I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on March 15, 2007.

Frank C. Eisenschenk, Ph.D., Patent Attorney

AMENDMENT UNDER 37 C.F.R. § 1.116
Examining Group 1617
Patent Application
Docket No. USF-106XC1
Serial No. 10/378,956

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Leonard M. Williams
Art Unit	:	1617
Applicants	:	Michael J. Zaworotko, Brian Moulton, Nair Rodriguez-Hornedo
Serial No.	:	10/378,956
Filed	:	March 3, 2003
Conf. No.	:	4742
For	:	Multiple-Component Solid Phases Containing at Least One Active Pharmaceutical Ingredient

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

AMENDMENT UNDER 37 C.F.R. § 1.116

Sir:

Applicants request that the period for response be extended one month through and including March 15, 2007, the fees for which have been paid at the time this Amendment was filed.

In response to the Office Action dated November 15, 2006, please amend the above-identified patent application as follows:

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In the Claims

1-24 (canceled).

25 (currently amended). A method for identifying complementary chemical functionalities in order to form a desired supramolecular synthon, said method comprising:

(a) evaluating the structure of an active pharmaceutical ingredient;

(b) determining whether the active pharmaceutical ingredient contains chemical functionalities capable of forming supramolecular synthons with itself (a first supramolecular synthon);

(c) identifying, from a plurality of chemical functionalities that are known to form a supramolecular synthon, at least one functionality that will form a second supramolecular synthon with the first supramolecular synthon formed by the active pharmaceutical ingredient, wherein the identified chemical functionality is not capable of disrupting non-covalent bonding within the supramolecular synthon formed by the active pharmaceutical ingredient, and wherein the selected chemical functionality is capable of forming a noncovalent bond to the supramolecular synthon formed by the active pharmaceutical ingredient;

(d) identifying co-crystal formers having at least one functionality identified in step (c); and

(e) preparing a multiple-component solid phase composition, wherein the multiple-component solid phase composition is a crystal that comprises the active pharmaceutical ingredient and at least one of the identified co-crystal formers.

26 (canceled).

27 (previously presented). The method of claim 25, wherein the at least one co-crystal former is selected from the group consisting of a different active pharmaceutical ingredient, a GRAS compound, a food additive, a low toxicity organic, and a metal-organic complex.

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28 (previously presented). The method of claim 25, wherein the multiple-component solid phase composition is formed by one or more methods selected from the group consisting of crystallization from solution, cooling the melt, sublimation, and grinding.

29-36 (canceled).

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Remarks

Claims 1-24 and 29-36 are pending in the subject application. Applicants acknowledge that claims 1-24 and 29-36 stood withdrawn from further consideration as being drawn to a non-elected invention. By this Amendment, Applicants have amended claim 25 and canceled claims 1-24 and 29-36. Support for the amendments can be found throughout the subject specification and in the claims as originally filed (see, for example, paragraphs 38, 42 and 46). Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 25, 27, and 28 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

At the outset, Applicants thank the Examiner for the courtesy of the interview conducted on 21 February 2007 where issues related to the prior art reference of record were discussed (*e.g.*, issues related to the effective filing dates of various passages within the reference). Applicants also acknowledge the indication that the previous rejection of claims 25-28 under 35 U.S.C. §112, second paragraph, as indefinite has been withdrawn.

Claims 25-28 are rejected under 35 U.S.C. § 102(e) as anticipated by Almarsson *et al.* (United States Patent No. 6,559,293, hereinafter referred to as the "'293 patent"). The Office Action argues that the '293 patent states:

> The present invention involves the unexpected discovery that the sulfamate (--OSO_2 NH_2) group of topiramate is slightly acidic and thus may be a handle for generation of salts, co-crystals, and complexes with basic compounds such as, but not limited to, caffeine, N-methyl pyrrolidine, nicotine, nicotinamide, and ethers such as PEGs (examples include but are not limited to PEG 200 and PEG 300). Salts are often associated with improved chemical stability and increased solubility of drugs leading to better delivery of drug to the body, by reducing unwanted degradation product exposure and increasing levels of drug in the body. Salt forms of drugs therefore constitute a useful set of options for development of drug formulations.

The Office Action further states:

> Co-crystals and complexes of topiramate and other compounds can be prepared using conventional crystallization techniques, e.g., from solutions comprising topiramate and the other compounds. Without being limited by theory, it is believed that the compounds within co-crystals and complexes can interact via hydrogen bonding, ionic, or other interactions. Crystallization from melts of topiramate and other

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> compounds may also be used to prepare co-crystals or complexes of topiramate. For example, a co-crystal or complex of topiramate and caffeine can be prepared by melting and recrystallizing caffeine, allowing such to cool, then contacting topiramate melt with the recrystallized caffeine, and allowing this to cool. In a particular method, caffeine is melted and recrystallized between a glass slide and glass cover slip on a hot-stage microscope (such as a Mettler-Toledo FP950tstage mounted on a Zeiss Axioplan II polarized light microscope). The hot-stage is allowed to cool to about 30° C. Topiramate is then placed on a glass slide in contact with the edge of the glass cover slip. The solid topiramate is melted and the melt is allowed to come into contact with the recrystallized caffeine. The temperature of the hot stage is lowered (e.g., to about 70° C.) and held there overnight. During that time the melted topiramate recrystallizes and a cocrystalline phase crystallizes between the caffeine and topiramate regions. The slide can then be heated to determined the melting point of the caffeine:topiramate co-crystal.

Applicants respectfully submit that the '293 patent is not prior art to the subject invention as certain of the passages relied upon in establishing this rejection under section 102(e) of Title 35 are not present in the priority document filed February 15, 2002 and a rejection under § 102(e) is not appropriate under such circumstances.

For example, the paragraph beginning at column 14, line 60, is not present in United States Provisional Patent Application 60/256,764 (filed February 15, 2002). Rather, this application contains the following passage (see page 14, lines 24-29):

> The present invention involves the unexpected discovery that the sulfamate ($-OSO_2NH_2$) group of topiramate is slightly acidic and thus may be a handle for generation of salts. Salts are often associated with improved chemical stability and increased solubility of drugs leading to better delivery of drug to the body, by reducing unwanted degradation product exposure and increasing levels of drug in the body. Salt forms of drugs therefore constitute a useful set of options for development of drug formulations.

Applicants respectfully submit that the passage referred to in the rejection of record is first disclosed in United States Provisional Patent Application 60/380,288 (filed May 15, 2002) at page 16, last paragraph of the priority document. With respect to the passage at column 14, lines 14-26, the language related to ", co-crystals, and complexes with basic compounds such as, but not limited to, caffeine, N-methyl pyrrolidine, nicotine, nicotinamide, and ethers such as PEGs (examples include but are not limited to PEG 200 and PEG 300)" is not found in the '764 application. The '288 patent application states this passage as "The present invention involves the unexpected discovery that the

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sulfamate ($-OSO_2NH_2$) group of topiramate is slightly acidic and thus may be a handle for generation of salts, or a co-crystal or complex with the basic compound caffeine. Salts are often associated with improved chemical stability and increased solubility of drugs leading to better delivery of drug to the body, by reducing unwanted degradation product exposure and increasing levels of drug in the body. Salt forms of drugs therefore constitute a useful set of options for development of drug formulations" (see page 15, line 29 through to page 16, line 2). The current version of this passage first appears in the paragraph bridging pages 15-16 of United States Provisional Patent Application 60/406,974 (filed August 30, 2002). Finally, Applicants respectfully submit that the Example relied upon in establishing this rejection is also not found in the earliest priority document for the '293 patent. Rather, Example 7 of the '293 patent is first disclosed as Example 6 in United States Provisional Patent Application 60/380,288 (filed May 15, 2002) at page 37. Accordingly it is respectfully submitted that the portions of the '293 patent relied upon for establishing the rejection of record are not prior art under 35 U.S.C. § 102(e) to the claimed invention and withdrawal of the rejection is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

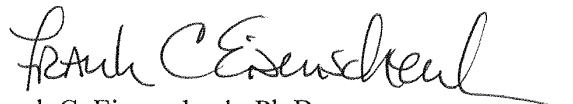
In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

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Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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FCE/sl

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Electronic Patent Application Fee Transmittal

Application Number:	10378956
Filing Date:	03-Mar-2003
Title of Invention:	Multiple-component solid phases containing at least one active pharmaceutical ingredient
First Named Inventor/Applicant Name:	Michael J. Zaworotko
Filer:	Frank Christopher Eisenschenk/Sherry Loke
Attorney Docket Number:	USF-106XC1
Filed as Small Entity	

Utility Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 1 month with $0 paid	2251	1	60	60

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**60**

Electronic Acknowledgement Receipt	
EFS ID:	1594744
Application Number:	10378956
International Application Number:	
Confirmation Number:	4742
Title of Invention:	Multiple-component solid phases containing at least one active pharmaceutical ingredient
First Named Inventor/Applicant Name:	Michael J. Zaworotko
Customer Number:	23557
Filer:	Frank Christopher Eisenschenk/Sherry Loke
Filer Authorized By:	Frank Christopher Eisenschenk
Attorney Docket Number:	USF-106XC1
Receipt Date:	15-MAR-2007
Filing Date:	03-MAR-2003
Time Stamp:	12:52:27
Application Type:	Utility

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$60
RAM confirmation Number	1718
Deposit Account	190065
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 and 1.17	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)
1		Amd-final.pdf	344597	yes	7
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Amendment After Final		1	1	
	Claims		2	3	
	Applicant Arguments/Remarks Made in an Amendment		4	7	
Warnings:					
Information:					
2	Fee Worksheet (PTO-06)	fee-info.pdf	8204	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	352801		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT APPLICATION FEE DETERMINATION RECORD
Effective January 1, 2003

Application or Docket Number: 10378986

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	36	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	36 minus 20 =	* 16
INDEPENDENT CLAIMS	9 minus 3 =	* 6
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	$375	OR	BASIC FEE	$750
X$ 9=	144	OR	X$18=	234
X42=	252	OR	X84=	504
+140=		OR	+280=	
TOTAL	771	OR	TOTAL	

7-27-06

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 35	Minus	** 36	=
Independent	* 9	Minus	*** 9	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

3-15-07

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 3	Minus	** 36	= —
Independent	* 1	Minus	*** 9	= —
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

		OR		
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=	—	OR	X$18=	
X42=	—	OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE	—	OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

		OR		
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

FORM PTO-875 (Rev. 1/07) — Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

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UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/378,956	03/03/2003	Michael J. Zaworotko	USF-106XC1	4742

23557 7590 04/24/2007

SALIWANCHIK LLOYD & SALIWANCHIK
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PO BOX 142950
GAINESVILLE, FL 32614-2950

EXAMINER	
WILLIAMS, LEONARD M	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
04/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

UM00014271
NOVARTIS EXHIBIT 1017
Novartis v. Regents, IPR2023-01346
Page 3010 of 4460

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/378,956	Applicant(s) ZAWOROTKO ET AL.	
	Examiner Leonard M. Williams	Art Unit 1617	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 15 March 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: _____.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

LMW

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER

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Page 3011 of 4460

Continuation of 11. does NOT place the application in condition for allowance because: The applicants have argued that the prior art applied does not constitute prior art under 102(e). The examiner respectfully does not agree. The amendment propsed by the applicants would require additional searching to fully evaluate thus it is not entered.

UM00014273
NOVARTIS EXHIBIT 1017
Novartis v. Regents, IPR2023-01346
Page 3012 of 4460

I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on March 15, 2007.

Frank C Eisenschenk

Frank C. Eisenschenk, Ph.D., Patent Attorney

AMENDMENT UNDER 37 C.F.R. § 1.116
Examining Group 1617
Patent Application
Docket No. USF-106XC1
Serial No. 10/378,956

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Leonard M. Williams
Art Unit	:	1617
Applicants	:	Michael J. Zaworotko, Brian Moulton, Nair Rodriguez-Hornedo
Serial No.	:	10/378,956
Filed	:	March 3, 2003
Conf. No.	:	4742
For	:	Multiple-Component Solid Phases Containing at Least One Active Pharmaceutical Ingredient

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

DO Not Enter

AMENDMENT UNDER 37 C.F.R. § 1.116

Sir:

Applicants request that the period for response be extended one month through and including March 15, 2007, the fees for which have been paid at the time this Amendment was filed.

In response to the Office Action dated November 15, 2006, please amend the above-identified patent application as follows:

J:\USF\106XC1\Amend-Resp\Amd.final.doc/DNB/sl

FACSIMILE COVER SHEET

SALIWANCHIK, LLOYD & SALIWANCHIK
A Professional Association
P.O. Box 142950
Gainesville, FL 326142950
Telephone (352) 375-8100
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RECEIVED
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MAY 15 2007

TO:	Examiner Leonard Williams	**FROM:**	Frank C. Eisenschenk, Ph.D.
COMPANY:	U.S. Patent Office	**DATE:**	May 15, 2007
FAX NO.:	(571)273-8300	**NO. OF PAGES (INCLUDING COVER SHEET):**	3

SUBJECT/MESSAGE:

Re: U.S. Patent Application Docket No. USF-106XC1
MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT
(Zaworotko, Moulton, Rodriguez-Hornedo)
Serial No. 10/378,956; filed March 3, 2003

Attachments: Request for Continued Examination (RCE) Transmittal (1 page)
Request for a Limited Suspension of Action After a Request for Continued Examination (RCE) (1 page)

THIS IS AN OFFICIAL DOCUMENT.

PLEASE DELIVER IMMEDIATELY.

The information contained in this facsimile message is intended only for the personal and confidential use of the designated recipients named above. This message may be an attorney-client communication, and as such is privileged and confidential. If the reader of this message is not the intended recipient or an agent responsible for delivering it to the intended recipient, you are hereby notified that you have received this document in error, and that any review, dissemination, distribution, or copying of this message is strictly prohibited. If you have received this communication in error, please notify us immediately by telephone and return the original message by mail. Thank you.

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MAY 15 2007

PTO/SB/30 (09-03)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	10/378,956
Filing Date	March 3, 2003
First Named Inventor	Michael J. Zaworotko
Art Unit	1617
Examiner Name	Leonard M. Williams
Attorney Docket Number	USF-106XC1

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).
   - a. [✓] Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
     - i. [ ] Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
     - ii. [ ] Other _____
   - b. [✓] Enclosed
     - i. [ ] Amendment/Reply
     - ii. [ ] Affidavit(s)/ Declaration(s)
     - iii. [ ] Information Disclosure Statement (IDS)
     - iv. [✓] Other Req. for a Limited Suspension of Action
2. Miscellaneous
   - a. [ ] Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)
   - b. [ ] Other _____
3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
   The Director is hereby authorized to charge the following fees, or credit any overpayments, to
   - a. [✓] Deposit Account No. 10-0065
     - i. [✓] RCE fee required under 37 CFR 1.17(e) ($790.00 BASED ON LARGE ENTITY STATUS)
     - ii. [✓] Extension of time fee (37 CFR 1.136 and 1.17) ($960 FOR THE DIFFERENCE BETWEEN A 1 AND 3 MONTH EOT)
     - iii. [ ] Other _____
   - b. [ ] Check in the amount of $ _____ enclosed
   - c. [ ] Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Name (Print/Type)	FRANK C. EISENSCHENK, PH.D.	Registration No. (Attorney/Agent)	45,332
Signature		Date	May 15, 2007

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Name (Print/Type)	FRANK C. EISENSCHENK, PH.D.		
Signature		Date	May 15, 2007

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.
If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2

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05/16/2007 HVUONG1 00000039 190065 10378956
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MAY 15 2007

I hereby certify that this correspondence is being facsimile transmitted to the United States Patent and Trademark Office on May 15, 2007.

Frank C. Eisenschenk, Ph.D., Patent Attorney

REQUEST FOR A LIMITED SUSPENSION OF ACTION
Docket No. USF-106XC1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Leonard Williams
Art Unit	:	1765
Applicants	:	Michael J. Zaworotko, Brian Moulton, Nair Rodriguez-Hornedo
Serial No.	:	10/378,956
Filed	:	March 3, 2003
Conf. No.	:	4742
For	:	Multiple-Component Solid Phases Containing at Least One Active Pharmaceutical Ingredient

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

REQUEST FOR A LIMITED SUSPENSION OF ACTION AFTER A REQUEST FOR CONTINUED APPLICATION (RCE)

Sir:

Applicants hereby request a suspension of action in this matter under 37 C.F.R. §1.103(c). This paper is being filed with a request for continued examination in compliance with § 1.114 and Applicants request that action in this application be suspended for a period of three (3) months. The processing fee of $130.00, set forth in § 1.17(i) may be charged to Deposit Account No. 190065.

The Commissioner is hereby authorized to charge any other necessary fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 190065.

Respectfully submitted,

05/16/2007 HVUONG1 00000039 190065 10378956
03 FC:1464 130.00 DA

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

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NOVARTIS EXHIBIT 1017
Novartis v. Regents, IPR2023-01346
Page 3016 of 4460

I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on August 3, 2007.

Frank C. Eisenschenk

Frank C. Eisenschenk, Ph.D., Patent Attorney

AMENDMENT UNDER 37 C.F.R. § 1.111
Examining Group 1617
Patent Application
Docket No. USF-106XC1
Serial No. 10/378,956

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Leonard M. Williams
Art Unit	:	1617
Applicants	:	Michael J. Zaworotko, Brian Moulton, Nair Rodriguez-Hornedo
Serial No.	:	10/378,956
Filed	:	March 3, 2003
Conf. No.	:	4742
For	:	Multiple-Component Solid Phases Containing at Least One Active Pharmaceutical Ingredient

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

SUPPLEMENTAL AMENDMENT UNDER 37 C.F.R. § 1.111

Sir:

In response to the Office Action dated November 15, 2006 and the Advisory Action dated April 24, 2007, please amend the above-identified patent application as follows:

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In the Claims

1-24 (canceled).

25 (previously presented). A method for identifying complementary chemical functionalities in order to form a desired supramolecular synthon, said method comprising:

(a) evaluating the structure of an active pharmaceutical ingredient;

(b) determining whether the active pharmaceutical ingredient contains chemical functionalities capable of forming supramolecular synthons with itself (a first supramolecular synthon);

(c) identifying, from a plurality of chemical functionalities that are known to form a supramolecular synthon, at least one functionality that will form a second supramolecular synthon with the first supramolecular synthon formed by the active pharmaceutical ingredient, wherein the identified chemical functionality is not capable of disrupting non-covalent bonding within the supramolecular synthon formed by the active pharmaceutical ingredient, and wherein the selected chemical functionality is capable of forming a noncovalent bond to the supramolecular synthon formed by the active pharmaceutical ingredient;

(d) identifying co-crystal formers having at least one functionality identified in step (c); and

(e) preparing a multiple-component solid phase composition, wherein the multiple-component solid phase composition is a crystal that comprises the active pharmaceutical ingredient and at least one of the identified co-crystal formers.

26 (canceled).

27 (previously presented). The method of claim 25, wherein the at least one co-crystal former is selected from the group consisting of a different active pharmaceutical ingredient, a GRAS compound, a food additive, a low toxicity organic, and a metal-organic complex.

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28 (previously presented). The method of claim 25, wherein the multiple-component solid phase composition is formed by one or more methods selected from the group consisting of crystallization from solution, cooling the melt, sublimation, and grinding.

29-36 (canceled).

37 (new). The method according to claim 25, wherein said active pharmaceutical ingredient is selected from aspirin, ibuprofen, flurbiprofen, carbamazepine, phenytoin or acetaminophen.

38 (new). A method for identifying complementary chemical functionalities in order to form a desired supramolecular synthon, said method comprising:

(a) selecting an active pharmaceutical ingredient and evaluating the structure of said active pharmaceutical ingredient;

(b) determining whether the active pharmaceutical ingredient contains chemical functionalities capable of forming supramolecular synthons with itself (a first supramolecular synthon);

(c) identifying, from a plurality of chemical functionalities that are known to form a supramolecular synthon, at least one functionality that will form a second supramolecular synthon with the first supramolecular synthon formed by the active pharmaceutical ingredient, wherein the identified chemical functionality is not capable of disrupting non-covalent bonding within the supramolecular synthon formed by the active pharmaceutical ingredient, and wherein the selected chemical functionality is capable of forming a noncovalent bond to the supramolecular synthon formed by the active pharmaceutical ingredient;

(d) identifying co-crystal formers having at least one functionality identified in step (c) and selecting said identified co-crystal formers for the preparation of a multiple component solid phase composition; and

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Novartis v. Regents, IPR2023-01346
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(e) preparing a multiple-component solid phase composition, wherein the multiple-component solid phase composition is a crystal that comprises the active pharmaceutical ingredient and at least one of the identified co-crystal formers.

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Remarks

Claims 25, 27 and 28 are pending in the subject application. By this Amendment, Applicants have added claims 37 and 38. Support for the new claims can be found throughout the subject specification and in the claims as originally filed (see, for example, paragraphs 8-10, 49-55 and Figure 24). Entry and consideration of the new claims presented herein is respectfully requested. Accordingly, claims 25, 27, 28 and 37-38 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

On March 15, 2007, Applicants submitted an after-final Amendment amending claim 25 and canceling claims 1-24 and 29-36. Applicants note that a Request for Continued Examination was filed on May 15, 2007 requesting that the previously submitted after-final Amendment be entered and considered. Applicants note that in this supplemental Amendment, claim 25 has been indicated as previously amended and claims 1-24 and 29-36 have been indicated as canceled (previously amended via the request for entry of the non-entered after-final amendment in the RCE of May 15, 2007). Applicants have also added new claims 37-38 in this supplemental Amendment.

Submitted with this Amendment is a supplemental Information Disclosure Statement for the Examiner's consideration. Applicants request that the references in the IDS be made of record in the subject application.

At the outset, Applicants thank the Examiner for the courtesy of the interview conducted on 21 February 2007 where issues related to the prior art reference of record were discussed (*e.g.*, issues related to the effective filing dates of various passages within the reference). Applicants also acknowledge the indication that the previous rejection of claims 25-28 under 35 U.S.C. §112, second paragraph, as indefinite has been withdrawn.

Claims 25-28 are rejected under 35 U.S.C. § 102(e) as anticipated by Almarsson *et al.* (United States Patent No. 6,559,293, hereinafter referred to as the '"293 patent"). The Office Action argues that the '293 patent states:

> The present invention involves the unexpected discovery that the sulfamate (--OSO_2 NH_2) group of topiramate is slightly acidic and thus may be a handle for generation of salts, co-crystals, and complexes with basic compounds such as, but not limited to, caffeine, N-methyl pyrrolidine, nicotine, nicotinamide, and ethers such as PEGs (examples include but are not limited to PEG 200 and PEG 300). Salts are

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> often associated with improved chemical stability and increased solubility of drugs leading to better delivery of drug to the body, by reducing unwanted degradation product exposure and increasing levels of drug in the body. Salt forms of drugs therefore constitute a useful set of options for development of drug formulations.

As is apparent, this passage relates to the formation of salts, not crystals comprising at least one active pharmaceutical ingredient (API) and a co-crystal former. Thus, this passage cannot be said to anticipate the claimed invention.

The Office Action further states:

> Co-crystals and complexes of topiramate and other compounds can be prepared using conventional crystallization techniques, e.g., from solutions comprising topiramate and the other compounds. Without being limited by theory, it is believed that the compounds within co-crystals and complexes can interact via hydrogen bonding, ionic, or other interactions. Crystallization from melts of topiramate and other compounds may also be used to prepare co-crystals or complexes of topiramate. For example, a co-crystal or complex of topiramate and caffeine can be prepared by melting and recrystallizing caffeine, allowing such to cool, then contacting topiramate melt with the recrystallized caffeine, and allowing this to cool. In a particular method, caffeine is melted and recrystallized between a glass slide and glass cover slip on a hot-stage microscope (such as a Mettler-Toledo FP950tstage mounted on a Zeiss Axioplan II polarized light microscope). The hot-stage is allowed to cool to about 30° C. Topiramate is then placed on a glass slide in contact with the edge of the glass cover slip. The solid topiramate is melted and the melt is allowed to come into contact with the recrystallized caffeine. The temperature of the hot stage is lowered (e.g., to about 70° C.) and held there overnight. During that time the melted topiramate recrystallizes and a cocrystalline phase crystallizes between the caffeine and topiramate regions. The slide can then be heated to determined the melting point of the caffeine:topiramate co-crystal.

Applicants respectfully submit that the '293 patent is not prior art to the subject invention as certain of the passages relied upon in establishing this rejection under section 102(e) of Title 35 are not present in the priority document filed February 15, 2002 and a rejection under § 102(e) is not appropriate under such circumstances.

For example, the paragraph beginning at column 14, line 60, is not present in United States Provisional Patent Application 60/256,764 (filed February 15, 2002). Rather, this application contains the following passage (see page 14, lines 24-29):

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Novartis v. Regents, IPR2023-01346
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> The present invention involves the unexpected discovery that the sulfamate ($-OSO_2NH_2$) group of topiramate is slightly acidic and thus may be a handle for generation of salts. Salts are often associated with improved chemical stability and increased solubility of drugs leading to better delivery of drug to the body, by reducing unwanted degradation product exposure and increasing levels of drug in the body. Salt forms of drugs therefore constitute a useful set of options for development of drug formulations.

Again, as stated above, this passage relates to the formation of topiramate salts and does not anticipate the presently claimed method of forming a crystal comprising at least one API and a co-crystal former. Applicants further respectfully submit that the passage referred to in the rejection of record is first disclosed in United States Provisional Patent Application 60/380,288 (filed May 15, 2002) at page 16, last paragraph of the priority document.

With respect to the passage at column 14, lines 14-26, the language related to ", co-crystals, and complexes with basic compounds such as, but not limited to, caffeine, N-methyl pyrrolidine, nicotine, nicotinamide, and ethers such as PEGs (examples include but are not limited to PEG 200 and PEG 300)" is not found in the '764 application. The '288 patent application states this passage as "The present invention involves the unexpected discovery that the sulfamate ($-OSO_2NH_2$) group of topiramate is slightly acidic and thus may be a handle for generation of salts, or a co-crystal or complex with the basic compound caffeine. Salts are often associated with improved chemical stability and increased solubility of drugs leading to better delivery of drug to the body, by reducing unwanted degradation product exposure and increasing levels of drug in the body. Salt forms of drugs therefore constitute a useful set of options for development of drug formulations" (see page 15, line 29 through to page 16, line 2). Applicants again respectfully submit that the current version of this passage first appears in the paragraph bridging pages 15-16 of United States Provisional Patent Application 60/406,974 (filed August 30, 2002).

Finally, Applicants respectfully submit that the Example (related to the formation of co-crystals and complexes of topiramate and other compounds) relied upon in establishing this rejection is also not found in the earliest priority document for the '293 patent. Rather, Example 7 of the '293 patent is first disclosed as Example 6 in United States Provisional Patent Application 60/380,288 (filed May 15, 2002) at page 37. Accordingly, it is respectfully submitted that the portions of the

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'293 patent relied upon for establishing the rejection of record are not prior art under 35 U.S.C. § 102(e) to the claimed invention and withdrawal of the rejection is respectfully requested.

While Applicants maintain that the '293 patent is not appropriate prior art to the instantly claimed invention, Applicants also submit, herewith, a Declaration under 37 C.F.R. § 1.131 antedating the '293 patent. As stated in the Declaration, the claimed invention was conceived and reduced to practice prior to February 15, 2002 in the United States. Accordingly, it is respectfully submitted that the cited reference is not prior art to the instantly claimed invention and reconsideration and withdrawal of the rejection of record is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

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Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/sl

Attachments: Supplemental Information Disclosure Statement
Declaration Under 37 C.F.R. § 1.131

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Leonard M. Williams
Art Unit	:	1617
Applicants	:	Michael J. Zaworotko, Brian Moulton, Nair Rodriguez-Hornedo
Serial No.	:	10/378,956
Filed	:	March 3, 2003
For	:	Multiple-Component Solid Phases Containing at Least One Active Pharmaceutical Ingredient

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF MICHAEL J. ZAWOROTKO, BRIAN MOULTON, AND NAIR RODRIGUEZ-HORNEDO UNDER 37 C.F.R. §1.131

Sir:

Michael J. Zaworotko, Brian Moulton and Nair Rodriguez-Hornedo declare:

1. That we are co-inventors of the invention disclosed and claimed in U.S. Application Serial No. 10/378,956;

2. That said invention was conceived and reduced to practice on, or before, February 15, 2002 (the critical date) in the United States;

3. That we conceived and reduced to practice methods for identifying complementary chemical functionalities that comprised evaluating the structure of an active pharmaceutical ingredient (API), determining whether the API contained chemical functionalities capable of forming supramolecular synthons with itself, identifying at least one other functionality that would form a second supramolecular synthon, identifying cocrystal formers having at least one

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Novartis v. Regents, IPR2023-01346
Page 3026 of 4460

functionality identified in the identifying step and preparing a multiple-component solid phase composition that is a crystal and that contains the API and at least one of the identified cocrystal formers;

4. That Exhibit 1 contains copies of abstracts discussing this technology that were submitted to the American Chemical Society on, or before, February 15, 2002 (see Abstracts 30 and 76). We hereby attest that the submission date of the abstracts to the American Chemical Society was prior to the critical date of February 15, 2002; and

5. Exhibit 2 contains a copy of an invention disclosure to the University of South Florida regarding the currently claimed technology. We hereby attest that the submission date of the invention disclosure has been redacted from the attached invention disclosure; however, the invention disclosure was submitted to the University of South Florida Division of Patents and Licensing prior to the critical date of February 15, 2002.

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NOVARTIS EXHIBIT 1017
Novartis v. Regents, IPR2023-01346
Page 3027 of 4460

We hereby further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Further, Declarants sayeth not.

By: _____ Date: 08/01/07
Michael J. Zaworotko

By: _____ Date: _____
Brian Moulton

By: _____ Date: _____
Nair Rodriguez-Hornedo

Attachment: Exhibit 1; Abstracts from the American Chemical Society, Division of Industrial and Engineering Chemistry
Exhibit 2; Invention Disclosure to the University of South Florida Division of Patents and Licensing

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Leonard M. Williams
Art Unit	:	1617
Applicants	:	Michael J. Zaworotko, Brian Moulton, Nair Rodriguez-Hornedo
Serial No.	:	10/378,956
Filed	:	March 3, 2003
For	:	Multiple-Component Solid Phases Containing at Least One Active Pharmaceutical Ingredient

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF MICHAEL J. ZAWOROTKO, BRIAN MOULTON, AND NAIR RODRIGUEZ-HORNEDO UNDER 37 C.F.R. §1.131

Sir:

Michael J. Zaworotko, Brian Moulton and Nair Rodriguez-Hornedo declare:

1. That we are co-inventors of the invention disclosed and claimed in U.S. Application Serial No. 10/378,956;

2. That said invention was conceived and reduced to practice on, or before, February 15, 2002 (the critical date) in the United States;

3. That we conceived and reduced to practice methods for identifying complementary chemical functionalities that comprised evaluating the structure of an active pharmaceutical ingredient (API), determining whether the API contained chemical functionalities capable of forming supramolecular synthons with itself, identifying at least one other functionality that would form a second supramolecular synthon, identifying cocrystal formers having at least one functionality

NOVARTIS EXHIBIT 1017
Novartis v. Regents, IPR2023-01346
Page 3029 of 4460

identified in the identifying step and preparing a multiple-component solid phase composition that is a crystal and that contains the API and at least one of the identified cocrystal formers;

4. That Exhibit 1 contains copies of abstracts discussing this technology that were submitted to the American Chemical Society on, or before, February 15, 2002 (see Abstracts 30 and 76). We hereby attest that the submission date of the abstracts to the American Chemical Society was prior to the critical date of February 15, 2002; and

5. Exhibit 2 contains a copy of an invention disclosure to the University of South Florida regarding the currently claimed technology. We hereby attest that the submission date of the invention disclosure has been redacted from the attached invention disclosure; however, the invention disclosure was submitted to the University of South Florida Division of Patents and Licensing prior to the critical date of February 15, 2002.

UM00014291
NOVARTIS EXHIBIT 1017
Novartis v. Regents, IPR2023-01346
Page 3030 of 4460

We hereby further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Further, Declarants sayeth not.

By: _____ Date: _____
Michael J. Zaworotko

By: _____ Date: 8/1/07
Brian Moulton

By: _____ Date: _____
Nair Rodriguez-Hornedo

Attachment: Exhibit 1; Abstracts from the American Chemical Society, Division of Industrial and Engineering Chemistry
Exhibit 2; Invention Disclosure to the University of South Florida Division of Patents and Licensing

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Patent Application
Docket No. USF-106XC1
Serial No. 10/378,956

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Leonard M. Williams
Art Unit	:	1617
Applicants	:	Michael J. Zaworotko, Brian Moulton, Nair Rodriguez-Hornedo
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For	:	Multiple-Component Solid Phases Containing at Least One Active Pharmaceutical Ingredient

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF MICHAEL J. ZAWOROTKO, BRIAN MOULTON, AND NAIR RODRIGUEZ-HORNEDO UNDER 37 C.F.R. §1.131

Sir:

Michael J. Zaworotko, Brian Moulton and Nair Rodriguez-Hornedo declare:

1. That we are co-inventors of the invention disclosed and claimed in U.S. Application Serial No. 10/378,956;

2. That said invention was conceived and reduced to practice on, or before, February 15, 2002 (the critical date) in the United States;

3. That we conceived and reduced to practice methods for identifying complementary chemical functionalities that comprised evaluating the structure of an active pharmaceutical ingredient (API), determining whether the API contained chemical functionalities capable of forming supramolecular synthons with itself, identifying at least one other functionality that would form a second supramolecular synthon, identifying cocrystal formers having at least one

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NOVARTIS EXHIBIT 1017
Novartis v. Regents, IPR2023-01346
Page 3032 of 4460

functionality identified in the identifying step and preparing a multiple-component solid phase composition that is a crystal and that contains the API and at least one of the identified cocrystal formers;

4. That Exhibit 1 contains copies of abstracts discussing this technology that were submitted to the American Chemical Society on, or before, February 15, 2002 (see Abstracts 30 and 76). We hereby attest that the submission date of the abstracts to the American Chemical Society was prior to the critical date of February 15, 2002; and

5. Exhibit 2 contains a copy of an invention disclosure to the University of South Florida regarding the currently claimed technology. We hereby attest that the submission date of the invention disclosure has been redacted from the attached invention disclosure; however, the invention disclosure was submitted to the University of South Florida Division of Patents and Licensing prior to the critical date of February 15, 2002.

UM00014294
NOVARTIS EXHIBIT 1017
Novartis v. Regents, IPR2023-01346
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We hereby further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Further, Declarants sayeth not.

By: _____ Date: _____
Michael J. Zaworotko

By: _____ Date: _____
Brian Moulton

By: _____ Date: July 31, 2003
Nair Rodriguez-Hornedo

Attachment: Exhibit 1; Abstracts from the American Chemical Society, Division of Industrial and Engineering Chemistry
Exhibit 2; Invention Disclosure to the University of South Florida Division of Patents and Licensing

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Exhibit 1

NOVARTIS EXHIBIT 1017
Novartis v. Regents, IPR2023-01346
Page 3035 of 4460



American Chemical Society
Division of Industrial & Engineering Chemistry

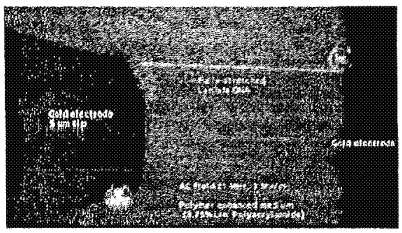
ABSTRACTS

223rd ACS NATIONAL MEETING
ORLANDO, FL
APRIL 7–11, 2002

R. M. Chamberlin, Program Chair

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27.
OPTIMIZED SYSTEM FOR IMMOBILIZATION AND STRETCHING OF SINGLE DNA MOLECULES IN MICROFLUIDIC DEVICES. *Vijay Namasivayam, Department of Chemical Engineering, The University of Michigan, 2300 Hayward, #3085 HH Dow, Ann Arbor, MI 48109, Fax: 734-763-0459, nvijay@engin.umich.edu, Ronald G. Larson, Dept. of Chemical Eng, University of Michigan, David Burke, Department of Human Genetics, University of Michigan, and Mark A. Burns, Department of Chemical Engineering and Department of Biomedical Engineering, University of Michigan*



28.
CRYSTAL ENGINEERING. *Gautam R. Desiraju, School of Chemistry, University of Hyderabad, Hyderabad 500 046, India, Fax: 91-40-3010567, desiraju@uohyd.ernet.in*

Crystal engineering, the design of organic solids, has emerged as an important cross-disciplinary field of basic and applied endeavour and is representative of both established and upcoming streams of chemistry. It is traditional in that it focuses on the relationships between structure and properties. In this respect, it is like physical organic chemistry. Being a synthetic activity, it is also like organic synthesis. It is modern in that it is based on supramolecular chemistry wherein reversibility, kinetics and entropy are all-important contributors to both structure and function. Crystallisation is a supramolecular reaction, and it is important that one is able to understand it before systematic crystal design is a reality. The essence of synthetic strategy in crystal engineering is to select molecules/systems wherein the intermolecular interactions are obtained hierarchically, in other words the strongest interactions are also the most predictable. Accordingly, the element of modularity is introduced into crystal design. In general, supramolecular function is not modular. But, by choosing the system appropriately the chemist tries to obtain a situation which approximates to the modular. Ideal hierarchic situations are not found often. One of the aims of crystal engineering is to recognise these situations, if possible try and avoid them and in the best cases overcome the problems presented by them. Crystal engineering is the planned synthesis of an organic or metal–organic crystal structure associated with a particular predesired property. If one can predict and control crystal structure of molecules, then one can in principle control the properties of the resulting solids. One moves therefore from structure design to property design. However, because the physical origin of many properties of general and practical interest differs from case to case, there can be no unified concept of design. Properties involving mainly cooperative effects of coupling will certainly be the most difficult to access by rational routes, if such a goal is ever achieved. Others that can be more or less derived logically from molecular attributes, such as the majority of chemical properties are to a great extent realisable. These and related issues will be covered in this talk.

29.
POLYTYPISM, REACTION CAVITIES AND MECHANISTIC EXPERIMENTS: TOOLS FOR THE DESIGN, DISCOVERY AND UNDERSTANDING OF NEW SOLID-STATE REACTIONS. *Bruce M. Foxman, Magali Bourghol, and Wen Shang, Department of Chemistry, Brandeis University, 415 South Street, P. O. Box 549110, Waltham, MA 02454-9110, Fax: 781-736-2516, foxman1@brandeis.edu*

Metal coordination polymers containing ligands with pendant unsaturated groups are excellent synthons for stereospecific solid-state syntheses. Recent results to be discussed include (i) the occurrence of polytypes in simple metal carboxylate salts such as potassium acrylate or sodium trans-2 butenoate, and their comparative effects on solid-state reactivity; and (ii) use of deuterium-labeling experiments to explore the mechanism of the γ-ray induced cyclodimerization reaction of bis(trans-2-butenoato) calcium. In addition to the use of bilayer formation as a steering device to produce reactive crystals, very recent work in our laboratory focuses on the creation of "ionic cavities" in crystals, where reaction between localized sets of unligated, unsaturated carboxylates can occur. This technique has allowed us to explore a unique one reaction of trans-2-butenoate, as well as to plan small-molecule syntheses starting with acrylates and methacrylates, species which usually undergo polymerization in the solid state.

30.
BINARY CRYSTALS BY DESIGN. *Michael J. Zaworotko, Chemistry, University of South Florida, 4202 E. Fowler Avenue, SCA 400, Tampa, FL 33620, Fax: 813-974-1733, zaworo@chuma1.cas.usf.edu*

The design of binary crystalline compounds relies upon understanding how complementary supramolecular synthons influence composition and structure in the solid state. In this paper we shall present details concerning a range of new binary cocrystals that involve carboxylic acid, amide or ether moieties. The molecular components generate the expected stoichiometry and, in some cases, predictable crystal packing motifs. An analysis of the structure and physical properties of the new binary cocrystals will be presented. The results will be discussed in the context of how one might exploit our results in order to generate novel pharmaceutical phases.

31.
C-H···X HYDROGEN BONDING IN THE CRYSTALLINE STATE. *Kenneth R. Seddon, and Jan Albert van den Berg, QUILL Research Centre, The Queen's University of Belfast, David Keir Building, Stranmillis Road, Belfast BT9 5AG, United Kingdom, Fax: +44 28 90665297, k.seddon@qub.ac.uk*

We examined the C-H···Cl interaction and analysed it statistically. It was shown that the concept of Van der Waals radii was not sufficient to predict the presence or absence of hydrogen bonds in the crystalline state. Here, we have extended this survey of the crystallographic database to determine the contact characteristics of type C-H···X, where X=F, Cl, Br, I, N, P, O or S. We also looked at some of the structures from an ab initio perspective using modern AIM ('Atoms in Molecules') theory to determine the characteristics of hydrogen bonds obtained within the database. This enabled us to statistically quantify parameters within the limits of the crystalline phase. Ultimately, we show that C-H···X hydrogen bonds are a general phenomenon, and cannot be adequately described using the Van der Waals formalism.

32.
ORGANIC ION-RADICAL CRYSTALS. PACKING PARAMAGNETIC ORGANIC MOLECULES. *Silas C. Blackstock, Peera Acharasatian, Kye-Young Kim, and Byron J. McGee, Department of Chemistry, The University of Alabama, P. O. Box 870336, Tuscaloosa, AL 35487, blackstock@ua.edu*

The crystal packing of a series of stable organic radical ions will be presented with an emphasis on dissecting effects of specific, weak, (even some covalent-based) anion-cation attractions on aggregation geometry. Nitrosyl sulphonates and their aggregation in the solid state as a function of cation identity will be discussed. Within this context, high resolution x-ray structures of the two polymorphs of Fremy's Salt will presented for the first time. Another series of structures to be presented contain the radical cation of tetra-anisyl-p-phenylene-diamine (TAPD). Specific cation-anion CH—O interactions are proposed to play a role in packing of TAPD+ salts. Finally, a case of charge-transfer crystallization will be presented. Here, an extremely endothermic electron transfer between a donor (D) and an acceptor (A) in solution yields a D+A- crystal structure. The basis of an energetic payoff for ionization during crystallization and possible mechanisms of crystal growth will be discussed.

33.
STUDIES OF THE GROWTH AND MORPHOLOGY OF CRYSTALS TEMPLATED ON CRYSTALS. *G. Tayhas R. Palmore, and Tzy-Jiun Mark Luo, Division of Engineering, Box D, Brown University, 182 Hope Street, Providence, RI 02912, Tayhas_Palmore@brown.edu*

We are interested in how chemical additives influence the kinetics of crystal growth for the purpose of controlling the size, shape and quality of crystals templated on the surface of other crystals. We have studied the growth of crystals comprised of bis(imidazolium 2,6-pyridinedicarboxylate)Cu(II)trihydrate

zeolite supported POM was more efficient, with the highest kobs (3.18*10-3 min-1) at pH 7.0, 300nm. The role of HCO3- was found less significant in the photodegradation kinetics of OCB with zeolite/ Preyssler system than with TiO2.

71.
SYNTHETIC LUBRICANTS FROM EPOXIDIZED SOYBEAN OIL: STRUCTURAL EFFECTS ON POUR POINT AND OXIDATIVE STABILITY. *Sevim Z. Erhan, National Center for Agricultural Utilization Research/ARS/USDA, 1815 N. University St., Peoria, IL 61604, Fax: (309)681-6340, erhansz@ncaur.usda.gov, and Hong-Sik Hwang, National Center for Agriculatural Utilization Research/ARS/USDA*

A variety of lubricant base fluids have been prepared from epoxidized soybean oil by chemical modification. Epoxidized soybean oil has been transformed to ring-opened products by reaction with various alcohols in the presence of sulfuric acid as a catalyst. Considerable amounts of transesterification products are observed during the ring-opening reaction. Acid anhydride has been then used to esterify the hydroxy groups in the ring-opened product. Structural effect of substituents on pour points of the product in the presence and absence of 1% PPD (pour point depressant) will be discussed. A modified Penn State micro-oxidation test of three selected products shows these lubricant candidates to have similar or better oxidative stability relative to synthetic lubricant base fluids such as PAO and adipate.

72.
SYNTHESIS OF 4-(TRIALKYLAMMONIUM) PROPANSULTANS AND THEIR APPLICATIONS TO NEW PHASE-TRANSFER CATALYSTS. *Maw-Ling Wang, Department of Chemical Engineering, Tung Hai University, Taichung Port Road, Section 3, Taichung 407, Taiwan, Fax: (04)-2359-0009, chmmlw@mail.thu.edu.tw, and Wei-Hung Chen, Department of Chemical Engineering, Chung Cheng University*

In this work, 4-(trialkylammonium) propansultan (TAAPS) was first developed as the new phase transfer catalyst. The addition reactions of 1,3-propane sultone (PS) and trialkylammines (TAAs) were successfully carried out to synthesize sulfobetaines (i.e. 4-(trialkylammonium) propansultans, TAAPSs) in a homogeneous solution. For the first time, five different TAAPSs, which possess high reactivity, stability, selectivity and performance, were employed as phase-transfer catalysts in synthesis dialkoxymethanes in this work. The reaction of alcohols and dibromomethane in an high alkaline solution of KOH/organic solvent two-phase medium to produce dialkoxymethanes were carried out under phase-transfer catalysis using 4-(trialkylammonium) propansultans as the catalysts. From the experimental observation, a rational reaction mechanism using this new phase-transfer catalyst was proposed. Kinetics of the reaction was studied in detail.

73.
SIMULATION OF SO2 TO SO3 IN A NON-ISOTHERMAL MULTI-TUBE FIXED-BED REACTOR. *Selahattin Gultekin, Department of Sciences/Chemistry Divisison, Dogus University, Zeamet Sok. No. 21, Acibadem, Kadikoy, Istanbul 81010, Turkey, Fax: +90 216 3279631, sgultekin@dogus.edu.tr, and Nurdan Ilhan, Evyap Chemical Co*

In this study, the oxidation of SO2 to SO3 was considered in a non-isothermal multi-tube fixed-bed reactor. The reaction SO2 + * O2—SO3 DH <0 is exothermic and reversible like ammonia and methanol synthesis reactions. The reactor simulation, therefore, is rather involved. Especially, the effects of the variations of some parameters such as inlet feed temperature, coolant initial temperature, pressure, feed rate, pipe diameter and pipe length on the conversion rate of the reaction were investigated. Changes of the conversion rate with respect to each of these parameters are given in graphical forms and interpreted accordingly. In the model equations that were derived for the system, the variables (like T, P, D, F, L...) affecting directly the process were used.Mathematical package program MATLAB was used to solve these equations. The numerical results obtained from the solutions of the simultaneous differential equations are examined and compared with the expected results from the theory of the related reaction. The results were then interpreted accordingly by considering the nature of the reaction under study.

74.
ELECTROCHEMICALLY GENERATED SUPEROXIDE ION IN IONIC LIQUIDS: APPLICATIONS TO GREEN CHEMISTRY. *Ines M AlNashef, Michael A. Matthews, and John W. Weidner, Department of Chemical Engineering, University of South Carolina, 301 Main, Columbia, SC 29208, Fax: 803-777-8265, alnashef@engr.sc.edu*

Green chemical technology is concerned with reducing the waste from an industrial chemical process to zero. Its implementation will lead to a cleaner environment. The introduction of greener technologies has become a major concern throughout both industry and academia. Room temperature ionic liquids (RTILs) are emerging as potential replacements for volatile organic compounds. They are nonvolatile and non-flammable. The superoxide ion can be electrochemically generated in RTILs. We have shown that the superoxide ion in RTIL can be used to destroy polyhalogenated aromatic hydrocarbons, which represent a major environmental problem. The electrochemically generated superoxide ion can also activate CO_2 to give a carboxylating reagent, which can be used for the synthesis of a number of organic compounds.

75.
EFFECT OF EMULSIFIED STOCK ON PRODUCT DISTRIBUTION OF FCC. *Chao-He Yang, and Yu-dong Sun, State Key Lab of Heavy Oil Processing, University of Petroleum, 271 North Second Road, Dongying 257061, China, yangch@hdpu.edu.cn*

FCC reaction property was contrasted between two kinds of emulsified oil and atmospheric residue in a confined fluidized bed reactor (CFBR). According to the "demolition atomization" theory that secondary atomization can form smaller oil drop in riser, and the invigorating effect of emulsifier to FCC which can promote the heavy oil FCC reactions. The CFBR experimental results indicate that emulsions have better FCC reaction characteristics than atmospheric residue. Under the same reaction conditions, the conversion of emulsified residue increase by 4 to 7 percent, gasoline yield 1 to 4 percent, LPG yield 1.3 to 2 percent, dry gas yield about 0.8 percent, diesel oil yield decrease by 0.2 to 1.5 percent, heavy oil yield about 5 percent, and coke yield is similar. At the approximate conversion, the selectivity of emulsions are superior to that of atmospheric residue. The difference of FCC reaction property of two emulsified oil is small.

76.
CRYSTAL ENGINEERING OF BINARY CRYSTALS THAT CONTAIN PHARMACEUTICAL MOLECULES. *Scott Fleischman, Leslie Ann Morales, and Michael J. Zaworotko, Department of Chemistry, University of South Florida, University of South Florida, 4202 E Fowler Ave SCA 400, Tampa, FL 33620, s_fleisch@yahoo.com, lmorales@chuma.cas.usf.edu*

The design of binary compounds using complementary molecules represents an example of an application of crystal engineering. Pharmaceutical molecules are inherently predisposed for such crystal engineering studies since they already contain molecular recognition sites that bind selectively to biomolecules, and they are prone to supramolecular self-assembly. Pharmaceutical molecules that we have explored and have been able to form co-crystals include ibuprofen and flurbiprofen. The co-crystals of ibuprofen/4,4'-dipyridyl, flurbiprofen/4,4'-dipyridyl and flurbiprofen/trans-1,2-bis(4-pyridyl)ethylene have been characterized by various techniques and exhibit physical properties different from the parent compound as a direct result of hydrogen bonding interaction. These crystalline assemblies could afford improved drug solubility, dissolution rate, stability and bioavailability.

77.
COVALENTLY BONDING THE BONE CEMENT-METAL INTERFACE OF ORTHOPEDIC JOINTS WITH A SILOXANE LINKER. *Amy L. Vickers, and Marya Lieberman, Department of Chemistry and Biochemistry, University of Notre Dame, 251 Nieuwland Science Hall, Notre Dame, IN 46556, avickers@nd.edu*

Present joint implants have a finite lifetime, usually within ten to fifteen years. The major mechanism of failure in orthopedic joint implants is the debonding of the metal-bone cement interface. Any improvement to increase interfacial adhesion might extend and improve the implants' lifetimes. Current available formulas of bone cement consist of methyl methacrylate (MMA) that is mixed with polymethyl methacrylate (PMMA) and an initiator. The mixture polymerizes in a free radical mechanism, bonding the bone and metal implant surfaces

Exhibit 2

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BACKGROUND TO INVENTION

The last decade has witnessed tremendous advances in our understanding of and ability to manipulate molecular and supramolecular assemblies.[1] Indeed, it is fair to state that there are new paradigms concerning the design and synthesis of a new generation of functional materials and molecules. Such advances are a consequence of the fundamental importance of intermolecular interactions, structure and cooperativity in many aspects of molecular science, from environmental science to molecular biology to pharmacology to materials science. Thus, the prospects for control and manipulation of materials at the molecular level, particularly in areas related to non-covalent bonding and nanotechnology, are now truly exceptional. However, whereas crystal structure determination has been a tool used by scientists since the 1920's, crystal structure prediction remains a largely unmet goal.[2,3] Furthermore, the existence of more than one crystalline form of a given molecular compound, typically in the form of polymorphs or solvates, represents both a problem and an opportunity.[4,5] This is particularly true for the pharmaceutical industry and forms both the scientific basis for this invention and its potential commercial significance.

The concept of crystal engineering[6,7] represents the scientific basis of the invention since it is predicated on the assumption that crystals are *de facto* examples of self-assembly, i.e. crystals are comprised from a series of molecular recognition events or *supramolecular synthons*.[8] It also offers a more realizable goal than crystal structure prediction since it relies on design and allows for careful selection of substrates, i.e. substrates that are predisposed to form predictable self-assembled superstructures can be targeted for study. Furthermore, the prototypal molecules used in crystal engineering contain exofunctional molecular recognition sites and they can be complementary with themselves (self-assembly)[9] or with other molecules (modular self-assembly).[10;11] Coincidentally, most pharmaceutical molecules also contain exterior molecular recognition sites and, although this makes them susceptible to polymorphism and solvate formation, it also makes them attractive candidates for crystal engineering studies.

SUMMARY OF INVENTION

This invention relates to the application of the concepts of crystal engineering towards the design of new pharmaceutical phases. In terms of superstructure, there are three likely ways in which a drug molecule might interact with another molecule:

- *Binary compounds* in which superstructure is generated by two or more molecules, both of which are integral components of the network and complementary.
- *Clathrate inclusion compounds* in which superstructure is generated by self-assembly of one or more molecules and a guest molecule is enclosed within the superstructure.
- *Porous inclusion compounds* in which the superstructure is open framework in nature.

In this invention we focus on the former and demonstrate for the first time that the concepts of crystal engineering and supramolecular synthons can be applied to prepare a wide range of novel pharmaceutical materials that are based on rational design. They therefore can be generated in such a fashion that they have desirable composition, structure and properties. More specifically, we address an issue that is particularly relevant to pharmaceutical composition of matter and processing: the diversity of compositions, superstructures and solubilities that can be generated when drug molecules form binary phases with complementary molecules. We report such binary phases involving the following drugs: aspirin, acetaminophen, ibuprofen (and related compounds), phenytoin and carbamazepine and appropriate molecular additives. These novel phases include

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both "model binary phases" that illustrate the concept of crystal engineering and binary phases that incorporate pharmaceuticals with GRAS[†] compounds.

WHY IS THIS WORK SCIENTIFICALLY RELEVANT? The ability of crystalline self-assemblies to be built from a bottom-up approach[12] leads to exceptional control of the design of new phases at a molecular level. This contrasts with the current state-of-the-art: "*The number of forms known for a given compound is proportional to the time and money spent in research on that compound*".[13] This statement summarizes the predicaments and opportunities that one faces when dealing with a need to assert control over the composition and structure of pharmaceutical compounds in the solid state:

- That physical properties of crystalline solids are critically dependent on the internal arrangement of molecules or ions makes prediction of composition, crystal structure and morphology from knowledge of molecular structure a scientific challenge of the highest order.
- However, crystal structure prediction and even prediction of composition remains a largely unmet goal.
- Yet crystal engineering offers the intriguing possibility of using molecular components for their ability to impart functional characteristics (such as solubility, dissolution rate and stability) for the development of new delivery systems

In the context of organic and pharmaceutical solids, our invention addresses these issues by demonstrating that crystal engineering offers a paradigm for the supramolecular synthesis[14] of a wide range of new multiple component phases that have predetermined composition and, in some instances, predetermined topology. Such an ability to build hierarchical structures from molecular or supramolecular modules facilitates precise control of structure and function of solid phases. These binary phases have the following advantages over single component phases and traditional multiple component phases (solid dispersions): high thermodynamic stability (thereby reducing problems associated with solid phase transformations), modified bioavailability (finely tunable solubility and delivery), and enhanced processability (crystal morphology, mechanical properties, hygroscopicity).
The invention therefore means the following from a scientific perspective:

- **Protocols for the rational design of a new generation of pharmaceutical phases that contain at least two components that are sustained by *supramolecular synthons*.**
- **Correlation of structure and function of the new pharmaceutical phases via characterization of structure, crystal energy, solubility, dissolution rate, and stability.**
- **A new range of novel phases for the treatment of human and animal diseases.**

WHY IS THIS WORK PRACTICALLY RELEVANT? Undesirable physicochemical properties, physiological barriers, or issues of toxicity often limit the therapeutic benefit of drugs. This has motivated research in drug delivery systems for poorly soluble, poorly absorbed and labile substances. Crystalline self-assemblies represent a promising delivery modality for improving drug solubility, dissolution rate, stability and bioavailability. In addition, enhancement of drug activity can be achieved by means of inclusion complexation or molecular encapsulation. These systems offer various advantages over amorphous polymeric delivery systems both from design and stability perspectives. In this context, the existence of more than one crystalline form of a given compound,

[†] Compounds that are FDA certified as Generally Regarded As Safe

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typically in the form of polymorphs or solvates, represents both a problem and an opportunity and awareness of this matter continues to grow. The following factors further complicate the situation:

- The FDA's strict purity requirements effectively mean that a particular crystalline phase of a drug must be selected and that its composition must be established. This has typically meant that a consistent X-ray powder diffraction (XPD) pattern is required.[15]
- The US Patent Office's definition that a new phase[16] (i.e. polymorph, solvate or binary compound) of a drug can be patented if there is any processing (e.g. filtering, drying, speed of crystallization, morphology) or bioavailability (e.g. solubility) advantage to a new solid phase. This can have significant commercial relevance because patents can be extended (e.g. ranitidine HCl form II – worth $30billion to Glaxo over 10 years) or effectively voided (the subsequent use of ranitidine HCl form I by a generic drug manufacturer).
- The need to ensure that processing produces both purity and ease of processing. The former is problematic because many drug molecules are prone to form multiple phases and crystal size and morphology can vary for a given phase. The commercial and public image costs of not ensuring that processing is reliable and reproducible is at best very high (e.g. recent pull back and reformulation of Norvir® by Abbott Laboratories).[17]

That XPD's have been relied on for intellectual property and quality control is convenient but is in many ways unfortunate since XPD is not as foolproof as single crystal X-ray crystallography (e.g. similar patterns can be obtained for different phases, composition is not unambiguously determined) and XPD does not determine crystal packing. Knowledge of crystal packing is important since it helps explain the solubility and composition of a particular phase and it **provides information that can be used to design new phases**. The materials properties of pharmaceuticals and the existence of polymorphs are generally investigated at the tail end of the drug development process. We intend to demonstrate that it will be possible to generate dozens or hundreds of phases involving a given pharmaceutically active moiety. Furthermore, these phases will offer a wide range of physical properties including melting point, solubility and hydrophobicity. Therefore, the invention described herein will likely make crystal engineering of pharmaceutical phases an early and critical part of drug discovery and development.

We therefore extend the state-of-the-art in at least three ways:

1) By generating a rational, supramolecular strategy for the design of novel, multiple component crystalline phases.

2) By extending this strategy to pharmaceutical phases.

3) By using this strategy to control the delivery properties and stability of pharmaceutical compounds.

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APPENDICES

1. Carbamazepine 5H-Dibenz(b,f)azepine-5-carboxamide (CBZ) has been shown to exist in at least three anhydrous forms and two solvated forms (a dihydrate and an acetonate). The aqueous solubilities of the dihydrate and the monoclinic anhydrous forms are 0.125 and 0.38 mg/ml at 25°C, respectively. The crystal structures of all forms except the triclinic and the acetonate forms have been solved[45-47]. One of the primary intermolecular interactions in these crystal forms is the dimer formed between the carboxamide moieties of each CBZ molecule. In the tricyclic framework of CBZ the central azepine ring has a boat conformation and the dihedral angle between the planar benzene moieties is 126.6. Intermolecular hydrogen bonding between carboxamide groups forms centrosymmetric dimers. The anhydrous polymorphs are monoclinic, trigonal, and triclinic. The polymorphs are enantiotropically related with the monoclinic form being the most thermodynamically stable at room temperature. The 10,11-Dihydro-5Hdibenz(b,f)azepine-5-carboxamide derivative displays a different bonding pattern from that of CBZ with the carboxamide groups building dimers as well as a continuous chain of hydrogen bonds. As in the crystal structures of anhydrous CBZ, the dihydrate exhibits intermolecular hydrogen bonding between carboxamide groups and thereby builds centrosymmetric dimers. The two independent water molecules form hydrogen bonds with a CBZ molecule, one water molecule as an acceptor NH---O(water) and the other as a donor to the carbonyl group of the carboxamide C=O---H(water). Three of the four hydrogen bonds per water molecule are between water molecules that create a continuous hydrogen bonded chain between water and CBZ molecules.

More details to be added on this and other drugs

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I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on August 3, 2007.

Frank C Eisenschenk

Frank C. Eisenschenk, Ph.D., Patent Attorney

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT
Patent Application
Docket No. USF-106XC1
Serial No. 10/378,956

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Leonard M. Williams
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Applicants	:	Michael J. Zaworotko, Brian Moulton, Nair Rodriguez-Hornedo
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Filed	:	March 3, 2003
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For	:	Multiple-Component Solid Phases Containing at Least One Active Pharmaceutical Ingredient

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT
UNDER 37 C.F.R. §§ 1.97 AND 1.98

Sir:

In accordance with 37 CFR §1.56, the references listed on the attached form PTO/SB/08 are being brought to the attention of the Examiner for consideration in connection with the examination of the above-identified patent application. A copy of each cited reference is attached.

It is respectfully requested that the references cited on the attached form PTO/SB/08 be considered in the examination of the subject application and that their consideration be made of record.

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Applicants respectfully assert that the substantive provisions of 37 CFR §§1.97 and 1.98 are met by the foregoing statements.

Respectfully submitted,



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Attachments: Form PTO/SB/08; copies of references cited therein.

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Substitute for form 1449B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	10/378,956
Filing Date	March 3, 2003
First Named Inventor	Michael J. Zaworotko
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Concomitant Polymorphs

Joel Bernstein,* Roger J. Davey, and Jan-Olav Henck

Chemists who encounter polymorphism for the first time are often unaware of its existence and baffled by its manifestations. Experimental problems might include, for example, variable or diffuse melting point, crystal batches with inconsistent physical properties (electrical or thermal conductivity, filtering, drying, flow, tabletting, dissolution), or two (or more) different colored or different shaped crystals in the same batch of (chemically) "pure" material. These problems arise because the conditions of the particular crystallization have led to the production of a number of polymorphs, which are present in the crystallizing medium or vessel at the time the crystals are harvested. The fact that polymorphs of a substance can appear concomitantly has long been recognized but rarely noted or studied. Is the phenomenon of concomitant polymorphs a curse or a blessing? It can be both. It is a curse for the chemist seeking a pure substance and a robust procedure to repeatedly and consistently produce the pure material, and the existence of concomitant polymorphs corrupts that procedure. It is a blessing, however, because (the recognition of) the existence of polymorphs in general, and concomitant polymorphs in particular, can provide the information and the opportunity to gain control over the crystallization process, and to achieve the desired specificity and robustness. An understanding of the competing thermodynamic and kinetic factors that govern the crystallization of polymorphs in general, or of a particular substance in particular, facilitates the control over the production of the desired polymorph, to the exclusion of undesired ones. Such control has important implications in a variety of industrial applications, of which pharmaceutical production and formulation is but one important example. This review covers the factors that govern competitive polymorphic crystallization and the rationale behind concomitantly crystallizing polymorphs, followed by a survey of concomitant polymorphs of a variety of chemical systems and a variety of crystallization procedures and conditions.

Keywords: concomitant polymorphs · crystallization · kinetics · polymorphism · thermodynamics

You can observe a lot just by watching.
Yogi Berra

1. Introduction

Even the title of this paper[1] requires close examination: are we referring to a description of the phenomenon of polymorphs that crystallize simultaneously or is this meant to be a practitioner's recipe for obtaining two or more polymorphs at the same time? The intent is the former, but in describing the phenomenon we certainly can provide hints on how one might accomplish the crystallization of polymorphs, if that were the desired experimental goal.

A polymorph has been defined as "a solid crystalline phase of a given compound resulting from the possibility of at least two crystalline arrangements of the molecules of that compound in the solid state".[2] Different polymorphs have different structures and hence, in effect, each is a unique material with its own physical and chemical properties. Every student learns early on that crystallization is one of the principal methods of purification, and indeed most industrial processes that lead to solid products rely on this technique almost exclusively to prepare active materials which meet the regulatory and market demands of reproducibility and purity. In a polymorphic system, crystallization can result in the production of more than one material, in fact a mixture of materials; hence a knowledge of the processes that govern nucleation, crystal growth, and phase transformation in these systems is essential, on the one hand, for process control and, on the other hand, to ensure that maximum data and understanding are generated from experiments. This review

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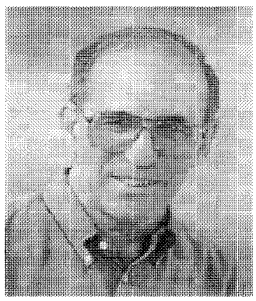
deals with a particular phenomenon which is not widely recognized but is associated with crystallization in polymorphic systems—namely that of concomitant crystallization of polymorphic crystal forms. We shall show that this is of particular relevance on two counts. First, from a scientific point of view, experiments that simultaneously yield crystals of different polymorphic structures potentially offer both structural and thermodynamic information not available when only one phase crystallizes. Second, from a commercial perspective, process conditions that result in concomitant crystallization are to be strenuously avoided since they lead to variable materials that do not meet prescribed specifications. We will address a number of questions related to this phenomenon:

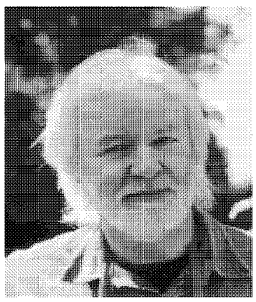
1) Why do different polymorphs crystallize concomitantly?
2) How can concomitant polymorphic crystallization be achieved or avoided?
3) What information can be obtained by the observation and study of such systems?
4) What use can be made of such information?
5) What examples of concomitant polymorphs are available?

Although in the course of addressing these questions a number of examples will be given in demonstration, this paper is not intended to be exhaustive or comprehensive. It is meant to provide an introduction and an entry to a generally unrecognized phenomenon which, when properly recognized and studied, can provide useful information for a variety of disciplines.

2. Why do Polymorphs Crystallize Concomitantly?—The Qualitative Picture

Crystallization is a remarkable process that brings approximately 10^{20} molecules or ions into an essentially ordered array, and results in the same structure—or limited number of structures, in the case of polymorphism—for every crystal, in every laboratory, and, in principle, every time it is done. There


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Joel Bernstein was born in Cleveland, Ohio, in 1941. After obtaining a BA degree at Cornell University, he earned a PhD degree in physical chemistry at Yale University for research on the solid-state spectroscopy of organic compounds. Following two-year postdoctoral stints in X-ray crystallography with the late Ken Trueblood at UCLA and in organic solid-state chemistry with the late Gerhardt Schmidt at the Weizmann Institute of Science in Rehovoth, Israel, he joined the faculty of the newly established Ben-Gurion University of the Negev, where he is now Professor of Chemistry. His research interests center on the organic solid state, with particular emphasis on understanding and utilizing polymorphism, structure–property relationships, hydrogen-bonding patterns and graph sets, and organic conducting materials. His career has been punctuated by visiting professorships at the University of Illinois, Cornell University, and the University of Minnesota, and as a visiting scientist at the Cambridge Crystallographic Data Centre.

Roger Davey graduated as a chemist from Bristol University. He earned a PhD degree on crystal-habit modification with Professor J. W. Mullin at University College London and spent four years studying the growth of molecular crystals at the ETH in Zurich, Switzerland. He then joined ICI at their Corporate Laboratory in Cheshire where he became a Company Research Associate, eventually transferring to ZENECA's Process Studies Group at Huddersfield. He joined UMIST in 1995 and now holds the Chair in Molecular Engineering in the Department of Chemical Engineering and leads the Department's activities in the area of colloids, crystals, and interfaces. His research interests in solid-state and surface chemistry form the basis for a range of activities in crystallization, precipitation, phase transitions, and the design of surface-active molecules.

Jan-Olav Henck obtained his Diplom in chemistry from the Universität Essen (Germany) in 1993. During the experimental work on his master thesis on phase transitions of drug substances under pressure, at the pharmaceutical division of Bayer AG in Wuppertal-Elberfeld (Germany), he came in contact with the topic of polymorphism of drug substances. For further studies in this research field he moved to the University of Innsbruck (Austria), where he received his PhD degree at the Institute of Pharmacognosy with Prof. Dr. Artur Burger in 1996. His thesis on conformational polymorphism of n-butyl-substituted drug substances was awarded the State Capitol Prize from the city of Innsbruck for scientific research at the University of Innsbruck. During 1996–1997 he was an Alexander von Humboldt Foundation Postdoctoral Fellow (Feodor Lynen Program) with Prof. Joel Bernstein at the Ben-Gurion University of the Negev in Israel.

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are exceptions, but it is these characteristics of the crystallization process that make it so attractive as a purification technique. As generations of chemists have learned, it is possible to define experimentally for any substance the solvent, temperature, rate of evaporation or cooling, and other conditions under which a material will crystallize.[6] This has been termed the *occurrence domain*.[7] This domain exists for any substance, but rarely, if ever, are its contents completely known. The contents of the occurrence domain for any material—in the present context, any polymorph—are not necessarily unique. In regions in which there is overlap of domains, one may expect that two or more polymorphs would crystallize under essentially identical conditions, thus leading to the phenomenon discussed in this review.

3. Polymorphism—Some Fundamentals

Like most chemical processes, crystallization in polymorphic systems is governed by a combination of thermodynamic and kinetic factors. We shall see in this and the following Section that it is in fact the interplay between thermodynamics and kinetics that makes concomitant crystallization possible. This section deals with the essentials of the thermodynamic processes involved. More detailed accounts may be found elsewhere.[8–13]

3.1. Thermodynamic and Kinetic Stability Amongst Polymorphs

Thermodynamic theory tells us that crystallization must result in an overall decrease in the free energy of the system. This means that, in general, the crystal structures that appear will be those with the greater (negative) lattice (free) energies. In polymorphic systems there are evidently a number of possible structures with similar lattice energies.

This drive towards free energy minimization will be balanced, as in all chemical changes, by the kinetic tendency of the system to crystallize as quickly as possible to relieve the imposed supersaturation. From the molecular point of view, the process of crystallization is one of supramolecular assembly in which the building blocks of the crystal assemble through the utilization of molecular recognition forces involving an array of intermolecular interactions as well as stereochemical packing constraints. If some structures are able to form more quickly than others then the system may, in the short term, settle for less than the maximum energy decrease, providing such a situation can be achieved at speed. A secondary transformation to a lower energy state can take place later.

The distinction between thermodynamic and kinetic influences is often demonstrated using the example of the graphite and diamond forms of carbon. The former is the thermodynamically preferred crystalline form, but kinetic factors (in particular, a high activation barrier) make the rate of transformation from diamond to graphite infinitely slow.[14]

3.1.1. *Energy versus Temperature Diagrams*

The energy versus temperature (E/T) diagram was introduced into crystallography by Buerger[15] in 1951 without application to any specific example. The theoretical derivation and practical application of this diagram have been described and discussed by Burger and Ramberger[11, 12] and by Grunenberg et al.[13] For simplicity we will limit the discussion to two polymorphic solids, although the extension to a larger number is based on the same principles.

The relative stability of two polymorphs depends on their free energies, the more stable polymorph having a lower free energy. The Gibbs free energy of a substance is expressed as Equation (1), where G and H are clearly functions of temper-

$$G = H - TS \tag{1}$$

ature and this variation may be plotted for one possible relationship between the two polymorphs and the melt (liquid) as in Figure 1. Such diagrams contain a great deal of information in a compact form, and provide a visual and readily interpretable summary of the often complex relationships among polymorphs.

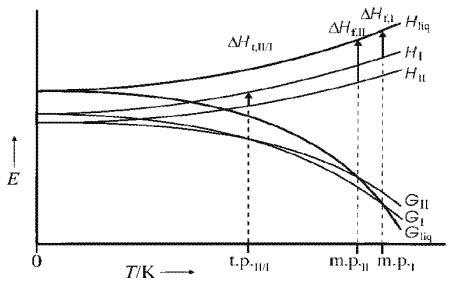


Figure 1. Energy versus temperature (E/T) diagram of a dimorphic system. G is the Gibbs free energy and H is the enthalpy. The Roman numerals indicate the two polymorphs; m.p. is the melting point and t.p.$_{II/I}$ is the transition point between the two polymorphs. This diagram represents the situation for an enantiotropic system, in which form II is the stable form below the transition point. (Reprinted from ref. [13] with permission.)

At absolute zero, TS vanishes so that the enthalpy is equal to the Gibbs free energy. As a consequence, at absolute zero, the most stable polymorphic modification should have the lowest Gibbs free energy. As mentioned above, at absolute zero the entropy term will play a role which may differ for the two polymorphs so that the free energy as a function of the temperature follows a different trajectory for the two polymorphs, as represented by the G_I and G_{II} curves in Figure 1. The two curves cross at the thermodynamic transition point t.p.$_{II/I}$, but since the enthalpy of II is lower than that of I, a quantity of energy $\Delta H_{t,II/I}$ is required to be input for the phase transition, which must be endothermic for the transition above t.p. and exothermic below t.p. for the situation that is depicted in Figure 1. The endothermic solid-to-liquid transitions at the melting points may be understood in the same way, with $\Delta H_{f,I}$ and $\Delta H_{f,II}$ denoting the respective enthalpies of fusion. Figure 1 represents an *enantiotropic* situation, since

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t.p.$_{II/I}$ lies at a temperature below the melting points for the two polymorphs.

The *monotropic* situation is represented in Figure 2. In this case, there is no transition point below the melting points of the two polymorphs. The phenomenological manifestation of enantiotropism is that there can be a reversible transition from one phase to another without going through the gas or liquid phase. If the thermodynamic relationship is one of

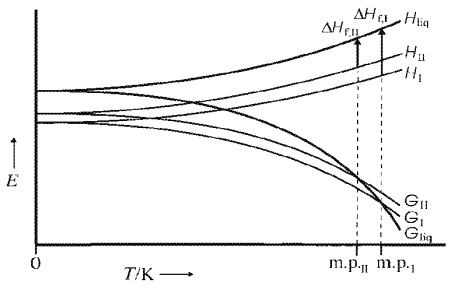


Figure 2. The E/T diagram of a monotropic dimorphic system. All symbols have the same meaning as in Figure 1. (Reprinted from ref. [13] with permission.)

monotropism the two modifications are not interconvertible.[16] In the context of simultaneously crystallizing polymorphs, the thermodynamic aspects are clear. First, only at thermodynamic transition points can two forms have the same stability and hence coexist as mixtures at equilibrium. At any other temperature there will be a thermodynamic tendency to transform to the more stable structure. This implies that mixtures of polymorphs will have limited lifetimes, except at the thermodynamic transition point, with transformation kinetics playing a role in those lifetimes.

3.1.2. *Vapor Pressure versus Temperature Diagram*

Another common representation of phase relationships is the pressure versus temperature (p/T) diagram. Figure 3 shows prototypical p/T plots for the enantiotropic and monotropic cases. These are best understood by traversing along various curves, which represent equilibrium situations between two phases. The liq./v. line in the high-temperature region of Figure 3a is the boiling point curve for the (common) melt of the two polymorphs. Moving to lower temperatures along that line, one encounters the II/v. line, which is the sublimation curve for form II. The intersection is the melting point for form II. Under thermodynamic conditions form II would crystallize out at this point and the solid part of the II/v. line would govern the behavior. However, if kinetic conditions prevail (for example, if the temperature is lowered rapidly) the system may proceed along the broken liq./v. line to the intersection with the I/v. line, at which point form I would crystallize. Continuing downward along the solid part of the II/v. curve, the crossing point with the I/v. sublimation curve is the transition point between the two polymorphic phases. Once again, if thermodynamic conditions prevail, form II will transform to form I. Under kinetic conditions form II may continue to exist (even indefinitely in some cases) along the II/v. sublimation curve. Figure 3a represents the enantiotropic case because the transition point between the two phases is found at a temperature below the melting point of form II, while Figure 3b represents the monotropic situation, in which the transition point is above the melting points of both forms.

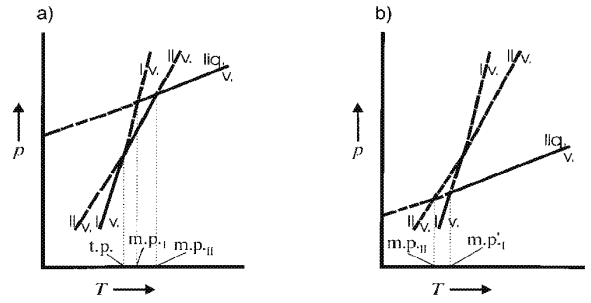


Figure 3. Pressure *versus* temperature plots: I/v. and II/v. represent sublimation curves, liq.v. is the boiling point curve. Broken lines represent regions which are thermodynamically unstable or inaccessible. a) Enantiotropic system; b) monotropic system. The labeling corresponds to that of Figures 1 and 2 to indicate that form I is stable at room temperature, which is below the transition point in the enantiotropic case. (Adapted from ref. [2] with permission.)

3.2. Some Practical Aspects of Relative Stabilities of Polymorphs

Knowledge of the enantiotropic or monotropic nature of the relationship between polymorphs can be used to steer crystallization processes to obtain a desired polymorph at the exclusion of an undesired one. For a dimorphic system there are four possibilities:

1) The thermodynamically stable form in a monotropic system: no transformation can take place to another form, and no precautions need be taken to preserve that form or to prevent a transformation.
2) The thermodynamically stable form in an enantiotropic system: precautions must be taken to maintain the thermodynamic conditions (temperature, pressure, relative humidity, etc.) at which the G curve for the desired polymorph is below that for the undesired one.
3) The thermodynamically metastable form in a monotropic system: a kinetically controlled transformation may take place to the undesired thermodynamically stable form. To prevent such a transformation it may be necessary to employ drastic conditions to reduce kinetic effects (e.g. very low temperatures, very dry conditions, storage in the dark).
4) The thermodynamically metastable form in an enantiotropic system: the information for obtaining and maintaining this form is essentially found in the E/T diagram.

Therefore, it is of practical importance (e.g. preformulation studies of a drug substance[10, 13]) to determine whether a system of concomitant polymorphs is monotropic or enantiotropic to enable the choice of and control over the desired

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polymorphic form. The combination of experience with polymorphic systems and the accumulation of sufficient thermodynamic and structural data have permitted the development of some useful "rules" for determining the relative positions of the G and H isobars, as well as the enantiotropic or monotropic nature of the relationship between polymorphs.[11–13]

3.2.1. Heat-of-Transition Rule[11]

If an endothermic phase transition is observed at a particular temperature, this experimental transition temperature lies above the thermodynamic transition temperature. An endothermic phase transition is observed if two modifications are enantiotropically related and is represented in the E/T diagram by the intersection point of the G isobars of two modifications. If the phase transition is exothermic, there is no thermodynamic transition point below the experimentally observed transition temperature. This is generally observed if two modifications are monotropically related. Exceptions to this rule were discussed by Burger and Ramberger.[12]

3.2.2. Entropy-of-Fusion Rule

The entropy of fusion is easily accessible by means of differential scanning calorimetry (DSC), since the enthalpy of fusion and the melting point of a crystal can be obtained in one experiment ($\Delta H_f/T_f = \Delta S_f$). At the melting point, the difference between the Gibbs free energy of a modification and its melt is zero. If a modification with the higher melting point has the lower entropy of fusion, the two forms are enantiotropic. Monotropism is realized if the lower melting form shows the lower entropy of fusion.[13]

3.2.3. Enthalpy-of-Sublimation Rule

The enthalpy of sublimation of a particular crystal form is the sum of its enthalpy of fusion and enthalpy of vaporization. The latter is identical for all polymorphs of a compound. Therefore the enthalpy of transition for the transformation of one modification into another is the same as the difference in their enthalpies of sublimation[9] and their enthalpies of fusion. Thus, if the modification with the higher melting point has the lower enthalpy of sublimation, the two forms are enantiotropic. Monotropism is realized if the lower melting form shows the lower enthalpy of fusion.

3.2.4. Density Rule[11]

If a particular modification exhibits a lower density than another one at ambient conditions, then it may be assumed that, at absolute zero, this form is thermodynamically metastable. The energetically most favorable packing of molecules in a crystal has the strongest interactions between the molecules and hence the greatest density. The best possible packing also corresponds to thermodynamic stability. This energetically favorable modification requires more energy than any other modification to melt. At absolute zero, the form with the greatest density is thermodynamically stable. This approximation assumes that there is no great variation in the density of solids over a wide range of temperature. The two modifications are monotropically related if the higher melting modification shows the higher density. Otherwise they are enantiotropically related. Exceptions to this rule (e.g. resorcinol[17] or acetazolamide[18]) are discussed by Burger and Ramberger.[11]

3.2.5. Heat-Capacity Rule[13]

If the higher melting modification shows a higher heat capacity at a given temperature than another modification, these two crystal forms are enantiotropically related. Otherwise the two modifications are monotropically related.

3.2.6. Solubility and Dissolution Rates

In addition to differences in melting points, heats of fusion, entropies of fusion, densities, heat capacities, and virtually every chemical and physical property, different modifications can also exhibit different solubilities and dissolution rates. Since the solubility is directly proportional to the free energy of a modification, determination of solubility curves is the most reliable method of assessing the relative free energies of polymorphs. The difference in solubility of two polymorphs is a direct measure of the ΔG between them. It is important to note that although the absolute solubility (and hence the dissolution rate) of a polymorph will be solvent dependent, the relative solubility of different forms will not depend on the solvent used.

As discussed in Sections 4 and 5, the situations in which polymorphs concomitantly crystallize are determined by the experimental conditions in relation to both the free energy–temperature relationships and the relative kinetic factors. These situations may arise either because specific thermodynamic conditions prevail or because the kinetic processes have equivalent rates. In thermodynamic terms we have seen that polymorphs can only exist in true equilibrium at the thermodynamic transition temperature (where the G curves cross). The chance of carrying out a crystallization precisely at such a temperature must be small, with the inevitable conclusion that kinetics play at least some role in the overall process. The final consequence of this, of course, is that a system of concomitantly crystallizing polymorphs will be subject to change in the direction that favors the formation of the most stable structure. If the crystals have grown from and remain in contact with solution, the most likely route for this transformation is via the solution by dissolution and recrystallization.[2, 19] If the crystals have formed from the melt or vapor phase or have been isolated from their mother phase, solid-state transformation is possible.[20] Either way, keen observation is vital to recognize the phenomenon, as discussed in Section 5.

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4. Why do Polymorphs Appear Together?—Kinetic Factors

The starting point for a discussion of the kinetic factors is the traditional energy–reaction coordinate diagram in Figure 4. This shows G_0, the free energy per mole of a solute in a supersaturated fluid which transforms by crystallization into one of two crystalline products, I or II, in which II is the more stable ($G_I > G_{II}$). Associated with each reaction pathway is a transition state and an activation free energy which is implicated in the relative rates of formation of the two structures. Unlike a chemical reaction, crystallization is complicated by the nature of the activated state since it is not a simple bi- or trimolecular complex as would be expected for a process in which a covalent bond is formed; rather it relates to a collection of self-assembled molecules with not only a precise packing arrangement but which also exist as a new separate solid phase.

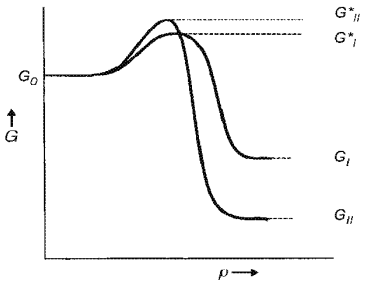


Figure 4. Schematic representation of the reaction coordinate ρ for crystallization in a dimorphic system to show the activated barriers for the formation of polymorphs I and II.

It is the existence of the phase boundary that complicates matters since this is associated with an increase in free energy of the system which must be offset by the overall loss of free energy. For this reason the magnitudes of the activated barriers are dependent on the size (i.e., the surface-to-volume ratio of the new phase) of the supramolecular assembly (crystal nucleus). This was recognized in 1939 by Volmer in his development of the kinetic theory of nucleation from homogeneous solutions which remains our best guide today.[21]

One of the key outcomes of this theory is the concept of critical size which an assembly of molecules must have in order to be stabilized by further growth. The higher the operating level of supersaturation, the smaller this size is (typically a few tens of molecules). In Figure 4, the supersaturation with respect to I is simply $G_0 - G_I$ and is lower than $G_0 - G_{II}$ for structure II. However, it can now be seen that if the critical size is lower for I than for II for a particular solution composition then the activation free energy for nucleation is lower and kinetics will favor form I. Ultimately form I will have to transform to form II, a process that we discuss later. Overall we can say that the probability that a particular form i will appear is given by Equation (2) in which

$$P(i) = f(\Delta G, R) \quad (2)$$

ΔG is the free energy for forming the ith polymorph and R is the rate of some kinetic process associated with the formation of a crystal by molecular aggregation. Thus, for example, if we follow the above reasoning we could equate the rate process with J, the rate of nucleation of the form. If all polymorphs had the same rates of nucleation then their appearance probability would be dominated by the relative free energies of the possible crystal structures.

The rates of nucleation as expressed by the classical expression of Volmer are related to various thermodynamic and physical properties of the system such as bulk and surface free energy (γ), temperature (T), degree of supersaturation (σ), solubility (hidden in the preexponential factor A_n) which will not be the same for each structure but will correctly reflect the balance between changes in bulk and surface free energies during nucleation. This is seen in Equation (3), which relates the rate of nucleation to the above parameters (v is the molecular volume).

$$J = A_n \exp(-16\pi\gamma^3 v^2/3\kappa^3 T^3 \sigma^2) \quad (3)$$

From this analysis it can be seen that the tradeoff between kinetics and thermodynamics is not at all obvious. Consider a monotropic, dimorphic system (for simplicity) whose solubility diagram is shown schematically in Figure 5. It is quite clear that for the occurrence given by solution compositions and temperatures that lie between the form I and II solubility curves, only polymorph II can crystallize. However, the outcome of an isothermal crystallization that follows the crystallization pathway indicated by the vector in Figure 5 is not so obvious since the initial solution is now supersaturated with respect to both polymorphic structures, with thermodynamics favoring form II and kinetics form I.

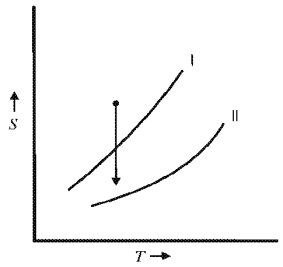


Figure 5. Schematic solubility diagram for a dimorphic system (polymorphs I and II) showing a hypothetical crystallization pathway at constant temperature.

Experimentally, the reality of this overall scenario of kinetic versus thermodynamic control was known long before the development of nucleation theory and is encompassed by Ostwald in his Rule of Stages in 1897.[22, 23] The German scientific literature between 1870 and 1914 contains many examples from organic and inorganic chemistry in which crystallization from melts and solutions yields an initial metastable form which is ultimately replaced by a stable structure, and Ostwald was led to conclude that "when leaving a metastable state, a given chemical system does not seek out the most stable state, rather the nearest metastable one that can be reached without loss of free energy".[24] Figure 6 shows an example of Ostwald's rule for potassium nitrate. It shows a group of rhombic (β form) crystals in contact with their mother liquor and their solution-mediated conversion to the more stable needle morphology (α form) by means of dissolution and recrystallization.

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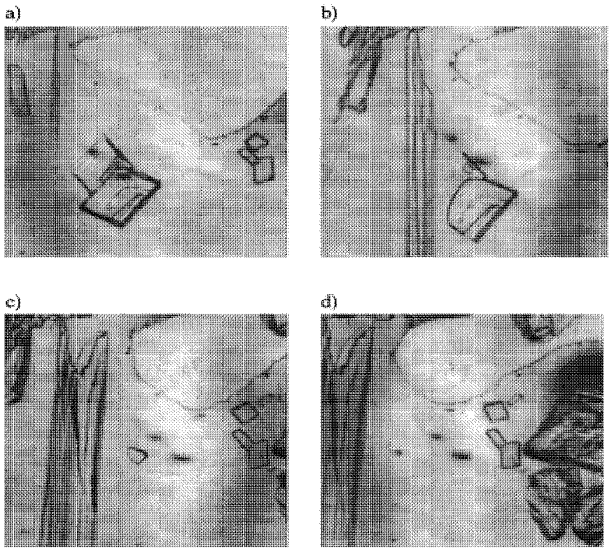


Figure 6. Time-lapse micrographs (× 50) of the crystallization of potassium nitrate from aqueous solution at room temperature. a) After 1 min, showing well formed rhombs and a single needle (upper left quadrant); b) after 5 min—note the rounded edges of the rhombs due to dissolution and the enlargement of the needle; c) and d) after 10 and 15 min—note the further dissolution of the rhombs and growth of the needle.

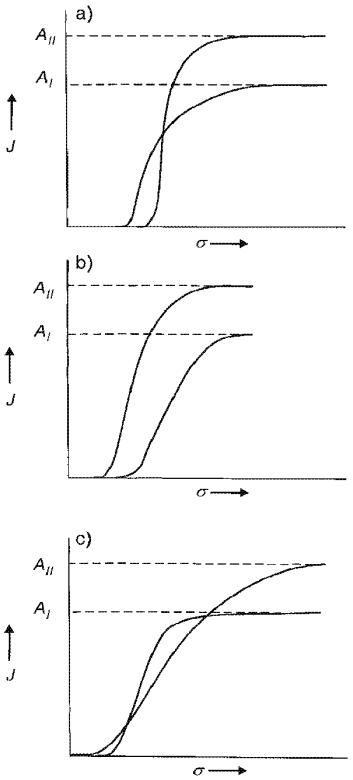


Figure 7. The rates of nucleation as functions of supersaturation for the dimorphic system defined in Figure 5. The three diagrams a, b, and c represent the three possible solutions for the simultaneous nucleation of two polymorphs each of which follows a rate equation of the form of Equation (3). Note that solutions a and c both allow for simultaneous nucleation of the forms at supersaturation levels corresponding to the crossover of the curves.

Of course this conclusion is significantly flawed: when a crystallization experiment yields only a single form there is no way of knowing whether it contradicts the rule or whether the material is simply not polymorphic. There is no way of answering this question. However, a sufficient number of cases of successively crystallizing polymorphic forms have been observed to warrant consideration of the principles behind Ostwald's rule as guidelines for understanding the phenomenon.

By making use of Volmer's equations, some attempts have been made by Becker and Doering, Stranski and Totomanov, and Davey to explain the rule in kinetic terms.[25] In doing so it becomes apparent that the situation is by no means as clear cut as Ostwald might have led us to believe. Figure 7 shows the three possible simultaneous solutions of the nucleation equations which indicate that, by careful control of the occurrence domain, there may be conditions in which the nucleation rates of the two forms are equal and hence their appearance probabilities are nearly equal. Under such conditions we might expect the polymorphs to crystallize concomitantly.

5. How Can Concomitant Polymorphs be Recognized?

Most cases of concomitant polymorphs have been recognized visually simply by a combination of curiosity, thoroughness, and keen observation. In the first years following the discovery of polymorphism by Mitscherlich in 1822,[26] the principal method of the study of crystals was observation and measurement on the microscope, particularly the polarizing microscope, and the measurement of interfacial angles on an appropriate goniometer. Differences in habit are indicative (but not necessarily conclusive) evidence of polymorphism, which could be confirmed by physical measurements such as index of refraction, melting behavior (including, of course, the melting point itself) and others. Groth's landmark compilation of such data contains many examples of polymorphism.[27] He was apparently also intrigued by the instances of concomitant crystallization of polymorphs, and compiled a list of examples in his book on chemical crystallography in 1904.[28]

With the emergence of X-ray diffraction and the development of more sophisticated methods of analysis, the discovery of concomitant polymorphs should have become more frequent—provided one is aware of the phenomenon. Even a variable melting point may be a sign of concomitant polymorphs since mixtures of different polymorphic composition can result from the crystallization, but also a peak on a DSC scan, or a broadening or doubling of lines in a solid-state IR or solid-state NMR spectrum may be signs for the existence of concomitant polymorphs. Still, probably the best

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method for discovering them is careful thermomicroscopic examination on the hot-stage polarizing microscope,[29, 30] and three examples of the facility with which concomitant polymorphs may be observed on the hot-stage polarizing microscope are given in Figure 8.

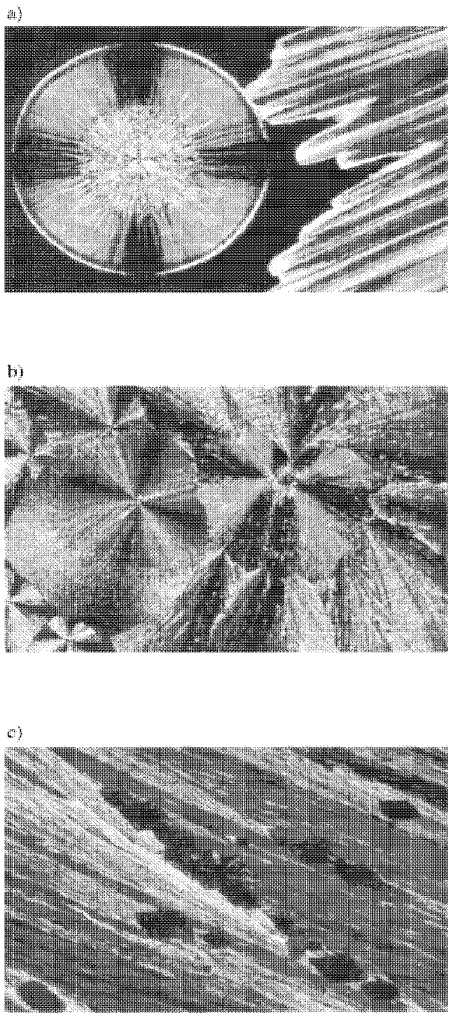


Figure 8. Cocrystallizing polymorphs as observed on the hot-stage microscope. a) Two crystal modifications of phenobarbital; b) three crystal modifications of nicotinamide; c) growth of the stable (diamond-shaped) crystals of sulfethidole from the unstable form. (Reprinted from ref. [30] with permission.)

6. What Are Concomitant Polymorphs Good For?

Polymorphs are of general interest because they represent special situations for the study of structure–property relations in systems with limited numbers of variables. They are also of interest since they provide unique data on the factors that govern molecular packing. Finally they are, as pointed out earlier, of extreme interest to those involved in the large-scale preparation of solid forms of specialty chemical and pharmaceutical materials.

Thus, if concomitant crystallization occurs, it offers the crystallographer the chance to maximize the data from a single crystallization experiment. It offers the formulation chemist the chance to measure physical properties and hence to select the structure that best matches the needs of the product. It gives the process chemist and chemical engineer a choice of which morphology might separate more effectively and also a warning that the process will have to be robust if a single polymorph is to be consistently isolated. For these reasons we believe that chemists should be aware of this phenomenon and maximize the information it offers.

Finally, we comment that since concomitant polymorphs are very nearly energetically equivalent structures, they provide excellent and demanding benchmarks for the validation of lattice energy programs[31] and so-called "polymorph predictor" programs.[32, 33] The programs and the force fields employed in those programs must reproduce the near equivalency of the crystal energetics, even if the absolute lattice energy is not reproduced or even not known.[34]

7. Examples of Concomitant Polymorphs

Apart from the above-mentioned section in Groth's book we are not aware of any other attempt to collect and document examples of concomitant polymorphs. It is a daunting, perhaps even impossible task to systematically extract additional instances from the literature.[35] Most examples given here were taken from our own experience, from chance encounters of descriptions of crystal growth procedures in the experimental sections of papers in the literature[24] or from responses to appeals by the authors at scientific meetings for testimonial cases from colleagues. One of the objects of this paper is to increase awareness of the phenomenon so it can become a keyword for indexing and abstracting, to enable future workers to take advantage of the useful information to be extracted from situations in which polymorphs crystallize concomitantly.

7.1. The Earliest Reported Concomitant Polymorphs

The first recognized example of a polymorphic organic substance was also an example with concomitant polymorphs. In 1832 Wöhler and Liebig described the dimorphism of benzamide.[36] They synthesized the material for the first time and initially found a melting point of 115 °C (later called modification II).[37] Reexamination led to a melting point of 128 °C (modification I). The lower melting modification crystallizes in featherlike needles while the higher melting modification shows blocks (Figure 9). It is of interest that if a hot saturated aqueous solution of benzamide is allowed to cool rapidly, one is able to observe by microscopy that the two modifications crystallize concomitantly, and in accord with Ostwald's rule. With increasing time the blocks of modification I grow at the expense of the feathery needles.

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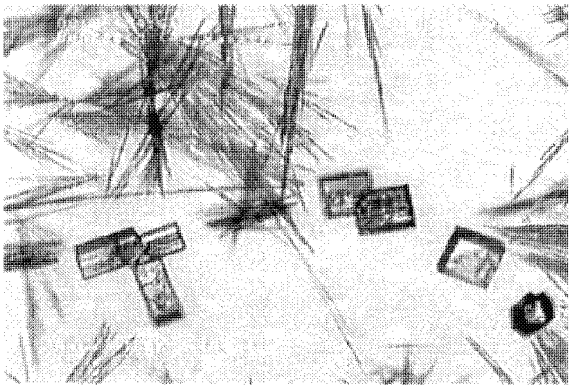
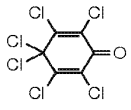


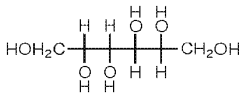
Figure 9. Photograph of the two forms of benzamide growing in aqueous solution. Form I are the blocklike crystals which grow at the expense of the featherlike needles of the less stable form II.

7.2. Groth's Collection

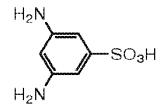
As noted above, Groth was apparently the first to collect a number of cases of the phenomenon of concomitant polymorphism from the literature until roughly the turn of the 20th century.[28] He noted that concomitant crystallization can occur for an enantiotropic system such as sulfur as well as in a monotropic dimorphous material such as "hexachloro-keto-dihydrobenzene, C_6Cl_6O" (**1**). He characterized the phenomenon as a "peculiarity" which is "analogous to the...indifference towards direct transformation" between polymorphic forms.



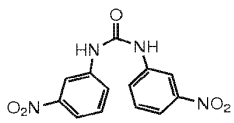
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2



3



4

Groth presents examples across a wide range of compound types, but what appears to be common among these examples is that keen observation was combined with considerable time and effort to study and characterize the compounds. Among the inorganic examples cited by Groth are telluric acid (H_6TeO_6),[38] ammonium fluorosilicate $(NH_4)_2SiF_6$,[39] sodium beryllium fluoride (Na_2BeF_4),[40] rubidium dichromate $(Rb_2Cr_2O_7)$,[41] and ammonium paratungstate $(NH_4)_{10}W_{12}O_{41}\cdot H_2O$,[42] while the organic examples include mannitol $C_6H_{14}O_6$ (**2**),[43, 44] *m*-diaminobenzenesulfonic acid $(C_6H_3(NH_2)_2SO_3H)$ (**3**),[45] and di-*m*-nitro-*s*-diphenylcarbamide $CO(NHC_6H_4NO_2)_2$ (**4**).[46] An organometallic salt exhibiting the phenomenon is dimethylammonium chloroplatinate $[\{NH_2(CH_3)_2\}_2PtCl_6]$.[47]

7.3. *m*-Nitrophenol: 120 Years of History

In spite of their generally keen powers of observation, the giants of 19th and early 20th century chemical microscopy and morphology certainly could have been aided by modern technology in the discovery of concomitant polymorphs. *m*-Nitrophenol is a case in point. The description of the material appears in Groth's book.[48] The two melting points quoted by Groth, 96 °C[49] and 93 °C,[50] and the description of the crystals might have suggested that the phase was not pure but the difference was within the acceptable range for different determinations. Groth himself had determined the interfacial angles in 1875, and Barker[51, 52] and Steinmetz[50] obtained similar results, with no hint of polymorphism.

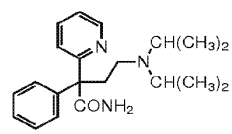
In 1934 Davis and Hartshorne[53, 54] determined indices of refraction as a technique for the identification of organic solids, including *m*-nitrophenol. They did note "occasional individuals (of crystals) with more or less rhombic outlines" amid monoclinic prismatic crystals (m.p. 96 °C) from water and benzene.

In 1972 Shigorin and Shipulo[55] reported that the compound exhibited a strong second harmonic generation (SHG), an effect known to require a non-centrosymmetric space group,[56] but Groth's morphological description indicated a centrosymmetric space group. In an attempt to resolve this discrepancy, Pandarese et al. carried out the crystal structure determination of the material described by Groth and others on crystals grown from the melt and from benzene.[57] The crystals were indeed centrosymmetric, in the common space group $P2_1/n$.

With the dilemma not resolved, they carefully reexamined many individual crystals from the benzene-grown batch, and discovered that approximately 20% belonged to the non-centrosymmetric orthorhombic space group $P2_12_12_1$, thus explaining the source of the SHG. A method for purifying *m*-nitrophenol and growing single crystals was developed by Wojack and Marqueton in 1989[58] and the structure of the orthorhombic form was published in 1996.[59]

7.4. Similar and Dissimilar Solubilities

One example from our own collection of concomitant polymorphs from solution is the dimorphic drug substance disopyramide **5**. Crystallization from *n*-hexane at 25 °C led to both modifications simultaneously. Gunning et al.[60] have described the solubility behavior and dissolution rates of two modifications of this material. They found no significant differences in the solubilities and the dissolution rates of the crystal forms at 37 °C. No thermodynamic or structural studies have been published until now.



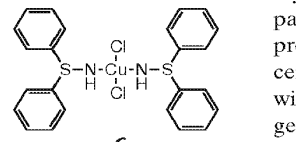
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We prepared single crystals of the two forms, determined their thermodynamic properties, and solved their structures, which will be published in a separate contribution. The two crystal forms are enantiotropically related with a t.p. at about

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40 °C. Modification II (m.p. 86 °C) crystallizes in rough blocks, while modification I (m.p. 96 °C) shows a needlelike habit. This example shows that similar solubilities and dissolution rates favor concomitant crystallization of different modifications.

The recent report of work on a neutral copper complex reveals some possible additional features of concomitant crystallization. Kelly et al.[61] prepared blue crystals of **6**, which precipitate from "reasonably concentrated (acetonitrile) solutions" with square-planar coordination geometry around the copper center (Figure 10). When the precipitate was filtered off and the remaining mother liquor treated with diethyl ether, followed by cooling in a freezer, concomitant crystallization of the blue crystals with green crystals occurred, in which the molecular structure exhibits pseudotetrahedral coordination geometry around the copper center.



6

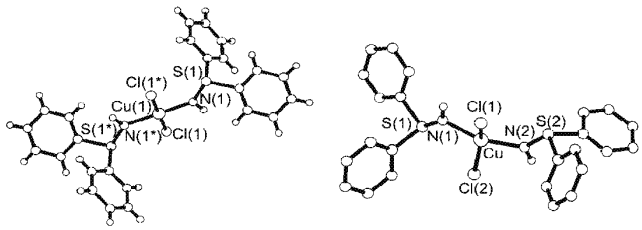


Figure 10. Molecular structure of the concomitant polymorphs of **6**. Left: the square-planar geometry found in the blue crystals. Right: The pseudotetragonal geometry found in the green crystals. (Reprinted from ref. [61] with permission.)

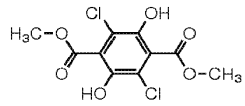
There is ample evidence that this also is a genuine case of polymorphism. The blue square-planar form can be dissolved to obtain the green tetrahedral one; indeed the authors state that the two form intergrowths, which apparently grow coincidentally. The green form is obtained only from dilute solutions, and once it is obtained the blue form cannot be regenerated. The sequence of events and the experimental conditions are compatible with Ostwald's Rule of Stages: the slight thermodynamic preference for the green form over the blue one (at least in dilute solutions—the melting points are essentially identical) and the phenomenon of "disappearing polymorphs".[62] Once seeds of the (even slightly) preferred green form are present in the immediate environment, the blue form cannot be obtained.

7.5. Trimorphic Concomitant Crystallization

The "diphenylcarbamide" **4** is, in fact, a urea derivative, and was recently studied by Etter et al. for apparently entirely different reasons.[63] As a symmetrically substituted urea derivative it was expected to exhibit a tendency to form polar chains,[64] while the substituents may be considered derivatives of *m*-nitroaniline and therefore might exhibit the known tendency of such compounds to avoid a centrosymmetric structure.[56, 65] However, it is the concomitant trimorphic crystallization behavior of this compound, which was extensively studied almost a century ago, that is of interest here.

The three reported forms are α, yellow prismatic needles; β, white needles; and γ, yellow tablets. Upon crystallization from 95% ethanol in the range 30–75 °C, the α and β forms always crystallize concomitantly, even in the presence of seeds of one form. The relative amounts can be regulated by varying the temperature; α is preferred at higher temperatures. Upon evaporation of the mother liquid at "the ordinary temperature (13 °C)" γ crystallizes out alone; warming the same mother liquor leads also to some crystals of β; at 40 °C γ no longer appears, but small amounts of α appear. The authors conclude that on the basis of the experiments with 95% alcoholic solutions, γ is the stable form at room temperature (considerably lower than room temperature today), and with increasing temperature, β and then α are the stable forms. However, this behavior may be modified by solvent. This is clearly a rich system with a very delicate balance between the relative stabilities of the three forms, as well as the kinetic factors that govern their appearance.

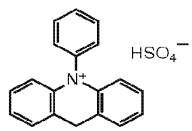
There are other examples of trimorphic concomitant crystallizations, generally recognized by differences in color. One, also originating in the early literature,[66] but on which a great deal of work has subsequently been done is methyl 2,5-hydroxy-3,6-dichloroterephthalate (**7**). The white and yellow forms were reported by Hantzsch in 1916[66] and studied by Byrn et at. in 1972,[67] but it was not until a thorough study was undertaken in 1989 that a third light yellow form was discovered by Dunitz and co-workers.[68] As the latter authors point out, visual observation during heating often reveals changes that are not detected by instrumental analytical methods, and it was this observation that led to the discovery of the previously undetected form.



7

Crystallization of the dibromo derivative of **7** from concentrated ethanolic solutions yields first polymorphic modification I, which transforms over a period of a week to a second modification II, upon which small crystals of the first form adhere. Crystals of both modifications are recognizable and separable by their morphology and color: the first are colorless blocks or plates, while the second are colorless on some faces and light violet on others.[69]

The term coined by Hantzsch[70] for polymorphs that exhibit different colors is *chromoisomerism*, recently discussed in historical perspective by Kahr and co-workers.[71] An example given by Kahr, which is also one of concomitant polymorphs, is that of 9-phenylacridinium hydrogen sulfate (**8**) which yields equal masses of red and green forms from acetonitrile/DMSO (10/1). The physical basis for the color difference remains an enigma.

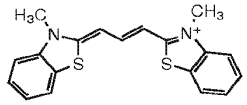


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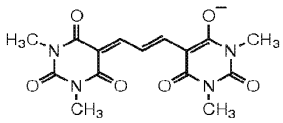
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7.6. Concomitant Crystallization of Multicomponent Systems

Concomitant crystallization is not limited to single component systems. For the remarkable cyanine/oxonol system (**9**/**10**) at least fourteen different polymorphs or solvates have been identified.[72] Two of these, a gold and a red form (each containing a molecule of $CHCl_3$ solvent per 1:1 complex, and



9



10

hence true polymorphs) crystallize concomitantly and have been structurally characterized.[72] Three of these polymorphs are shown in Figure 11. Despite the fact that both of these dyes are known to be individually self-aggregating,[73] the two

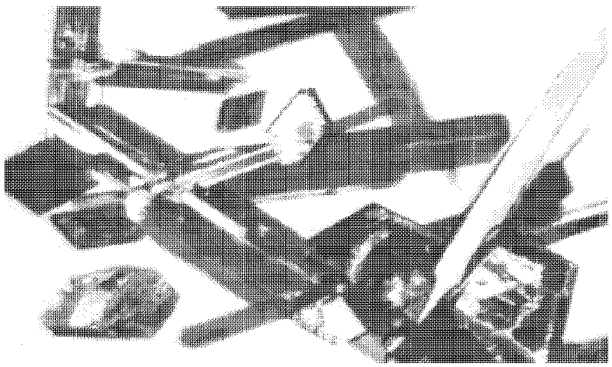
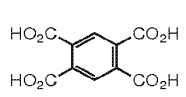


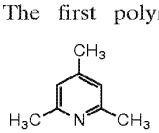
Figure 11. Three of the concomitant polymorphs of the cyanine/oxonol dyes **9** and **10**. The gold (by reflection; otherwise red by transmission) and red forms mentioned in the text are easily distinguishable. The third form is purple, normally diamond shaped as on the middle right, but many of these crystals are undergoing conversion, as indicated by varying degrees of mottled surfaces.

structures exhibit mixed stacks, with very significant differences in the relative orientation of neighboring molecules along the stack (Figure 12): in the case of the gold structure the molecular long axes are oriented nearly perpendicular to each other, while in the red polymorph the molecular long axes are very nearly parallel. Recently Bonafede and Ward have shown how edge-directed epitaxy on single crystal succinic acid substrates may be used for the selective nucleation and growth of the less stable red polymorph.[74]

The often serendipitous nature of the discovery of concomitant polymorphs is illustrated by another recent example of a two-component system, pyromellitic acid (**11**) and 2,4,6-trimethylpyridine (**12**).[75] The first polymorph (A) was



11



12

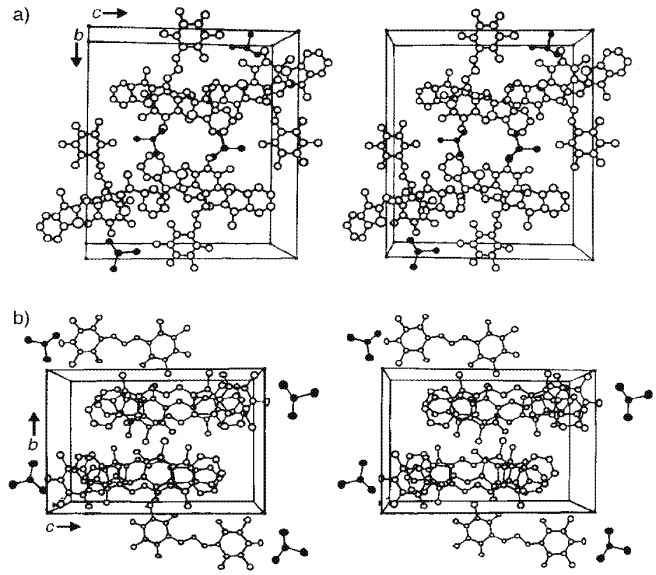


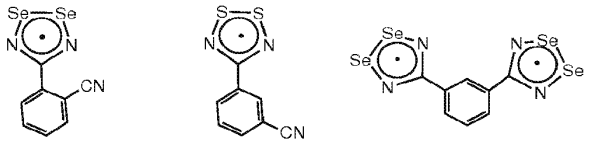
Figure 12. Stereoviews of the unit cells of the gold (a) and red (b) forms of the salt of **9** and **10**. a) View along [100] of the entire cell. Chloroform molecules of solvation (shaded black in the figure) fill (010) planes of the structure, providing stabilization by hydrogen-bond interaction with the oxonol dye. b) [100] view of the entire cell of the red form. Chloroform molecules represented in a similar manner. Both figures are viewed down the stack axis and indicate the relative orientation of cation and anion which is one feature of the overall packing. (Reprinted from ref. [72] with permission.)

obtained by the reaction of **11** with four equivalents of **12** in a methanolic solution. When **12** was used as the solvent, a second polymorph (B) crystallized in fifteen minutes. Form A was found to have crystallized as well in the same reaction vessel after about 24 hours. These two polymorphs are not readily distinguishable by their morphology. However, the authors point out that the experimental evidence indicates that form B is the kinetically controlled one, while form A is the thermodynamically preferred one.

7.7. Concomitant Crystallization by Sublimation

Concomitant crystallization is by no means limited to crystallization from solution, nor to preservation of constant molecular conformation. As noted in Section 3.1.2, the classic p/T phase diagram for two solid phases (Figure 3) of one material exhibits two lines corresponding to the solid/vapor equilibrium for each of two polymorphs. At any one temperature one would expect the two polymorphs to have different vapor pressures. This, in fact, is the basis for purification of solids by sublimation. Nevertheless there are examples where the two have nearly equal vapor pressures at a particular temperature and cosublime. For instance, the two compounds **13** and **14** both yield two phases upon vacuum sublimation.[76] For **13** slow sublimation at 140 °C and 0.1 Torr led to a mixture of a "few feathery needles" (m.p. 192–193 °C) among the main product of "lustrous coppery blocks" (m.p. 220–223 °C),

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13 14 15

which could be separated manually for further characterization. Compound **14** was also purified/crystallized by vacuum sublimation (120 °C, 10^{-2} Torr) to yield manually separable deep red needles (α phase, m.p. 157–160 °C) and blocks (β phase 165–168 °C). The crystal structure determinations of the two phases of **14** indicated significantly different molecular geometry (Figure 13), a cofacial dimer in the α phase, and a *trans* antarafacial dimer in the β phase.[77]

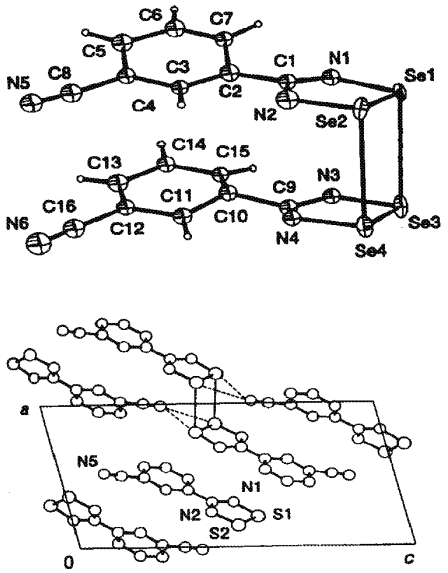
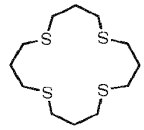


Figure 13. Molecular geometry in the two polymorphs of the dimers of **14** obtained by sublimation. Top: α phase, cofacial dimer; bottom: β phase, antarafacial dimer. (Reprinted from ref. [76] with permission.)

Another example of cosublimed phases is the compound **15** for which it appears that the sublimation conditions were systematically varied in an attempt to obtain a second polymorph.[78] The α form was initially prepared as a single phase of golden needles by slow sublimation over several weeks at 10^{-6} Torr during which the sample was heated to 180 °C and the cold finger was maintained at 100 °C. Raising the pressure to 10^{-1}–10^{-2} Torr and increasing the sample temperature to 220 °C, with a cold finger in the range 120–140 °C also led to the same α-phase needles, but they were accompanied by blocks of an additional β phase. The two can be separated manually. Clearly, the authors moved along the solid/vapor line of the α phase towards the intersection with the solid/vapor line of the β phase (see Figure 3).

7.8. Concomitant Crystallization by Solvent Diffusion

Concomitant crystallization has also been reported from solvent diffusion crystallization, which means that the concomitant forms have very similar solubilities in the same *mixture* of solvents—under the same thermodynamic and kinetic conditions. Such is the case for 1,5,9,13-tetrathiacyclohexadecane (**16**).[79] The material is reported to be trimorphic; all three forms crystallize in polar space groups [needles, $Pbc2_1$ (α); plates, $P2_1$ (β); and twinned, apparently $Fdd2$ (γ)]. The α and β forms are obtained simultaneously at ambient temperature by diffusion of hexane into dichloromethane solutions of **16**. Lowering the temperature to −130 °C for the same diffusion process leads exclusively to the γ form. The forms that crystallize concomitantly have unusual, but similar molecular conformations. Not surprising for the phenomenon observed, in particular for the α and β forms, the three melting points (59.5–60.2 (α), 57.8–59.0 (β), 60.0–60.9 °C (γ)) are very similar, and the authors used the technique of mixed melting points to verify the existence of the three polymorphs.

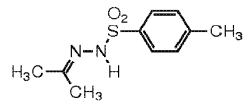


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7.9. Concomitant Crystallization of Conformational Polymorphs

One of the definitions of polymorphism[2, 5, 80] requires that all polymorphic structures of a material dissolve, melt, or vaporize to give the same species or equilibrium mixture of species. If this is accepted as a definition, the time necessary for equilibrium to be achieved becomes an issue, as well as the temperature of the dissolution, melting, or vaporization process. Clearly, years is too long to meet this criterion, but are hours or days too long? The question is still open. Nevertheless, a number of cases of concomitant polymorphs demonstrate the principles.

Gleason and co-workers[81] recently reported the crystallization of two *conformational polymorphs*[82] of acetone tosylhydrazone (**17**). A triclinic form and a monoclinic form are obtained from anhydrous ethanol, sometimes together. If the crystallizing solution is allowed to evaporate completely, only the monoclinic form is obtained, which suggests that it is the thermodynamically preferred form at room temperature. This is consistent with Ostwald's Rule of Stages[22] and McCrone's test for relative stability of polymorphs:[2] the more stable polymorph will grow at the expense of the less stable one. The crystal structure determination indicates that the conformations differ by ≈15° about the S–C exocyclic bond. In this case, the solution has an equilibrium mixture of (at least) these two molecular conformations. Lattice energy calculations (Cerius2)[83] are consistent with this observation, and indicate that the triclinic polymorph is more stable than the monoclinic form by about 1 kcal mol^{-1}.



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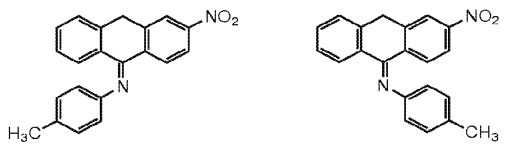
Another issue in the definition of polymorphs is that of *tautomerism*. An example of the crystallizing tautomeric structures of 2-amino-3-hydroxy-6-phenylazopyridine (**18**) has been reported by Desiraju,[84] **18a** being the "low temperature" form as lustrous blue needles and red **18b** being the



18a **18b**

"high temperature" form, both with melting points of 181–182 °C. They were obtained simultaneously from recrystallization of the crude synthetic product from ethanol, but the relative amounts varied from batch to batch in subsequent crystallizations when concentration and temperature were varied. The high temperature form was always obtained; the amount of low temperature form varied with the crystallization conditions. The tautomeric separation clearly takes place upon crystallization. To complete the picture and to make this, arguably, a case of polymorphism, it must be shown that the blue and red crystals dissolve to yield the same equilibrium mixture.

A case of concomitant crystallization which involves *configurational isomerism* has been reported by Matthews et al.[85] which again called into question the definition of polymorphism. The benzophenone anil **19** can exist in two configurational isomers, designated *E* and *Z*. The material has been shown to be trimorphic: a yellow form (triclinic, $P\bar{1}$, $Z=6$, m.p. 91 °C) and an orange form (triclinic, $P\bar{1}$, $Z=4$, m.p. 78–80 °C) often crystallizing from ethanol or benzene/diethyl ether at 0 °C. The third form (monoclinic $P2_1/c$, $Z=4$, m.p. 91 °C) is obtained from ethanol at room temperature.



(*E*)-**19** (*Z*)-**19**

In the first polymorph, all molecules exhibit the *Z* configuration. In the second, concomitant polymorph all molecules are in the *E* configuration. The third polymorph also contains molecules with *E* configuration. The conformations of the molecules in the second and third polymorphs differ slightly, which suggests that they might qualify as conformational polymorphs.[82]

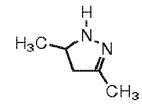
But should the first two structures be considered as properly belonging to a polymorphic system? Again, we can revert to McCrone's tests.[2] As Matthews et al. point out, these configurational isomers can interconvert at rates which vary by up to 10^{14}. If they interconvert quickly (i.e., on the order of hours) then they will give the same equilibrium mixture and may properly be called polymorphs according to the McCrone definition.

McCrone suggests some additional tests.[2] Two crystals of the same compound suspected of being polymorphic are placed side by side on a microscope slide in a mutually suitable solvent. If they are polymorphs of different thermodynamic stability the more stable one will grow at the expense of the less stable one. While it is not clear how soluble the polymorphs of **19** are in Nujol, when both the *E*-containing polymorphs were allowed to stand in Nujol for a few days the result was a conversion to the *Z*-containing polymorph. On the basis of the available evidence this does seem to be a case of polymorphism, in spite of the original authors' preference to avoid the use of the term.

7.10. Concomitant Crystallization of Racemates and Enantiomers

Another issue in the definition of polymorphs deals with racemic mixtures versus enantiomerically pure crystals or conglomerates.[2, 5, 80] In principle, enantiomerically pure crystals are different from racemic ones, but if they racemize quickly in solution and/or spontaneously resolve upon crystallization, it is still debatable whether these are to be considered polymorphic substances. Sironi and co-workers[86] have recently characterized a concomitantly crystallized system that incorporates and illustrates many of these features, and in addition, provides an example of a substance in which the synthetic approach to the material apparently plays a role in determining which polymorph is initially obtained.

The molecule under study was $[Pd\{(dmpz)_2(Hdmpz)_2\}_2]$ (**20**). The material is trimorphic. The reaction mixture yields mostly (90%) the monoclinic ($C2/c$, racemic) α phase, the remainder being the triclinic ($P\bar{1}$, racemic) γ phase. The latter can be removed by recrystallization from 1,2-dichloroethane, which suggests that it is the more soluble and hence less stable polymorph in that solvent. Sironi and co-workers found that mixtures of various amounts of α and γ polymorphs could be obtained by varying the solvent and precipitation temperature (−70 °C to +50 °C), with α preferred at higher temperatures, consistent with the earlier observation of relative stabilities. Pure polymorph γ may be obtained by a different synthetic route, which, with an excess of 3,5-dimethylpyrazole, leads to an approximately 50:50 mixture of polymorphs α and γ. This system thus also represents a case in which the polymorph obtained, or the polymorphic mixture obtained, depends on the synthetic route to the desired material. It is probably more correct to state that as usual, the polymorph or polymorphic mixture depends on the crystallization conditions, and these will clearly differ in the solvent/reagent/product compositions that result from different synthetic conditions and routes.[87]



Hdmpz

The tetragonal ($I422$, chiral) β "polymorph" is obtained quantitatively by a solid–liquid synthesis. The product is a conglomerate of enantiomeric crystals, which the authors claim does not transform into the α phase because of the impossibility of a solid–solid transformation. Dissolution of the β phase in 1,2-dichloroethane and subsequent evaporation quantitatively restores a mixture of α and γ forms. Despite the

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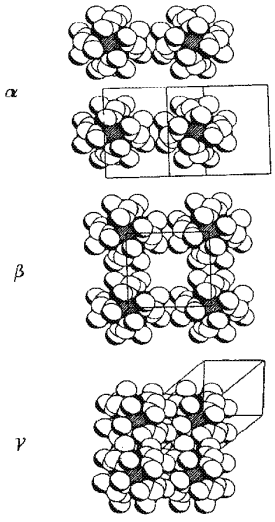


Figure 14. Packing of the $[Pd(dmpz)_2(Hdmpz)_2]_2$ (**20**) molecules in the three polymorphs, viewed approximately down the pseudo-fourfold axis. (Reprinted from ref. [86] with permission.)

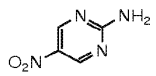
different space groups, the gross features of the packing modes are very similar, the molecules being arranged about a pseudo (α, γ) or real (β) fourfold axis (Figure 14). Such a view of the crystal structure is consistent with observations of Gavezzotti and Desiraju[91] and Braga and Grepioni[92] on the general similarities of packing features and coordination numbers of organic and organometallic compounds.

7.11. Concomitant Crystallization and Crystal Engineering

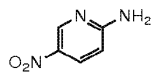
The growing interest in crystal engineering is certain to lead to more recognized cases of concomitant polymorphs. Indeed, if crystal engineering can be considered as control over the design and preparation of desired crystal structures then the phenomenon of polymorphism—and concomitantly crystallizing polymorphs—is antithetical to such an approach.[93] One popular strategy in crystal engineering is to build up structures from systems of two molecular components between which the intermolecular interactions are well defined, usually by the potential formation of hydrogen bonds.[94]

A recent example from this realm of chemistry, which again illustrates the role of the synthetic route in determining the generation of polymorphic structures comes from the work of Biradha and Zaworotko on **11** and **12** (see Section 7.6).

Another attempt at crystal engineering led to a remarkable number of concomitant crystallized materials. Aakeroy et al. dissolved **21** and **22** in a 1:1 ratio in butanol. Upon slow evaporation they obtained *five* crystalline materials, three polymorphs of **21** (thick, diamond-shaped plates, white needles and colorless blocks)[95] and yellow platelike crystals of **22** along with yellow/colorless dichroic blocks of a monohydrate of **22**. Only keen observation could be responsible for the discovery and characterization of all five crystalline materials in this mixture.

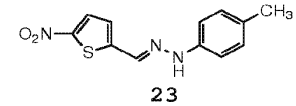


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22

One practical mission-driven aspect of crystal engineering is the attempt to design and prepare nonlinear optical materials. This goal has led to the variation of crystallization conditions in the search for crystals of potential SHG materials, and has resulted in the discovery of polymorphic systems,[96] as well as the development of a number of strategies for obtaining structures with the required symmetry properties.[97] Recently Pan et al. reported many crystallization studies on **23**, which is at least trimorphic, the three modifications being easily recognized by habit and color: form I, red greenish plates ($P2_1/n$); form II, red orange prisms ($Pna2_1$); form III, black needles ($P2_1/n$). Hence only form II is SHG active. Solvent evaporation or controlled lowering of the temperature lead to form I from all solvents used, but rapid cooling of highly supersaturated solutions of protonic solvents (e.g. methanol or ethanol) sometimes led to concomitant crystallization of forms II and III. The crystal structures of these three modifications could also be distinguished by the nature of the intermolecular interactions dominating them.[98]



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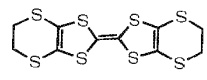
7.12. Organic Conductors and Magnets

It is not surprising that quite a few examples of concomitant polymorphs are found amongst the compounds and salts of potential use as organic conductors and magnetic materials. Considerable effort is generally expended in growing crystals and fine tuning conditions for obtaining crystals of sufficient quality for further structural and physical characterization. Thus a wide variety of crystallizing conditions are often tested and many individual crystals from a single crystallization might be subjected to structural and physical characterization.[99] These are favorable circumstances for the preparation and recognition of polymorphism and concomitant polymorphs.

7.12.1. Organic Conductors by Electrocrystallization

Perhaps most prominent of these materials are the organic conducting and superconducting salts based on so-called ethylenedithio ("ET") compounds, in which bis(ethylenedithio)tetrathiafulvalene (BEDT-TTF; **24**) is the donor (cation in the salt), generally in a 2:1 ratio with the acceptor (anion in the salt).[100a]

One of the most widely studied of these salts is $(ET)_2I_3$, for which at least 14 different phases have been reported,[100] although the α and β phases tend to dominate.[101] Most of the 2:1 salts are obtained by electrochemical crystallization which affords additional degrees of freedom of crystallization conditions compared to "conventional" crystallization: voltage, current density, counterion (for the salt anion), supporting electrolyte, electrode materials, and so on. So, for $(ET)_2I_3$ for instance, it has been shown that the α phase is the kinetically favored product (>90%) under conditions of high current density and a small amount of water or oxidant in the crystallization medium. Under more nearly equilibrium conditions (i.e., much lower



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current density) and dry solvent (tetrahydrofuran), pure β phase can be obtained, which suggests that it is the thermodynamically preferred form. Intermediate conditions apparently lead to concomitant crystallization of the two forms.[100]

When the crystallization is carried out as an oxidation of ET in tetrahydrofuran with a mixture of $(n\text{-}C_4H_9)_4NI_3$ and $(n\text{-}C_4H_9)_4NAuI_2$ (16/1 w/w) with an intermediate current to that described above, the α form is the main product, concomitantly crystallized with small amounts of θ and κ polymorphs.[102] The authors note the difficulty in identifying the three forms on the basis of crystal shape alone, and the three were characterized by a combination of X-ray diffraction and other physical measurements.

Two distinct superconducting κ phases (labeled κ_H and κ_L) are obtained simultaneously in the electrocrystallization of the salt of ET with the anion $[Cu(CF_3)_4]^-$ in 1,1,2-trichloroethane.[103] After four days black needles of the κ_H form appeared on the anode, and within a week black plates of the κ_L form appeared amongst the needles (Figure 15). Both salts are, in fact, solvates of $(ET)Cu(CF_3)_4$, with κ_L containing one molecule per salt formula unit, and κ_H containing slightly less than one molecule per salt formula unit. The authors note that the growth of the plates apparently inhibits the growth of the needles, which after 14 days amounted to approximately 5% by weight of the product. These results were reproducible. The addition of 10% ethanol to the electrolyte solution led to a slight increase in crystal quality in some experiments, but otherwise did not alter the results. ET also forms a concomitant dimorphic salt with $Pt(CN)_4$, with the stoichiometry $(ET)_4Pt(CN)_4$; the two forms are designated α and β.[104, 105]

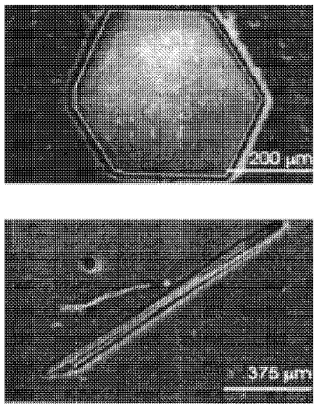
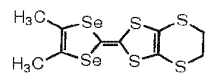
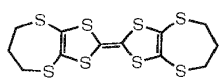
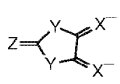


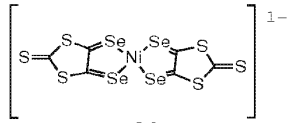
Figure 15. Photograph of the two κ phases of $(ET)_2Cu(CF_3)_4$. (Reprinted from ref. [103] with permission.)

In another example that involves similar materials, the dimethyl ethylenedithio donor is DMET **25** and the acceptor is $AuBr_2$ to form both rhombs and platelike crystals of $(DMET)_2AuBr_2$;[106, 107] no further information on crystallization conditions, color, habit, and so on are given. The crystal structure and temperature-dependent resistivities differ significantly for the two polymorphs.


25


26


27: X, Y, Z = S, Se


28

Montgomery et al.[108] have shown that, in systems in which attempts were made to prepare alloys of β-$(ET)_2I_3$ with β-$(PT)_2I_3$ (PT = **26**, a propylenethio donor), they apparently obtained "single crystals" of $(ET)_2I_3$ which were in fact mixtures of the α and β forms. The phenomenon in this system was initially detected and then confirmed by ESR spectroscopy, which was subsequently used to develop a quantitative procedure for the determination of the polymorphic composition of such "mixed single crystals". There are other scattered reports in the literature of this phenomenon,[109] which has been termed "composite crystals" and has been discussed in detail by Coppens et al.[110]

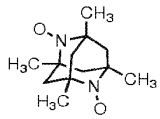
Another widely studied series of conducting organic salts is based on the ligand **27**. In the case where X = Se, Y = Z = S, known as dsit, the organometallic monovalent anion **28** can be formed with Ni^{III} to give a dimorphic salt with composition $(Bu_4N)_2[Ni(dsit)_2]_2$.[111] Concomitant crystallization of the α and β forms was noted upon recrystallization of the crude material, the α form being chunky blocks, while the β form crystallizes as needles. Slow evaporation of a solution prepared by dissolution of both forms leads to the α form, which suggests that it is the more stable form.

7.12.2. Organic Conductors by Interdiffusion

Interdiffusion of saturated solutions (as opposed to electrocrystallization) is another method for obtaining crystals of potentially conducting salts. In most of the preparations of $TTF[Pd(dmit)_2]_2$ (dmit: **27**, X = Y = Z = S) by diffusion of $(TTF)_3(BF_4)_2$ and $(nBu_4N)[Pd(dmit)_2]$, mainly black shiny needles of the α phase were obtained. However, some experiments yielded, in addition, a so-called α' phase (due to its structural similarity to the α phase, but different electrical behavior), and occasionally it was possible to separate a third δ phase of plate-shaped crystals from the batch.[112–114]

7.12.3. Organic Magnetic Materials

The significant increase in interest and activity in the design, preparation, and study of organic magnetic materials has led to the discovery of a number of polymorphic systems.[116, 117] One of the few purely organic materials shown to undergo a well-characterized ferromagnetic transition is the azaadamantane derivative **29**.[118] The material is dimorphic, and both forms appear simultaneously by evaporation of a diethyl ether solution at room temperature. The authors note that they have not succeeded in determining the conditions for selectively crystallizing either form.


29

The structures of the α and β forms are shown in Figure 16. It can be seen that there is indeed a subtle difference in the environment of the oxygen atom on which the unpaired electrons are formally located, and in other intermolecular interactions, but the concomitant crystallization suggests that

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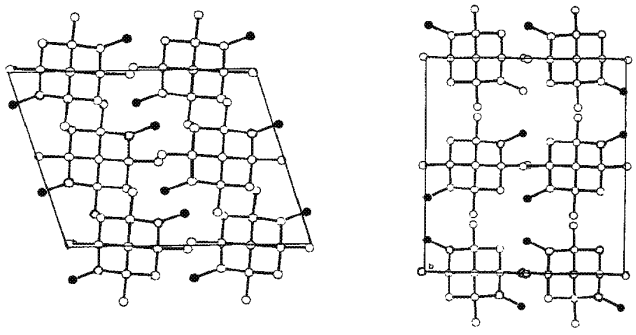
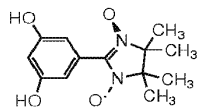


Figure 16. Representation of the packing of the two forms of **29**. Oxygen atoms are denoted by solid circles. Left: the monoclinic α form; right: the orthorhombic β form. (Reprinted from ref. [118] with permission.)

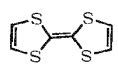
the energetic consequences of the sum of these differences are very small.

This lack of control over the polymorph obtained is in contrast to the dimorphic system HQNN **30**. Sugawara et al. reported in a preliminary communication[119] that the bluish-purple blocks of the α phase could be obtained above 4 °C and the needle-shaped β phase can be crystallized below 0 °C. In addition, they add that "both crystals can be obtained selectively by using a seed crystal at room temperature". In a later publication[120] it was noted that the α phase was obtained in a refrigerator, "(≈4 °C) under a nitrogen atmosphere" while the β form was obtained from a solution "stored in a freezer (≈ −10 °C)".

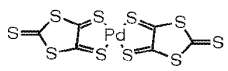


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Legros and Valade reported the concomitant (α and γ) forms of **31** and **32**. The crystals are obtained from the slow interdiffusion of saturated solutions of $(TTF)_3(BF_4)_2$ and



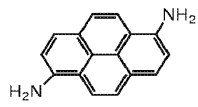
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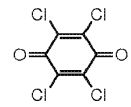
32

$(n\mathrm{Bu_4N})[\mathrm{Pd(dmit)_2}]$.[112] The α form is the main product as shiny black needles, with some platelets of the γ phase usually present. Occasionally, a so-called α' phase is also obtained in this crystallization procedure. The α and γ forms have very different crystal structures and correspondingly different electrical behavior. The former are built up of segregated stacks of donor and acceptor molecules and undergoes a metal–semiconductor transition. The latter has stacks of dimers of **32**, and exhibits metallic behavior in the range 120–300 K.

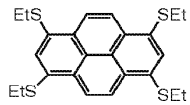
A recent study on the system of 1,6-diaminopyrene (**33**) and chloranil (**34**) is edifying with regard to the connection between structure and electrical conductivity. Compound **33** is a relatively strong donor that was an early subject of study as a component of potential electrically conducting complexes,[121, 122] and quite a few complexes of this donor were prepared.[123, 124] The complex of **33** with **34** was investigated in



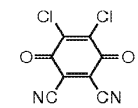
33



34



35



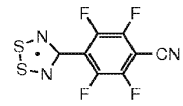
36

detail recently[124, 125] with results that indicate both the utility and some of the limitations of studies of polymorphic systems. The 1:1 complex is polymorphic, with a dark brown α form and a green β form. Both may be obtained *simultaneously* from benzene solution by both slow cooling and "prolonged" slow evaporation.[124] Under cooling or grinding, the resistivity of the α form is reduced by eight orders of magnitude, with no detectable structural changes by X-ray crystallography.

Modification of the substituents on the pyrene donor and the benzoquinone acceptor leads to the 1:1 complex of **35** with **36**, which was studied by Lee et al.[126] Slow evaporation of an equimolar mixture of the compounds in dichloromethane led to a mixture of black crystals; the α phase were "branchy" microcrystals and the β phase were large platelets.

7.12.4. Free Radicals by Sublimation

The recently reported 1,2,3,5-dithiadiazolyl radical **37** is the first to retain its paramagnetic behavior in the solid state.[127, 128] It also provides another example of concomitant crystallization by sublimation. Large black blocks of the α phase may be obtained pure by very rapid vacuum sublimation at 120 °C and 10^{-2} Torr. The long, plastically deformable needles or small red blocks of the β phase are prepared at the same pressure and 80–100 °C, with the crystals collecting just above the level of the oil bath or heating tape of the source vessel (i.e., small temperature gradient).[129] The two phases appear simultaneously under vacuum in a sublimation tube subjected to a temperature gradient. The difference in color of the latter two types of β crystals is most likely a size effect, the larger crystals being opaque and hence reflecting.



37

7.13. Concomitant Crystallization of Proteins

In view of the many experiments carried out on the crystallization of proteins and subsequently refinement of the conditions to maximize crystal size and quality for X-ray structure determination, it is not surprising that examples of concomitant crystallization are found among proteins. Wang and co-workers reported the simultaneous crystallization of three polymorphs of a m-class glutathione S-transferase from

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rat liver[130] (Figure 17). Day and McPherson reported crystallization of two crystalline forms in stages in accord with Ostwald's Rule for cytochrome c from *Valida membranaefaciens*[131] (Figure 18). In every case of crystallization they obtained arrays of thin triclinic plates (Figure 18a), some of which grew up to 0.5 mm along the largest physical dimension (Figure 18b). In some cases, some of these dissolved (in accord with Ostwald's Rule of Stages) to give rectangular prisms (Figure 18c), which turned out to be orthorhombic.

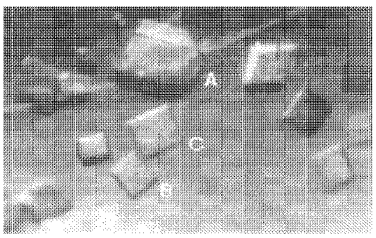


Figure 17. Photograph of cocrystallizing forms of rat liver glutathone S-transferase. The three forms are labeled. (Reprinted from ref. [130] with permission.)

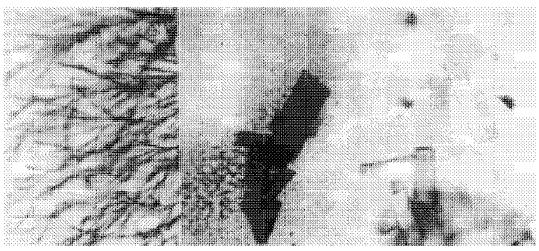
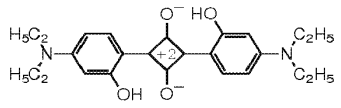


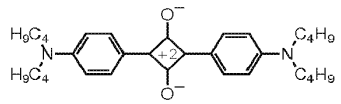
Figure 18. Example of the stagelike growth in cytochrome c from *Valida membranaefaciens*. a) Treelike arrays of small triclinic crystals. b) Triclinic crystals, which are frequently seen to dissolve at the expense of the orthorhombic prism (c). (Reprinted from ref. [131] with permission.)

8. A Structural Approach to Concomitant Crystallization

Up to this point this account of instances of concomitant polymorphs has been phenomenological. We have discussed the thermodynamic and kinetic crystallization of polymorphs. There is still the question of whether any insight can be gained from the study of the crystal structures of concomitantly crystallized polymorphs. A qualitative attempt was made to see if details of the crystal structures may provide clues to the reasons for concomitant crystallization. The squarylium dye **38** crystallizes from dichloromethane in a triclinic violet form and a monoclinic green form.[132] The cell constants (Table 1) do not suggest any similarity of the structures. However, a projection on the molecular plane which includes two neighboring molecules (Figure 19) indicates that the stacking of the planar molecules is virtually identical in the two structures. In both cases the two molecules are related by a lattice translation: in the triclinic structure it is along the *c* axis and in the monoclinic structure along the *b* axis. Although the



38



39

Table 1. Crystallographic cell constants for the two polymorphic forms of **38**.

	Triclinic	Monoclinic
a [Å]	11.911	15.72
b [Å]	7.401	7.283
c [Å]	6.501	9.591
α [°]	92.78	90
β [°]	111.9	106.11
γ [°]	98.08	90
space group	$P\bar{1}$	$P2_1/c$

views appear the same to the eye, the vertical separation between planes differs (3.40 Å vs 3.86 Å), which is a manifestation of the different axial lengths involved. The similarity of these diagrams strongly suggests that the stacking

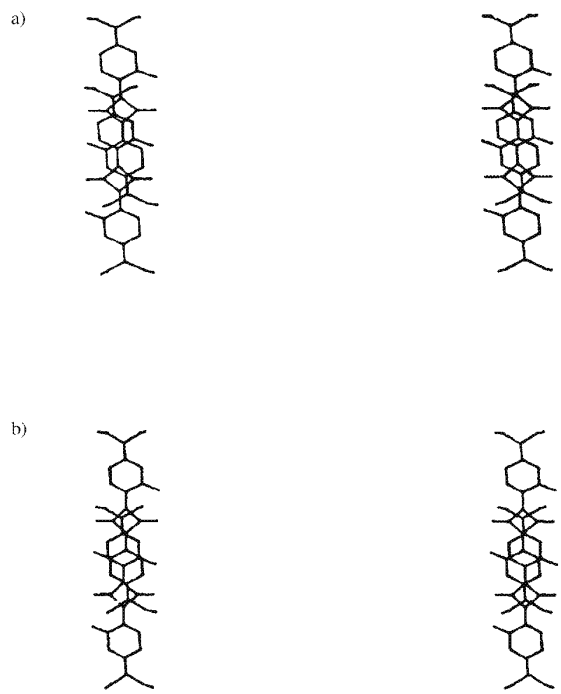


Figure 19. Stereoviews of the overlap of translationally related molecules in the two structures of **38**. In both cases the view is on the plane of the reference molecule. a) Triclinic structure, *c*-axis translation; b) monoclinic structure, *b*-axis translation. (Reprinted from ref. [132] with permission.)

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is the dominant influence in the crystal growth process for both—hence the concomitant crystallization. The crystal structures differ, of course, in that stacks are related by translation in the triclinic structure and by a screw axis in the monoclinic one, as shown in Figure 20, but the fact that these phases crystallize concomitantly would be consistent with the assumption that energetically, at least, these interstack interactions contribute in a less significant way than those within the stack.

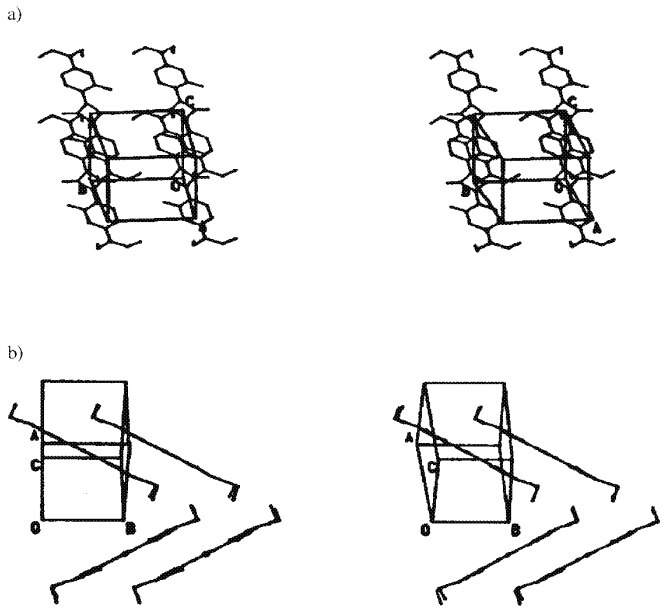


Figure 20. Stereoviews showing the relationship between the stacks shown in Figure 19 for **38**. a) Triclinic structure, translational relationship. b) Monoclinic structure, screw-axis relationship. (Reprinted from ref. [132] with permission.)

It is of interest to note that another similar squarylium dye **39** has also been shown to concomitantly crystallize in a green monoclinic phase and a purple triclinic phase.[133] The structure has been reported for the former, but crystals of the latter were not of sufficient quality to determine the crystal structure. The monoclinic phase crystallizes in space group $P2_1/c$ with cell constants $a = 9.046$, $b = 19.615$, $c = 9.055$ Å, $\beta = 116.1°$, which precludes any molecular overlap of the type seen in Figure 19 for **38**. The crystal structures of **38** and **39** are significantly different so that the similarity in the colors of the polymorphs of the two compounds appears to be entirely coincidental, albeit unusual.[115]

9. Summary and Outlook

Sironi and co-workers have described the current situation of the discovery of polymorphs in general and of concomitantly crystallizing polymorphs in particular:[86] "Normally, after a good-looking single crystal is randomly picked out of a bunch of crystals, or more frequently, from a complex mixture containing also (morphologically) amorphous, microcrystalline or powdered material, no scattering measurements characterizing the nature of the bulk are routinely performed, thus overlooking the possibility of finding [the] coexistence of different crystalline phases of the same composition in the same sample."

Sironi and co-workers advocate the use of fast (≈30 min) diffraction patterns as a "routine control of reaction products". We have no argument with this: any suitable technique could and should be used. We still prefer the initial careful optical examination with the polarizing, and preferably, hot-stage microscope. Very little material is required, the method is usually non-destructive, and a great deal can be learned with a very small investment in time and money.

We have described a phenomenon that can be useful in the investigation of solid materials, and in understanding the relative crystal energetics of polymorphic materials. In general no sophisticated technique or instrumentation is required to detect concomitant polymorphs. All that is necessary is the willingness to observe crystalline samples carefully, the awareness that such samples may contain more than one polymorphic modification, and the understanding that such a situation can provide a great deal more information than one polymorphic modification can yield. We hope that this awareness will stimulate those dealing with crystallizations and with crystals to look a little closer at the batch of crystals before moving on to further study or relegating them to storage, and to describe the associated crystallizing procedures, crystal habits, color, and so on in more detail than is the common practice today.[134]

As the awareness of polymorphism has grown, there has been increasing effort to understand the phenomenon and to gain control over the crystallization process in order to selectively obtain a desired polymorph or suppress the growth of an undesired one. Historically, this was done by a combination of trial and error, intuition, serendipity, varying solvents, temperature,[2, 18] and occasionally additives.[135] The availability of detailed structural data, combined with strategic design of substrates and additives, has led to significant advances in the control over the polymorphs obtained in a particular crystallization.[136–139]

Although the phenomenon of concomitant crystallization has a long history, many of our examples have been taken from the very recent literature. This is not totally by accident. The relative ease with which crystal structures can be solved compared, say, to a generation ago has facilitated the structural investigation of crystals per se. However, a large proportion of the papers cited have been authored by what might be called practitioners of the organic solid state who, through training and experience, tend to benefit from an awareness of polymorphism and an interest in polymorphic systems. It is hoped that this review will promote that awareness throughout the general chemical community.

We are grateful to many enthusiastic colleagues who responded to our call for examples of concomitant polymorphs and to subsequent follow-ups for details. Many of the examples presented here benefited from some extra effort or assistance

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from them. Helpful discussions with Dr. Nick Blagden are appreciated. Special thanks to R. Goddard for permission to describe his independent results on the preparation of the second form of tetrathiafulvalene. We also wish to thank the Alexander von Humboldt Foundation for a postdoctoral fellowship to J.-O.H., the Academic Study Group (London) for a travel grant to R.J.D. to Israel, and an Austria–Israel Cultural and Scientific Exchange Program for J.B. to travel to Innsbruck and J.-O.H. to travel to Beer Sheva. The warm hospitality and availability of resources of the Cambridge Crystallographic Data Centre during a sabbatical leave of J.B. are greatly appreciated.

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[1] This phrase has been chosen with some consideration, and a number of other options were available. Our intention is to refer to polymorphs that are observed in the crystallization medium, usually simultaneously, although we do not rule out the possibility that they occur in stages, a later modification replacing an earlier one. This is compatible with the choice of "concomitant", which is defined as "accompanying, or happening together". Another possibility was "cocrystallizing", but this term is already in use with reference to the formation of solid solutions of enantiomers and also in the formation of crystalline complexes of two or more molecules, usually as a result of hydrogen bonding. Other options (with definitions) included concurrent (happening together), concrescent (the growing together of related parts), convergent (becoming similar or identical), simultaneously crystallizing (crystallizing at the same time). None of these portrayed more aptly than "concomitant" the phenomenon we wish to describe here.

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[35] Part of the difficulty in searching and interpreting the literature on polymorphic behavior of materials is due to the inconsistent labeling of polymorphs. In many cases, the inconsistency arises from lack of an accepted standard notation. However, often, and perhaps more important, it is due to the lack of various authors' awareness of previous work or lack of attempts to reconcile their own work with earlier studies. While many polymorphic minerals and inorganic compounds actually have different names (e.g., calcite, aragonite, and vaterite for calcium carbonate or rutile, brookite, and anatase for titanium oxide) this has not been the practice for molecular crystals, which have been labeled with Arabic (1, 2, 3,...) or Roman (I, II, III,...) numerals, lower or upper case Latin (a, b, c,... or A, B, C,...) or lower case Greek (α, β, γ,...) letters, or by names descriptive of properties (red form, low-temperature polymorph, metastable modification, etc.). As Threlfall has pointed out, arbitrary systems for naming polymorphs should be discouraged to avoid confusion as regards the number and identity of polymorphs for any compound.[5] Those based on relative stability or order of melting point do not allow for the discovery of forms with intermediate values; also small differences in stability or melting point might lead to different order and different labeling by different workers. McCrone[2] proposed the use of Roman numerals for the polymorphs in the order of their discovery, with the numeral I specifying the most stable form at room temperature. By Ostwald's Rule[22, 23] the order of discovery should in general follow the order of stability. McCrone also supported the suggestion by the Koflers that the Roman numeral be succeeded by the melting point in parentheses. In fact, the successors of the Koflers at the Innsbruck school have attempted to follow this practice,[11, 30] although in general it has not been widely adopted by others. In view

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of the body of literature already extant and the questions surrounding the definition of a polymorph, it is clearly not practical to define strict rules for labeling polymorphs. The Kofler method has some obvious advantages, since the melting point identifier may eliminate some questions of identity; hence its use should be encouraged. The important point for those studying polymorphic systems is to be fully aware of previous work, to try to identify the correspondence between their own polymorphic discoveries and those of earlier workers, and to avoid flippancy in the use of nomenclature in the naming of truly new polymorphs. In this review we have carried over the nomenclature adopted by the original workers.

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Science 17 October 1997:
Vol. 278. no. 5337, pp. 404 – 405
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PERSPECTIVES

SOLID-STATE CHEMISTRY:

Crystal Gazing: Structure Prediction and Polymorphism

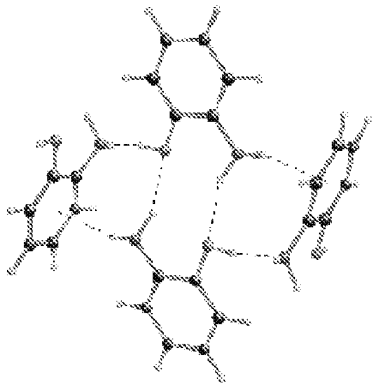
Gautam R. Desiraju

Crystal engineering, the design of organic solids with specified architectures and therefore particular physical or chemical properties, continues to elicit intense interest (1, 2). Crystals are built with molecules, and ideally one would like to predict the crystal structure of an organic substance from nothing more than its molecular structure. Indeed, given the molecular basis of organic chemistry, such a goal seems almost intuitive. A particular molecular structure can also yield more than one crystal structure, and this phenomenon of polymorphism (3) has been in the forefront, most notably in litigation surrounding the widely used ulcer medication Zantac (4).

The major obstacle in routinely predicting crystal structures from molecular structures is that in any kind of molecular recognition, and this includes the recognition between identical molecules during crystallization, it is the dissimilar functionalities that come into closest contact and not the similar surfaces (5). Steric and electronic complementarity thus characterize the crystallization event. The functional group approach, so central to molecular chemistry, is of limited applicability because the supramolecular behavior of a particular functional group depends acutely on the nature and even the location of the other functionalities in the molecule. This issue is greatly complicated by the fact that hydrocarbon residues, not normally considered functional groups in molecular chemistry, are quite respectable supramolecular functionalities. All this means that the crystal structures of many "simple" organic compounds need not be simple at all. What is surprising, however, and this is what provides the vital impetus to the subject, is that although the energy differences between the plethora of putative crystal structures for a given molecule can be quite small, many organic compounds are not polymorphic. Molecules seem to know exactly how to crystallize, even as chemists seem unable to accurately foresee such events.

Sometimes, it is possible to predict the outcome of crystallization. In seminal papers, Ermer (6) and Hanessian (7) and their colleagues showed that predictable structures can be obtained in systems containing equal stoichiometries of NH_2 and OH groups. This predictability arises from the 2:1 and 1:2 hydrogen bond donor:acceptor ratios in these functional groups, leading (i) to tetrahedral configurations at both heteroatoms in the hydrogen bond network and consequently (ii) to variants of the arsenic and wurtzite structures. In particular, 4-aminophenol is identifiable as an archetype of this family. Yet, how predictable are these crystal structures? We determined the structures of the isomeric 2- and 3-aminophenols with single-crystal low-temperature neutron diffraction, and rather than the expected tetrahedral network, an unusual N-H. .p hydrogen bond was observed (8) (see figure). The reason for this unexpected structure is

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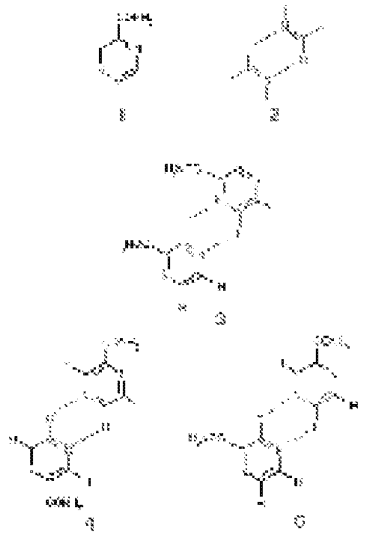


Odd bonds. An unusual NH···π hydrogen bond is found in the crystal structure of 2-aminophenol. Although conventional OH···N and NH···O hydrogen bonds are also seen, saturation of the hydrogen bonding capabilities of the NH_2 and OH groups with conventional hydrogen bonds, as predicted (6, 7), is not observed.

that the packing in all three aminophenols is dominated by the herringbone packing of aromatic rings rather than by hydrogen bonding. In 4-aminophenol, the aromatic packing is able to coexist with the hydrogen-bonded wurtzite network; in other words, the interference between these two sets of interactions is minimal. In 2- and 3-aminophenols, however, the same packing of aromatic rings is incompatible with the tetrahedral network that is replaced by the unconventional hydrogen-bond arrangement.

If functional groups do not adequately reflect molecule-to-crystal transforms, how then does one attempt to understand crystallization events in chemical terms? The descriptor "supramolecular synthon" signifies larger multimolecular units, within the most robust and useful of which is encoded the optimal information inherent in the mutual recognition of molecules to yield solid-state supermolecules, that is, crystals (9). Pyrazine carboxamide (see **1** in scheme 1) is a bizarre compound that exists in no less than five distinct polymorphic forms, and the supramolecular synthon **2** found in all of them is indicative of the importance of CH···N hydrogen bonding. The multiple yet distinctive occurrences of the heterocyclic N atom and the aromatic =CH group in the molecular skeleton of **1** means that synthon **2** can be generated in several ways, as shown in **3** through **5**, leading more or less directly to polymorphism.

Just as a given molecule may adopt different crystal structures, a given network structure may be accessed by distinct molecules. In this sense, there is some flexibility in crystal engineering strategies that are aimed at networks, if a particular network structure can lead to a property of interest. However, there are some areas wherein a molecule-based approach is still mandated. A good example is the crystallization of pharmaceuticals.



Scheme 1. The CH. ..N hydrogen-bonded supramolecular synthon **2** is optimized in the polymorphs of pyrazinc carboxamidc (**1**) in alternative arrangements **3** through **5**.

The complex legal issues raised by the Zantac litigation demonstrate how state-of-the-art scientific knowledge can impinge on purely legal issues with tremendous commercial ramifications (4). In general, for any given drug molecule, one needs to know if it is likely to be polymorphic or pseudopolymorphic, that is, if it crystallizes with variations in the nature or amount of solvent. Such efforts at crystal structure prediction are usually computational in nature with a greater or lesser reliance on crystallographic and close-packing arguments (10-13). These methods have been moderately successful, but there is still much that can be learned. A Monte Carlo simulated-annealing process is the basis for a well-known software package (14). Molecular dynamics-based approaches offer new perspectives, and recent studies by Gavezzotti (15) show how solvent and kinetic effects can be simulated. Experimental methods are less common, but the recent work of Davey *et al.* (16) on the stabilization of a metastable form of L-glutamic acid by conformational mimicry is of considerable relevance because it highlights the importance of kinetic and thermodynamic factors in crystallization.

An appreciation of polymorphism is fundamental to an understanding of the crystallization process itself. It is possible that a molecule with more recognition sites can more easily cascade into a stable crystal structure, with alternative crystallization possibilities being more efficiently excluded (17). In this respect, a certain resemblance between the crystallization of a small organic molecule and the folding of a protein may be noted. Both processes could proceed through intermediate (and perhaps kinetically stabilized) states, which could be semicompact random globules for proteins (18) and structure-determining clusters that contain robust supramolecular synthons for small

molecules. These intermediate states could result in a considerable increase in crystallization or folding efficiency, even as the correction of mistakes is facile.

Crystallization and polymorphism are complex phenomena, and a distinct branch of crystal engineering has developed that attempts to sidestep the difficult issues involved in their understanding. In the study of coordination polymers, use is made of relatively strong bonds between ligands and metal ions with unambiguous coordination geometries to generate open networks, some of which are stable to the loss of included solvent (19). But microporosity is not the only beneficial property in the world of solids and the design of crystal structures of small organic molecules remains an attractive research area with considerable intellectual challenge and potentialities for further applications as materials (20).

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http://euch3i.chem.emory.edu/~childs/supramolecular.html

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There's Plenty of Room at the Bottom

An Invitation to Enter a New Field of Physics

 *by Richard P. Feynman*

This transcript of the classic talk that Richard Feynman gave on December 29th 1959 at the annual meeting of the American Physical Society at the California Institute of Technology (Caltech) was first published in the February 1960 issue of Caltech's *Engineering and Science*, which owns the copyright. It has been made available on the web at http://www.zyvex.com/nanotech/feynman.html with their kind permission.

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For an account of the talk and how people reacted to it, see chapter 4 of *Nano!* by Ed Regis, Little/Brown 1995. An excellent technical introduction to nanotechnology is *Nanosystems: molecular machinery, manufacturing, and computation* by K. Eric Drexler, Wiley 1992.

I imagine experimental physicists must often look with envy at men like Kamerlingh Onnes, who discovered a field like low temperature, which seems to be bottomless and in which one can go down and down. Such a man is then a leader and has some temporary monopoly in a scientific adventure. Percy Bridgman, in designing a way to obtain higher pressures, opened up another new field and was able to move into it and to lead us all along. The development of ever higher vacuum was a continuing development of the same kind.

I would like to describe a field, in which little has been done, but in which an enormous amount can be done in principle. This field is not quite the same as the others in that it will not tell us much of fundamental physics (in the sense of, ``What are the strange particles?'') but it is more like solid-state physics in the sense that it might tell us much of great interest about the strange phenomena that occur in complex situations. Furthermore, a point that is most important is that it would have an enormous number of technical applications.

What I want to talk about is the problem of manipulating and controlling things on a small scale.

As soon as I mention this, people tell me about miniaturization, and how far it has progressed today. They tell me about electric motors that are the size of the nail on your small finger. And there is a device on the market, they tell me, by which you can write the Lord's Prayer on the head of a pin. But that's nothing; that's the most primitive, halting step in the direction I intend to discuss. It is a staggeringly small world that is below. In the year 2000, when they look back at this age, they will wonder why it was not until the year 1960 that anybody began seriously to move in this direction.

Why cannot we write the entire 24 volumes of the Encyclopedia Brittanica on the head of a pin?

Let's see what would be involved. The head of a pin is a sixteenth of an inch across. If you magnify it by 25,000 diameters, the area of the head of the pin is then equal to the area of all the pages of the Encyclopaedia Brittanica. Therefore, all it is necessary to do is to reduce in size all the writing in the Encyclopaedia by 25,000 times. Is that possible? The resolving power of the eye is about 1/120 of an inch---that is roughly the diameter of one of the little dots on the fine half-tone reproductions in the Encyclopaedia. This, when you demagnify it by 25,000 times, is still 80 angstroms in diameter---32 atoms across, in an ordinary metal. In other words, one of those dots still would contain in its area 1,000 atoms. So, each dot can easily be adjusted in size as required by the photoengraving, and there is no question that there is enough room on the head of a pin to put all of the Encyclopaedia Brittanica.

Furthermore, it can be read if it is so written. Let's imagine that it is written in raised letters of metal; that is, where the black is in the Encyclopedia, we have raised letters of metal that are actually 1/25,000 of their ordinary size. How would we read it?

If we had something written in such a way, we could read it using techniques in common use today. (They will undoubtedly find a better way when we do actually have it written, but to make my point conservatively I shall just take techniques we know today.) We would press the metal into a plastic material and make a mold of it, then peel the plastic off very carefully, evaporate silica into the plastic to get a very thin film, then shadow it by evaporating gold at an angle against the silica so that all the little letters will appear clearly, dissolve the plastic away from the silica film, and then look through it with an electron microscope!

There is no question that if the thing were reduced by 25,000 times in the form of raised letters on the pin, it would be easy for us to read it today. Furthermore; there is no question that we would find it easy to make copies of the master; we would just need to press the same metal plate again into plastic and we would have another copy.

How do we write small?

The next question is: How do we *write* it? We have no standard technique to do this now. But let me argue that it is not as difficult as it first appears to be. We can reverse the lenses of the electron microscope in order to demagnify as well as magnify. A source of

ions, sent through the microscope lenses in reverse, could be focused to a very small spot. We could write with that spot like we write in a TV cathode ray oscilloscope, by going across in lines, and having an adjustment which determines the amount of material which is going to be deposited as we scan in lines.

This method might be very slow because of space charge limitations. There will be more rapid methods. We could first make, perhaps by some photo process, a screen which has holes in it in the form of the letters. Then we would strike an arc behind the holes and draw metallic ions through the holes; then we could again use our system of lenses and make a small image in the form of ions, which would deposit the metal on the pin.

A simpler way might be this (though I am not sure it would work): We take light and, through an optical microscope running backwards, we focus it onto a very small photoelectric screen. Then electrons come away from the screen where the light is shining. These electrons are focused down in size by the electron microscope lenses to impinge directly upon the surface of the metal. Will such a beam etch away the metal if it is run long enough? I don't know. If it doesn't work for a metal surface, it must be possible to find some surface with which to coat the original pin so that, where the electrons bombard, a change is made which we could recognize later.

There is no intensity problem in these devices---not what you are used to in magnification, where you have to take a few electrons and spread them over a bigger and bigger screen; it is just the opposite. The light which we get from a page is concentrated onto a very small area so it is very intense. The few electrons which come from the photoelectric screen are demagnified down to a very tiny area so that, again, they are very intense. I don't know why this hasn't been done yet!

That's the Encyclopaedia Brittanica on the head of a pin, but let's consider all the books in the world. The Library of Congress has approximately 9 million volumes; the British Museum Library has 5 million volumes; there are also 5 million volumes in the National Library in France. Undoubtedly there are duplications, so let us say that there are some 24 million volumes of interest in the world.

What would happen if I print all this down at the scale we have been discussing? How much space would it take? It would take, of course, the area of about a million pinheads because, instead of there being just the 24 volumes of the Encyclopaedia, there are 24 million volumes. The million pinheads can be put in a square of a thousand pins on a side, or an area of about 3 square yards. That is to say, the silica replica with the paper-thin backing of plastic, with which we have made the copies, with all this information, is on an area of approximately the size of 35 pages of the Encyclopaedia. That is about half as many pages as there are in this magazine. All of the information which all of mankind has every recorded in books can be carried around in a pamphlet in your hand---and not written in code, but a simple reproduction of the original pictures, engravings, and everything else on a small scale without loss of resolution.

What would our librarian at Caltech say, as she runs all over from one building to another, if I tell her that, ten years from now, all of the information that she is struggling to keep track of--- 120,000 volumes, stacked from the floor to the ceiling, drawers full of cards, storage rooms full of the older books---can be kept on just one library card! When the University of Brazil, for example, finds that their library is burned, we can send them a copy of every book in our library by striking off a copy from the master plate in a few hours and mailing it in an envelope no bigger or heavier than any other ordinary air mail letter.

Now, the name of this talk is ``There is *Plenty* of Room at the Bottom"---not just ``There is Room at the Bottom." What I have demonstrated is that there *is* room---that you can decrease the size of things in a practical way. I now want to show that there is *plenty* of room. I will not now discuss how we are going to do it, but only what is possible in principle---in other words, what is possible according to the laws of physics. I am not inventing anti-gravity, which is possible someday only if the laws are not what we think. I am telling you what could be done if the laws *are* what we think; we are not doing it simply because we haven't yet gotten around to it.

Information on a small scale

Suppose that, instead of trying to reproduce the pictures and all the information directly in its present form, we write only the information content in a code of dots and dashes, or something like that, to represent the various letters. Each letter represents six or seven ``bits" of information; that is, you need only about six or seven dots or dashes for each letter. Now, instead of writing everything, as I did before, on the *surface* of the head of a pin, I am going to use the interior of the material as well.

Let us represent a dot by a small spot of one metal, the next dash, by an adjacent spot of another metal, and so on. Suppose, to be conservative, that a bit of information is going to require a little cube of atoms 5 times 5 times 5---that is 125 atoms. Perhaps we need a hundred and some odd atoms to make sure that the information is not lost through diffusion, or through some other process.

I have estimated how many letters there are in the Encyclopaedia, and I have assumed that each of my 24 million books is as big as an Encyclopaedia volume, and have calculated, then, how many bits of information there are (10^15). For each bit I allow 100 atoms. And it turns out that all of the information that man has carefully accumulated in all the books in the world can be written in this form in a cube of material one two-hundredth of an inch wide--- which is the barest piece of dust that can be made out by the human eye. So there is *plenty* of room at the bottom! Don't tell me about microfilm!

This fact---that enormous amounts of information can be carried in an exceedingly small space---is, of course, well known to the biologists, and resolves the mystery which existed before we understood all this clearly, of how it could be that, in the tiniest cell, all of the information for the organization of a complex creature such as ourselves can be stored. All this information---whether we have brown eyes, or whether we think at all, or

that in the embryo the jawbone should first develop with a little hole in the side so that later a nerve can grow through it---all this information is contained in a very tiny fraction of the cell in the form of long-chain DNA molecules in which approximately 50 atoms are used for one bit of information about the cell.

Better electron microscopes

If I have written in a code, with 5 times 5 times 5 atoms to a bit, the question is: How could I read it today? The electron microscope is not quite good enough, with the greatest care and effort, it can only resolve about 10 angstroms. I would like to try and impress upon you while I am talking about all of these things on a small scale, the importance of improving the electron microscope by a hundred times. It is not impossible; it is not against the laws of diffraction of the electron. The wave length of the electron in such a microscope is only 1/20 of an angstrom. So it should be possible to see the individual atoms. What good would it be to see individual atoms distinctly?

We have friends in other fields---in biology, for instance. We physicists often look at them and say, ``You know the reason you fellows are making so little progress?" (Actually I don't know any field where they are making more rapid progress than they are in biology today.) ``You should use more mathematics, like we do." They could answer us---but they're polite, so I'll answer for them: ``What *you* should do in order for *us* to make more rapid progress is to make the electron microscope 100 times better."

What are the most central and fundamental problems of biology today? They are questions like: What is the sequence of bases in the DNA? What happens when you have a mutation? How is the base order in the DNA connected to the order of amino acids in the protein? What is the structure of the RNA; is it single-chain or double-chain, and how is it related in its order of bases to the DNA? What is the organization of the microsomes? How are proteins synthesized? Where does the RNA go? How does it sit? Where do the proteins sit? Where do the amino acids go in? In photosynthesis, where is the chlorophyll; how is it arranged; where are the carotenoids involved in this thing? What is the system of the conversion of light into chemical energy?

It is very easy to answer many of these fundamental biological questions; you just *look at the thing!* You will see the order of bases in the chain; you will see the structure of the microsome. Unfortunately, the present microscope sees at a scale which is just a bit too crude. Make the microscope one hundred times more powerful, and many problems of biology would be made very much easier. I exaggerate, of course, but the biologists would surely be very thankful to you---and they would prefer that to the criticism that they should use more mathematics.

The theory of chemical processes today is based on theoretical physics. In this sense, physics supplies the foundation of chemistry. But chemistry also has analysis. If you have a strange substance and you want to know what it is, you go through a long and complicated process of chemical analysis. You can analyze almost anything today, so I am a little late with my idea. But if the physicists wanted to, they could also dig under the

chemists in the problem of chemical analysis. It would be very easy to make an analysis of any complicated chemical substance; all one would have to do would be to look at it and see where the atoms are. The only trouble is that the electron microscope is one hundred times too poor. (Later, I would like to ask the question: Can the physicists do something about the third problem of chemistry---namely, synthesis? Is there a *physical* way to synthesize any chemical substance?

The reason the electron microscope is so poor is that the f- value of the lenses is only 1 part to 1,000; you don't have a big enough numerical aperture. And I know that there are theorems which prove that it is impossible, with axially symmetrical stationary field lenses, to produce an f-value any bigger than so and so; and therefore the resolving power at the present time is at its theoretical maximum. But in every theorem there are assumptions. Why must the field be symmetrical? I put this out as a challenge: Is there no way to make the electron microscope more powerful?

The marvelous biological system

The biological example of writing information on a small scale has inspired me to think of something that should be possible. Biology is not simply writing information; it is *doing something* about it. A biological system can be exceedingly small. Many of the cells are very tiny, but they are very active; they manufacture various substances; they walk around; they wiggle; and they do all kinds of marvelous things---all on a very small scale. Also, they store information. Consider the possibility that we too can make a thing very small which does what we want---that we can manufacture an object that maneuvers at that level!

There may even be an economic point to this business of making things very small. Let me remind you of some of the problems of computing machines. In computers we have to store an enormous amount of information. The kind of writing that I was mentioning before, in which I had everything down as a distribution of metal, is permanent. Much more interesting to a computer is a way of writing, erasing, and writing something else. (This is usually because we don't want to waste the material on which we have just written. Yet if we could write it in a very small space, it wouldn't make any difference; it could just be thrown away after it was read. It doesn't cost very much for the material).

Miniaturizing the computer

I don't know how to do this on a small scale in a practical way, but I do know that computing machines are very large; they fill rooms. Why can't we make them very small, make them of little wires, little elements---and by little, I mean *little*. For instance, the wires should be 10 or 100 atoms in diameter, and the circuits should be a few thousand angstroms across. Everybody who has analyzed the logical theory of computers has come to the conclusion that the possibilities of computers are very interesting---if they could be made to be more complicated by several orders of magnitude. If they had millions of times as many elements, they could make judgments. They would have time to calculate what is the best way to make the calculation that they are about to make. They could

select the method of analysis which, from their experience, is better than the one that we would give to them. And in many other ways, they would have new qualitative features.

If I look at your face I immediately recognize that I have seen it before. (Actually, my friends will say I have chosen an unfortunate example here for the subject of this illustration. At least I recognize that it is a *man* and not an *apple*.) Yet there is no machine which, with that speed, can take a picture of a face and say even that it is a man; and much less that it is the same man that you showed it before---unless it is exactly the same picture. If the face is changed; if I am closer to the face; if I am further from the face; if the light changes---I recognize it anyway. Now, this little computer I carry in my head is easily able to do that. The computers that we build are not able to do that. The number of elements in this bone box of mine are enormously greater than the number of elements in our ``wonderful'' computers. But our mechanical computers are too big; the elements in this box are microscopic. I want to make some that are *sub*microscopic.

If we wanted to make a computer that had all these marvelous extra qualitative abilities, we would have to make it, perhaps, the size of the Pentagon. This has several disadvantages. First, it requires too much material; there may not be enough germanium in the world for all the transistors which would have to be put into this enormous thing. There is also the problem of heat generation and power consumption; TVA would be needed to run the computer. But an even more practical difficulty is that the computer would be limited to a certain speed. Because of its large size, there is finite time required to get the information from one place to another. The information cannot go any faster than the speed of light---so, ultimately, when our computers get faster and faster and more and more elaborate, we will have to make them smaller and smaller.

But there is plenty of room to make them smaller. There is nothing that I can see in the physical laws that says the computer elements cannot be made enormously smaller than they are now. In fact, there may be certain advantages.

Miniaturization by evaporation

How can we make such a device? What kind of manufacturing processes would we use? One possibility we might consider, since we have talked about writing by putting atoms down in a certain arrangement, would be to evaporate the material, then evaporate the insulator next to it. Then, for the next layer, evaporate another position of a wire, another insulator, and so on. So, you simply evaporate until you have a block of stuff which has the elements--- coils and condensers, transistors and so on---of exceedingly fine dimensions.

But I would like to discuss, just for amusement, that there are other possibilities. Why can't we manufacture these small computers somewhat like we manufacture the big ones? Why can't we drill holes, cut things, solder things, stamp things out, mold different shapes all at an infinitesimal level? What are the limitations as to how small a thing has to be before you can no longer mold it? How many times when you are working on something frustratingly tiny like your wife's wrist watch, have you said to yourself, ``If I

could only train an ant to do this!" What I would like to suggest is the possibility of training an ant to train a mite to do this. What are the possibilities of small but movable machines? They may or may not be useful, but they surely would be fun to make.

Consider any machine---for example, an automobile---and ask about the problems of making an infinitesimal machine like it. Suppose, in the particular design of the automobile, we need a certain precision of the parts; we need an accuracy, let's suppose, of 4/10,000 of an inch. If things are more inaccurate than that in the shape of the cylinder and so on, it isn't going to work very well. If I make the thing too small, I have to worry about the size of the atoms; I can't make a circle of ``balls" so to speak, if the circle is too small. So, if I make the error, corresponding to 4/10,000 of an inch, correspond to an error of 10 atoms, it turns out that I can reduce the dimensions of an automobile 4,000 times, approximately---so that it is 1 mm. across. Obviously, if you redesign the car so that it would work with a much larger tolerance, which is not at all impossible, then you could make a much smaller device.

It is interesting to consider what the problems are in such small machines. Firstly, with parts stressed to the same degree, the forces go as the area you are reducing, so that things like weight and inertia are of relatively no importance. The strength of material, in other words, is very much greater in proportion. The stresses and expansion of the flywheel from centrifugal force, for example, would be the same proportion only if the rotational speed is increased in the same proportion as we decrease the size. On the other hand, the metals that we use have a grain structure, and this would be very annoying at small scale because the material is not homogeneous. Plastics and glass and things of this amorphous nature are very much more homogeneous, and so we would have to make our machines out of such materials.

There are problems associated with the electrical part of the system---with the copper wires and the magnetic parts. The magnetic properties on a very small scale are not the same as on a large scale; there is the ``domain" problem involved. A big magnet made of millions of domains can only be made on a small scale with one domain. The electrical equipment won't simply be scaled down; it has to be redesigned. But I can see no reason why it can't be redesigned to work again.

Problems of lubrication

Lubrication involves some interesting points. The effective viscosity of oil would be higher and higher in proportion as we went down (and if we increase the speed as much as we can). If we don't increase the speed so much, and change from oil to kerosene or some other fluid, the problem is not so bad. But actually we may not have to lubricate at all! We have a lot of extra force. Let the bearings run dry; they won't run hot because the heat escapes away from such a small device very, very rapidly.

This rapid heat loss would prevent the gasoline from exploding, so an internal combustion engine is impossible. Other chemical reactions, liberating energy when cold,

can be used. Probably an external supply of electrical power would be most convenient for such small machines.

What would be the utility of such machines? Who knows? Of course, a small automobile would only be useful for the mites to drive around in, and I suppose our Christian interests don't go that far. However, we did note the possibility of the manufacture of small elements for computers in completely automatic factories, containing lathes and other machine tools at the very small level. The small lathe would not have to be exactly like our big lathe. I leave to your imagination the improvement of the design to take full advantage of the properties of things on a small scale, and in such a way that the fully automatic aspect would be easiest to manage.

A friend of mine (Albert R. Hibbs) suggests a very interesting possibility for relatively small machines. He says that, although it is a very wild idea, it would be interesting in surgery if you could swallow the surgeon. You put the mechanical surgeon inside the blood vessel and it goes into the heart and ``looks" around. (Of course the information has to be fed out.) It finds out which valve is the faulty one and takes a little knife and slices it out. Other small machines might be permanently incorporated in the body to assist some inadequately-functioning organ.

Now comes the interesting question: How do we make such a tiny mechanism? I leave that to you. However, let me suggest one weird possibility. You know, in the atomic energy plants they have materials and machines that they can't handle directly because they have become radioactive. To unscrew nuts and put on bolts and so on, they have a set of master and slave hands, so that by operating a set of levers here, you control the ``hands" there, and can turn them this way and that so you can handle things quite nicely.

Most of these devices are actually made rather simply, in that there is a particular cable, like a marionette string, that goes directly from the controls to the ``hands." But, of course, things also have been made using servo motors, so that the connection between the one thing and the other is electrical rather than mechanical. When you turn the levers, they turn a servo motor, and it changes the electrical currents in the wires, which repositions a motor at the other end.

Now, I want to build much the same device---a master-slave system which operates electrically. But I want the slaves to be made especially carefully by modern large-scale machinists so that they are one-fourth the scale of the ``hands" that you ordinarily maneuver. So you have a scheme by which you can do things at one- quarter scale anyway---the little servo motors with little hands play with little nuts and bolts; they drill little holes; they are four times smaller. Aha! So I manufacture a quarter-size lathe; I manufacture quarter-size tools; and I make, at the one-quarter scale, still another set of hands again relatively one-quarter size! This is one-sixteenth size, from my point of view. And after I finish doing this I wire directly from my large-scale system, through transformers perhaps, to the one-sixteenth-size servo motors. Thus I can now manipulate the one-sixteenth size hands.

Well, you get the principle from there on. It is rather a difficult program, but it is a possibility. You might say that one can go much farther in one step than from one to four. Of course, this has all to be designed very carefully and it is not necessary simply to make it like hands. If you thought of it very carefully, you could probably arrive at a much better system for doing such things.

If you work through a pantograph, even today, you can get much more than a factor of four in even one step. But you can't work directly through a pantograph which makes a smaller pantograph which then makes a smaller pantograph---because of the looseness of the holes and the irregularities of construction. The end of the pantograph wiggles with a relatively greater irregularity than the irregularity with which you move your hands. In going down this scale, I would find the end of the pantograph on the end of the pantograph on the end of the pantograph shaking so badly that it wasn't doing anything sensible at all.

At each stage, it is necessary to improve the precision of the apparatus. If, for instance, having made a small lathe with a pantograph, we find its lead screw irregular---more irregular than the large-scale one---we could lap the lead screw against breakable nuts that you can reverse in the usual way back and forth until this lead screw is, at its scale, as accurate as our original lead screws, at our scale.

We can make flats by rubbing unflat surfaces in triplicates together---in three pairs---and the flats then become flatter than the thing you started with. Thus, it is not impossible to improve precision on a small scale by the correct operations. So, when we build this stuff, it is necessary at each step to improve the accuracy of the equipment by working for awhile down there, making accurate lead screws, Johansen blocks, and all the other materials which we use in accurate machine work at the higher level. We have to stop at each level and manufacture all the stuff to go to the next level---a very long and very difficult program. Perhaps you can figure a better way than that to get down to small scale more rapidly.

Yet, after all this, you have just got one little baby lathe four thousand times smaller than usual. But we were thinking of making an enormous computer, which we were going to build by drilling holes on this lathe to make little washers for the computer. How many washers can you manufacture on this one lathe?

A hundred tiny hands

When I make my first set of slave ``hands" at one-fourth scale, I am going to make ten sets. I make ten sets of ``hands," and I wire them to my original levers so they each do exactly the same thing at the same time in parallel. Now, when I am making my new devices one-quarter again as small, I let each one manufacture ten copies, so that I would have a hundred ``hands" at the 1/16th size.

Where am I going to put the million lathes that I am going to have? Why, there is nothing to it; the volume is much less than that of even one full-scale lathe. For instance, if I

made a billion little lathes, each 1/4000 of the scale of a regular lathe, there are plenty of materials and space available because in the billion little ones there is less than 2 percent of the materials in one big lathe.

It doesn't cost anything for materials, you see. So I want to build a billion tiny factories, models of each other, which are manufacturing simultaneously, drilling holes, stamping parts, and so on.

As we go down in size, there are a number of interesting problems that arise. All things do not simply scale down in proportion. There is the problem that materials stick together by the molecular (Van der Waals) attractions. It would be like this: After you have made a part and you unscrew the nut from a bolt, it isn't going to fall down because the gravity isn't appreciable; it would even be hard to get it off the bolt. It would be like those old movies of a man with his hands full of molasses, trying to get rid of a glass of water. There will be several problems of this nature that we will have to be ready to design for.

Rearranging the atoms

But I am not afraid to consider the final question as to whether, ultimately---in the great future---we can arrange the atoms the way we want; the very *atoms*, all the way down! What would happen if we could arrange the atoms one by one the way we want them (within reason, of course; you can't put them so that they are chemically unstable, for example).

Up to now, we have been content to dig in the ground to find minerals. We heat them and we do things on a large scale with them, and we hope to get a pure substance with just so much impurity, and so on. But we must always accept some atomic arrangement that nature gives us. We haven't got anything, say, with a ``checkerboard" arrangement, with the impurity atoms exactly arranged 1,000 angstroms apart, or in some other particular pattern.

What could we do with layered structures with just the right layers? What would the properties of materials be if we could really arrange the atoms the way we want them? They would be very interesting to investigate theoretically. I can't see exactly what would happen, but I can hardly doubt that when we have some *control* of the arrangement of things on a small scale we will get an enormously greater range of possible properties that substances can have, and of different things that we can do.

Consider, for example, a piece of material in which we make little coils and condensers (or their solid state analogs) 1,000 or 10,000 angstroms in a circuit, one right next to the other, over a large area, with little antennas sticking out at the other end---a whole series of circuits. Is it possible, for example, to emit light from a whole set of antennas, like we emit radio waves from an organized set of antennas to beam the radio programs to Europe? The same thing would be to *beam* the light out in a definite direction with very high intensity. (Perhaps such a beam is not very useful technically or economically.)

I have thought about some of the problems of building electric circuits on a small scale, and the problem of resistance is serious. If you build a corresponding circuit on a small scale, its natural frequency goes up, since the wave length goes down as the scale; but the skin depth only decreases with the square root of the scale ratio, and so resistive problems are of increasing difficulty. Possibly we can beat resistance through the use of superconductivity if the frequency is not too high, or by other tricks.

Atoms in a small world

When we get to the very, very small world---say circuits of seven atoms---we have a lot of new things that would happen that represent completely new opportunities for design. Atoms on a small scale behave like *nothing* on a large scale, for they satisfy the laws of quantum mechanics. So, as we go down and fiddle around with the atoms down there, we are working with different laws, and we can expect to do different things. We can manufacture in different ways. We can use, not just circuits, but some system involving the quantized energy levels, or the interactions of quantized spins, etc.

Another thing we will notice is that, if we go down far enough, all of our devices can be mass produced so that they are absolutely perfect copies of one another. We cannot build two large machines so that the dimensions are exactly the same. But if your machine is only 100 atoms high, you only have to get it correct to one-half of one percent to make sure the other machine is exactly the same size---namely, 100 atoms high!

At the atomic level, we have new kinds of forces and new kinds of possibilities, new kinds of effects. The problems of manufacture and reproduction of materials will be quite different. I am, as I said, inspired by the biological phenomena in which chemical forces are used in repetitious fashion to produce all kinds of weird effects (one of which is the author).

The principles of physics, as far as I can see, do not speak against the possibility of maneuvering things atom by atom. It is not an attempt to violate any laws; it is something, in principle, that can be done; but in practice, it has not been done because we are too big.

Ultimately, we can do chemical synthesis. A chemist comes to us and says, ``Look, I want a molecule that has the atoms arranged thus and so; make me that molecule." The chemist does a mysterious thing when he wants to make a molecule. He sees that it has got that ring, so he mixes this and that, and he shakes it, and he fiddles around. And, at the end of a difficult process, he usually does succeed in synthesizing what he wants. By the time I get my devices working, so that we can do it by physics, he will have figured out how to synthesize absolutely anything, so that this will really be useless.

But it is interesting that it would be, in principle, possible (I think) for a physicist to synthesize any chemical substance that the chemist writes down. Give the orders and the physicist synthesizes it. How? Put the atoms down where the chemist says, and so you make the substance. The problems of chemistry and biology can be greatly helped if our

ability to see what we are doing, and to do things on an atomic level, is ultimately developed---a development which I think cannot be avoided.

Now, you might say, ``Who should do this and why should they do it?'' Well, I pointed out a few of the economic applications, but I know that the reason that you would do it might be just for fun. But have some fun! Let's have a competition between laboratories. Let one laboratory make a tiny motor which it sends to another lab which sends it back with a thing that fits inside the shaft of the first motor.

High school competition

Just for the fun of it, and in order to get kids interested in this field, I would propose that someone who has some contact with the high schools think of making some kind of high school competition. After all, we haven't even started in this field, and even the kids can write smaller than has ever been written before. They could have competition in high schools. The Los Angeles high school could send a pin to the Venice high school on which it says, ``How's this?'' They get the pin back, and in the dot of the ``i'' it says, ``Not so hot.''

Perhaps this doesn't excite you to do it, and only economics will do so. Then I want to do something; but I can't do it at the present moment, because I haven't prepared the ground. It is my intention to offer a prize of $1,000 to the first guy who can take the information on the page of a book and put it on an area 1/25,000 smaller in linear scale in such manner that it can be read by an electron microscope.

And I want to offer another prize---if I can figure out how to phrase it so that I don't get into a mess of arguments about definitions---of another $1,000 to the first guy who makes an operating electric motor---a rotating electric motor which can be controlled from the outside and, not counting the lead-in wires, is only 1/64 inch cube.

I do not expect that such prizes will have to wait very long for claimants.

Crystal Engineering of Diamondoid Networks

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1 Introduction

That it might ultimately become feasible routinely to design and control solid-state architecture and therefore function, coupled with our growing understanding of supramolecular chemistry, has afforded the driving force behind the emergence of crystal engineering.[1,2] A fundamental principle of crystal engineering is that crystal structures can be regarded as *de facto* manifestations of self-assembly. Whereas this is not always a reasonable assertion in the absence of conventional (*i.e.* X–H···Y; X,Y = O or N) hydrogen or covalent bonds,[3] it is becoming increasingly clear that molecules or ions of dramatically variable chemical nature can have analogous crystal engineering functions. Therefore, the solid-state structures of moieties as different as a carbon atom, a water molecule, and a dihydrogenphosphate anion have similarities since they represent moieties that have similar geometry (T_d or pseudo T_d) and function (ability to self-assemble) at the molecule or ionic level. Indeed, ice and KH_2PO_4 (KDP) represent simple compounds which have long been known[4] to be capable of exhibiting diamondoid architecture in the solid state, well before the term crystal engineering was introduced by Schmidt.[5] Figure 1 schematically illustrates the similarities and differences between the structures of diamond, ice, and KDP by comparing adamantoid portions of their networks. Whereas all three structures are adamantoid, increased separations between the tetrahedral centres impart important physical consequences: diamond is well enough packed to be mechanically strong and possess one of the highest melting points known; ice is not as efficiently packed and is therefore less dense than water; KDP is so open an architecture that for an isolated network more than 50% of its volume would be vacuum. It is the latter which represents one of several reasons why a search for new diamondoid compounds is of more than aesthetic relevance:

(i) The ability of all 2-D and 3-D frameworks to pack optimally is prejudiced by the directionality and rigidity of the cohesive forces involved. Therefore, diamond is thermodynamically less stable than graphite under ambient conditions and the much larger amount of open space that is necessarily present in a 1-fold diamondoid array of $H_2PO_4^-$ anions has to be accommodated. In the case of KDP, space is addressed by interpenetration of a second independent network, *i.e.* KDP is a 2-fold diamondoid structure. If interpenetration could be reduced, or even avoided, then channels and cavities with very specific and predictable dimensions and chemical type would be generated. Enclathrated guest molecules that facilitate more efficient packing would be expected to promote lower levels of interpenetration and such is indeed the case for trimesic acid (1,3,5-benzenetricarboxylic acid), which is a 3-fold 2-D honeycomb grid when pure.[6] In principle, synthesis of a new generation of open solids with very selective zeolite-like inclusion capabilities is therefore achievable *via* diamondoid architecture.

(ii) Notwithstanding problems associated with packing efficiency, diamondoid solids would in general be expected to have high mechanical and thermal stability because the attractive forces extend isotropically in three dimensions. This includes hydrogen-bonded networks, which can be sustained by hydrogen bond energies of as high as 200 kJ/mol if ionic components are involved.[2]

(iii) Even a moiety with perfect T_d symmetry possesses no centre of inversion. It should therefore logically follow that diamondoid architecture is at the very least not predisposed to adapt non-polar space groups. This might seem obvious, or even trivial, but it should be remembered that around 75% of compounds crystallize in non-polar space groups and strategies for designing polarity into crystals are still in their infancy.[7] This is an important consideration since a number of important physical properties (*e.g.* ferroelectricity, piezoelectricity, pyroelectricity, second-order non-linear optics) are dependent upon bulk crystal polarity, which only occurs in compounds that adapt polar space groups. Indeed, a low-temperature polymorph of KDP is a commercial second-order non-linear optic.[8]

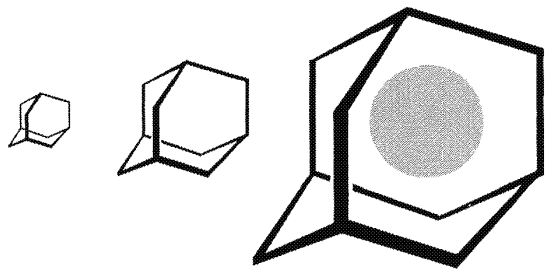
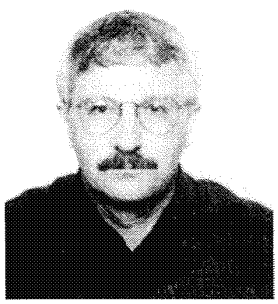


Figure 1 A schematic representation of the adamantoid portion of the diamondoid architectures exhibited by diamond, ice, and KDP. Ice I is a hexagonal network but two polymorphs of ice are diamondoid.

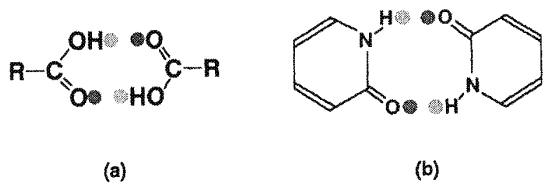
2 The Modular Approach to Crystal Engineering of Diamondoid Networks

The key to successful crystal engineering of new classes of diamondoid compound lies with recognition that, regardless of their chemical nature, molecules, ions or, importantly, combi-

Michael J. Zaworotko was born in Blackwood, Gwent and attended Bedwellty Grammer School before graduating from Imperial College in 1977. His Ph.D. was earned with Jerry Atwood at the University of Alabama (X-ray crystallograpy, organoaluminum chemistry, 1982) and this was followed by a postdoctoral fellowship with S. R. Stobart at the University of Victoria, Canada. A research programme dedicated to molecular recognition was initiated when he was appointed Assistant Professor of Chemistry at Saint Mary's University in 1985. The initial focus was ionic liquids but a sabbatical leave at the U.S. Air Force Academy facilitated a change of focus to the solid state, in particular structure–function relationships and crystal engineering in multi-component systems such as organic salts and cocrystals. Dr. Zaworotko is now Associate Professor and Chairperson.



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(a) (b)

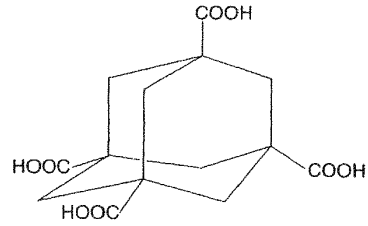
Figure 2 A schematic representation of the dimeric motifs adapted by (a) carboxylic acids and (b) pyridones. For this and subsequent diagrams the colour coding is red for hydrogen bond donors and blue for hydrogen bond acceptors. Complementarity therefore occurs when blue and red moieties are matched with one another.

nations thereof, should be capable of forming infinite diamondoid arrays if their geometry and functionality are appropriate. Whereas the structures of ice and KDP have long been understood, it was not until 1988 that diamondoid frameworks based upon organic molecules were first characterized. Otto Ermer's elegant studies on the tetragonally elongated diamondoid structures of adamantane-1,3,5,7-tetracarboxylic acid[9a] (1) and methanetetraacetic acid[9b] (2), detailed not only their crystal structures but provided an excellent introduction to the background and possible future applications of diamondoid solids. It should not be surprising that (1) and (2) are extensively interwoven (5-fold and 3-fold, respectively) since the separations between tetrahedral centres are 10.07 and 8.76 Å, respectively. The observed structures are based upon self-assembly sustained by the carboxylic acid dimer motif. Pyridones exhibit a similar ability to form dimeric motifs (Figure 2) and Wuest exploited this motif with the tetrakispyridone (3) which, remarkably, does not interpenetrate in the presence of butyric acid. Rather, (3) exists as a 1-fold framework with channels large enough to hold two molecules of butyric acid.[10] Structures (1)—(3) therefore represent molecules that, because of their inherent symmetry and functionality, are effectively programmed to self-assemble to form superdiamondoid arrays.

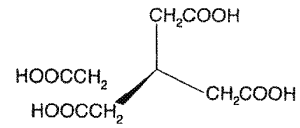
Unfortunately, tetrafunctionalized molecules with T_d or close to T_d symmetry are not that common. Furthermore, chemical modification of (1)—(3) could easily destroy their ability to self-assemble predictably, and generating new molecules is synthetically challenging. Bearing this in mind, we set out to investigate the possibility of generating diamondoid networks using complementary molecules, *i.e.* a modular or strict self-assembly[11] approach. In principle, such a strategy has distinct advantages over single-component self-assembly since it could permit fine-tuning of diamondoid structures without resorting to covalent modifications and would therefore be both facile and more generic (Figure 3). Therefore, although significant advances have recently been made with single-component self-assembly[9,10] and covalent systems such as polychalcogenides,[12] this review places particular emphasis upon systems which have been prepared *via* the modular approach. Such an approach could involve either non-covalent or covalent bonding and the remainder of this work is subdivided accordingly.

3 Non-covalent Diamondoid Networks

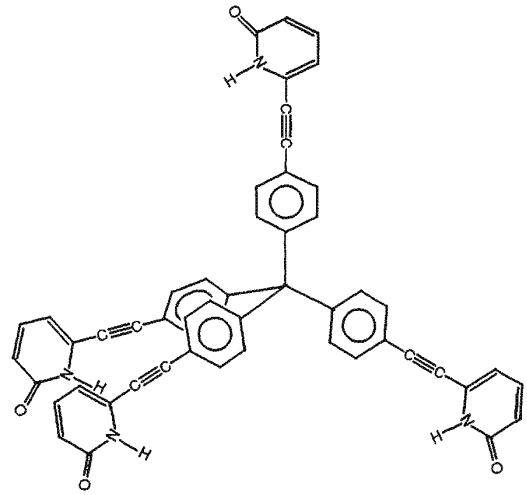
A T_d molecule that is either a tetrafunctional hydrogen bond donor or a tetrafunctional hydrogen bond acceptor that is NOT capable of self-assembling (*i.e.* it does not contain internal complementarity) should in principle strictly self-assemble with two equivalents of a complementary difunctional linear molecule to form a diamondoid array (Figure 3). The T_d molecule we chose to study is $[Mn(CO)_3(\mu_3\text{-}OH)]_4$, (4) an air- and water-stable cubane-like cluster that can be prepared quantitatively from Mn_2CO_{10}.[13] Structure (4) is illustrated in Figure 4 and it should be clear that it is ideally suited as a prototypal molecule for sustaining diamondoid architecture since it holds perfect T_d symmetry, meaning that all four of its μ_3-OH groups are oriented towards the vertices of a tetrahedron. Furthermore, (4)



(1)



(2)



(3)

is rigid and contains no strong hydrogen bond acceptor moieties. Given Etter's observations concerning hydrogen bonding in solids,[14] that (4) spontaneously self-assembles with 1,2-diaminoethane to form a diamondoid array[15] should therefore not be a surprise. 1,2-diaminoethane can be replaced with other complementary 'spacers' in a remarkably facile and general manner since the only criteria that matter are that a 'spacer' has two hydrogen bond acceptor moieties and that they can orient their vectors 180° apart from each other. Table 1 lists difunctional molecules that fit these criteria and have been successfully exploited as linear 'spacers'. The 'spacer' molecules employ several classes of hydrogen bond, both conventional (O–H···N, O–H···O) and weak (O–H···arene), and the levels of interpenetration are logical, based upon the length [molecules of (4) are separated by between 9.74 and 15.35 Å] and volume of the spacer molecule. Of particular interest is that every network except one adapts tetragonal or cubic space groups that allow (4) to retain at least S_4 or even T_d symmetry. In other words, the symmetry of (4) clearly manifests itself on the crystal architecture and space group symmetry. Several of the networks are polar or they contain microchannels that contain as many as four molecules of solvent (acetonitrile) per molecule of (4).[16] Figure 5 illustrates the 4-fold diamondoid structure of (4)·2(4,4′-dipyridyl)·2CH_3CN viewed down the tetragonal *c*-axis. The microchannels enclathrate two molecules of acetonitrile per molecule of (4). Several of the structures are diamondoid because μ_3-OH moieties form π-hydrogen bonds with each face of a range of arenes, including napthalenes. The π-hydrogen bonds can be assumed to be quite weak from a thermodynamic

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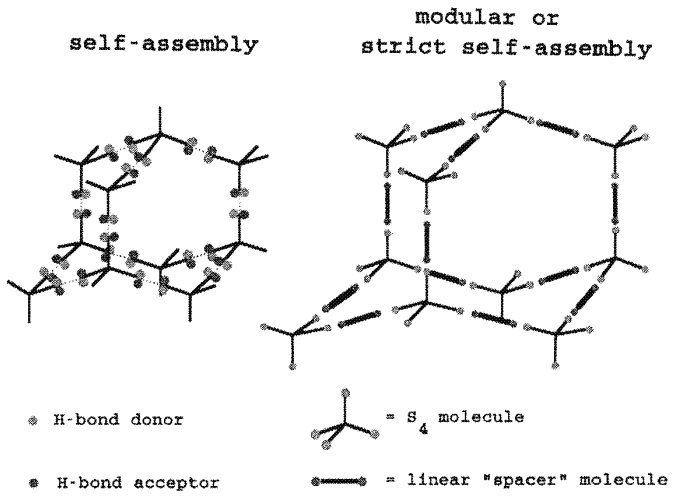
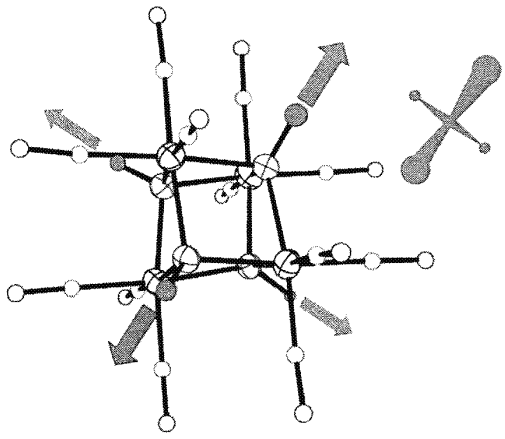


Figure 3 A schematic representation of single-component (self-assembly) *versus* multi-component (strict self-assembly) approaches to construction of diamondoid architectures. The modular nature of the latter makes it in principle facile to 'fine-tune' the bulk physical properties of the network by substituting components that have the same crystal engineering function of either the spacer or the S_4 molecule.



(4)

Figure 4 The molecular structure of $[Mn(CO)_3(\mu_3\text{-}OH)]_4$, (4). Note that (4) has four strong hydrogen bond donors (red) but no strong hydrogen bond acceptors.

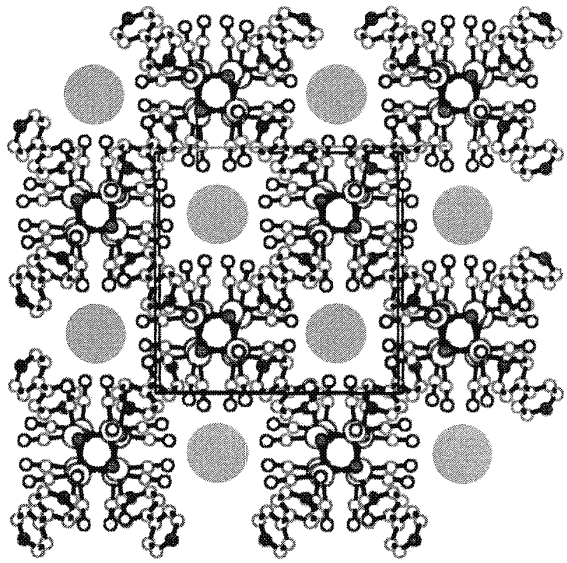


Figure 5 The 4-fold diamondoid structure of (4)·2(4,4′-dipyridyl) viewed down the crystallographic *c*-axis. The microchannels (green circles) are occupied by two molecules of acetonitrile per molecule of (4).

Table 1 Diamondoid networks based upon $[M(CO)_3(\mu_3\text{-}OH)]_4$ and A–A spacers

M	A–A	Intercube Å	Crystal System	*n*-fold
Mn	$Me_2NCH_2CH_2NMe_2$	11.35	Tetragonal	2
Mn	$H_2NCH_2CH_2NH_2$	11.59	Cubic	3
Re	1,4-Diaminobenzene	11.79	Tetragonal	2*
Mn	2-Cl-Pyrazine	11.82	Cubic	3
Mn	$Ph_2P(O)CH_2CH_2P(O)Ph_2$	13.53	Tetragonal	2*
Mn	4,4′-Dipyridyl	15.22	Tetragonal	4*
Mn	4,4′-Bipiperidine	15.35	Tetragonal	4*
Mn	Toluene	10.10	Tetragonal	2,*B*1
Mn	*p*-Xylene	10.35	Tetragonal	2,*B*1
Mn	*p*-Fluorotoluene	10.13	Tetragonal	2,*B*1
Mn	Benzene	9.74	Cubic	2,*A*
Mn	Naphthalene	10.40	Tetragonal	2,*B*2
Mn	Me-naphthalene	10.26	Hexagonal	2,*B*2

* Solvent enclathrated in microchannels. *A*: symmetric bridge; *B*1: unsymmetric bridge to same ring; *B*2: unsymmetric bridge to different rings.

perspective[17] but they are directional and hence capable of acting as linear 'spacers' to sustain the diamondoid architecture. An adamantoid portion of (4)·2*p*-xylene is illustrated in Figure 6. This plot is effectively generic for the (4)·2arene structures since all six we have thus far prepared and characterized exhibit 2-fold interpenetration because of similar intercube spacings.

It is important to recognize that the solvent used for re-crystallization can play a critical role in the self-assembly process and even determine the topology of the resulting network. The compounds in Table 1 were crystallized from acetonitrile or the pure 'spacer' molecule. However, if an alcohol is used it can play a crystal engineering function by using its OH group as a donor–acceptor moiety. Therefore, although (4)·2(4,4′-dipyridyl)·2ROH has the same stoichiometry as its acetonitrile analogue, it exhibits a radically different structure based upon interwoven 2-D square grids.[18] The alcohol molecules serve the function of angular 'spacers' that link one end of molecules of

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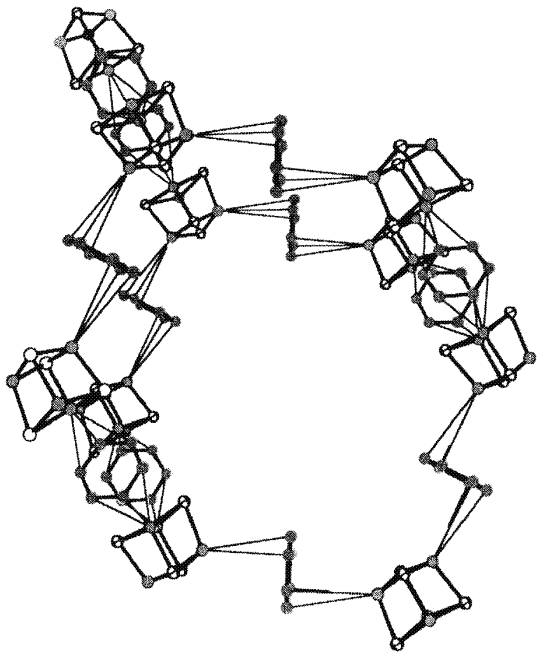


Figure 6 An ORTEP view of the adamantoid portion of one of the two diamondoid networks present in (4)·2(*p*-xylene). Methyl and carbonyl groups are omitted for the sake of clarity.

4,4′-dipyridyl to molecules of (4), thereby preventing propagation in the third dimension required for diamondoid architecture. (4)·2(4,4′-dipyridyl)·2ROH therefore represents strict self-assembly of three complementary molecules in a predictable manner. Difunctional hydrogen bond acceptor molecules that are angular in their own right (1,3-diaminopropane)[18] or linear difunctional acceptors that can form acute hydrogen bonds [1,2-bis(4-dipyridyl)ethane, 1,4-dicyanobenzene] afford co-crystals of the same stoichiometry which exhibit 2-D square grid instead of diamondoid topology. Figure 7 illustrates schematically how T_d molecules can play a modular role in construction of 2-D square grid frameworks.

4 Covalent Diamondoid Networks

There is virtually no limit to where one could begin in terms of designing covalent diamondoid networks since any tetrahedral moiety is in principle capable of sustaining diamondoid architecture and they are known to exist for most elements. Indeed, M_4X_4 analogues of (4) are known for many transition and main group elements. However, in terms of synthetic accessibility, tetrahedral transition metal cations offer a particularly tempting target for the following reasons: their simple coordination chemistry is generally well documented; geometry and lability can be readily controlled using redox; it would be conceivable to incorporate metal centres that are catalytically active. Tetrahedral metal centres would therefore serve the same crystal engineering function as the T_d donor molecule in Figure 3 and metal–ligand bonds would replace hydrogen bonds. It is not necessary to develop new synthetic methodology, rather one has simply to focus upon bridging (*i.e.* exodentate) rather than chelating (*i.e.* endodentate) ligands. General strategies for modular construction of infinite coordinate covalent frameworks were delineated by Robson and Hoskins in 1990[19] and in the past five years there have been several notable examples of diamondoid frameworks based upon Cu^{I}, Zn^{II}, Cd^{II}, and Ag^{I} that were rationally constructed: $Zn(CN)_2$ and $Cd(CN)_2$:$Zn(CN)_2$ and $Cd(CN)_2$ exist as isostructural 2-fold diamondoid networks and have been extensively investigated by at least two groups.[19,20] $Cd(CN)_2$ represents a simple and straightforward example of the modular approach described in Figure 3 and shows a rich array of chemistry because it can undergo a honeycomb–diamondoid topological rearrangement within a single crystal[21] and it can act as a host matrix when 1-fold or hexagonal.[20,22]

$Cd(SPh)_2$:$Cd(SPh)_2$ exists in the solid state as a 3-D array of phenylsulfide-linked $Cd_4(SPh)_6^{2+}$ adamantoid cages[23] as illustrated in Figure 8. $Cd(SPh)_2$ therefore represents an unusual example of a covalently linked T_d metal cluster. The authors suggested that $Cd(SPh)_2$ might exist as a higher-order tetraadamantoid cluster $Cd_{10}(SPh)_{20}$ in dimethylformamide, which represents yet another candidate for generating diamondoid architecture. Indeed, cubane-like and adamantoid clusters are known for a variety of metals but are yet to be exploited in a crystal engineering context. The possibility of cooperativity within and between linked clusters provides added impetus for further study in this area.

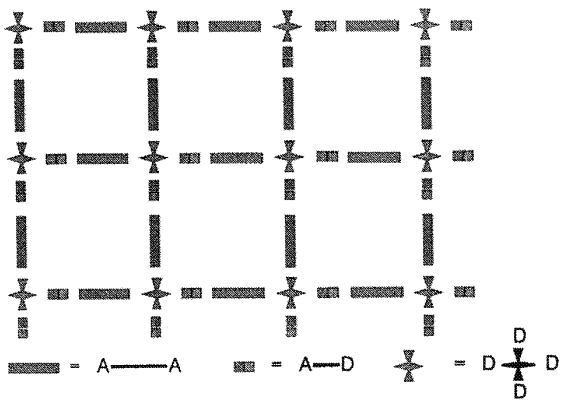


Figure 7 A schematic representation of how three types of molecule with the appropriate symmetry and functionality (1 × T_d donor, 2 × linear difunctional acceptor, 2 × angular donor–acceptor) can strictly self-assemble to form a square grid network.

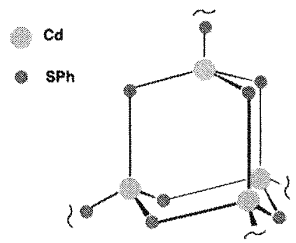


Figure 8 A schematic representation of the adamantoid units that exist in $Cd(SPh)_2$.

$[CuL_2]^+$:Cu^{I} commonly adapts a tetrahedral environment and as such sustains 5-fold, 4-fold, and 1-fold cationic diamondoid frameworks with 1,4-dicyanobenzene (BF_4^- salt),[22b] 4,4′-dipyridyl (PF_6^- salt[24]) and 2,5-Me_2pyrazine (PF_6^- salt[25]), respectively. Anions sit in microchannels and do not interact with the Cu^{I} moieties. Remarkably, the structure of the [Cu(4,4′-dipyridyl)$_2$]PF_6 salt closely resembles that of (4)·2(4,4′-dipyridyl)·2CH_3CN. Both compounds utilize 4,4′-dipyridyl as a 'spacer' molecule and crystallize as 4-fold diamondoid structures (Figure 9) that contain microchannels parallel to the crystallographic *c*-axis of tetragonal space groups (*P4/n* and *P4/nnc*, respectively). The former compound holds counterions in its microchannels whereas the latter contains acetonitrile (Figure 5).

Ag^+:[Ag_2(succinate)] dimerizes in the solid state to form linked planar tetranuclear [Ag_4(succinate)$_2$] clusters that have S_4 symmetry because of the disposition of the succinate moieties (Figure 10). The clusters are bridged to one another by succinate dianions, thereby forming a 3-fold diamondoid solid.[26] This is

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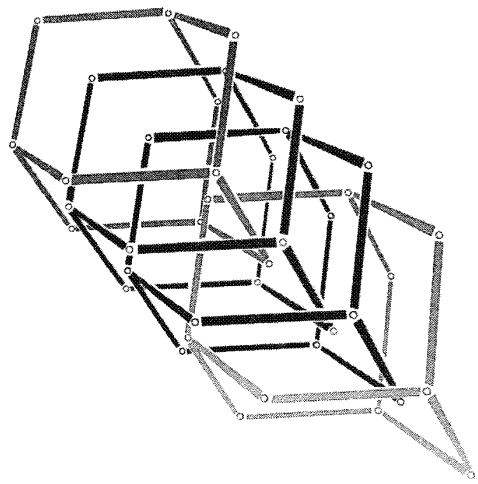


Figure 9 A schematic representation of how four adamantoid units can interweave.

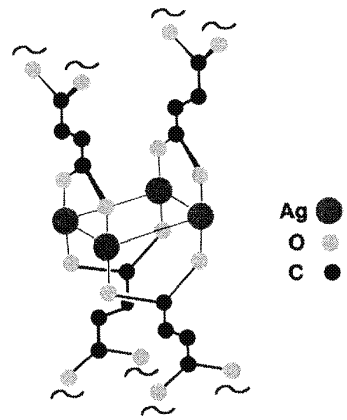


Figure 10 A schematic representation of the S_4 cluster formed by [Ag_2(succinate)].

another example of a cluster that links to form diamondoid networks and illustrates an important concept: overt S_4 symmetry is not necessary to form diamondoid arrays.

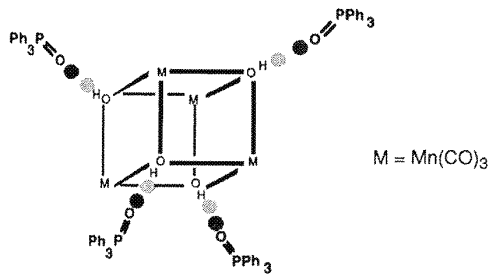
5 Summary and Future Directions

The focus of this review has been upon how modular approaches can be successfully applied to designing one particular type of structure: diamondoid solids. What do these results mean in a wider context? The author considers that the results are important not so much because of what was achieved but how it was achieved. The results presented herein demonstrate not only that the modular approach to crystal engineering of diamondoid networks is viable, but that it can be applied across a diverse range of chemical components (from organics to metal clusters) and bonds (π-hydrogen bond to coordinate covalent). Therefore, given that it is now possible rationally to exploit the directionality of both non-covalent and covalent bonds in order to crystal-engineer diamondoid solids, it is reasonable to assert that the same principles should be equally applicable to other structural classes. When such observations are coupled with recent advances in cognate fields such as computational, host–guest chemistry and materials characterization, scientists are finally in position to have gathered enough tools to understand and control solid-state structure–function relationships well enough to aim realistically at equalling or surpassing the functions of naturally occurring materials. The author is optimistic enough to believe that crystal engineering will evolve to the point where the only limits that the chemist will face in the context of designing new functional materials is his or her imagination. Minerals might therefore merely serve as prototypes for new classes of 'fine-tunable' mineralomimetic solid that can be crystal-engineered, for example, to have zeolitic, catalytic, specific bulk physical properties, or a combination thereof. Indeed, this is the ultimate goal of crystal engineering: control of solid-state structure to the extent that specific function can be routinely and rationally incorporated. Such optimism might have been very difficult to justify as recently as 1988 when Maddox made the following provocative statement '*One of the continuing scandals in the physical sciences is that it remains in general impossible to predict the structure of even the simplest crystalline solids from a knowledge of their chemical composition*'.[27] Whereas Maddox's statement was qualified by the remainder of his essay it still holds true for the majority of compounds. Indeed, such is the case for (4) when it is pure. However, as should be clear from this review, judicious choice of modular components can validate *ab initio* prediction of at least the gross features of crystal structures and in some cases significantly limit space group choice. Such is the case for several of the compounds listed in Table 1. Indeed, in cases where the 'spacer' moiety and its interaction with (4) is symmetrical enough to facilitate full retention of T_d symmetry [*i.e.* (4) sits around a crystallographic-43*m* position] the space group choices are limited to just six out of two hundred and thirty: *Fd*-3*m* (*cf.* diamond), *Pn*-3*m*, *I*-43*m*, *F*-43*m*, *Fm*-3*m*, or *P*-43*m*. (4)·2 benzene fits the necessary criteria because benzene holds 3-fold symmetry. Measurement of the cell volume of (4)·2benzene dictates that $Z = 2$ and therefore means that *Pn*-3*m* is the only possible space group. The precise structure, including its 2-fold nature, can therefore be determined even before crystallographic data are collected because the positions of molecules of (4) and benzene are fixed by space group symmetry. The lower crystallographic site symmetry of the other compounds in Table 1 is a reflection of the point group of the 'spacer' and the symmetry of its interaction with (4).

Finally, it should be stressed that the lessons that can be gained from crystal engineering would also be expected to be applicable to the design and assembly of discrete supramolecules and nanostructures, and, of course, *vice-versa*. The relationship between crystal engineering and supramolecular chemistry is already documented as are the ideas that, by virtue of their molecular symmetry and functionality, mixtures of molecules can be programmed for a particular structure and function.[28] Indeed, modular or 'molecular meccano'[29] approaches have already been successfully applied to synthesis of a wide range of discrete supramolecular complexes. We have started to investigate (4) in the context of discrete supramolecules since its T_d symmetry and functionality should in principle manifest towards discrete supramolecules if it is mixed with appropriate components. Compound (4) readily forms discrete 4:1 adducts with monofunctional hydrogen bond donors such as triphenylphosphineoxide, (5),[30] whereas in the presence of a crude mixture of dimethyldiazaanthracenes (*i.e.* angular or linear difunctional 'spacers'), the four-component nine-molecule centrosymmetric dimer (6) can be isolated (Figure 11).[31] We had anticipated that (4) would preferrentially recognize only one difunctional 'spacer' of those present in the diazaanthracene 'soup', but instead it sequestered two so as to generate (6). That (4) or any molecule with related symmetry and functionality will have a rich chemistry in the context of discrete supramolecules appears likely if one considers that structural analogies can be drawn between the compounds in Table 1, (5) and (6) and diamond, methane and ethane, respectively.

I would like to acknowledge my co-workers, whose names appear in the list of references, and the following sources of

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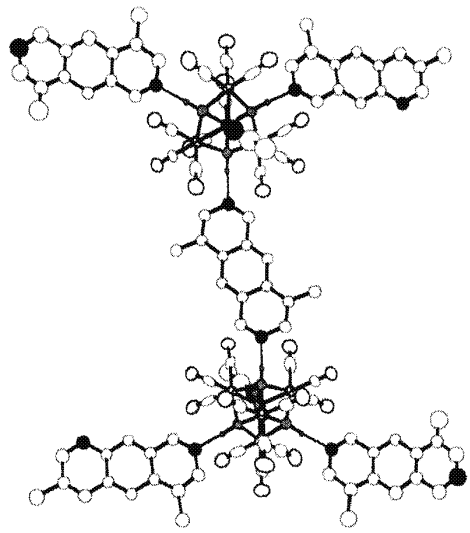


Figure 11 An ORTEP plot of the nine-molecule supramolecular aggregate formed when (4) is crystallized from acetonitrile in the presence of a mixture of dimethyldiazaanthracenes.

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the finger was pointing to CC-CKR-5 because it specifically binds RANTES, MIP-1α and MIP-1β. With the recent publication of its sequence[15], expression cloning was possible and it soon became apparent that CC-CKR-5 serves as the co-receptor to CD4 for fusion and entry of those NSI strains of HIV that infect peripheral-blood lymphocytes and macrophages[1–3].

Although two long-standing questions about HIV infection *in vivo* and *in vitro* have now been fused to a satisfactory conclusion, these novel findings are by no means the end of the story. Rather, they are opening up a new area of AIDS research. Other co-receptors are likely to come to light: for example, HIV-2 and simian immunodeficiency virus have distinct cell tropisms from HIV-1 (refs 16, 17). The actual mechanism by which the HIV envelope (see figure) and its cellular receptors trigger membrane fusion[18] remains to be elucidated, and we may look forward to a new class of inhibitors that block this interaction.

The effects of HIV envelope glycoproteins on the signalling by 7tm receptors for chemotaxis, mitogenesis, apoptosis, and the secretion of further cytokines may prove to be important in unravelling HIV pathogenesis in the immune system and the brain. As Feng *et al.*[5] point out, there is now a possibility of developing transgenic animals for HIV infection that express both human CD4 and the relevant co-receptor. Animal models may not be a simple solution, however; most mouse cells, for instance, exert post-penetration restrictions on HIV replication[17]. Nonetheless, these recent discoveries[1–5] have set AIDS researchers alight with enthusiasm. □

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MATERIALS CHEMISTRY

Scandal of crystal design...

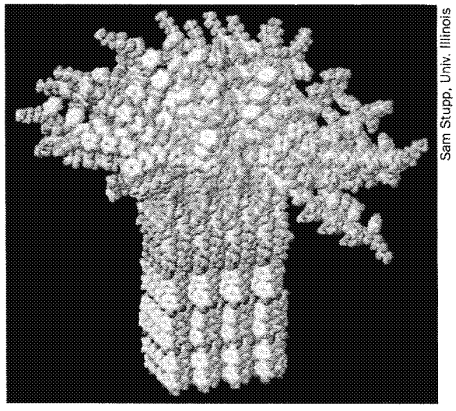
Philip Ball

IT'S how you say it that counts. When in 1988 John Maddox declared in this journal that the inability to predict *a priori* the structure of any crystalline material was a "scandal", he could not have more effectively thrown down the gauntlet. Eight years on, the smarting is still felt — and not least because in large part the scandal remains.

This lack of an infallible predictive tool is perhaps why it is so hard to identify any crystalline material in wide technological use that has been prepared by design. Piezoelectrics such as lead zirconate-titanate (PZT), nonlinear optical crystals such as lithium niobate, the copper-oxide superconductors — all are products of more or less chance discovery. Even zeolites, perhaps the favourite of crystal chemists' 'designer' materials, are either inorganic natural products or artificial variants thereof whose synthetic predictability is imperfectly developed.

What, then, are the prospects for using rational design to make new, useful crystalline materials? If we cannot yet with certainty predict the phase diagram of silica, what hope can there be for a drawing-board approach to engineering the solid state? This was the question faced by participants at a meeting last month*, who showed that rejoinders to Maddox's challenge now make an impressive list. While a set of universal rules for planning crystal structures remains a dream, there is now both a tool kit and something approaching an instruction manual for building solid-state materials to order.

At present, the price that must be paid is to declare large swathes of the periodic table out of bounds. Metals have some very appealing uses in crystal design, but by and large inorganic chemistry as such is still too daunting: prediction there demands a full quantum-mechanical treatment, with little guarantee of success and still less of qualitative guidelines for would-be crystal engineers. That notwithstanding, the ornate frameworks that can be constructed from inorganic building blocks alone are astonishing, and to the classic example of zeolites (whose microporous channels and cavities are made up of tetrahedral silicate and aluminate units) we can now add a dazzling array of microporous vanadate frameworks, where the square pyramidal VO_5 building block is predominant (Bob Haushalter, NEC Princeton).



Sam Stupp, Univ. Illinois

FIG. 1 Supramolecular mushrooms — these aggregates are formed from linear molecules in which a rod-like unit, which packs into an ordered stem, is connected to a flexible unit, which forms the disordered head.

But the strongest message of the meeting was that, to gain a good idea in advance of what to expect from a crystal structure, you are best off working with organic building blocks. Preformed organic units — called tectons by Jim Wuest (Univ. Montréal) — can make crystal engineering (a term now 30 years old) more a matter of construction-kit assembly than of *ab initio* number crunching. The idea is simple: you design your tectons so that there are only a very few ways, perhaps even a unique way, in which they can join together. If the design is good, and if the tectons are given 'sticky ends', they should self-assemble from (generally) solution, precipitating as the crystal structure of your choice.

Of this strategy, the last step (precipitating good single crystals) remains a black art. But the rest is, in principle, a purely rational matter. A favourite target is the diamondoid lattice: a three-dimensional network of tetrahedral vertices, like the carbon framework of diamond. This should result from tectons designed to self-assemble in tetrahedral geometry — four-armed molecules with each sticky end pointing to the corner of a tetrahedron. Wuest has made tectons of this sort in which the sticky ends form two hydrogen bonds with an identical partner. The diamondoid lattices constructed from these units contain large channels, up to a nanometre-and-a-half wide.

Hydrogen bonds are an attractive

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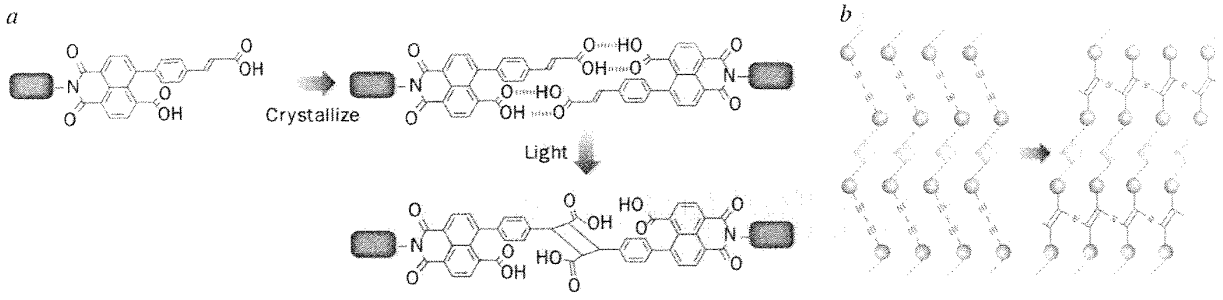


FIG. 2 *a*, Covalent links between self-assembling molecules can be forged by including unsaturated bonds in the 'sticky ends'. Here the appendages of some central molecular hub (blue rectangle) associate via hydrogen bonds in the crystal, and are then crosslinked by irradiation to induce cycloaddition of the adjacent carbon–carbon double bonds. *b*, Diacetylenes can be 'pre-organized' for covalent crosslinking by attaching to each end of the linear molecules chemical groups (blue balls) that form non-covalent links (dashed lines) with 'organizing centres' (red squares) in a co-crystal. Irradiation-induced crosslinking then generates one-dimensional polydiacetylene chains.

glue for this building-block approach to molecular crystals, for several reasons. They are directional in space, so that the disposition and orientation of sticky ends directs the topology of the network; they are weak enough (one should perhaps say reversible or 'labile' enough) to allow for annealing and editing during the assembly process, yet strong enough to generate stable crystals; and they are relatively deformable, allowing for some bending strain to be accommodated between the connected tectons (recalling the still greater flexibility of the Si–O–Si linkage, which enables zeolites to adopt such a variety of frameworks). At present, it is fair to say that hydrogen bonds are the most common glue in designed molecular assemblies of all sorts, be they crystals or solution-phase supramolecular complexes.

But greater geometric scope, more variety in bond strengths, and possibly greater potential to design functionality (optical, magnetic, electronic, catalytic) come from the use of coordination bonds to metal ions as the connections between tectons. Richard Robson (Univ. Melbourne) described a bewildering range of open-framework structures made from organic components linked via metal ions at their vertices. Square porphyrin-based tectons joined at the corners via tetrahedrally coordinated copper(I) ions, for instance, provide a tetragonal framework structure with rectangular channels 15 by 20 ångströms across (see *Nature* **369**, 727; 1994).

Any forces weaker than full covalent bonds might in principle be exploited to direct crystal self-assembly. Even so weak and non-directional an interaction as the van der Waals force has its value when combined with appropriate tecton geometry, as illustrated in the one-dimensional stacks reported by Wais Housseni (Univ. Louis Pasteur, Strasbourg). Here, back-to-back cup-shaped calixarenes ('exo-receptors' by virtue of their divergent binding-site orientations) are held together by linear diyne molecules inserted into opposed cups. And Sam Stupp (Univ. Illinois) showed that geometric packing effects alone, rather than short-range molecular interactions, can apparently force a molecular crystal into a non-intuitive structure that arguably contains an element of design. Stupp has made 'supramolecular mushrooms', finite-sized aggregates of surprisingly regular size and shape comprised of linear oligomeric molecules with a rod-like section, that can stack in a crystalline manner, and a flexible section that forms disordered aggregates. The molecules aggregate into a close-packed stem of rods and a mushroom head of disordered strands, whose size is ultimately limited (to 100 or so molecules) by the point at which the bulging of the head prevents further packing in the stem (Fig. 1).

These mushrooms form lamellar stacks, visible by transmission electron microscopy, in which one might expect a bilayer stem-to-stem packing configuration. But instead, efficient packing seems to favour a stem-to-head arrangement, giving the lamellar films different surface energies on each face, which is evident from their markedly different contact angles against water droplets.

The problems of a tectonic approach remain substantial, however. Predictability is often evident but far from guaranteed. In general it is made easier by restricting the dimensionality: two-dimensional sheets made from flat tectons are easier to design than three-dimensional networks, and because there is only one way that identical sheets can stack, the third dimension then takes care of itself. But polymorphism is a constant bugbear: for many tectons the intended crystal structure is not unique, and it is hard to know which of several possible connected networks will be preferred.

For crystals that incorporate large voids, meanwhile, abhorrence of a vacuum (more properly, the enthalpic benefit of high packing density) commonly leads to interpenetration: rather than a single network, one obtains several identical, topologically independent copies which interpenetrate to fill space. This happens for both Wuest's diamondoid nets and Robson's tetragonal nets, for example. If the aim is to achieve large voids or channels (so as to mimic the molecular sieving propensity of zeolites), this is a nuisance. One way of avoiding the problem may be to use tectons whose covalent structure predetermines the channel spaces — rigid, channel-forming rings, for instance, cannot interpenetrate (see *Nature* **371**, 591; 1994).

Another drawback of organic molecular crystals is their inherent lack of stability (thermal, and sometimes mechanical and/or chemical). Haushalter reminded the meeting that, for all the talk one hears of organic zeolites, no one is going to make an open-network organic crystal that can be boiled for hours in crude oil. Indeed, few of these channel-bearing crystals survive removal of the solvent that fills the pores. But improved stability might be obtained by incorporating into the tectons' sticky arms groups that can be covalently crosslinked once weaker interactions have directed the self-assembly. Ken Feldman (Pennsylvania State Univ.) described steps in this direction, whereby hydrogen-bonded dimers could be linked by cycloaddition between two unsaturated bonds in the linkers (Fig. 2*a*). Joe Lauher and Bill Fowler (SUNY at Stony Brook) have used the tectonic approach to pre-arrange diacetylene molecules into two-dimensional sheets in such a way as to facilitate crosslinking (by γ-irradiation) to give polydiacetylene chains (Fig. 2*b*).

Although there is still ample scope for refining the control of structure, the field of crystal engineering already faces a growing need to define some practical targets — in other words, to engineer function too. Here it seems to me that the agenda is set not so much by what might be possible as by what the competition is already capable of. For instance, microelectronic engineers have for years practised crystal engineering of a rather different kind, in which structural sophis-

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tication is secondary to the more important business of engineering electronic properties, namely band gaps. This can be achieved merely by adjusting the lattice spacing of III–V semiconductor alloys through control of composition or by careful introduction of strain into thin-layer, non-lattice-matched superlattices. Molecular-beam epitaxy has brought this technology to the status of a fine art, capable for instance of generating continuous compositional gradients with atomic-layer position. It is doubtful that molecular crystal engineering will easily make much impact here.

Although many such crystals are currently designed to have large pores, it is not clear (for the reasons stated) that there is much future in striving to make these selective industrial catalysts to rival zeolites. Rather, it is in the gentler arenas that inorganic microporous materials have entered — molecular sieving and sensor technologies, for example — that large-pore organic crystals might compete. Particularly attractive here is the possibility of designing helical pores for chiral separation.

In terms of dense materials one might wonder whether self-assembly could be used to pre-organize components for subsequent covalent linkage into materials that are otherwise hard or impossible to make: cubic boron nitride springs to mind, or the mythical β-C_3N_4 that is predicted to have the hardness of diamond. But that is ambitious, to say the least. Better, perhaps, to focus on functional materials such as non-centrosymmetric crystals for nonlinear optics, polar crystals for ferroelectrics and piezoelectrics, or magnetic materials in which the magnetic interactions of metal centres might be tuned by adjusting their symmetry and separation.

In getting function from form, nature is an old hand. But while those practising self-assembly in general draw much inspiration from biology, there are no perfect, structurally elegant molecular crystals to be found there. The materials of nature are composites, and long-range order is rare. In fact, properties and functions are arguably dictated more by defects than by regularities — in structural proteins, the parts of a peptide chain that break a propensity towards crystallization (β-sheet formation, say) are essential for conveying flexibility and preventing brittleness. Defects may turn out to be as important for obtaining useful engineered crystals as regularity, a point emphasized by Sam Stupp. They can, for instance, relieve strain or act as trapping sites for electronic excitations (as in photorefractive crystals). If ever we obtain absolute structural control over the solid state, we might then need to loosen our grip in order to make that facility useful. □

Philip Ball is an associate editor at Nature.

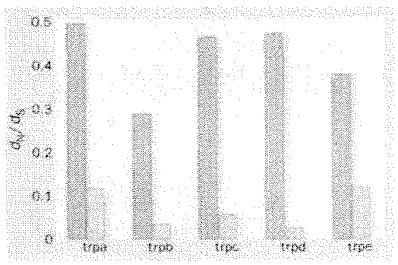
EVOLUTIONARY GENETICS

... and scandalous symbionts

Laurence D. Hurst and Gilean T. McVean

THE persistence over millions of years of lineages of organisms that never have sex is, in the words of John Maynard Smith[1], "an evolutionary scandal". Most theories[2] do indeed have it that in the long term asexuality will usually lead to extinction, but work by Nancy Moran, published in the *Proceedings of the National Academy of Sciences*[3], may help to explain why some asexual lineages persist.

Sex should promote evolutionary change and survival if selective forces fluctuate, as is thought to occur during antagonistic parasite–host coevolution, and it should also prevent the accumulation of deleterious mutations[4,5]. Models of the parasite–host interaction predict that asexual lineages die out rapidly because they are unable to keep up with faster evolving parasites (one need only look at the consequences of growing monocultures[6] — take the Irish potato famines of the last century, for example). Genome decay models, on the other hand, emphasize the vulnerability of small asexual populations to the accumulation of slightly deleterious mutations, which make a population smaller and by a positive feedback process can lead to 'mutational meltdown'[7].



Ratio of mean non-synonymous (d_N) to mean synonymous (d_S) substitutions per nucleotide site for five tryptophan biosynthetic enzymes in endosymbiotic and free-living bacteria. Red, the ratio in the endosymbiotic *Buchnera* from two aphid species. Blue, the ratio in the free-living enterics *Escherichia coli* and *Salmonella typhimurium*.

Moran has studied the endosymbiotic bacteria (*Buchnera*) of aphids. The bacteria are passed from mother to progeny every generation, and have apparently done so for some 100 million years[8]. The absence of biparental inheritance precludes genetic recombination between different clonal lineages, but a bacterial symbiont in an insect host inhabits a cosy world protected from both parasites and environmental fluctuations. So the asexuality of endosymbiotic bacteria has been considered to be consistent with the parasite theory of sex[9].

These bacteria do, however, pose a problem for the view that sex is a means of expunging deleterious mutations — populations of endosymbiotic bacteria go through a 'bottleneck' when they pass through the eggs of their hosts. This limits the population size and makes them prone to mutational meltdown. Why then have asexual endosymbionts such as *Buchnera* not decayed to extinction? There are two possible explanations. First, the mutational decay they suffer may happen only very slowly; second, they may have accelerated rates of accumulation of deleterious mutations, but accompanied by compensatory responses.

Moran compared the rate of evolution of *Buchnera* genes with that of the same genes in closely related, free-living bacteria that live in huge populations, some of which have recombination. Differences between genes in two lineages may be of one of two types: there are those that have no effect on the amino-acid composition of the protein concerned (synonymous substitutions) and those that do (non-synonymous). Moran could then ask whether the endosymbionts have relatively accelerated rates of non-synonymous substitution, as genome-decay models would predict. She found that this was indeed the case — see figure. The same has been found for one Y-linked gene in mammals[10,11] (the Y chromosome escapes recombination and also has a small effective 'population size', and so is essentially in the same boat as an endosymbiont). Moran also demonstrates that 16S RNA evolves much faster in five independently evolving symbiont lineages than in their free-living relatives.

The high ratio of non-synonymous to synonymous mutations is compatible with genome-decay models. But it could also be due to adaptive change, as could be argued for the Y chromosome. Moran, however, contends that adaptation is not the reason behind the pattern of change seen in endosymbionts, because the percentage of adenine (A) and thymine (T) in the endosymbiont genome is very high and many of the A/T substitutions occur in non-synonymous positions. The high A and T content could reflect adaptive genome-wide selection favouring As and Ts. But selection for base composition would be expected to act primarily on synonymous sites. So most non-synonymous substitutions are probably deleterious.

It seems, then, that the endosymbionts have tolerated accelerated rates of deleterious mutations while avoiding mutational meltdown and extinction. So how have they done it? The rate of accumulation of mutations could be slowed, in the absence of recombination, if the per genome mutation rate could be somehow reduced.

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An Approach to the Design of Molecular Solids. Strategies for Controlling the Assembly of Molecules into Two-Dimensional Layered Structures[1]

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Abstract: A design strategy for the synthesis of molecular crystals containing two-dimensional layers is formulated and demonstrated by the synthesis and structure determination of a series of dicarboxylic acid urea derivatives. The design strategy is based upon the selection of complementary hydrogen bond functionalities and an accounting of the specific symmetry operators that must correspond to each intermolecular interaction within the molecular crystal. Each of the molecules studied contained a disubstituted urea functionality that was expected to form a one-dimensional hydrogen-bonded network, an α-network, via urea hydrogen bonds. The molecules also contained terminal carboxylic acid or amide residues that were anticipated to unite the α-networks into two-dimensional β-networks via additional hydrogen bonds. In practice, it was found that symmetrical ureas, with C_2 point group symmetry, retained the two-fold axis within the crystal and reliably formed β-networks. When unsymmetrical ureas were studied, the anticipated β-network often failed to form. This was a particular problem when racemates were used. However, when a single enantiomer of an unsymmetrical chiral molecule was studied, the β-network formed in accordance with the design. The importance of chirality for the development of strategies for supramolecular synthesis is discussed.

Introduction

The properties of a material depend critically upon both the chemical nature of the constituent molecules *and* their relationships with respect to each other in the condensed phase.[2] Thus, the preparation of new materials must be concerned with the problems of both molecular and supramolecular[3] synthesis. Molecular synthesis has historically been a major focus of chemistry, and considerable progress has been made in the directed synthesis of complex molecules. However, supramolecular synthesis, or the control of molecular orientation in the condensed phase, is an extremely difficult problem and presents one of the greatest obstacles to the preparation of new materials.[4]

We have chosen two-dimensional layered materials for the development of strategies for supramolecular synthesis. Low-dimensional solid-state structures, such as one-dimensional rods and two-dimensional layers, are solid-state structures that have played an important role in materials science.[5] Two-dimensional materials, such as the copper oxide superconductors, molybdenum sulfide lubricants, or intercalated graphite materials, are generally inorganic and have many important applications. The inherent anisotropic properties of a two-dimensional solid-state structure are a result of very strong interactions, often covalent bonds, in two dimensions and weak interactions in the third dimension. Although not as extensively studied, molecular two-dimensional layers[6,7] can be envisioned where the molecules within the layer are held together by strong intermolecular interactions and the adjacent layers are held together by weak van der Waals interactions. Among the strong intermolecular interactions, hydrogen bonding[8] is of paramount importance for molecular organization in the solid state[6,7,9,10] and will be extensively employed in our design strategies.

Crystal Design Strategies

The formation of an intermolecular bond is a chemical process. The formation of an intermolecular bond in a crystal is governed by the same forces that govern such bonds in solution or in other less ordered phases. However, in a crystal *all* intermolecular interactions must conform to the laws of crystallography. These laws can be expressed in terms of symmetry relationships and group theory. Crystal design strategies that ignore these symmetry principles will often be futile. Properly understood, these symmetry principles can greatly simplify design strategies.

To demonstrate how symmetry principles can be used when designing molecular crystals, four fundamental supramolecular

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Table I. Four Fundamental Supramolecular Structures

structure type	translations	group symmetry
discrete assembly	no translations	point group symmetry
α-network	translations in one direction	rod group symmetry
β-network	translations in two directions	layer group symmetry
γ-network	translations in three directions	space group symmetry

structures, found in molecular crystals, must be defined (Table I). It will then be demonstrated how the chemical principles governing intermolecular hydrogen bonds can be combined with a rigorous symmetry analysis to design and predict specific crystal structures.

A *discrete assembly* is a supramolecular complex that lacks translational symmetry.[11] The assembly must be finite and will generally contain only a small number of molecules. A discrete assembly may be symmetric or asymmetric;[12] it may be composed of like molecules or of unlike molecules. Figure 1 shows two examples of discrete assemblies. One is the centrosymmetric benzoic acid dimer, an example of a symmetric discrete assembly, and the other is a molecular complex recently prepared by the Hamilton group,[10f] an example of an asymmetric discrete assembly.[13]

Often molecules form supramolecular structures that possess translational symmetry. These structures are networks and contain a theoretically infinite number of molecules. The simplest networks are one-dimensional α-networks with one degree of translational symmetry.[14] Hydrogen-bonded α-networks are common structural features. They may be composed of single molecules such as an α-network of secondary amides,[15] (Figure 2a) or they may be composed of translationally related discrete assemblies such as an α-network of primary amide dimers[16] (Figure 2b).

A supramolecular structure with two degrees of translational symmetry is a β-network. A two-dimensional β-network may contain, but is not required to contain, substructures that are classifiable independently as α-networks or as discrete assemblies.[17] Figure 3 shows an example of a β-network of primary diamides.[16a] Properly designed, a β-network supramolecular structure can naturally lead to a layered molecular solid.

The fourth and final type of supramolecular structure has three degrees of translational symmetry and is termed a γ-network. A γ-network will fill three-dimensional space, and in many cases, an entire crystal structure is defined by one γ-network.[18] A γ-network may contain α-networks and/or β-networks as substructures.[19]

The fundamental building block of each of the four structure types is an asymmetric assembly of atoms. The asymmetric assembly may consist of a single molecule, multiple like or unlike molecules, or a portion of a symmetric molecule.[20] Consider first the simplest and most common situation of a crystal with an asymmetric unit consisting of a single molecule. Crystallographic symmetry requires that all molecules within the crystal are related to any other molecule by some symmetry operation. This means that all molecules in the crystal must have either identical or enantiomorphic structures. This rule is well-known, but it has

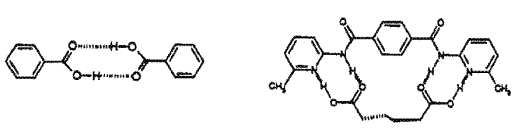


Figure 1. Examples of *discrete assemblies*. On the left is an example of a carboxylic acid dimer.[8,9a] Such dimers usually form about inversion centers, meaning that the complex is a *symmetric discrete assembly* with point group symmetry C_i. On the right is a host–guest complex.[10f] Such complexes most often form with no symmetry elements and thus are examples of *asymmetric discrete assemblies*.

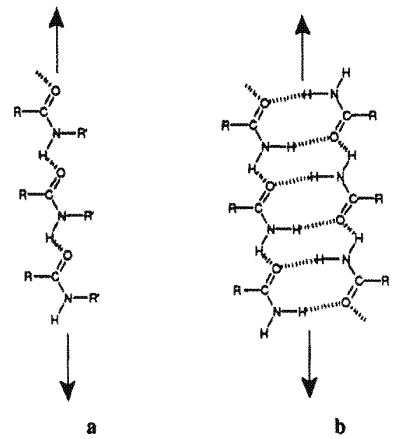


Figure 2. Examples of α-networks. The drawing on the left shows an α-network of a secondary amide.[15b] Such networks are commonly found with one of three different rod group symmetries, $P1$, $P2_1$, or Pa, depending upon the identity of the symmetry element (translation, screw axis, or glide plane) relating each molecule to its neighbor. On the right is an α-network of primary amides.[15a] Primary amide α-networks commonly contain inversion centers and have $P\bar{1}$ rod group symmetry.

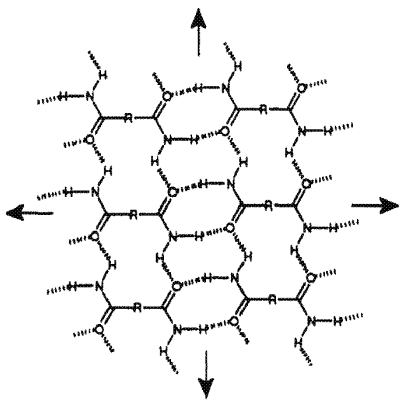


Figure 3. Common hydrogen bonding pattern for primary diamides.[15a] An example of a β-network.

a corollary rule that is perhaps not so well appreciated: *If all molecules in a molecular crystal are identical or enantiomorphic,*

(11) A discrete assembly can be characterized by its point group symmetry. If the discrete assembly is found in a crystal, its point group must be one of the 32 crystallographic point groups.

(12) The molecules in a symmetric assembly must be related by some symmetry operator such as an inversion center or symmetry axis. The molecules in an asymmetric assembly are not related by symmetry. If the assembly is of unlike molecules, then it must be asymmetric, since no symmetry operator can equate unlike molecules.

(13) The supramolecular structure shown in Figure 1b is just one combination of the many reported.[9f] Other pairs of compounds formed α-networks instead of discrete assemblies.

(14) An α-network has one degree of translational symmetry. It can be characterized by its rod group symmetry. See ref 6b for more details.

(15) (a)Leiserowitz, L.; Schmidt, G. M. J. *J. Chem. Soc. A.* **1969**, 2372. (b) Leisowitz, L.I; Tuval, M. *Acta Crystallogr.* **1978**, *B34*, 1230. (c) Weinstein, S.; Leiserowitz, L.; Gil-Av, E. *J. Am. Chem. Soc.* **1980**, *102*, 2768.

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(17) A β-network has two degrees of translational symmetry. It can be characterized by its layer group symmetry. See ref 6b for more details.

(18) An example of when this is not true is a crystal containing additional molecules, solvent molecules perhaps, that are not part of the γ-network.

(19) The space group of a γ-network is not required to be the same as the crystal space group. The crystal could contain additional symmetry operators . The space group of the γ-network must be at least a subgroup of the crystal space group.

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then all ***intermolecular interactions*** *will correspond to a specific symmetry operation.*[21,22] One normally thinks of intermolecular interactions in terms of chemical forces; however, in a crystal, one must also consider the symmetry operator that will generate the second molecule of any interacting pair. In any given case only certain symmetry operators will be chemically possible. This will greatly limit the number of possible supramolecular structures and greatly simplify the design process.

Network Designs. A logical strategy for the synthesis of molecular solids can be based upon the synthesis of molecular networks held together by hydrogen bonds.[9,10] This strategy is based upon a combination of chemical and crystallographic principles. The most important chemical concept is that of the complementary hydrogen bond functionality set, a combination of atoms with hydrogen bond donor and acceptors matched in terms of number, shape, and interatomic distances. The important crystallographic concept is an accounting of the symmetry operator that interrelates the two molecules of each intermolecular hydrogen bond. For a successful design, the hydrogen-bonding patterns must be persistent, maintaining both the chemical connectivity and the associated symmetry operator.

Examples of α-networks are common. Recently, α-networks have been the focus of studies directly concerned with the problem of supramolecular synthesis.[10b-i] An interesting example has been provided by Lehn and co-workers, who prepared a molecule designed to form an α-network via a total of six highly specific complementary hydrogen bonds. In related work reported by the Lehn,[10g,h] Whitesides,[10b-e] and Hamilton groups,[10f] α-networks were formed by hydrogen bonds between pairs of different but complementary molecules that cocrystallized to produce solid-state structures with the desired one degree of translational symmetry with the two molecules alternating along the α-network. In the Whitesides work,[10b-e] cocrystals of compounds of the cyanuric acid–melamine family of compounds were found to form three distinct supramolecular structures.[23] These strategies for the designed synthesis of α-networks are elegant in their simplicity, with a high probability of success due to the careful design of the hydrogen bond functionalities.

Our general synthetic strategy for the preparation of a two-dimensional β-network requires *two* independent complementary hydrogen bond functionality sets. One can envision the formation of a hydrogen-bonded α-network in the usual manner via a first set, but the molecules are chosen such that they have a second set available for linking the α-networks into a β-network.

This strategy will have potential problems not encountered in a one-dimensional α-network synthesis. One chemical problem is maintaining the independence of the two hydrogen bond functionality sets. If the complementarity breaks down and a donor atom from one set forms a hydrogen bond with an acceptor atom of the second set, then numerous alternative structures become possible. There are also potential crystallographic problems. For any supramolecular structure, molecules must be chosen with the proper size and shape for molecular packing; but as the dimensionality of the structure increases, the degrees of molecular freedom decrease and the problem becomes more serious.[24] Also, in a two-dimensional β-network, there will be more possible alternate symmetry operations than in an α-network and more ambiguity in the design process.

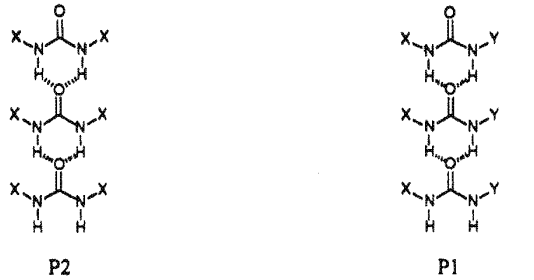


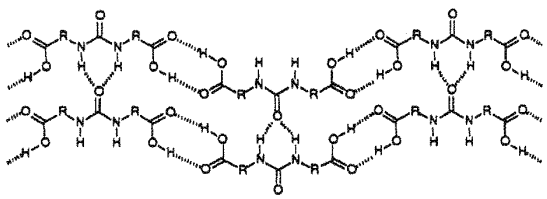
Figure 4. *N,N'*-Disubstituted ureas form α-networks by forming pairs of complementary hydrogen bonds. In our work, we have observed that symmetrical ureas usually retain their two-fold axis within the solid state and form α-networks of *P*2 symmetry. If the substituents differ, then there usually is no molecular symmetry and the ureas form α-networks with *P*1 rod group symmetry.

Symmetry Analysis. For a successful design of any molecular solid, one must properly account for the specific symmetry operators that correspond to each intermolecular interaction. Thus, a symmetry analysis of α- and β-networks is a necessary first step. The symmetry group of an α-network can be determined by taking the symmetry operators of the point group of the asymmetric assembly and combining them with the symmetry operator or operators corresponding to the intermolecular hydrogen bonds that tie together the α-network. One trivial but common case discussed previously has a secondary amide[15] forming an α-network of *P*1 rod symmetry by simple translation (Figure 2a). Alternate symmetries are possible for the generation of the intermolecular bond. A screw axis would generate $P2_1$ rod symmetry; a glide plane would generate *Pa* rod symmetry. These three different α-network symmetries are the only ones commonly observed.

In a slightly more complex case, primary amides[16] tend to use their *syn*-hydrogens to form centrosymmetric dimers of C_i symmetry, and these discrete assemblies further associate via the amide *anti*-hydrogen atoms to form α-networks of $P\bar{1}$ rod symmetry via simple translation (Figure 2b). In this case there are no commonly found alternate symmetries and the $P\bar{1}$ α-network symmetry can be predicted with a high reliability.

In our previous work[6] on the design and preparation of β-networks, the disubstituted urea functionality has been used to form primary α-networks. It has been found that the urea group most commonly will form a hydrogen-bonded α-network via simple translation. Unsymmetrical disubstituted ureas lack a molecular two-fold axis and form α-networks of *P*1 rod symmetry (Figure 4). Symmetrical disubstituted ureas usually retain a two-fold axis within the crystal, C_2 point group symmetry, and thus form α-networks of *P*2 rod symmetry.

To produce a β-network of disubstituted ureas, a second hydrogen bond functionality set must be introduced into the molecule. This second set can then link the urea α-networks into a β-network. In our initial work, a series of symmetrical urea dicarboxylic acids (**1**, **2**, and **3**) that formed α-networks of *P*2 rod symmetry was prepared. In each case the two carboxylic acid



(20) The asymmetric assembly is often identical to the crystallographic asymmetric unit, but this is not necessarily true. The asymmetric unit may contain additional molecules that are not part of the designated supramolecular structure.

(21) To say that an intermolecular interaction corresponds to a symmetry operation means that the two molecules are related by that symmetry operation.

(22) This rule can be stated without the restriction. In a molecular crystal, all intermolecular interactions between molecules of different asymmetric units will correspond to a specific symmetry operation.

(23) In the original papers[9b,e] the two forms of α-networks were termed linear tapes and crinkled tapes. The second form differs due to a reversal in the complementarity of one hydrogen bond set. The third form, a discrete assembly, requires two such reversals and was termed a rosette.

(24) Close packing has long been recognized as a primary determinent of molecular crystal structures. Kitaigorodskii, A. I. *Organic Chemical Crystallography*; Consultants Bureau: New York, 1961.

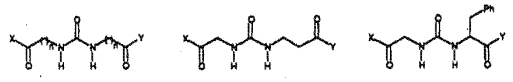
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Table II. Results of Adding Selected Additional Symmetry Operators to *P*1 and *P*2 Rod Groups[a]

	*P*1 rod group	*P*2 rod group
Chiral Groups		
translation, perpendicular to main axis	*P*1 layer group[a]	*P*2 layer group
two-fold axis, parallel to main axis	*P*2 rod group	*P*2 layer group
two-fold axis, perpendicular to but not intersecting main axis	*P*112 rod group	$P222_1$ layer group
2_1 screw axis, parallel to main axis	$P2_1$ rod group	*C*2 layer group
2_1 screw axis, perpendicular to and intersecting main axis	$P2_1$ layer group	$P222_1$ layer group
2_1 screw axis, perpendicular to but not intersecting main axis	$P2_1$ layer group	$P2_12_12$ space group
Achiral Groups		
inversion, off of main axis	$P\bar{1}$ rod group	*P*2/*c* layer group
glide plane, intersecting main axis, glide in perpendicular direction	*P*11b layer group[a]	*P*2*mb* layer group
glide plane, parallel to main axis but not intersecting, glide in parallel direction	*Pa* rod group	*P*2*an* layer group
glide plane, parallel to main axis but not intersecting, glide in perpendicular direction	*P*11*b* layer group[a]	*Pba*2 space group
glide plane, perpendicular to main axis	*Pb*11 layer group	*P*2/*c* layer group

[a] In this case the direction is not required to be perpendicular to the main axis but merely nonparallel to the main axis.

groups formed cyclic hydrogen bonds about inversion centers, linking the urea α-networks into a β-network. Adding an inversion operator to the *P*2 rod group yielded the observed layer group *P*2/*c*.



4 X = Y = NH_2, n = 3
5 X = Y = NH_2, n = 1
6 X = OH, Y = NH_2, n = 1
7 X = OH, Y = NH_2, n = 3
8 X = OH, Y = NH_2
9 X = NH_2, Y = OH
10 X = OH, Y = OH
11 X = OH, Y = OH (racemic)
12 X = OH, Y = NH_2 (racemic)
13 X = NH_2, Y = OH (racemic)
14 X = NH_2, Y = OH (chiral (S))

In these cases the symmetry of the β-network was relatively easy to predict, since there is a strong association between each intermolecular bond and a particular symmetry operator. The layer group symmetry *P*2/*c* resulted from a combination of the primary two-fold axis of the urea α-network and the inversion centers corresponding to the carboxylic acid intermolecular interactions. Other intermolecular interactions would have different associated symmetry operators and different predicted symmetry groups. In Table II the effect of adding selected symmetry operators to the *P*1 and *P*2 rod groups is shown.[25] As can be seen from the table, the resulting symmetry group may be another rod group, a layer group, or a space group. In chemical terms this means that adding an intermolecular interaction to an α-network can generate a larger α-network, a β-network, or a γ-network. In principle, real examples of networks characterized by any of the listed symmetry groups could be generated if a chemical functionality is identified that gives an intermolecular interaction corresponding to the given symmetry operation.[26]

The results for the *P*2 rod group are especially interesting. The addition of any of the more commonly encountered symmetry operators will give layer groups. The two exceptions generate rarely encountered space groups and are unlikely to occur.[27] Thus, it can be said with some confidence that an α-network of *P*2 rod symmetry will form a β-network whenever a second complementary hydrogen bond functionality set is added to the constituent molecule. The symmetry of the resulting β-network will depend upon the identity of the symmetry operator that corresponds to the second intermolecular hydrogen bond.

(25) Table II lists only a selection of the possible additional symmetry operators. High-order axes are not included. High-order axes are only found in trigonal, tetragonal, or cubic space groups. Since over 95% of organic structures are found to possess triclinic, monoclinic, or orthorhombic symmetry, we have not included high-order axes in this analysis. Mighell, A. D.; Himes, V. L.; Rogus, J. R. *Acta Crystallogr.* **1983**, *A39*, 737.

(26) It would be difficult to identify favorable intermolecular interactions corresponding to some of the listed symmetry operators. For example it is unlikely that one could identify a bonding intermolecular interaction corresponding to a mirror plane.

(27) The two exceptions generate the space groups $P2_12_12$ and *P*2*cn*. The former is a relatively rare space group; the latter is very unusual.

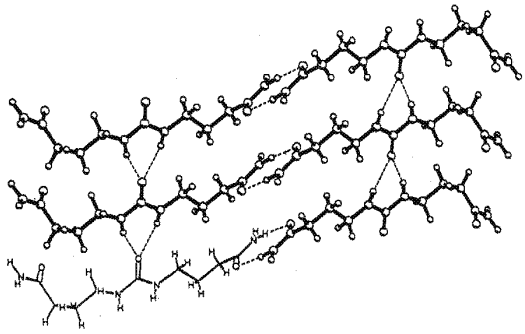


Figure 5. β-Network of the diamide **4**. There is a two-fold axis passing through the urea carbonyl groups and an inversion center at the center of the cyclic amide hydrogen bonds. The α-network defined by the urea hydrogen bonds has *P*2 rod symmetry; the layer symmetry of the β-network is *P*2/*c*.

This paper reports a solid-state structural investigation of urea acid and amide derivatives. The purpose of the study was to identify fundamental principles for the development of strategies for controlling molecular orientation in the solid state. The symmetry analysis discussed above is an integral component of these strategies.

Results

Urea Diamide Derivatives. The urea dicarboxylic acids (**1**, **2**, and **3**) form, via a urea-based α-network, β-networks with neighboring α-networks linked by the cyclic hydrogen-bonded dimers of the dicarboxylic acid functionality.[6] Primary amides are also known to form hydrogen bond dimers about centers of symmetry,[16] and analogous β-networks can be envisioned for symmetrical urea diamide derivatives **4** and **5**. Figure 5 shows the crystal structure of the diamide **4** possessing a propylene group linking the amide and urea functionalities. A β-network forms and has layer symmetry *P*2/*c*. It is completely analogous to the dicarboxylic acid structures found earlier. The amide groups form cyclic hydrogen bonds about inversion centers via the amide *syn*-hydrogen atom. The *anti*-hydrogen atoms form additional hydrogen bonds to amide carbonyl atoms of the neighboring β-networks, uniting the entire structure into a three-dimensional γ-network. Neighboring layers are related to each other via a two-fold screw axis so that the final space group symmetry for the γ-network and the crystal is *C*2/*c*.[28]

(28) A single molecule within this structure has a two-fold axis; the urea functionalities hydrogen bond to form the primary α-networks via simple translation. The primary α-networks are united to form β-networks via cyclic amide dimers about centers of symmetry. The β-networks are held together via hydrogen bonds formed between the *anti*-hydrogen atoms of the amides and amide carbonyls. These hydrogen bonds require an offset between successive layers that is generated by a two-fold screw axis. These symmetry operators, a two-fold axis, a translation, an inversion center, and a screw axis, serve as generating operators for the *C*2/*c* space group.

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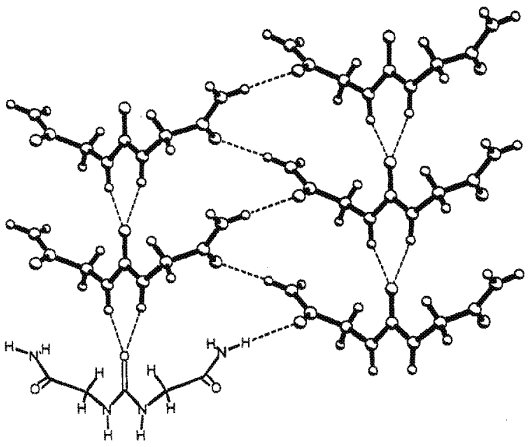


Figure 6. β-Network of the diamide **5**. The urea carbonyl groups lie on a two-fold axis and form an α-network of $P2$ rod symmetry. The amide hydrogen bonds form a helix about a two-fold screw axis. The layer symmetry of the β-network is $C2$.

The diamide **5** also forms a $P2$ α-network via urea hydrogen bonds, but in this case the primary amide groups form a catemer structure via a two-fold screw axis[29] (Figure 6). The combination of a screw axis with the original two-fold axis generates a β-network with $C2$ layer symmetry. In contrast to the β-network formed by compound **4**, the individual β-networks formed by compound **5** are polar with all urea carbonyl groups pointing in the same direction. However, successive layers are related by inversion centers, yielding a nonpolar $C2/c$ space group symmetry for the crystal.[30]

Urea Acid Amide Derivatives. Our initial studies of urea dicarboxylic acids, and their diamide derivatives, all involved molecules with molecular two-fold axes. These molecules formed primary α-networks with $P2$ rod symmetry. As a logical extension of this work, the monoamide derivatives **6** and **7** of the dicarboxylic acids **1** and **3** were also investigated. It was anticipated that the monoamide derivatives would form α-networks of $P1$ rod symmetry via urea hydrogen bonds. The terminal acid and amide groups could potentially hydrogen bond in two chemically distinct ways. They could form segregated *like to like* hydrogen-bonded pairs (acid–acid and amide–amide), or they could form *like to unlike* hydrogen bonded pairs (acid–amide).

The possible symmetry operators corresponding to each alternative are different. With *like to like* hydrogen bonds, an inversion operator is the most likely alternative, yielding a β-network with $P\bar{1}$ layer symmetry. With *like to unlike*, amide–acid hydrogen bonds, a simple translation operator is the most likely alternative, yielding a β-network with $P1$ layer symmetry. Work by others[31] and model studies[32] in our laboratories suggested that the acid–amide hydrogen bonds are somewhat more favorable in terms of energy. It was anticipated that a β-network with $P1$ layer symmetry was the most likely possibility.

When the crystal structures of compounds **6** and **7** were determined, the results were somewhat surprising (Figure 7). The best interpretation of the X-ray data indicates that in *both*

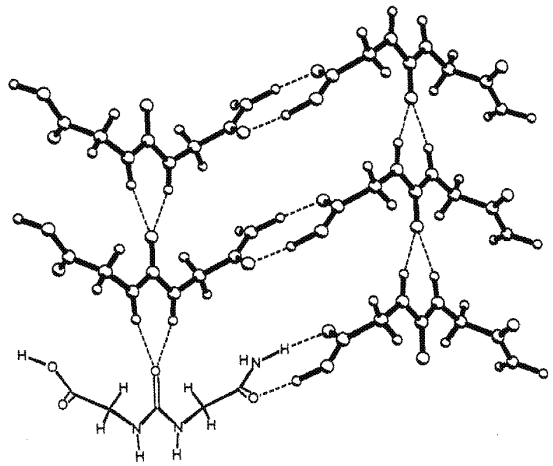


Figure 7. β-Network of the monoamide **6**. The compound has a disordered structure. There is a crystallographic two-fold axis passing through the urea carbonyl groups and an inversion center at the center of the cyclic acid–amide hydrogen bond. This disorder makes it impossible to distinguish the true structural relationships of the acid and amide functionalities. This figure shows one possibility.

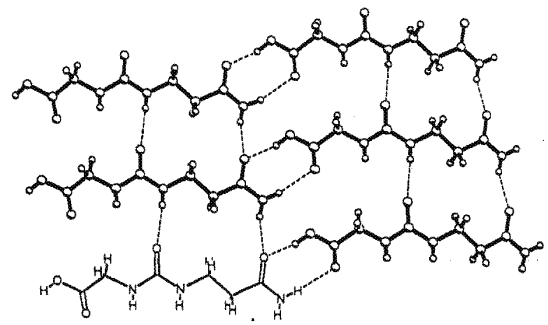


Figure 8. β-Network of the monoamide **8**. This β-network has $P1$ layer symmetry, with neighboring molecules related by simple translations only. The intermolecular urea to urea hydrogen bonds are unusual in this structure. Instead of the normal symmetrical structure there is only one urea hydrogen bond with a N–H···O distance of 2.11(3) Å. The second N–H···O distance is much longer, 2.91(3) Å.

cases the molecules are completely disordered about a pseudo-two-fold axis passing through the urea carbonyl group. Indeed, the crystal structure of the monoamide **6** is isomorphous with the structure of **1**. This apparent crystallographic disorder prevents us from unambiguously determining the amide and acid hydrogen bond patterns. The observed disorder was not anticipated in either case. Its presence illustrates one problem that can interfere with any design effort. This pseudosymmetry also illustrates the similarity of the amide and acid functionalities in terms of size and shape as well as intermolecular bonding capabilities.

Breaking the Pseudosymmetry. Clearly, to fully investigate the acid amide family of molecules, examples without the pseudo-two-fold axis were needed. The isomeric molecules **8** and **9** were prepared, and their crystal structures were determined (Figures 8 and 9). The crystal structure of **8** exhibits the *like to unlike* amide to acid hydrogen bond pattern and forms the predicted β-network of $P1$ symmetry. In this β-network, the amide group turns so that the amide *anti*-hydrogen atom can form a hydrogen bond within the layer. With an amide hydrogen bond within the layer, the neighboring urea functionalities cannot form their usual symmetric pair of hydrogen bonds. As a result of this situation, the urea groups adopt an unusual "slipped" configuration.

The monoamide **9** shows *like to like*, acid–acid and amide–amide, hydrogen bonds, but with two molecules in the asymmetric

(29) The amide *anti*-hydrogens link molecules into a helix about the two-fold screw axis. This helix is an α-network with $P2_1$ rod symmetry.

(30) Successive layers again are held together via hydrogen bonds formed by the *anti*-hydrogens of the primary amide groups. The generating symmetry operators are the same as in the crystal of compound **4**, but the chemical correspondence is different.

(31) (a) Leiserowitz, L.; Nader, F. *Acta Crystallogr.* **1977**, *B33*, 2719. (b) Leiserowitz, L. *Acta Crystallogr.* **1976**, *B32*, 775.

(32) It has been found that the glutaramide crystallizes in the space group Cc, with two molecules in the asymmetric unit. The molecules form an α-network of Pa symmetry via like to unlike amide to acid hydrogen bonds. Chang, Y.-L. Ph.D. Thesis, State University of New York, Stony Brook, NY, 1991.

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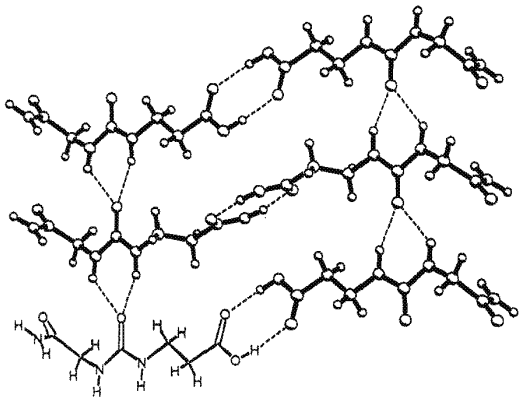


Figure 9. β-Network of the monoamide **9**. This structure contains two molecules in the asymmetric unit. The carboxylic acid ends of the two independent molecules have different conformations. The urea α-network of $P\bar{1}$ rod symmetry consists of alternate independent molecules. Neighboring α-networks are related to each other via inversion centers, yielding a β-network with layer symmetry.

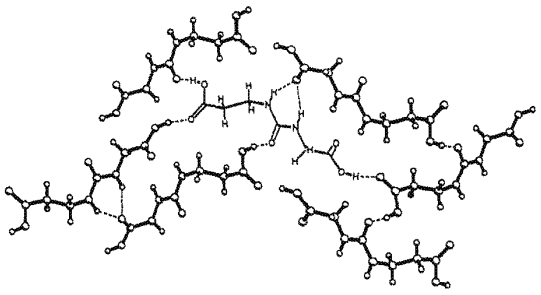


Figure 10. Crystal structure of the diacid **10**. In this structure the expected complementary hydrogen-bond patterns have been broken. The molecules form a γ-network of $P2_12_12_1$ space group symmetry. There is no β-network.

unit. The pairs of unlike molecules form a urea-based α-network of $P\bar{1}$ rod symmetry. The acid–acid and amide–amide hydrogen bonds form about inversion centers as expected. The resulting β-network has $P\bar{1}$ symmetry.[33]

A Break in Hydrogen Bond Complementarity Patterns. An Unsymmetrical Diacid. The structure of the diacid **10** was also determined. Again, β-networks of either $P\bar{1}$ or $P\bar{1}$ layer symmetry were anticipated, depending upon whether the two different carboxylic acid functionalities formed hydrogen bonds in a *like to like* or *like to unlike* pattern. However, Figure 10 shows that the hydrogen bond complementarity has been completely broken. The urea functionality serves as a double hydrogen bond donor forming hydrogen bonds to the carbonyl group of one of the carboxylic acid groups at the same time the urea carbonyl accepts a hydrogen bond from another carboxylic acid group. There is one acid–acid hydrogen bond, but it involves only one hydrogen atom and not the normal two. The space group is $P2_12_12_1$, and there is no β-network.

Introduction of a Stereogenic Center. Molecular chirality plays a fundamental role in determining solid-state structure. All of the urea derivatives discussed above have been achiral. It was of interest to determine the response of the solid-state structure of this class of compounds to the introduction of a stereogenic center. The urea dicarboxylic acids and their derivatives are prepared from amino acids, and most of the available amino acids are chiral. In our initial studies a relatively simple example was chosen: the urea formed from glycine and phenylalanine, a molecule possessing a single stereo center. The diacid **11** and the two isomeric monoamide derivatives **12** and **13** were prepared in racemic form, and their crystal structures were determined.

(33) It is interesting to note that the main difference between the two independent molecules is the "twist" of the carboxylic acid groups. A similar structural feature is found in the structure of the diacid **2**, a structure that also contains multiple molecules in the asymmetric unit.

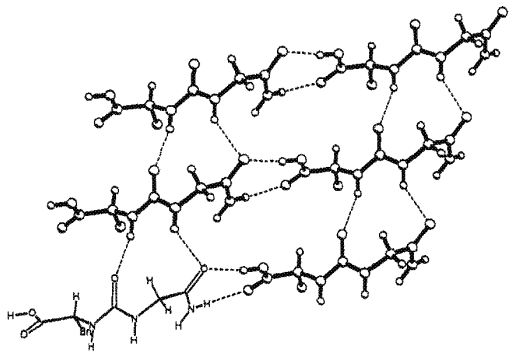


Figure 11. β-Network of the acid amide **14**. This β-network has $P\bar{1}$ layer symmetry, with neighboring molecules related by simple translations only. To simplify the figure, the benzyl groups have been omitted and are represented by a dummy atom labeled Bn. The distorted urea hydrogen-bond distance, N–H···O, is 1.99(2) Å. The unusual urea to amide carbonyl oxygen distance, N–H···O, is 2.22(1) Å.

As racemates, each of the three compounds can crystallize in a centrosymmetric space group. In each case there are two enantiomorphic molecules, the *R* and the *S*, each with acid or amide ends capable of forming complementary hydrogen bonds. There are several different β-networks that could be formed for each compound. However, neither the diacid nor either of the monoamide derivatives formed a β-network, as described above.

In the diacid **11**, the carboxylic acid functionality adjacent to the benzyl group forms a conventional dimer about an inversion center, but the other carboxylic acid group slips around to the urea carbonyl oxygen atom, forming a large hydrogen-bonded ring about an inversion center. The result is a β-network, but not one of those anticipated. With the "slipped" acid to urea hydrogen bond, the layer structure is not so readily discernible.

Both monoamide structures contain similar unconventional hydrogen bond patterns. Compound **12** contains a large hydrogen-bonded ring structure encompassing two urea functionalities as well as one carboxylic acid and one amide group. Compound **13** contains a large ring formed by acid to amide hydrogen bonds with the two ends of a pair of molecules forming a centrosymmetric dimer. Compound **13** also contains an unusual amide–amide hydrogen bond formed about a crystallographic two-fold axis instead of the more usual inversion center.

The chiral compound **14**, the urea derivative of the amide of glycine and L-phenylalanine, was prepared. The compound crystallized forming the β-network shown in Figure 11. This β-network has $P\bar{1}$ layer symmetry with only translational symmetry present. The β-network is formed by linking together the primary urea α-networks by *like to unlike* amide to acid hydrogen bonds. The *anti*-hydrogen of the amide group also forms an interlayer hydrogen bond, meaning that the entire structure is somewhat similar to that found for compound **8**. The benzyl groups are aligned all on one side of the layer (Figure 12). The space group is $C2$ with alternate layers related by 2_1 and 2 axes approximately parallel to the urea carbonyl group. The individual layers and the overall crystal have polar axes.

Thus, the designed β-network, that failed to form with *all* racemic derivatives of the ureas derived from phenylalanine, is produced with the nonracemic monoamide derivative **14**. Although the solid-state structures of the other chiral ureas (**11** and **12**) would be of interest, all attempts to obtain suitable crystals for X-ray crystallography have been unsuccessful.

Polymorphism is a common phenomenon for some classes of

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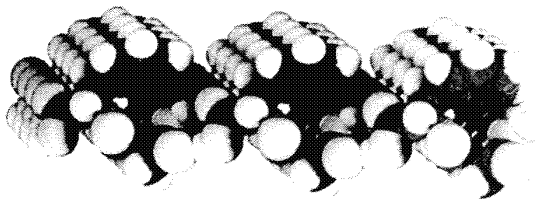


Figure 12. Edge view of the β-network of the acid amide **14**.

molecular crystals. For each of the compounds discussed above that did not form a β-network, it is possible there is an alternate polymorph with this hydrogen-bonding pattern. Although a systematic effort has not been made to identify polymorphs, they have not been observed for any of the ureylene dicarboxylic acid derivatives.

Discussion

Two-Fold Molecular Symmetry. The first disubstituted urea molecules studied[6] were symmetrical and formed crystals containing α-networks of $P2$ symmetry.[34] Often molecules that have a potential two-fold molecular axis will crystallize in a manner such that the potential two-fold axis is lost. In general, a crystallographic two-fold axis is not considered a favorable structural feature.[24] It was found with the symmetrical urea molecules that the two-fold axis persists in the crystal. This may be due to the fact that the intermolecular hydrogen bond formed between neighboring urea molecules is itself compatible with a two-fold axis. Indeed, the unsymmetrical monoamide molecules **4** and **5**, lacking a molecular two-fold axis, preserve a crystallographic two-fold axis by forming a disordered structure.

A molecular functionality that will yield an α-network of $P2$ symmetry is an ideal starting point for the formation of a β-network. This can be shown by examining Table II, where the results of adding a symmetry operator to the $P2$ rod group are shown. With the exception of two rarely encountered space groups, the additional operator combines with the operators of the $P2$ rod group to form a layer group. In chemical terms, this means that any intermolecular interaction that corresponds to a commonly encountered symmetry operator will unite neighboring $P2$ α-networks together to form a β-network with the designated layer symmetry.

With one exception, the urea-based $P2$ α-networks are related to neighboring α-networks via acid–acid or amide–amide hydrogen bonds[35] that form about inversion centers. As listed in Table II, the combination of an inversion center with the operators of the $P2$ rod group yields the layer group $P2/c$, as was observed in each of these structures. The diamide **5** was the exception; the amide groups form a catemer structure about a two-fold screw axis. Adding a 2_1 axis to the $P2$ rod group gives the layer group $C2$.

No Molecular Symmetry. With two different nitrogen substituents, the urea molecules cannot crystallize about a two-fold axis. In our studies such ureas tend to form α-networks of $P1$ symmetry. With a $P1$ α-network a single additional intermolecular interaction is *less* likely to give a β-network. This can be seen by examining Table II, where the results of adding various additional symmetry operators to the $P1$ rod group are shown. Some operator combinations yield new rod groups, layer groups, and space groups. For example, adding an inversion center to the $P1$ rod group yields the $P\bar{1}$ rod group. To form $P\bar{1}$ a layer group, two independent inversion centers would be required. Compound **9** (Figure 9) is such an example, but with two molecules per asymmetric unit, it is not a simple one.

For the purposes of molecular design, perhaps the most attractive symmetry operator to add to a $P1$ α-network would be a simple translation operator. This would yield a $P1$ layer group, meaning that the entire layer would possess only translational symmetry. In practice this means a molecule with hydrogen bond functionalities chosen such that the "top side of the molecule" complements the "bottom side" via simple translation and the "left side" complements the "right side" via simple translation. Compounds **8** and **14** (Figures 8 and 12) both form $P1$ layers via such a mechanism.

Breakdowns in Hydrogen Bond Complementarity. In the first compounds examined[6] the hydrogen bond patterns formed as anticipated, producing the designed β-networks. In compound **5** the proper complementarity was maintained; but the amide catemer structure was an unexpected geometry, and an alternate layer symmetry was observed for the β-network. As more complicated ureas were examined, examples were encountered (**10**, **11**, **12**, and **13**) where the hydrogen bonds formed in unexpected patterns. Without the expected hydrogen bond complementarity, the anticipated β-networks did not form. In most cases the number of hydrogen bonds that form is similar to the number of hydrogen bonds that would have formed in the anticipated patterns. The energies of individual hydrogen bonds may differ, but total energies of the hydrogen bonds would not likely differ by more than a few kcals/mol, even in the least satisfactory cases.[36] These results demonstrate the immense difficulty associated with the problem of developing rational strategies for supramolecular synthesis.

Strategies for Supramolecular Synthesis. The β Network. Important considerations for the development of any synthetic strategy are that it be simple to implement, have a high probability of success, and have flexibility for the preparation of related structures. For example, predictable hydrogen-bonding patterns are a requirement of our design efforts. The *N,N'*-disubstituted ureas and the carboxylic acid derivatives were chosen in our studies because they form persistent complementary hydrogen-bonding patterns. However, many exceptions to the required hydrogen-bonding patterns are known. A more complex functionality, such as the nucleic acids and their analogs, may ensure a greater degree of predictability, but if one adopts this strategy, there is a price to pay in terms of the difficulty of the molecular synthesis and a loss of the flexibility associated with simple functional groups.

Controlling the molecular packing by controlling the possible symmetry operators relating neighboring molecules can be a powerful strategy. The presence of an α-network, with $P2$ symmetry, readily leads to a β-network, since any of the common symmetry operators when added to the $P2$ rod group will generate a layer group. This means that essentially any additional intermolecular interaction will yield a β-network. The key to this strategy is the persistence of the crystallographic two-fold axis. The symmetrical ureas **1**–**5** are examples of a successful application of this concept. Similar strategies could likely be developed with other symmetrical molecules, such as those with persistent inversion centers or mirror planes.

If one considers a compound with no molecular symmetry, then there are many more alternative symmetry operators available and successful predictions of molecular packing will become more difficult. In particular, the situation becomes much more difficult when racemates are considered. In a racemate any given intermolecular bond may form between like molecules or between enantiomers; the two alternatives may often seem to be very similar in energy. Indeed none of the racemic ureas derived from phenylalanine formed the desired β-networks. In each case unanticipated patterns of hydrogen bonds were formed.

Chirality. There remains one powerful form of symmetry control that can be used in a design effort. One can turn to pure

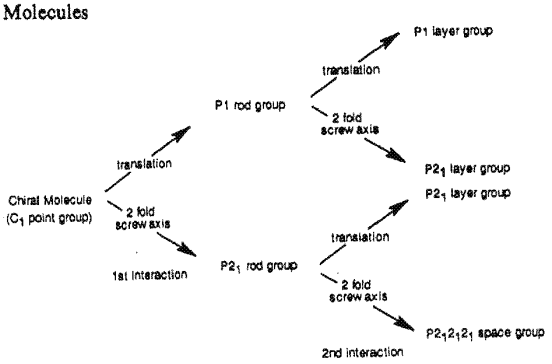
(34) The Cambridge Structural Data Base and our own work show that about 80% of symmetrical disubstituted urea molecules crystallize forming an α-network along a crystallographic two-fold axis.

(35) In the disordered acid amide structures **6** and **7**, neighboring α-networks were also related by inversion centers.

(36) Since crystal formation is undoubtedly under kinetic control, factors other than the relative stability of the final crystal may also play a role. For example, see the discussion of: McBride, J. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *69*, 295.

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Scheme I. Probable Self-Assembly Pathways for Chiral Molecules



enantiomers. The use of enantiomers greatly limits the crystallographic symmetry operators possible and, as a direct consequence, also limits the intermolecular interactions possible. Indeed, the only two commonly encountered intermolecular symmetry operators in a chiral crystal are simple translation and a two-fold screw axis. In this more limited universe, with fewer alternate structures, predictions become easier. In particular, the construction of a β-network of $P1$ symmetry with molecules related only by translational symmetry becomes an attractive structural goal. This concept is illustrated by the structure of molecule **14** (Figure 11). One can anticipate that similar ureas derived from other chiral amino acids will form similar β-networks. Chiral molecules would appear to be ideal candidates for the synthesis of layered structures of all types. Since there are only two commonly encountered symmetry operators corresponding to intramolecular interactions between chiral molecules, simple translation and the two-fold screw axis, there are only a few probable layer groups. Consider the following mental exercise that is also outlined in Scheme I.

In any molecular crystal structure there must be a net favorable intermolecular energy of interaction between neighboring molecules.[37] One particular intramolecular interaction and its symmetry related equivalents should be identifiable as the most favorable interaction. Some other intramolecular interaction should similarly be considered as the second most favorable interaction.[38] Consider the symmetry operators corresponding to these two intermolecular interactions. In a chiral crystal the first operator will most likely be either a translation operator or a two-fold screw axis operator. The same is true with the second operator. The first and second operators combine to give a higher order group. There are four possibilities: translation followed by translation gives the $P1$ layer group, translation followed by a screw axis or vice versa gives the $P2_1$ layer group, while two successive screw axes give the space group $P2_12_12_1$.[39,40] If either the strongest or second strongest intramolecular interaction corresponds to a simple translation operator, the formation of a layered structure is assured.[41] The chemical and physical significance of the layer formation depends upon the relative magnitude of interlayer versus intralayer forces, but any supramolecular structure containing the indicated symmetry operators will contain layers. However if both interactions are screw axes, then there is no layer formation. With some thought a design of a molecular solid could include molecular features that would favor at least one translation operator, thus favoring layer formation.

With achiral or racemic compounds these same rules apply, but the problem is that there are many more symmetry operators available. In particular, the single most favorable intramolecular interaction will often be an inversion center that will generate a centrosymmetric dimer. The presence of centrosymmetric dimers will not prevent layer formation but will often mean that the strongest forces between molecules in the supramolecular structure do not correspond to the translation symmetry operators needed for layer production. Compare the structure of the racemate **13** with that of the pure enantiomer **14**. The β-network of **14** has $P1$ layer symmetry. The racemate **13** could have contained this same supramolecular structure, but did not. Instead it formed centrosymmetric dimers that broke the designed hydrogen bond complementarity. *The fact that chiral crystals may exhibit special physical properties is well-known,*[42] *but the principle that it may be easier to design a given solid-state structure using chiral molecules is perhaps not so well appreciated.*

The organization of molecules into layers[43] is not restricted to molecular crystals. Molecular layers are important features of other structures such as surfaces, Langmuir–Blodgett (LB) films, and smectic liquid crystals. In a crystal it is easier to study and define such layers, but many of the essential properties and characteristics of crystalline layers may equally apply to the less ordered systems. For example, the role of chirality may be similar. In a film or liquid crystal, intramolecular interactions are also of great importance, and although the symmetry principles discussed in this paper do not apply strictly, the pseudosymmetry operator corresponding to each intramolecular interaction is still important. LB films and most smectic liquid crystals must be inherently acentric and polar, because of the forced alignment of head groups at one face of the layer. This means that the intramolecular interactions between molecules of a layer will most likely correspond to a translational symmetry operator. In a racemate the strongest intramolecular interaction often leads to a centrosymmetric dimer, incompatible with layer formation in a film or smectic liquid crystal. On the other hand the most favorable interaction between homochiral molecules is much more likely to correspond to a translational operator, consistent with layer formation.

In fact, Arnett[44] has found chiral recognition in the organization of monolayers formed at the air/water interface. Stupp has also observed that molecular chirality alters the behavior of liquid crystals[45] and is believed to be important for the preassembly of monomers for the formation of two-dimensional polymers shaped

(37) It must be noted that a structure containing a β-network is not necessarily a layered solid. The forces within the β-networks relative to the forces between the β-networks may not correspond to those associated with a layered solid. For example, the diacid **1** is a layered solid because there are hydrogen bonds within the layer but no strong intermolecular forces between successive β-networks. However, the corresponding diamide **5** is not a layered solid because the hydrogen bonds formed by the amide *anti*-hydrogens hold together successive β-networks. Consistant with this, qualitative observations indicate that crystals of compound **1** readily cleave between the layers formed by the β-networks, but crystals of **5** do not.

(38) The emphasis on specific symmetry related interactions has been addressed recently in theoretical studies. Gavezzotti, A. *J. Am. Chem. Soc.* **1991**, *113*, 4622. Perlstein, J. *J. Am. Chem. Soc.* **1992**, *114*, 1955.

(39) We are considering only the case with a nonintersecting second screw axis perpendicular to the first. The case with the two screw axes parallel is equivalent to that of a screw axis followed by translation. If the second screw axis intersects the first, then a real two-fold axis will be generated; this is generally not a favorable occurrence.

(40) The space group $P2_12_12_1$ is the most common space group for chiral molecules. It contains as subgroups all the groups outlined in Scheme I including the $P1$ and $P2_1$ layer groups.

(41) To go from the layer groups to a space group, a third independent symmetry operator must be added. Adding a third independent translation operator to the $P1$ layer group will generate the $P1$ space group. Adding an additional translation operator to the $P2_1$ layer group will generate the $P2_1$ space group. Adding a screw axis to the $P1$ layer group will generate the $P2_1$ space group. Adding a third independent screw axis to the $P2_1$ layer group will generate the $P2_12_12_1$ space group. The space groups $P2_12_12_1$, $P2_1$, and $P1$ are by far the most common chiral space groups.

(42) In particular, the use of chiral molecules to design non-centrosymmetric crystals for second-order nonlinear optical properties is well-known: Nicoud, J. F.; Twieg, R. J. In *Nonlinear Optical Properties of Organic Molecules and Crystals*; Chemla, D. S., Zyss, J., Eds.; Academic Press: Orlando, FL, 1987; Vol. 2, p 248.

(43) For a theoretical treatment of layers see: Scaringe, R. P. In *Electron Crystallography of Organic Molecules*; Fryer, J. R., Dorset, D. L., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1991.

(44) For a recent review, see: Rose, P. L.; Harvey, N. G.; Arnett, E. M. In *Advances in Physical Organic Chemistry*; Academic Press: San Diego, 1993; p 45.

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as molecular sheets.[46] In one dimension, Fuhrhop[47] has reported that chirality plays a role for the assembly of molecular rod structures. The origins of chiral discrimination have been discussed by Andelman and de Gennes.[46]

Summary

A design strategy for two-dimensional layered molecular crystals has been formulated. This strategy is based upon the application of complementary hydrogen bonding and the concept that, in a crystal, intermolecular bonds must correspond to specific crystallographic symmetry operators. The specific goal of forming two-dimensional β-networks was explored by preparing a series of disubstituted acid and/or amide derivatives of ureas. In the designed structures, the formation of one-dimensional α-networks based upon urea hydrogen bonds, with the α-networks linked in turn by hydrogen bonds between acid and/or amide functionalities to form two-dimensional β-networks, was anticipated. Our experiments showed that the β-networks formed as predicted whenever symmetrical disubstituted ureas with C_2 point group symmetry were studied. When less symmetrical disubstituted ureas were used, alternate and unpredicted network structures were found in several cases. This was a particular problem with racemates. However, when a single enantiomer of an unsymmetrical chiral urea was studied, the anticipated β-network was again observed, suggesting the importance of using chiral molecules for the design and preparation of layered solid-state structures.

Experimental Section

General Methods. Proton NMR spectra were recorded on a Nicolet QE-300 spectrometer, and TMS was used as internal reference. The NMR spectra of all urea carboxylic acid and amide derivatives were recorded on samples dissolved in a mixture of DMSO-d_6 and $CDCl_3$. Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR as KBr solid pellets without internal reference. Melting points were recorded on a Fisher-Johns melting point apparatus. Diimidazole, triphosgene, and the amino acids were purchased from Aldrich Chemical Company and were used without further purification.

***N,N*-Bis(3-carbamoylpropyl)urea (4).** Using the ammonolysis procedure *general method A* (described for the preparation of **5**) and *N,N'*-bis(((methyloxy)carbonyl)propyl)urea[6] afforded 1.0 g (70%) of compound **4** as colorless plates: mp 196–198 °C; ^{1}H NMR (DMSO/$CDCl_3$, 5/1) δ 1.65 (t, J = 7 Hz, 2H), 2.10 (t, J = 7.2 Hz, 2H), 3.04 (m, 2H), 5.78 (t, J = 1.2 Hz, 1H), 6.57 (b, 1H), 7.25 (b, 1H); IR (KBr) 3377, 3342, 3189, 1660, 1613, 1572, 660 cm^{-1}. Samples suitable for crystallographic analysis were obtained by recrystallization from H_2O.

***N,N'*-Bis(carbamoylmethyl)urea (5).** To 3.03 g of ethyl glycinate in 2 mL of water was slowly added 4 mL of triphosgene (trichloromethyl carbonate, 0.75 g) solution in toluene. A total of 0.42 g of Na_2CO_3 was added to the solution mixture to maintain the pH above 10 while adding triphosgene. The solution was allowed to stir in the ice bath for 30 min, and the bis((ethoxycarbonyl)methyl)urea precipitated. The precipitate was removed by filtation, washed with a small amount of ice water, and purified by recrystallization (H_2O/C_2H_5OH) to give 1.5 g (26%) of the diester: mp 138–140 °C (lit. 146 °C).[47]

The ammonolysis of the above ester was adapted from the literature[48] using a procedure referred to as *general method A*: *N,N'*-Bis((ethoxycarbonyl)methyl)urea (1.0 g) was dissolved in 30 mL of anhydrous methanol. A stream of NH_3 gas was introduced while the reaction mixture was cooled in an ice/water bath. After 1.5 h, introduction of the ammonia was discontinued and the flask was closed with a rubber stopper. The reaction mixture was allowed to warm up to room temperature and stand for 3 days. The solvent was removed *in vacuo* to give urea **5** as colorless plates (0.61 g (82%)): mp 228–230 °C dec (lit.[49] 228–229 °C dec); ^{1}H NMR 300 MHz (DMSO) δ 3.62 (d, J = 5.4 Hz, 2H), 6.38 (d, J = 5.4 Hz, 2H), 6.94 (s, 1H), 7.24 (s, 1H); IR (KBr) 3377, 3345, 3190, 1660, 1654, 1625, 1570, 650 cm^{-1}. A sample suitable for crystallographic analysis was obtained by recrystallization from H_2O/MeOH.

***N*-(Carboxymethyl)-*N'*-(carbamoylmethyl)urea (6).** *N,N'*-Bis((ethoxycarbonyl)methyl)urea was prepared using a procedure subsequently referred to as *general method B*: To a solution of 3.00 g (40 mmol) of glycine in 13 mL of 3 N NaOH (40 mmol) was added 5.16 g (40 mmol) of ethyl isocyanatoacetate cooled in an ice/water bath. The mixture was allowed to warm to room temperature and stir until TLC (methylene chloride/methanol/ethyl acetate (2:1:1)) indicated the amino acid had been consumed. The reaction mixture was carefully acidified with 6 N HCl to pH 2. The *N,N'*-bis((ethoxycarbonyl)methyl)urea precipitated and was removed by filtration, washed with iced water, and recrystallized from ethanol to give 4.5 g (55%) of pure product that was used directly in the next step. The ammonolysis was performed using *general method A*, described above for the preparation of **5**, with the following modification. Once the reaction was completed, the solvent was removed *in vacuo* and the dry residue was treated with 6 N HCl to pH 2 to give 3.6 g (80%) of compound **6** as colorless needles: mp 209–214 °C (lit. 209–210 °C);[52] ^{1}H NMR 300 MHz (DMSO/$CDCl_3$, 5/1) δ 3.65 (d, J = 4 Hz, 2H), 3.75 (d, J = 4 Hz, 2H), 6.41 (b, 2H), 6.91 (s, 1H), 7.16 (s, 1H); IR (KBr) 3389, 3342, 3160, 1719, 1660, 1625, 1584, 910, 660 cm^{-1}. Samples suitable for crystallographic analysis were obtained by recrystallization from ethanol.

***N*-(3-Carboxypropyl)-*N'*-(3-carbamoylpropyl)urea (7).** To a solution of 10.86 g of methyl 4-aminobutyrate hydrochloride and 10.1 g of triethylamine in anhydrous dioxane (40 mL) at room temperature under nitrogen was added 14.27 g of trimethylsilyl 3-isocyanatopropanate.[53] The reaction mixture was refluxed for 8 h. The triethylamine hydrochloride was removed by filtration and the solvent removed *in vacuo*. The residue was dissolved in $CHCl_3$ and extracted with H_2O (3 × 50 mL). The aqueous extracts were concentrated *in vacuo* and chilled in an ice bath until a colorless precipitate formed. The product was collected by filtration and recrystallized from H_2O/ethanol to give 8.0 g of *N*-(3-carboxypropyl)-*N'*-((3-methoxycarbonyl)propyl)urea, mp 95–98 °C. This ester, without further purification, was converted to the amide using *general method A* (with the modification described above for the preparation of **6**) to give the monoamide **7** as colorless long needles: mp 136–138 °C; ^{1}H NMR (DMSO/$CDCl_3$, 9/1) δ 1.6 (t, J = 6.3 Hz, 4H), 2.03 (m, 4H), 2.16 (m, 4H), 6.02 (b, 2H), 6.71 (b, 1H), 7.36 (b, 1H); IR (KBr) 3412, 3318, 3210, 1701, 1649, 1613, 1578, 908, 660 cm^{-1}. A crystal suitable for crystallographic analysis was obtained by recrystallization from H_2O/C_2H_5OH.

***N*-(Carboxymethyl)-*N'*-(2-carbamoylethyl)urea (8).** To a solution of 0.91 g of 3-aminopropionamide in 18 mL of isopropanol was slowly added 1.33 g of ethyl isocyanatoacetate at room temperature. After the reaction mixture stirred for 20 min, the solvent was removed *in vacuo*. The residue was recrystallized from ethanol to afford 2.1 g of *N*-((methoxycarbonyl)methyl)-*N'*-(2-carbamoylethyl)urea, mp 110–113 °C. Without further purification, hydrolysis of this monoester was accomplished using the following procedure. To a solution of 0.460 g of NaOH and 5 mL of methanol in 30 mL of H_2O was added 2.5 g of *N*-((ethoxycarbonyl)methyl)-*N'*-(2-carbamoylethyl)urea. The reaction mixture was heated to reflux for 5 h. Removal of the solvent *in vacuo* produced a residue that was redissolved in a minimum amount of H_2O and neutralized by passing it through an acidic cation-exchange column (Rexyn 101) to afford 1.29 g of *N*-(carboxymethyl)-*N'*-(2-carbamoylethyl)urea as colorless thin plates: mp 174–175 °C; ^{1}H NMR (DMSO/$CDCl_3$, 10/1) δ 2.18 (t, J = 6.6 Hz, 2H), 3.15 (q, J = 6.3 Hz, 2H), 3.65 (d, J = 6 Hz, 2H), 6.11 (t, J = 6 Hz, 1H), 6.20 (t, J = 6 Hz, 1H), 6.8 (b, 1H), 7.3 (b, 1H); IR (KBr) 3395, 3336, 3210, 1719, 1650, 1635, 1576, 640 cm^{-1}. A sample suitable for crystallographic analysis was obtained by recrystallization from H_2O.

***N*-(Carbamoylmethyl)-*N'*-(2-carboxyethyl)urea (9).** This compound was prepared from ethyl isocyanatoacetate and β-alanine using *general method B* followed by *general method A* (described above for monoamide **6**) to give monoamide **9** as colorless plates: mp 187–188 °C; ^{1}H NMR (DMSO/$CDCl_3$) δ 2.47 (t, J = 6 Hz, 2H), 3.43 (m, 2H), 3.79 (d, J = 3 Hz, 2H), 6.14 (b, 2H), 6.22 (b, 1H), 6.82 (b, 1H). Crystals suitable for crystallographic analysis were obtained by recrystallization from H_2O.

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Table III. Crystal Data

compound	4	5	6	7	8	9	10	11	12	13	14
a (Å)	23.908(8)	19.297(4)	9.031(4)	9.326(3)	12.159(5)	5.218(3)	4.719(1)	32.334(5)	9.338(4)	23.228(9)	29.010(8)
b (Å)	4.704(3)	4.616(1)	4.612(2)	4.625(2)	4.951(4)	8.194(4)	8.075(2)	9.597(2)	7.618(3)	5.202(3)	5.104(2)
c (Å)	9.958(2)	8.705(3)	18.240(7)	26.312(8)	13.79(1)	20.323(8)	21.193(2)	8.400(2)	37.360(12)	21.460(8)	8.730(4)
α (deg)						95.48(2)					
β (deg)	90.30(3)	91.35(3)	90.38(3)	97.87(3)	95.89(3)	92.28(2)		103.18(3)		101.72(4)	94.39(2)
γ (deg)						96.32(3)					
space group	$C2/c$	$C2/c$	$C2/c$	$C2/c$	$P2_1/c$	$P\bar{1}$	$P2_12_12_1$	$C2/c$	$Pca2_1$	$C2/c$	$C2$
Z	4	4	4	4	4	4	4	8	8	8	4
max 2θ (deg) – radiation	50.0 – Mo	60.0 – Mo	60.0 – Mo	50.0 – Mo	50.0 – Mo	50.0 – Mo	100.0 – Cu	50.0 – Mo	100.0 – Cu	100.0 – Cu	150.0 – Cu
observations ($I > 3\sigma$)	775	939	573	659	941	1325	512	623	1025	1117	1182
variables	78	56	56	74	162	235	118	172	342	172	171
R	0.054	0.051	0.048	0.089	0.037	0.048	0.086	0.057	0.061	0.038	0.081
R_w	0.073	0.072	0.064	0.114	0.043	0.057	0.092	0.066	0.070	0.050	0.103

***N*-(Carboxymethyl)-*N'*-(2-carboxyethyl)urea (10).** *N*-((Ethoxycarbonyl)methyl)-*N'*-(2-carboxyethyl)urea was prepared from ethyl isocyanatoacetate and β-alanine using *general method B*. Hydrolysis was accomplished using a procedure subsequently referred to as *general method C*: To a solution 0.545 g of NaOH in 5 mL of methanol and 30 mL of water was added 3.0 g (0.014 mol) of the ester. The reaction mixture was refluxed for 18 h. The solution was concentrated to about half of its original volume, cooled to 5 °C, and acidified with 6 N HCl to pH 2. The precipitate was filtered, recrystallized from ethanol, and dried to give 1.5 g of the diacid **10** as colorless long needles: mp 173–175 °C; ^{1}H NMR (DMSO/$CDCl_3$, 5/1) δ 2.39 (t, J = 8 Hz, 2H), 3.47 (m, 2H), 3.84 (d, J = 6 Hz, 2H), 6.22 (b, 2H); IR (KBr) 3408, 3311, 1728, 1716, 1650, 1568, 610 cm^{-1}. Samples suitable for crystallographic analysis were obtained by recrystallization from H_2O with a few drops of 6 N HCl.

(*R,S*)-*N*-(Carboxymethyl)-*N'*-((carboxybenzyl)methyl)urea (11). This compound was prepared from DL-phenylalanine and ethyl isocyanatoacetate according to *general method B*, described above for the preparation of **6**. The monoester was filtered, washed with iced water, and recrystallized from ethanol to give colorless needles: mp 196–198 °C; ^{1}H NMR ($CDCl_3$) 1.23 (t, J = 8 Hz), 3.00 (m, 3H), 3.80 (d, J = 6 Hz, 1H), 4.10 (q, J = 8 Hz, 2H), 4.41 (dd, 1H), 6.38 (d, J = 6 Hz, 1H), 6.56 (t, J = 6 Hz, 1H), 7.21 (m, 5H); IR (KBr) 3389, 3330.6, 1746.4, 1726, 1630.4, 1558.5 cm^{-1}. Without further purification, the above ester (0.28 g, 0.9 mmol) was dissolved in 2 mL of 3 N NaOH and the solution was refluxed for 3 h. The reaction mixture was acidified with 6 N HCl to pH 2 while it was cooled in an ice/water bath. The product was removed by filtration, washed with a small amount of iced water, and recrystallized from ethanol to give **11** as colorless needles: mp 182–184 °C; ^{1}H NMR ($CDCl_3$/DMSO, 5/1) 2.99–3.10 (dd, J_1 = 6 Hz, J_2 = 6 Hz, 2H), 3.87 (t, J = 5 Hz, 2H), 4.62 (td, J_1 = 6 Hz, J_2 = 8 Hz, 1H), 6.30 (d, J = 8 Hz, 1H), 6.41 (t, J = 5 Hz, 1H), 7.26 (m, 5H); IR (KBr) 3403, 3388, 1739, 1704, 1578 cm^{-1}. A sample suitable for crystallographic analysis was obtained by recrystallization from ethanol.

(*R,S*)-*N*-(Carboxymethyl)-*N'*-((carbamoylbenzyl)methyl)urea (12). To a solution of 7.23 g (0.044 mol) of (*R,S*)-2-amino-3-phenylpropionamide in 100 mL of 2-propanol was added 5.69 g (0.044 mol) of ethyl isocyanatoacetate at room temperature. The reaction mixture was noticably exothermic and became cloudy. The reaction mixture was stirred at room temperature for 30 min. Concentration of the solvent *in vacuo*, filtration, and recrystallization from H_2O/ethanol gave 7.0 g (80%) of the ester as colorless crystals, mp 189 °C. The above ester (2.5 g) was hydrolyzed using *general method C* to give 2.2 g of the monoamide **12** as colorless thin plates: mp 182–185 °C; ^{1}H NMR ($CDCl_3$/DMSO, 2/1) δ 3.01–3.145 (dd, J_1 = 6 Hz, J_2 = 8 Hz, 2H), 3.86 (d, J = 5 Hz, 2H), 4.62 (q, J = 6 Hz, 1H), 6.30 (d, J = 8 Hz, 1H), 6.39 (t, J = 5 Hz, 1H); IR (KBr) 3420, 3366, 1740, 1701, 1660, 1556 cm^{-1}. A sample suitable for X-ray analysis was obtained by recrystallization from ethanol.

(*R,S*)-*N*-(Carbamoylmethyl)-*N'*-((carboxybenzyl)methyl)urea (13). Using *general method A*, ammonolysis of the above ethyl ester (for the preparation of **11**) afforded compound **13** as colorless needles (50%): mp 169–170 °C; ^{1}H NMR (DMSO) δ 2.82–3.31 (dd, J_1 = 8 Hz, J_2 = 5 Hz, 2H), 3.34 (b, 1H), 3.52 (d, J = 5 Hz, 2H), 4.32 (q, J = 5 Hz, 1H), 6.28 (t, J = 5 Hz, 1H), 6.43 (d, J = 8 Hz, 1H), 6.99 (b, 1H), 7.25 (m, 5H); IR (KBr) 3445, 3430, 3342, 3254, 1709, 1655, 1557 cm^{-1}. A sample suitable for X-ray analysis was obtained by recrystallization from ethanol.

(*S*)-*N*-(Carbamoylmethyl)-*N'*-((carboxybenzyl)methyl)urea (14). Using *general method B*, (*S*)-*N*-(ethoxycarbonyl)-*N'*-((carboxybenzyl)-methyl)urea was prepared from L-phenylalanine and ethyl isocyanatoacetate. The ammonolysis was performed according to *general method A*, giving the chiral mono amide **14** (50%) as colorless needles: mp 183–185 °C; ^{1}H NMR (DMSO/$CDCl_3$, 2/1) δ 2.86–3.08 (dd, J_1 = 5 Hz, J_2 = 7 Hz, 2H), 3.61 (t, J = 6 Hz, 2H), 4.43 (q, J = 5 Hz, 1H), 6.39 (d, J = 6 Hz, 2H), 6.87 (b, 1H), 7.08 (b, 1H), 7.25 (m, 5H); IR (KBr) 3449, 3366, 3312, 3261, 1710, 1660, 1644, 1548 cm^{-1}. A sample suitable for X-ray analysis was obtained by recrystallization from H_2O.

X-ray Diffraction Studies. Crystals of the eleven compounds **4–14**, obtained as described above, were selected and mounted on glass fibers using epoxy cement. The crystals were optically centered on an Enraf Nonius CAD4 diffractometer, and X-ray data were collected using graphite-monochromated Cu or Mo radiation. The unit cells were determined by a least squares analysis of the setting angles of 25 high-angle reflections. Data were collected as indicated in the tables, and the structures were solved and refined using the TEXAN crystallographic program package of the Molecular Structure Corporation. All non-hydrogen atoms were refined with aniosotropic temperature factors with hydrogen atoms added with fixed isotropic contributions in calculated positions, except for structures **8** and **13**, for which the hydrogen atoms were refined. Figures were drawn using the program CHARON.[54] The data obtained for some of the compounds were less than ideal due to crystal imperfections. The forces within the crystals, by design, were anisotropic. This anisotropy at a molecular level leads to macroscopic crystals with anisotropic properties. Most of the crystals grew preferentially along the axis corresponding to the urea hydrogen bonds forming small flat needles, often exhibiting numerous cracks. This made selection of a quality crystal difficult. Compounds **7**, **9**, **10**, **12**, and **14** had the most problems. The final least squares refinements for these three compounds gave higher than desired agreement factors, and some of the anisotropic thermal parameters were abnormal. The data and refinements for the remaining compounds were normal. Compounds **6** and **7** were refined in the space group $C2/c$. With four molecules in the cell, this requires the molecules to be disordered about the crystallographic two-fold axis. Dropping the symmetry to Cc gave an ordered structure and an equally good refinement, but with high correlation coefficients and bond distances that deviated from expected values. Thus, the disordered $C2/c$ structures were considered the better models. Table III gives crystal data for the eleven compounds. Full crystallographic details and tables of coordinates, temperature factors, and bond distances and angles are given in the supplementary material.

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Supplementary Material Available: Tables of crystal data, isotropic and anisotropic temperature factors, and bond distances and angles (48 pages). Ordering information is given on any current masthead page.

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Use of Hydrogen Bonds To Control Molecular Aggregation. Behavior of Dipyridones and Pyridone–Pyrimidones Designed To Form Cyclic Triplexes

Éric Boucher,[1] Michel Simard, and James D. Wuest*,[2]

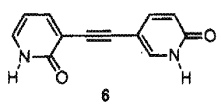
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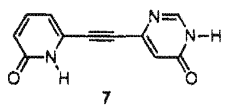
The tendency of 2-pyridones and related heterocycles to form cyclic hydrogen-bonded dimers allows them to be used as sticky sites that induce molecules in which they are incorporated to associate in particular ways. Compound **7**, which is constructed from pyridone and pyrimidone subunits linked to a rigid linear acetylenic spacer, incorporates an array of hydrogen-bonding sites designed to favor the formation of a cyclic triplex. Pyridone–pyrimidone **7** was synthesized and the structure of its DMSO solvate was determined by X-ray crystallography. Aggregation does not produce a cyclic triplex but rather gives chains in which adjacent molecules of compound **7** are linked by single hydrogen bonds.

The tendency of 2-pyridones and related heterocycles to form cyclic hydrogen-bonded dimers allows them to be used as sticky sites that induce molecules in which they are incorporated to associate in particular ways.[3] For example, linking two pyridones to linear spacers at the 3 and 6′ positions creates self-complementary molecules **1** that are able to form strong antiparallel duplexes **2** joined by four hydrogen bonds (Scheme 1, eq 1).[3g] In contrast, isomeric 6,6′-linked dipyridone **3** and the analogous 3,3′-linked structure are not fully self-complementary and must therefore form linear oligomers (Scheme 1, eq 2). These simple examples show that the systematic attachment of sticky heterocyclic subunits to well-chosen frameworks can be a powerful strategy for constructing molecules predisposed to associate in particular ways.[3] A notable advantage of this strategy is that it provides access to markedly different patterns of aggregation by the simple expedient of reorienting the sticky heterocyclic subunits, rather than by the more complex process of synthesizing entirely new types of associating molecules.

In principle, dipyridones **4** created by linking pyridones to rigid linear spacers at the 3 and 5′ positions contain arrays of hydrogen-bonding sites that are perfectly self-complementary in cyclic triplexes **5** (Scheme 1, eq 3).[3f,4] The rigidity of dipyridone **4** allows us to estimate that $\Delta H°$ for the trimerization of eq 3 will be approximately −17.7 kcal/mol in $CHCl_3$, three times $\Delta H°$ for the dimerization of 2-pyridone,[5,6] and that $\Delta S°$ will be approximately −21.4 eu, twice $\Delta S°$ for the dimerization of 2-pyridone.[5,8] As a result, $\Delta G°$ for the trimerization of eq 3 should be about −11 kcal/mol in $CHCl_3$ at 25 °C, making triplex **5** a potentially important species even in relatively dilute solutions. In this paper, we describe the synthesis and chemical behavior of two compounds, acetylenic dipyridone **6** and the closely related pyridone–pyrimidone **7**, that have been designed to form cyclic triplexes of this type.

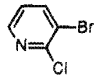


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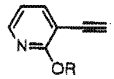


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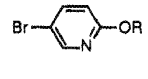
Acetylenic dipyridone **6** was prepared in the following way. An improved procedure was devised for converting 2-chloro-3-pyridinamine into 3-bromo-2-chloropyridine (**8**),[9] which was then used to make 3-ethynyl-2-(phenylmethoxy)pyridine (**9**) by the published method.[3g] In addition, the known 5-bromo-2-(phenylmethoxy)pyridine (**10**)[10] was prepared from 2,5-dibromopyridine by an improved method. Deprotonation of ethynylpyridine **9**



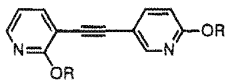
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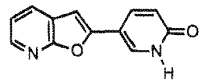
9 (R = CH_2Ph)



10 (R = CH_2Ph)



11 (R = CH_2Ph)



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(2) Killam Research Fellow, 1992–1994.

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(6) Separation of the pyridone subunits by a rigid linear spacer ensures that each subunit will make an approximately additive contribution to the overall enthalpy of association. Secondary electrostatic interactions in the aggregate will be similar to those in the dimer of 2-pyridone itself.[7]

(7) Pranata, J.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991,** *113,* 2810.

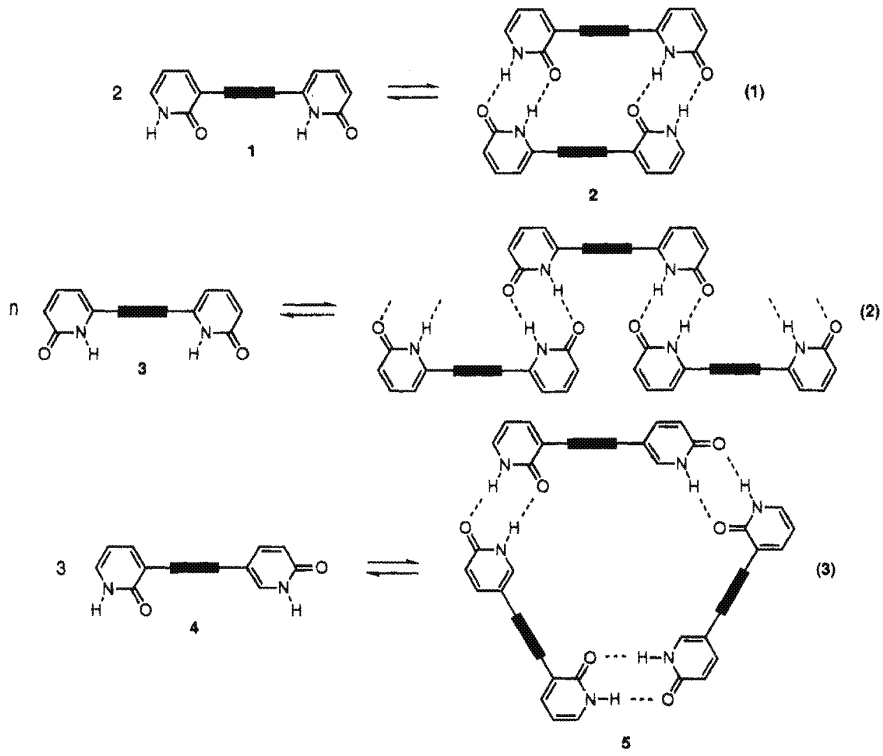
(8) (a) This is a very crude approximation that neglects the loss of entropy of rotation around the spacer as well as other factors. (b) For a discussion of $\Delta S°$ in the formation of hydrogen-bonded dimers, see: Doig, A. J.; Williams, D. H. *J. Am. Chem. Soc.* **1992,** *114,* 338. Williams, D. H. *Aldrichim. Acta* **1992,** *25,* 9.

(9) Den Hertog, H. J.; Boelrijk, N. A. I. M. *Recl. Trav. Chim. Pays-Bas* **1951,** *70,* 578.

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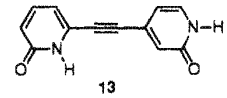
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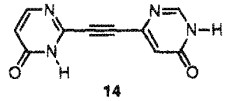
Scheme 1

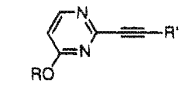


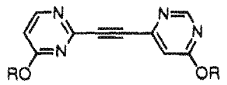
(BuLi), followed by the addition of $ZnCl_2$, bromopyridine **10**, and a catalytic amount of $Pd(PPh_3)_4$, then provided the coupled product **11** in 74% yield.[11] Careful deprotection (CF_3COOH, 25 °C)[12] then gave the the corresponding 3,5′-dipyridone **6** in quantitative yield. Although compound **6** could be isolated and partially characterized, it proved to be unstable in solution and was transformed rapidly into furopyridine **12** by intramolecular addition to the triple bond.[3d,13] As a result, we were unable to crystallize dipyridone **6**, purify it, or study its aggregation in solution or in the solid state.

A similar cyclization cannot occur in isomeric dipyridone **13**. Unfortunately, however, its synthesis would require coupling an acetylene with suitable 4-substituted derivatives of 2-pyridone, which are not readily available.

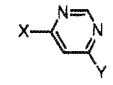

13

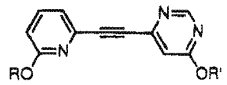

14


15 (R = CH_3, R′ = $Si(CH_3)_3$)
16 (R = CH_3, R′ = H)


17 (R = CH_3)

We expected the related dipyrimidone **14** and the pyridone-pyrimidone **7** to be more accessible, and we were able to synthesize protected derivatives by the following procedures. Coupling of (trimethylsilyl)acetylene with 2-chloro-4-methoxypyrimidine,[14] carried out in $N(C_2H_5)_3$ containing catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI,[15] gave an 89% yield of compound **15**, which was converted by treatment with tetrabutylammonium fluoride into ethynylpyrimidine **16** in 70% yield. Compound **16** was then converted into the protected derivative **17** of dipyrimidone **14** in 69% yield by a similar coupling with 4-iodo-6-methoxypyrimidine (**18**), which was prepared in


18 (X = OCH_3, Y = I)
19 (X = Y = I)


20 (R = CH_2Ph, R′ = CH_3)

69% overall yield by using aqueous HI to convert 4,6-dichloropyrimidine into 4,6-diiodopyrimidine (**19**),[16] followed by the addition of an equimolar amount of sodium methoxide. Unfortunately, all attempts to deprotect compound **17** led only to products of degradation, and the desired dipyrimidone **14** could not be isolated. Standard coupling[15] of 2-ethynyl-6-(phenylmethoxy)-pyridine[3g] with 4-iodo-6-methoxypyrimidine (**18**) provided an 80% yield of pyridopyrimidine **20**, which could be

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(13) For similar observations, see: Sakamoto, T.; Kondo, Y.; Watanabe, R.; Yamanaka, H. *Chem. Pharm. Bull.* **1986**, *34*, 2719. Castro, C. E.; Gaughan, E. J.; Owsley, D. C. *J. Org. Chem.* **1966**, *31*, 4071.
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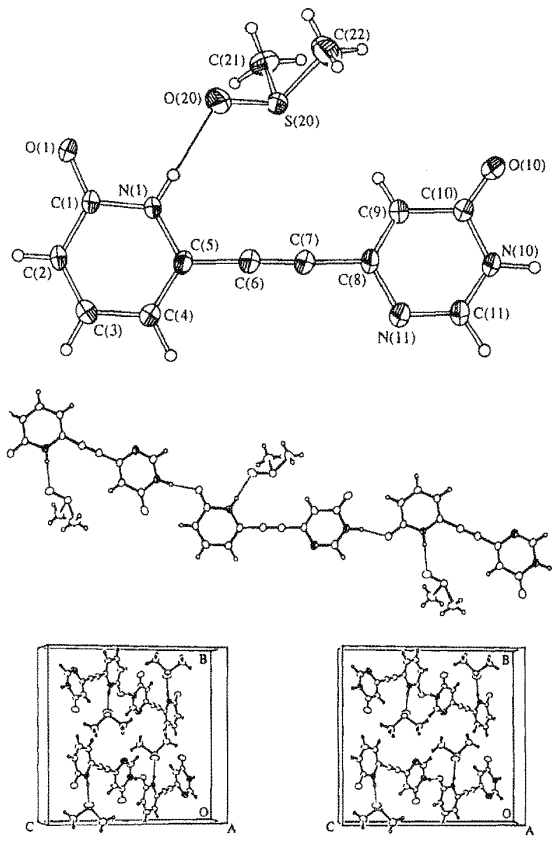


Figure 1. ORTEP drawings of the structure of the 1:1 solvate of pyridone–pyrimidone **7** with DMSO. The upper figure shows the atomic numbering, the middle figure shows the hydrogen-bonded chains present in the structure, and the lower figure provides a stereoview of the unit cell along the *a* axis. Hydrogen atoms appear as spheres of arbitrary size, while other atoms are represented by ellipsoids corresponding to 40% probability. Atoms of nitrogen are distinguished by shading, and hydrogen bonds are indicated by narrow lines. Important bond lengths include O(1)–C(1) = 1.246(2), O(10)–C(10) = 1.223(2), C(2)–C(3) = 1.341(3), C(3)–C(4) = 1.406(3), C(4)–C(5) = 1.356(3), N(10)–C(11) = 1.344(3), N(11)–C(11) = 1.298-(2), C(5)–C(6) = 1.433(2), C(6)–C(7) = 1.192(3), and C(7)–C(8) = 1.445(2) Å.

converted into the desired pyridone–pyrimidone **7** in 82% yield by a two-step deprotection using KOH in dioxane followed by CF_3COOH.

The solubility of pyridone–pyrimidone **7** proved to be too low to allow study of its aggregation in solution, so we examined its association in the solid state. The preparation of crystals suitable for X-ray diffraction was difficult but could finally be achieved by adding benzene to a solution of compound **7** in DMSO. The structure was solved and is shown in Figure 1, along with selected bond lengths. The short O(1)–C(1) and O(10)–C(10) distances, the observed alternation in the C(2)–C(3), C(3)–C(4), and C(4)–C(5) distances, and the short N(11)–C(11) distance indicate that the pyridone–pyrimidone adopts tautomeric structure **7** in the solid state rather than one of the five alternatives. Moreover, the pyridone and pyrimidone rings are approximately coplanar, and rotation around the acetylenic spacer has yielded the particular conformer required for formation of a cyclic triplex. Nevertheless, the expected association does not occur. Instead, the pyridone subunit of each molecule of compound **7** donates a hydrogen bond to the oxygen atom of DMSO and accepts a hydrogen bond from the pyrimidone subunit in a second molecule, creating chains in which adjacent molecules of compound **7** are linked by single hydrogen bonds (Figure 1). The origins of the failure of compound **7** to produce a cyclic triplex under these conditions are undoubtedly complex; however, it is tempting to attribute the failure to the presence of DMSO, which is presumably a stronger acceptor of hydrogen bonds than the oxygen atom of pyrimidone.

Experimental Section

$N(C_2H_5)_3$ was dried by distillation from CaH_2, and tetrahydrofuran (THF) was dried by distillation from the sodium ketyl of benzophenone. $Pd(PPh_3)_4$[17] and $PdCl_2(PPh_3)_2$[18] were prepared by known methods, $ZnCl_2$ was dried in an oven before use, and CuI was purified by a standard procedure.[19] Other commercial reagents were used without further purification. Flash chromatography was performed in the normal way.[20]

3-Bromo-2-chloropyridine (8).[9] A solution prepared by dissolving 2-chloro-3-pyridinamine (12.3 g, 95.7 mmol) in 48% aqueous HBr (30 mL) was stirred at 0 °C and treated with a cold solution of $NaNO_2$ (7.08 g, 103 mmol) in water (20 mL), added at a rate that kept the temperature of the mixture from exceeding 10 °C. CuBr (7.08 g, 49.4 mmol) was then added, the mixture was heated at reflux, and the organic product was removed by steam distillation. The distillate was extracted with CH_2Cl_2, and volatiles were removed by evaporation under reduced pressure. This left a white solid residue of 3-bromo-2-chloropyridine (**8**; 16.7 g, 86.8 mmol, 91%),[9] which could be used for the preparation of 3-ethynyl-2-(phenylmethoxy)-pyridine (**9**) without further purification.

5-Bromo-2-(phenylmethoxy)pyridine (10).[10] A mixture of 2,5-dibromopyridine (1.00 g, 4.22 mmol), dibenzo-18-crown-6 (0.0814 g, 0.226 mmol), benzyl alcohol (0.598 g, 5.53 mmol), and KOH (0.571 g, 10.2 mmol) in toluene (15 mL) was heated at reflux for 3 h in an apparatus fitted with a Dean-Stark trap. Toluene was then removed by evaporation under reduced pressure, water was added to the residue, and the resulting mixture was extracted with $CHCl_3$. Volatiles were removed from the organic extracts by evaporation under reduced pressure. Kugelrohr distillation of the residue then provided 5-bromo-2-(phenylmethoxy)pyridine (**10**; 1.10 g, 4.16 mmol, 99%)[10] as a colorless liquid: bp 110–120 °C/0.15 Torr (lit.[10] bp 178–185 °C/14 Torr); ^1H NMR (300 MHz, $CDCl_3$) δ 5.34 (s, 2H), 6.73 (d, ^3J = 8.8 Hz, 1H), 7.30–7.50 (m, 5H), 7.66 (dd, ^3J = 8.8 Hz, ^4J = 2.6 Hz, 1H), 8.21 (d, ^4J = 2.6 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 67.8, 111.7, 112.7, 127.8, 127.8, 128.3, 136.7, 141.0, 147.2, 162.2; MS (FAB) *m/e* 264; HRMS (EI) calcd for $C_{12}H_{10}$ $^{79}BrNO$ 262.9946, found 262.9952.

2-(Phenylmethoxy)-3-[2-[2-(phenylmethoxy)-5-pyridinyl]ethynyl]pyridine (11). A solution of 3-ethynyl-2-(phenylmethoxy)pyridine (**9**; 205 mg, 0.980 mmol)[9g] in THF (1 mL) was stirred at 0 °C under dry N_2 and treated dropwise with a solution of BuLi (0.70 mL, 1.48 M in hexane, 1.0 mmol). The resulting deep red solution was kept at 0 °C for 30 min, and then a solution of $ZnCl_2$ (157 mg, 1.15 mmol) in THF (1 mL) was added. The mixture was kept at 25 °C for 90 min and was then transferred to a stirred solution of 5-bromo-2-(phenylmethoxy)pyridine (**10**; 278 mg, 1.05 mmol) and $Pd(PPh_3)_4$ (19.9 mg, 0.0172 mmol) in THF (6 mL). The mixture was heated at reflux for 12 h, volatiles were removed by evaporation under reduced pressure, the residue was partitioned between water and $CHCl_3$, and solvent was removed from the organic phase by evaporation under reduced pressure.

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Crystallization of the residue from ethanol provided analytically pure 2-(phenylmethoxy)-3-[2-[2-(phenylmethoxy)-5-pyridinyl]ethynyl]pyridine (**11**; 281 mg, 0.716 mmol, 73%) as a beige solid: mp 108.5–109.5 °C; IR (KBr) 2210 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.41 (s, 2H) 5.51 (s, 2H), 6.79 (d, ^3J = 8.6 Hz, 1H), 6.91 (dd, ^3J = 7.4 Hz, ^3J = 5.1 Hz, 1H), 7.31–7.55 (m, 10H), 7.69 (dd, ^3J = 8.6 Hz, ^4J = 2.4 Hz, 1H), 7.76 (dd, ^3J = 7.4 Hz, ^4J = 1.9 Hz, 1H), 8.13 (dd, ^3J = 5.1 Hz, ^4J = 1.9 Hz, 1H), 8.36 (d, ^4J = 2.4 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 67.7, 67.9, 85.6, 91.7, 107.6, 111.0, 113.3, 116.6, 127.2, 127.6, 127.9, 128.0, 128.3, 128.4, 131.6, 136.9, 137.3, 141.2, 146.2, 150.0, 162.9, 163.0; MS (FAB) *m/e* 393, 301; HRMS (FAB) calcd for $C_{26}H_{20}N_2O_2$ + H 393.1603, found 393.1615. Anal. Calcd for $C_{26}H_{20}N_2O_2$: C, 79.57; H, 5.14. Found: C, 79.37; H, 5.36.

2-(1,2-Dihydro-2-oxo-5-pyridinyl)furo[2,3-*b*]pyridine (12). A suspension of 2-(phenylmethoxy)-3-[2-[2-(phenylmethoxy)-5-pyridinyl]ethynyl]pyridine (**11**; 605 mg, 1.54 mmol) in CF_3COOH (6 mL) was heated at reflux for 2 h. Volatiles were then removed by evaporation under reduced pressure, toluene was added, and volatiles were again removed by evaporation under reduced pressure. The residual solid was triturated with $N(C_2H_5)_3$ (1 mL) and acetone (3 mL), the supernatant liquid was decanted after centrifugation, and the solid was washed with additional acetone and dried. Recrystallization from 1-butanol provided analytically pure 2-(1,2-dihydro-2-oxo-5-pyridinyl)furo[2,3-*b*]pyridine (**12**; 182 mg, 0.858 mmol, 56%) as fine yellow needles: mp 260–262 °C; IR (KBr) 3200–2300, 1666, 1632 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 6.49 (d, ^3J = 10.4 Hz, 1H), 7.17 (s, 1H), 7.28 (dd, ^3J = 7.6 Hz, ^3J = 4.9 Hz, 1H), 7.95 (m, 2H), 8.00 (dd, ^3J = 7.6 Hz, ^4J = 1.7 Hz, 1H), 8.19 (dd, ^3J = 4.9 Hz, ^4J = 1.7 Hz, 1H), 12.03 (s, 1H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 98.9, 108.3, 120.1, 120.7, 121.2, 129.7, 131.3, 137.5, 143.1, 152.4, 161.1, 162.0; MS (EI) *m/e* 212; HRMS (EI) calcd for $C_{12}H_8N_2O_2$ 212.0586, found 212.0594.

3-[2-(1,2-Dihydro-2-oxo-5-pyridinyl)ethynyl]-2(1*H*)-pyridinone (6). A similar procedure in which 2-(phenylmethoxy)-3-[2-[2-(phenylmethoxy)-5-pyridinyl]ethynyl]pyridine (**11**) was stirred in CF_3COOH under milder conditions (25 °C, 2 h) produced 3-[2-(1,2-dihydro-2-oxo-5-pyridinyl)ethynyl]-2(1*H*)-pyridinone (**6**) as an unstable yellow solid: ^1H NMR (300 MHz, DMSO-d_6) δ 6.20 (t, ^3J = 6.7 Hz, 1H), 6.35 (d, ^3J = 9.5 Hz, 1H), 7.43 (m, 1H), 7.46 (m, 1H), 7.67 (m, 2H), 11.9 (bs, 2H).

4-Methoxy-2-[(trimethylsilyl)ethynyl]pyrimidine (15). A mixture of 2-chloro-4-methoxypyrimidine (1.87 g, 12.9 mmol),[14] $PdCl_2(PPh_3)_2$ (0.282 g, 0.402 mmol), CuI (0.129 g, 0.677 mmol), and (trimethylsilyl)ethyne (1.56 g, 15.9 mmol) in $N(C_2H_5)_3$ (10 mL) was degassed and sealed under vacuum in a glass tube. The tube was heated at 100 °C for 12 h, its contents were poured into water, the mixture was extracted with $CHCl_3$, and volatiles were removed from the combined extracts by evaporation under reduced pressure. Kugelrohr distillation of the residue provided analytically pure 4-methoxy-2-[(trimethylsilyl)ethynyl]pyrimidine (**15**; 2.37 g, 11.5 mmol, 89%) as a colorless liquid: bp 120 °C/1 Torr; ^1H NMR (300 MHz, $CDCl_3$) δ 0.30 (s, 9 H), 4.01 (s, 3H), 6.67 (d, ^3J = 5.8 Hz, 1H), 8.38 (d, ^3J = 5.8 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ −0.6, 53.9, 93.0, 102.3, 107.8, 151.5, 156.9, 169.0; MS (EI) *m/e* 206; HRMS (EI) calcd for $C_{10}H_{14}N_2OSi$ 206.0875, found 206.0876.

2-Ethynyl-4-methoxypyrimidine (16). A stirred solution of 4-methoxy-2-[(trimethylsilyl)ethynyl]pyrimidine (**15**; 3.64 g, 17.6 mmol) and CH_3COOH (1.05 g, 17.5 mmol) in THF (25 mL) was treated with a solution of tetrabutylammonium fluoride (17.7 mL, 1.0 M in THF, 17.7 mmol). After 5 min, 10% aqueous K_2CO_3 (50 mL) was added, volatiles were removed by evaporation under reduced pressure, the residue was extracted with $CHCl_3$, and volatiles were removed from the organic extracts by evaporation under reduced pressure. Sublimation (50 °C/0.5 Torr) of the residue provided analytically pure 2-ethynyl-4-methoxypyrimidine (**16**; 1.65 g, 12.3 mmol, 70%) as a white solid: mp 88.0–89.5 °C; IR (melt) 2118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.09 (s, 1H), 4.00 (s, 3H), 6.71 (d, ^3J = 5.8 Hz, 1H), 8.38 (d, ^3J = 5.8 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 54.0, 74.9, 81.8, 108.4, 151.2, 157.0, 169.2; MS (EI) *m/e* 134; HRMS (EI) calcd for $C_7H_6N_2O$ 134.0480, found 134.0480. Anal. Calcd for $C_7H_6N_2O$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.78; H, 4.71; N, 21.20.

4,6-Diiodopyrimidine (19).[16] A solution prepared by dissolving 4,6-dichloropyrimidine (14.9 g, 100 mmol) in 48% aqueous HI (200 mL) was stirred at 25 °C in the dark for 72 h. The precipitated solid was then removed by filtration and added to a mixture of 10% aqueous K_2CO_3 (200 mL) and 10% aqueous $Na_2S_2O_3$ (10 mL). The mixture was extracted with $CHCl_3$, and volatiles were removed from the combined extracts by evaporation under reduced pressure. Crystallization of the residue from hexane provided 4,6-diiodopyrimidine (**19**; 27.0 g, 81.4 mmol, 81%)[16] as a white solid: mp 107–109 °C (lit.[16] mp 107.5–108.5 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, ^5J = 1.0 Hz, 1H), 8.55 (d, ^5J = 1.0 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 128.5, 142.8, 157.7.

4-Iodo-6-methoxypyrimidine (18). At 0 °C under dry N_2, a solution of $NaOCH_3$ (9.3 mL, 4.4 M in CH_3OH, 41 mmol) was added slowly by syringe pump to a stirred solution of 4,6-diiodopyrimidine (**19**; 13.8 g, 41.6 mmol) in CH_3OH (250 mL). The mixture was kept at 25 °C for 2 h, and volatiles were then removed by evaporation under reduced pressure. The residue was treated with $CHCl_3$, the resulting mixture was filtered, and volatiles were removed from the organic phase by evaporation under reduced pressure. Kugelrohr distillation of the residue provided analytically pure 4-iodo-6-methoxypyrimidine (**18**; 8.36 g, 35.4 mmol, 85%) as a white solid: mp 68.0–69.5 0 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 3H), 7.23 (s, 1H), 8.45 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 54.2, 119.1, 127.3, 157.5, 168.6; MS (EI) 236, 109; HRMS (EI) calcd for $C_5H_5IN_2O$ 235.9447, found 235.9443. Anal. Calcd for $C_5H_5IN_2O$: C, 25.45; H, 2.14; N, 11.87. Found: C, 25.36; H, 2.14; N, 11.78.

4-Methoxy-2-[2-(6-methoxy-4-pyrimidinyl)ethynyl]pyrimidine (17). A stirred mixture of 2-ethynyl-4-methoxypyrimidine (**16**; 136 mg, 1.01 mmol), 4-iodo-6-methoxypyrimidine (**18**; 204 mg, 0.864 mmol), $PdCl_2(PPh_3)_2$ (35.0 mg, 0.0499 mmol), and CuI (18.0 mg, 0.0945 mmol) in $N(C_2H_5)_3$ (6 mL) was heated at reflux under N_2 for 12 h. Volatiles were removed by evaporation under reduced pressure, the residue was extracted with $CHCl_3$, and volatiles were removed from the extracts by evaporation under reduced pressure. The residue was purified by flash chromatography (silica, hexane (50%)/ethyl acetate (50%)), and recrystallization from acetone provided analytically pure 4-methoxy-2-[2-(6-methoxy-4-pyrimidinyl)ethynyl]pyrimidine (**17**; 145 mg, 0.599 mmol, 69%) as a white solid: mp 184–186 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 4.02 (s, 6H), 6.74 (d, ^3J = 5.9 Hz, 1H), 7.03 (d, ^5J = 1.1 Hz, 1H), 8.45 (d, ^3J = 5.9 Hz, 1H), 8.80 (d, ^5J = 1.1 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 54.0, 54.1, 82.3, 89.3, 108.5, 111.7, 149.1, 151.2, 157.0, 158.5, 169.1, 169.4; MS (EI) *m/e* 242; HRMS (EI) calcd for $C_{12}H_{10}N_4O_2$ 242.0804, found 242.0805.

4-Methoxy-6-[2-[6-(phenylmethoxy)-2-pyridinyl]ethynyl]pyrimidine (20). A stirred mixture of 2-ethynyl-6-(phenylmethoxy)pyridine (3.90 g, 18.6 mmol),[3g] 4-iodo-6-methoxypyrimidine (**18**; 4.27 g, 18.1 mmol), $PdCl_2(PPh_3)_2$ (0.307 g, 0.437 mmol), and CuI (0.172 g, 0.903 mmol) in $N(C_2H_5)_3$ (200 mL) was heated at reflux under N_2 for 12 h. The crude product was isolated by the procedure described for compound **17** and purified by flash chromatography (silica, hexane (60%)/ethyl acetate (40%)) to give 4-methoxy-6-[2-[6-(phenylmethoxy)-2-pyridinyl]ethynyl]pyrimidine (**20**; 4.59 g, 14.5 mmol, 80%) as a yellow solid. Recrystallization from cyclohexane provided analytically pure yellow needles: mp 109.5–110.5 °C; IR (melt) 2225 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.02 (s, 3H), 5.42 (s, 2H), 6.85 (dd, ^3J = 8.4 Hz, ^4J = 0.8 Hz, 1H), 7.00 (d, ^5J = 1.1 Hz, 1H), 7.25 (dd, ^3J = 7.3 Hz, ^4J = 0.8 Hz, 1H), 7.27–7.42 (m, 3H), 7.47–7.51 (m, 2H), 7.60 (dd, ^3J = 8.4 Hz, ^3J = 7.3 Hz, 1H), 8.79 (d, ^5J = 1.1 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 54.0, 67.9, 85.0, 91.1, 111.2, 112.8, 121.9, 127.9, 128.1, 128.4, 136.9, 138.5, 138.6, 149.9, 158.5, 163.4, 169.6; MS (EI) 317; HRMS (EI) calcd for $C_{19}H_{15}N_3O_2$ 317.1164, found 317.1161. Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76. Found: C, 71.15; H, 4.99.

6-[2-(1,6-Dihydro-6-oxo-2-pyridinyl)ethynyl]-4(3*H*)-pyrimidinone (7). A suspension of 4-methoxy-6-[2-[6-(phenylmethoxy)-2-pyridinyl]ethynyl]pyrimidine (**20**; 3.37 g, 10.6

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mmol) in a mixture of dioxane (25 mL) and 1 N aqueous KOH (35 mL) was heated at reflux for 4 h. When the solid had dissolved, volatiles were partially removed by evaporation under reduced pressure, and the pH of the residual solution was lowered to 7 by the addition of 3 N aqueous HCl. The precipitated solid was separated by centrifugation, washed with water, and dried. It was then heated for 2 h in boiling CF_3COOH (100 mL). Volatiles were removed by evaporation under reduced pressure, water (50 mL) was added, and the pH was raised to 7 by the addition of $N(C_2H_5)_3$. The precipitated solid was separated by centrifugation, washed with water and acetone, dried, and crystallized from 1-butanol. This provided analytically pure 6-[2-(1,6-dihydro-6-oxo-2-pyridinyl)-ethynyl]-4(3*H*)-pyrimidinone (**7**; 1.86 g, 8.72 mmol, 82%) as fine yellow needles: mp 250 °C dec; IR (KBr) 3500–2500, 2220, 1686, 1654 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 6.53 (dd, ^3J = 9.1 Hz, ^4J = 0.8 Hz, 1H), 6.63 (d, ^5J = 1.0 Hz, 1H), 6.73 (dd, ^3J = 6.9 Hz, ^4J = 0.8 Hz, 1H), 7.50 (dd, ^3J = 9.1 Hz, ^3J = 6.9 Hz, 1H), 8.20 (d, ^5J = 1.0 Hz, 1H), 12.3 (bs, 2H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 86.6, 88.6, 114.2, 119.7, 120.1, 130.0, 140.3, 146.0, 151.0, 160.3, 162.6.

X-ray Crystallographic Study of the 1:1 DMSO Solvate of 6-[2-(1,6-Dihydro-6-oxo-2-pyridinyl)ethynyl]-4(3*H*)-pyrimidinone (7).[21] Crystals of solvate **7**·DMSO belong to the monoclinic space group $P2_1/c$ with a = 4.7695(8) Å, b = 16.7966(18) Å, c = 17.0526(17) Å, β = 94.067(12)°, V = 1362.7-(3)Å^3, D_{calcd} = 1.420 g cm^{-3}, and Z = 4. Data were collected at 295 K, and the structure was refined to R_f = 0.040, R_w = 0.044 for 2259 reflections with $I > 1.96\sigma(I)$.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada, the Ministère de l'Éducation du Québec, and the Canada Council for financial support.

Supplementary Material Available: ^1H NMR spectra of compounds **12**, **15**, **17**, and **20** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9412692

(21) The authors have deposited X-ray crystallographic data, a description of the structure determination, and tables of atomic coordinates and isotropic thermal parameters, bond lengths and angles, anisotropic thermal parameters, and refined and calculated hydrogen atom coordinates with the Cambridge Crystallographic Data Centre. The data can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ UK.

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From Molecules to Crystal Engineering: Supramolecular Isomerism and Polymorphism in Network Solids

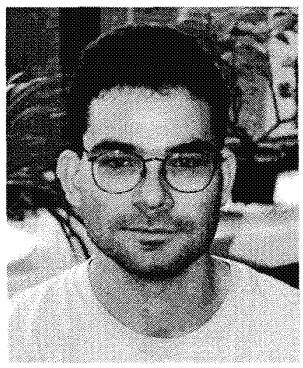
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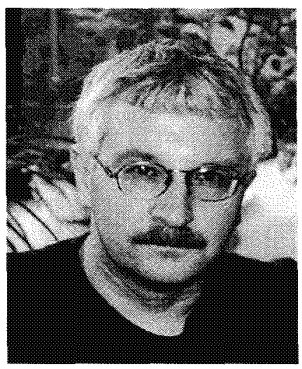
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I. Introduction

Whereas single-crystal X-ray crystallography has represented an active area of research since shortly after the discovery of X-rays, the subjects of crystal design and crystal engineering have developed rapidly only in recent years. This is presumably an artifact of a number of factors. For example, the development of relatively low-cost and powerful computers has not only enhanced crystal structure determination, but also crystal structure visualiza-

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tion, database development and analysis, and reflection analysis and processing. Simply put, X-ray crystallographic analysis has become less time consuming, relatively inexpensive, and more readily available, even for larger and/or difficult structures. The growth of crystal engineering has also coincided with advances in our understanding of intermolecular interactions and supramolecular chemistry and the realization that several aspects of solid-state chemistry are of increasing relevance and can only be resolved with a better understanding of structure–function relationships. It is the latter that will be the primary focus of this review, which is to present an overview of how advances in supramolecular chemistry have impacted the manner in which chemists view the existence of single crystals and, perhaps even more importantly, the design of new crystalline phases.

A. From Molecules to Crystal Engineering

"*One of the continuing scandals in the physical sciences is that it remains in general impossible to predict the structure of even the simplest crystalline solids from a knowledge of their chemical composition.*" This provocative comment by Maddox[1] illuminates an issue that continues to represent a challenge of the highest level of scientific and technological importance. Simply put, to quote Feynman, "*What would the properties of materials be if we could really arrange the atoms the way we want them?*"[2] Such a dream generally remains to come to fruition, at least in terms of molecular self-assembly in the crystalline state. However, it has spawned and fuelled a seemingly exponential growth in research activity devoted to the subjects of crystal design and crystal engineering. Furthermore, the implications go beyond materials science since structure–function relationships in the solid state are of relevance to opportunities in the context of areas of interest that are as diverse as solvent-free synthesis and drug design and development. The term crystal engineering was first coined in a contribution by G. M. J. Schmidt concerning the subject of organic solid-state photochemistry.[3] Schmidt's article marked a thought evolution in at least two important ways. First, as implicit by use of the term crystal engineering, it became clear that, in appropriate circumstances, crystals could be thought of as the sum of a series of molecular recognition events, self-assembly, rather than the result of the need to "avoid a vacuum". It has subsequently become clear that crystal engineering, especially in the context of organic solids, is intimately linked to concepts that have been developed in supramolecular chemistry, another field that has undergone explosive growth in recent years. Supramolecular chemistry, defined by Lehn as chemistry beyond the molecule,[4,5] and "supramolecular assemblies" are inherently linked to the concepts of crystal engineering. In this context, crystals might be regarded as being single chemical entities and as such are perhaps the ultimate examples of supramolecular assemblies or supermolecules. Dunitz referred to organic crystals as "supermolecule(s) *par excellence*".[6,7] As revealed herein, this interpretation is fully consistent with the approaches to crystal engineering practiced by ourselves and others who are presently active in the field.

Second, Schmidt's work emphasized that the physical and chemical properties of crystalline solids are as critically dependent upon the distribution of molecular components within the crystal lattice as the properties of its individual molecular components. Therefore, crystal engineering has implications that extend well beyond materials science and into areas as diverse as pharmaceutical development and synthetic chemistry. In the context of the former, there are important processes and intellectual property implications related to polymorphism.[8–12] In the context of the latter, solid-phase organic synthesis can be solvent free and offer significant yield and regioselectivity advantages over solution-phase reactions. In other words, crystals should not be regarded as chemical graveyards. To the contrary, it is becoming increasingly clear that binary or inclusion compounds can be used to effect a diverse range of thermal and photochemical reactions in the solid state,[13–16] including some that cannot be effected in solution.[17–19]

In this contribution we concentrate upon advances that were spawned by a series of papers and monographs in the 1980s by Desiraju[20–22] and Etter[23–25] that concentrated upon using the Cambridge Structural Database[26] (CSD) for analysis and interpretation of noncovalent bonding patterns in organic solids. It should be noted that a considerable body of work devoted to the subjects of crystal nucleation, growth, and morphology was developed concurrently. This research, which could be perhaps termed "engineering crystals", is not the intended focus of this review and is exemplified by the work of research groups such as those of Cohen,[27] Green,[28] Addadi,[29–33] Mann and Heywood,[34,35] Thomas,[36,37] and Davey.[38,39] The seminal work by Desiraju and Etter in solid-state organic chemistry afforded the concept of *supramolecular synthons*[22] and led to hydrogen bonds being perhaps the most widely exploited of the noncovalent interactions in the context of crystal engineering. Their research programs addressed the use of hydrogen bonding as a design element in crystal design and delineated the nature (strength and directionality) of the interaction. It is now readily accepted that these forces include weak hydrogen-bonding interactions such as C–H···X and CH···π. Although Professor Desiraju continues his valuable contributions to the discipline, Professor Etter passed away in 1992.

In this contribution, we attempt to address the challenges and opportunities represented by crystal engineering with particular emphasis upon how supramolecular concepts are important in helping us to understand supramolecular isomerism and superstructural diversity in the context of two classes of structure: coordination polymers and organic molecular networks.

B. Crystal Engineering vs Crystal Structure Prediction

It is important to stress the significant conceptual difference between crystal engineering and crystal

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structure prediction. In short, crystal structure prediction is precise (i.e., space group and exact details of packing are defined) and deals primarily with known molecules or compositions of molecules. Crystal engineering is less precise (e.g., network prediction) and most typically deals with entirely new phases, sometimes, but not necessarily, involving well-known molecules. Technological advances in experimental and computational methodology have accelerated the evolution of crystal engineering. In particular, the advent of CCD diffractometers facilitated the solution of crystal structures within hours or minutes rather than weeks or days and computational advances have made use of databases and visualization software inexpensive and straightforward. Therefore, although ab initio crystal structure prediction remains at best a significant challenge,[40-43] even for small molecules, crystal engineering has been able to develop rapidly because its objectives and *modus operandi* are distinctly different from crystal structure prediction. The *raison d'etre* and strategies of crystal engineering are somewhat different from those of crystal structure prediction since the former is primarily concerned with design and, although more restrictive in terms of molecular components that might be employed, is becoming increasingly synonymous with the concept of supramolecular synthesis of new solid-state structures. In other words, crystal engineering represents a paradigm for synthesis of new solid phases with predictable stoichiometry and architecture. In contrast, predicting a crystal structure requires analysis of the recognition features of a molecular component in the context of how they will generate crystallographic symmetry operations and optimize close packing, i.e., it requires space group determination.

Engineering and design are far less restrictive from a conceptual perspective since they focus more broadly upon the design of new and existing architectures. In effect, the principles of design are based upon a blueprint, in many cases a blueprint that is first recognized via a serendipitous discovery, and allow the designer to select components in a judicious manner. Therefore, a desired network structure or blueprint can be limited to chemical moieties, in many cases commercially available moieties, that are predisposed to a successful outcome.

C. Supramolecular Isomerism

Closely related to the well-documented (but not necessarily well understood) subject of polymorphism in crystalline solids is the existence of supramolecular isomerism[44] in polymeric network structures. Supramolecular isomerism in this context is the existence of more than one type of network superstructure for the same molecular building blocks and is therefore related to structural isomerism at the molecular level. In other words, the relationship between supramolecular isomerism and molecules is similar to that between molecules and atoms. In some instances, supramolecular isomerism can be a consequence of the effect of the same molecular components generating different supramolecular synthons and could be synonymous with polymorphism. However, in other situations, supramolecular isomerism is the existence of different architectures (i.e., architectural isomerism[45]) or superstructures. In this context, the presence of guest or solvent molecules that do not directly participate in the network itself, especially in open framework structures, is important to note as it means that polymorphism represents an inappropriate term to describe the superstructural differences between network structures. Indeed, it is reasonable to assert that polymorphism can be regarded as being a type of supramolecular isomerism but not necessarily vice versa. Pseudopolymorphism is a related term that has been coined to categorize solvates,[46,47] especially in the context of pharmaceutical solids. Since solvent molecules are often integral parts of the resulting network structures, a pseudopolymorph is, at least from a supramolecular perspective, a binary phase and an entirely different class of compound.

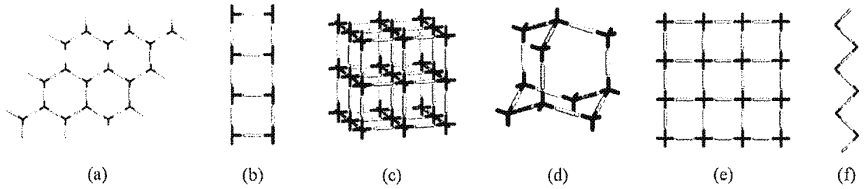
The subject of supramolecular isomerism is important for a number of reasons. (1) Investigation of the relationship between supramolecular isomerism and polymorphism represents a fundamental scientific challenge. However, when one considers that bulk properties of solids are critically dependent upon architecture and that crystal structure confirms composition of matter from a legal perspective, the applied relevance also becomes immediately apparent. Polymorphism in molecular crystals represents a phenomenon that is particularly important and ubiquitous in the context of pharmaceuticals and is receiving increasing attention from a scientific perspective.[48-53] It should also be noted that McCrone was prompted to suggest that the "*number of forms known for a given compound is proportional to the time and money spent in research on that compound*".[54] However, the generality of McCrone's statement remains ambiguous despite indications that polymorphism is more general than expected from the CSD.[55] For example, Desiraju[47] demonstrated that the frequency of occurrence of polymorphic modifications is not necessarily uniform in all categories of substance. His analysis revealed that the phenomenon is probably more common with molecules that have conformational flexibility and/or multiple groups capable of hydrogen bonding or coordination. Coincidentally and importantly, this is inherently the situation for many pharmaceuticals and conformational polymorphism is a subject in its own right.[56,57] Desiraju also suggested that polymorphism can be strongly solvent-dependent. In summary, the relevance of polymorphism is clear but remains a subject that is not fully or widely understood at a fundamental level.

(2) Control over supramolecular isomers and polymorphs lies at the very heart of the concept of crystal engineering (i.e., design of solids). However, there is presently very little understanding concerning even the existence of supramolecular isomers, never mind how to control them.

(3) Supramolecular isomerism also lies at the heart of gaining a better understanding of supramolecular synthons and, by inference, how they develop and occur in other solid phases and even solution. The

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Scheme 1. Schematic Representation of Some of the Simple Network Architectures Structurally Characterized for Metal–Organic Polymers: (a) 2D Honeycomb, (b) 1D Ladder, (c) 3D Octahedral, (d) 3D Hexagonal Diamondoid, (e) 2D Square Grid, and (f) 1D Zigzag Chain



Cambridge Structural Database remains a very powerful tool in this context, but it must be remembered that even such a large database will not necessarily be reflective of the full range of compounds that will be isolated and characterized in future years.

The conceptual link between polymorphism and supramolecular isomerism in organic and metal–organic networks is not immediately apparent. However, since polymorphs can be rationalized on the basis of supramolecular interactions, polymorphism can be regarded as a type of supramolecular isomerism. Implicitly, all sets of polymorphs can therefore be regarded as being supramolecular isomers of one another but the reverse is not necessarily the case. It should also be noted that solvates are almost always different compounds from a crystal engineering perspective. The only exception would be in the case of inclusion compounds where the host framework remains intact in the presence of different solvent molecules, i.e., the solvent serves the function of being a guest molecule. Supramolecular isomerism as seen in metal–organic and organic networks may be classified based upon analogies drawn with isomerism at the molecular level. Thus far it is appropriate to categorize the following classes of supramolecular isomerism.

Structural. The components of the network (i.e., the metal moiety and the ligands the or exofunctional organic molecule) remain the same but a different superstructure exists.[44] In such a situation, the networks are effectively different compounds even though their empirical formula and chemical components are identical.

Conformational. Conformational changes in flexible ligands such as bis(4-pyridyl)ethane generate a different but often related network architecture.[44] Conformational polymorphism is a closely related subject.[56,57]

Catenane. The different manner and degrees in which networks interpenetrate or interweave can afford significant variations in overall structure and properties depending upon the molecular building blocks that are utilized.[58] Interpenetrated and noninterpenetrated structures are effectively different compounds because their bulk properties will be so different.

Optical. Networks can be inherently chiral and can therefore crystallize in chiral (enantiomorphic) space groups. Therefore, an analogy can be drawn with homochiral compounds. This type of supramolecular isomerism lies at the heart of an important issue: spontaneous resolution of chiral solids.[59–65]

The remainder of this contribution reviews the subject of supramolecular isomerism and how it leads to superstructural diversity in network solids. Emphasis is placed upon metal–organic or coordination polymers and organic solids, respectively. However, it should be noted that the subject matter is divided along these lines for convenience only since the basic concepts apply equally well to both classes of compound.

II. Coordination Polymers

Coordination polymers exemplify how crystal engineering has become a paradigm for the design of new supramolecular structures. In this context, the work of Wells is exhaustive and seminal and can serve as a reference point. Wells was primarily concerned with the overall structure of solids, particularly inorganic compounds.[66,67] He defined crystal structures in terms of their topology by reducing them to a series of points (nodes) of a certain geometry (tetrahedral, trigonal planar, etc.) that are connected to a fixed number of other points. The resulting structures, which can also be calculated mathematically, can be either discrete (zero-dimensional) polyhedra or infinite (one-, two-, and three-dimensional) periodic nets.

It is perhaps surprising that it took until the 1990s for the approach of Wells to bear fruit in the laboratory. Robson[68–75] was primarily responsible for the initial studies that facilitated rapid development of the field of coordination polymers alongside that of crystal engineering of organic solids. Robson extrapolated Wells work on inorganic network structures into the realm of metal–organic compounds and coordination polymers. In this context, the resulting "node and spacer" approach has been remarkably successful at producing predictable network architectures. Scheme 1 illustrates some of the simplest architectures that can be generated by using commonly available metal moieties and linking them with linear "spacer" ligands. Whereas diamondoid networks represent a class of structure that could be described as mineralomimetic because there are many naturally occurring analogues, that is not the case for any of the other architectures illustrated in Scheme 1.

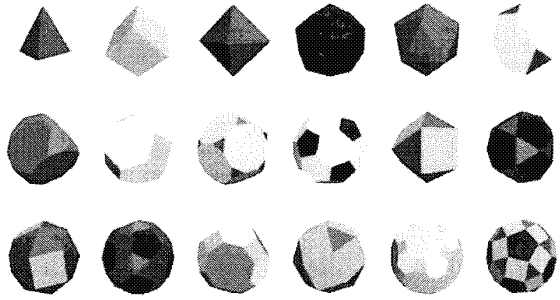
The nature of these novel structures and their organic analogues and the diversity exhibited by their *supramolecular isomers*[44] represent the primary focus for the remainder of this contribution. Such structures are of interest for both conceptual reasons and because of their interesting properties. They are

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ideally suited to illustrate the concepts of crystal engineering for the following reasons. (1) The diversity of structures that can be obtained from the simplest of components is quite remarkable, not only in the context of coordination polymers but also in the context of organic solids and even, for that matter, discrete architectures. (2) Coordination polymers can be relevant in the context of inclusion chemistry. As should be clear from Scheme 1, a recurring feature of even the simplest network structures is the presence of voids or cavities that are inherently present because of the architecture itself and the dimensions of the spacer ligands. This feature is attracting considerable interest, and there are a number of recent reports concerning open framework coordination polymers that exhibit hitherto unprecedented levels of porosity and high levels of thermal stability. Indeed, there already exists a diverse range of coordination polymers with higher effective surface areas than zeolites and stability to loss of guest.[76-84] (3) From a design perspective, it should be clear from Scheme 1 that each of the networks illustrated is based upon at least two components (i.e., the node and the spacer) and, as will become clear herein, such components can be preselected for their ability to self-assemble. The network structures can therefore be regarded as examples of blueprints for the construction of networks that, in principle, can be generated from a diverse range of chemical components, i.e., they are prototypal examples of modular frameworks. It should be noted that the construction of networks from single-component systems also represents an important area of activity. Self-assembly of a single-molecular component, or "molecular tectonics", represents a different approach to crystal design, and it must be remembered that most existing crystal structures are based upon a single component. However, in order for single-component self-assembly to be directly relevant in the context of crystal engineering, all the molecular recognition features that lead to supramolecular synthons must be present in a single molecule. 1,3,5,7-Adamantanetetraacetic acid[85,86] and methanetetraacetic acid[87] can be regarded as being prototypal for self-assembled diamondoid architectures. Both structures are sustained by one of the most well recognized supramolecular synthons—the carboxylic acid dimer.[88] Pyridone dimers have been used in a fashion similar to build diamondoid networks, in this case from tetrahedral tetrakispyridones.[89] A number of well-known inorganic structures can also be regarded as examples of self-assembly (e.g., ice, potassium dihydrogenphosphate), and one might even consider covalent bonds as conceptually related: diamond, Si, Ge, ZnS, BP, GaAs, ZnSe, CdS, $CuInSe_2$, $CuFeS_2$ (chalcopyrite). However, this contribution will focus primarily upon the modular or multicomponent approach to crystal design. Coordination polymers and hydrogen-bonded structures with multiple complementary components can be regarded as being the consequence of modular self-assembly.[90]

The remainder of this section will be organized according to the dimensionality of the observed structures. However, it should be stressed that the modular self-assembly approach applies equally well to all levels of dimensionality since the dimensionality is often determined directly by the node. Therefore, it is appropriate to include discrete 0D structures in the discussion.

Scheme 2. 3D Models of the Regular (Platonic) and Semiregular (Archimedean) Solids



A. 0D (Discrete) Architectures

In addition to research that has focused upon infinite structures, the principles of self-assembly have also been applied toward the design and isolation of discrete molecular structures. Such structures are exemplified by molecular squares[11,91-108] and, more recently, by striking examples of new high molecular weight compounds that can be described as spheroid architectures.[109-127] The design principles behind the isolation and development of these new classes of compounds are based upon the concept of self-assembly in the context of geometric considerations found in regular (Platonic) and semiregular (Archimedean) solids. Such structures are also known in zeolites (e.g., Linde A, which is based upon an edge-skeleton generated by fused truncated octahedra[128]) and in biological self-assembled systems such as mammalian picornaoviruses[93,99,129-131] and proteins.[132] The 5 Platonic and 13 Archimedean solids[133] are illustrated in Scheme 2. They can be constructed at the molecular level by sharing of the edges of molecular moieties that have the shape of regular polygons,[118] i.e., triangles, squares, pentagons, hexagons, and octagons, or by connecting molecular vertexes with linear bifunctional rodlike ligands.[100,112] In the case of the former closed convex surfaces are generated, whereas for the latter all the faces are open windows. This subject is highly topical, and several recent review articles have appeared.[100,112,114,117,134] We shall therefore provide no further details. The primary purpose of highlighting such structures is that they have been developed using the same principles as those used for generating the infinite structures described herein. Structures such as molecular squares are in effect supramolecular isomers of some of the infinite 1D structures described herein.

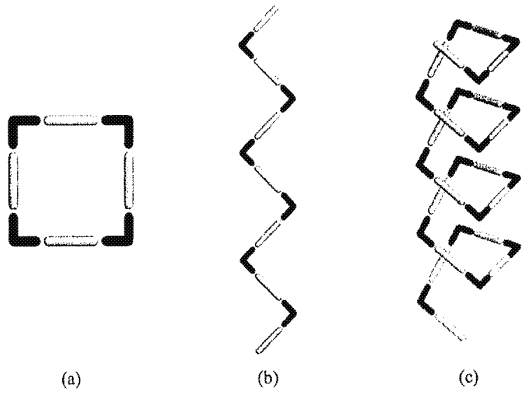
B. 1D Coordination Polymers

1. Stoichiometry of Metal to Ligand = 1:1

Structural supramolecular isomerism is exemplified by the range of structures that has thus far been

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Scheme 3. Schematic Representation of the Three Structural Supramolecular Isomers Observed for Angular Nodes Generated by *cis*-Substituted Metal Moieties: (a) 0D Square, (b) 1D Zigzag Chain, and (c) 1D Helix



observed in coordination polymers, in particular network structures that have been observed for some of the simplest building blocks and stoichiometries. Scheme 3 illustrates the possible structures that can result from self-assembly of either a *cis*-octahedral or a *cis*-square planar metal and a linear "spacer" ligand. There are three obvious architectures that might result, and they are dramatically different from one another. The "square box" or "molecular square" architecture represents a discrete species that has been developed extensively in recent years by the groups of Fujita,[106] Stang,[11,100,102–104,107,112,120] and Hupp.[92,94–96,98,101,135] The other two architectures are both examples of 1D coordination polymers, but they are quite different from one another. The zigzag polymer[136–146] has been fairly widely encountered, and such structures tend to pack efficiently and eschew open frameworks or cavities. The helix[147–158] remains quite rare in the context of coordination polymers, but there is added interest because it is inherently chiral regardless of what its components might be. The inherent chirality of this architecture comes from spatial disposition rather than the presence of chiral atoms, thereby illustrating an important aspect of the solid state: it is possible for achiral molecules to generate chiral crystals. To illustrate the potential for generation of chiral architectures from simple achiral building blocks, let us consider how one might design a homochiral crystal from simple molecular components.

There would appear to be at least four strategies for the design of polar crystals that are independent of the need for homochiral molecular components: (1) achiral building blocks that crystallize in a chiral space group, (2) achiral molecular building blocks to build a chiral framework, (3) achiral host framework built from achiral molecular components with chiral guest(s), and (4) achiral host framework built from achiral molecular components with achiral guest(s).

Whereas exploitation of homochiral components represents the most obvious approach because the absence of a crystallographic center of inversion is guaranteed, it in no way implies or affords any control over molecular orientation and, therefore, bulk polarity. Furthermore, reliance upon the use of pure enantiomers raises the substantial problem of requiring control over stereochemistry at the molecular level without yet solving the problem of controlling stereochemistry at the supramolecular level. Indeed, strategy 1, which basically relies upon serendipity, offers just as much chance of optimal control of crystal packing as the use of homochiral components. However, there are three types of polar architecture that do not need to be sustained by homochiral molecular components: helical networks,[149,153,154,159–166] 1D acentric networks sustained by head-to-tail stacking of complementary molecules,[167–175] and host–guest networks which are polar because of the presence of acentric guest molecules or guest aggregates.[65,176,177]

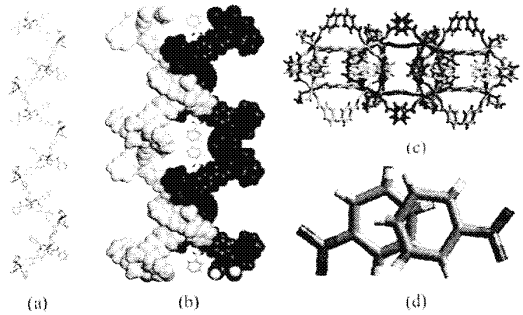


Figure 1. Illustration of the crystal structure for [Ni(bipy)-$(PhCO_2^-)_2(MeOH)_2]\cdot PhNO_2$: (a) portion of a single helical chain, (b) space-filling model illustrating the packing of adjacent helices and the resulting cavities occupied by $(nitrobenzene)_2$ adducts, (c) overhead view of packing of helices, and (d) illustration of the dissymmetric nitrobenzene dimer.

Although the crystallization process for strategies 1–4 can inherently afford homochiral single crystals, only the use of homochiral components guarantees that all crystals in a batch will be of the same enantiomorph. Batches of crystals will often be heterochiral as both enantiomers tend to be formed equally during crystallization. Fortunately, it has been demonstrated that formation of homochiral bulk materials can be afforded by seeding with the desired enantiomer.[153]

$[Ni(bipy)(benzoate)_2(MeOH)_2]$[154] (bipy = 4,4-bipyridine), **1**, illustrates the issues raised above. **1** self-assembles as a helical architecture that is sustained by linking of octahedral metal moieties with linear spacer ligands. Furthermore, it persists in the presence of several guests, even if 4-hydroxybenzoate ligands (i.e., ligands that are capable of forming strong hydrogen bonds) are employed. The crystal structure of the nitrobenzene clathrate is presented in Figure 1 and reveals the presence of large chiral cavities that induce the guest molecules to form chiral dimers. The guest molecules are trapped in a closed environment since helices from adjacent planes close off the 500 Å^3 cavities. The helical chains generated by **1** pack such that they are staggered but align in a parallel fashion. Therefore, the bulk crystal is polar as every helix in an individual crystal is of the same handedness.

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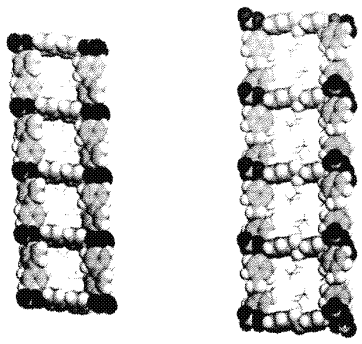


Figure 2. Illustration of the crystal structures two molecule ladders: (a) $[Co(bipy)_{1.5}(NO_3)_2]\cdot 2CHCl_3$ and (b) $[Co(bipy\text{-}eta)_{1.5}(NO_3)_2]\cdot 3CHCl_3$.

1 illustrates the attractiveness of self-assembly and crystal engineering for generation of polar architectures. In particular, there is no prerequisite for homochiral molecular components and host−guest compounds have the potential to be modular and fine-tunable since the guest molecule might be used to impart functional properties. It should also be stressed that, at least in principle, all existing achiral moieties can be incorporated into polar structures. The problem that has yet to be solved is how reliably and predictably to avoid crystallographic centers of inversion and how to control alignment of molecular dipoles.

Another example of a coordination polymer that self-assembles into a helical architecture is represented by the result of complexation of a 2,2′-bipyridine-based exo-ditopic macrocyclic ligand with Ag^+ cations. The single-strand helical assembly is one of four possible arrangements and contains channels that run through the center of the assembly. These channels contain acetonitrile solvent molecules. The helices align antiparallel with respect to each other, and therefore, a racemic mixture of the right- and left-handed helices is obtained.[155]

2. Stoichiometry of Metal and Spacer Ligand = 1:1.5

Molecular ladders represent another type of 1D coordination polymer.[59,91,178−185] They differ in two important ways from molecular chains and helices. Most obviously, their stoichiometry is different since they are the result of self-assembly of 1.5 spacer ligands per metal. Therefore, the molecular building unit is effectively a "T-shape" moiety. Second, they necessarily contain cavities within the individual molecular ladders. These cavities are determined by the length, shape, and orientation of the spacer ligand. Simple examples of molecular ladders are represented by the coordination polymers $[M(\mu\text{-}L)_{1.5}(NO_3)_2]_n$ (L = bipy,[186] **2a**, or bis(4-pyridyl)ethane),[44] **2b**). Examples of these structures are illustrated in Figure 2, which reveals how **2a** and **2b** contain cavities that are large enough to sustain individual or pairs of molecules. The cavities are hydrophobic in nature, and their diagonal dimensions are defined by M−M separations of ca. 16 and 19 Å, respectively. This means that the effective dimensions of the cavities are ca. 13 and 16 Å, respectively.

C. 2D Coordination Polymers

The strategy of exploiting known coordination geometries of metals to propagate 2D structures via coordination with linear bifunctional spacer ligands has yielded many examples of coordination polymers with various metal moieties and architectures. The ratio of metal and ligand and the nature of the coordination of terminal ligands (i.e., degree of chelation) are the primary factors that determine the topology of the network. Scheme 4 illustrates some of the 2D network structures that have thus far been observed in coordination polymers.

1. Square Grids

Square grid networks exemplify a particularly simple and commonly reported example of a predictable 2D metal−organic network. Square grid coordination polymers are based upon 1:2 metal:ligand complexes with linear bifunctional spacer ligands. They were first reported using cyano ligands[187−190] and have recently been expanded in terms of chemical type and cavity size to include pyrazines,[191−193] bipy,[78,194−199] and longer analogues of bipy.[197,200] These compounds can be regarded as being analogues of clays since they would be expected to have the ability to intercalate guest molecules. However, they have added features that are not likely to be present in clays. For example, cavities lie within the plane of the structure. These cavities are suitable for either interpenetration or enclathration of a possibly wide range of organic guest molecules. There also exists potential for incorporating catalytically active sites into such structures.[70] Furthermore, the cavities are tunable as the length and width of the spacer ligand controls the size of the cavities that occur within the polymeric structure, although interpenetration can mitigate against the existence of frameworks with very large cavities.[58]

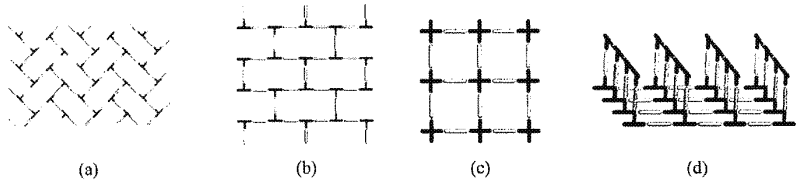
Open framework square grid networks generated with bipy spacer ligands were first reported by Fujita et al.[70] Fujita's structures are based on Cd(II), and other examples have subsequently been reported based on a number of other transition metals, including Co(II), Ni(II), and Zn(II). Although these 2D coordination networks are isostructural within the coordination grid (effective dimensions of the diagonals are ca. 13 × 13 Å), the crystal structures of compounds can differ in the manner in which the networks stack with respect to each other (interlayer separations range from 6 to 8 Å).

The compounds $[M(bipy)_2(NO_3)_2]\cdot$guest (M = Co, Ni) have been studied extensively[201] by us, and we have only observed three basic crystal structure types (Figure 3).

Type A compounds crystallize with similar cell parameters (monoclinic $C2/c$; $a = 21.5$ Å, $b = 11.5$ Å, $c = 13$ Å; $\beta = 102°$), have 2:1 guest:host stoichiometry and interplanar separations of ca. 6 Å. The crystal packing appears to be influenced by C−H···O hydrogen-bond interactions between the bipy ligands of one square grid and the nitrate anions of adjacent square

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Scheme 4. Schematic Representation of 2D Networks Recently Reported for Metal–Organic Polymers: (a) Herringbone or 'Parquet Floor', (b) Brick Wall, (c) Square Grid, and (d) Bilayer



grids. The square grids do not align with a unit cell face, and adjacent grids are slipped in one direction by ca. 20%, i.e., every sixth layer repeats. The crystal packing of type B compounds is also controlled by weak interactions between adjacent layers. They generally crystallize with 2.5 guest molecules per metal center, and cell parameters are fairly consistent (monoclinic $P2_1/c$; $a = 16$ Å, $b = 14.75$ Å, $c = 16$ Å; $\beta = 100°$). The interlayer separation is ca. 8 Å. Type C compounds have interlayer separations that are similar to those seen for type B compounds. Four examples of type C compounds have 3:1 stoichiometry: three crystallize in space group $C2/c$ (monoclinic; $a = 16$ Å, $b = 11.5$ Å, $c = 23$ Å; $\beta = 100°$), and the other crystallizes in space group Cc. The latter compound exhibits similar cell parameters except that there is a tripling of the a-axis and the cell volume. Another example of a type C grid crystallizes in space group Pn (monoclinic; $a = 11.4$ Å, $b = 22.8$ Å, $c = 15.9$ Å; $\beta = 93.3°$). Although these cell parameters are inconsistent with the previous four structures, the packing of the grids is appropriate for type C grids. The positioning of the grids facilitates inclusion of one guest molecule in the center of each grid. The other guest molecules lie between the grids and engage in stacking interactions between the bipy ligands and themselves.

In all of these compounds the proportion of the crystal that is occupied by guest molecule is ca. 50 vol %. In such a situation it becomes reasonable to question whether interactions between the guest molecules determine the cavity shape and crystal packing of the square grid polymers rather than vice versa. This issue is addressed later.

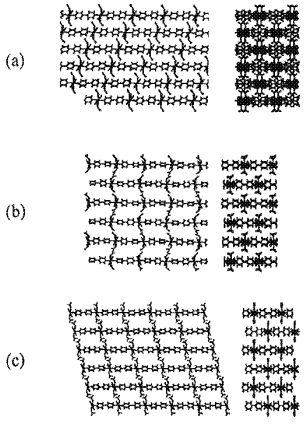


Figure 3. Perspective views of the stacking of square grid network architectures of formula $[M(bipy)_2(NO_3)_2]$: (a) A-type grids, (b) B-type grids, and (c) C- type grids.

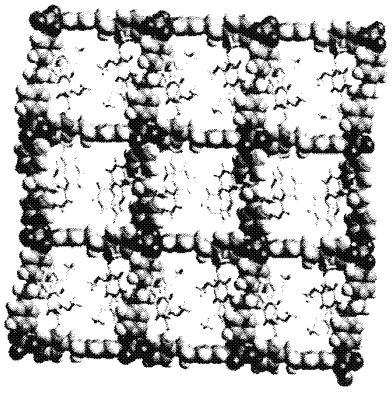


Figure 4. Illustration of the square grid architecture $[Ni(bipy\text{-}eta)_2(NO_3)_2]\cdot 2Ph(OMe)_2$.

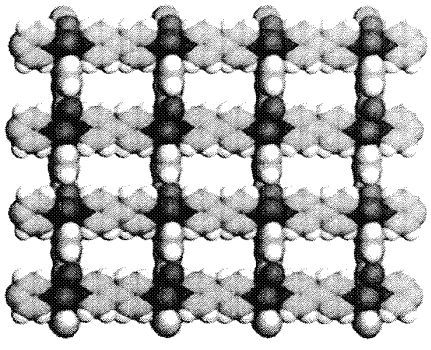


Figure 5. Space-filling illustration of $[Co(pyca)(bipy)(H_2O)_2]\cdot[NO_3]\cdot(bipy)(H_2O)_{1.5}$; an example of a rectangular grid resulting from the coordination of a metal to two types of spacer ligand.

As these square grid architectures are inherently modular, it should be possible to extend their dimensions by simply using longer spacer ligands. An example of such a structure, $[Ni(1,2\text{-bis}(4\text{-pyridyl})\text{-ethane})_2(NO_3)_2]_n\cdot 2$veratrole, is illustrated in Figure 4. This structure has grid dimensions ca. 20% larger than the smaller grids (diagonal dimensions are ca. 16 × 16 Å), large enough to enclathrate more than one aromatic guest. Larger grids (ca. 20 × 20 Å) have also been reported using tetra(4-pyridyl)porphyrin.[202]

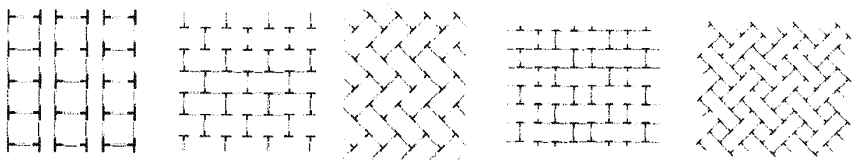
Grids in which there are two types of spacer ligand have also been reported.[199,203] Figure 5 reveals the structure of such a compound, which is appropriately termed a rectangular grid.

2. Other 2D Architectures

Another metal geometry or node that is of particular interest because of its potential range of su-

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Scheme 5. Schematic Illustration of Calculated Tiling Patterns Characterized or Might Be Expected To Occur: (a) 1D Ladder (finite second dimension), (b) Brick Wall, (c) Herringbone, (d) Long and Short Brick, (e) Basket Weave. (d, e) Yet To Be Realized



pramolecular isomers is the T-shaped geometry, i.e., a *mer*-substituted octahedral metal moiety or a trisubstituted square planar metal moiety with a 1:1.5 metal:spacer ligand ratio. This node has thus far produced examples of 1D, 2D, and 3D networks. Three distinct 2D supramolecular isomers have already been reported: brick wall,[78,178,180,204–209] herringbone,[78,210–212] and bilayer.[213–216] It is interesting to note that if one calculates the possible tiling patterns (i.e., all points lie in the same plane) that are possible for T-shaped nodes (Scheme 5), three of the five possibilities have already been realized.

The brick architecture (**5b**) is observed as the product of the reaction between heptacoordinate Cd(II) and 1,4-bis((4-pyridyl)methyl)-2,3,5,6-tetrafluorophenylene.[70] The T-shape geometry is the result of two terminal nitrate ligands chelating in a bidentate manner, thereby occupying four of the seven coordination sites. The structure is triply interpenetrated and, as such, does not possess channels or cavities. In a similar system using the nonfluorinated pyridyl-based ligand, a 1D ladder structure (**5a**) was observed. The brick architecture was also seen in $[Ni(4,4'\text{-azopyridine})_{1.5}(NO_3)_2]_n$, which interpenetrates with two perpendicular $[Ni(4,4'\text{-azopyridine})_2(NO_3)_2]_n$ square grid networks.[208]

The herringbone or 'parquet floor' architecture (**5c**) has recently been observed by several groups.[204,210,211] In these structures, the coordination sphere is similar to that of the brick architectures: heptacoordinate Cd(II) or Co(II) with two terminal bidentate nitrate ligands and coordination to one end of three 4,4′-azopyridine bridging ligands; an isostructural example has also been reported with 1,2-bis(4-pyridyl)-ethyne as the bridging ligand.[214]

The bilayer architecture has been observed in at least three compounds.[213–215] It has been observed as the product from the reaction of $Co(NO_3)_2$ and bipy, which also generates ladder, square grid, and herringbone architectures. The bilayer form of $[Co(bipy)_{1.5}(NO_3)_2]$ is observed if crystallization occurs in the presence of CS_2 or H_2O. The bilayers pack by partial interdigitation, which allows 1D channels to run through the structure. This structure is particularly relevant since it represents one of the first reported examples of a compound that might be termed a "metal–organic zeolite", i.e., the structure is porous and stable to loss of guest.[215] The bilayer architecture has also been reported for systems using 1,2-bis(4,-pyridyl)ethane.[217]

The number of supramolecular isomers already observed in the $Co(NO_3)_2$/bipy system indicates how important selection of template and crystallization conditions are. It seems reasonable to assert that it is only a matter of time and effort before the weave (**5e**) and long-and-short brick (**5d**) motifs illustrated in Scheme 5 will also be realized.

In terms of topology, it should be noted that brick and herringbone motifs are both examples of (6,3) nets and can therefore be regarded as being closely related to honeycomb (6,3) nets.[67] Honeycomb networks are quite common in organic structures because of the availability of trigonal nodes (i.e., 1,3,5-trisubstituted benzenes such as trimesic acid and species such as the guanidinium cation) but they seldom occur in the context of metal–organic polymers because trigonal and trigonal bipyramidal coordination geometries are rare. However, $[Cu(pyrazine)_{1.5}]BF_4$[218] is based upon trigonal Cu(I), and it should therefore be unsurprising that it crystallizes as a honeycomb (6,3) net. That a number of ligands with trigonal geometry[100,112,114,118,123,125,219–225] now exist means that it is likely that a wider range of honeycomb structures will be generated soon.

D. 3D Coordination Polymers

It might be anticipated that the challenge of designing 3D network architectures represents an added level of complexity in comparison with 2D architectures, and it in many ways represents the ultimate challenge to crystal engineers since it leads most directly to crystal structure control and prediction. For example, in most situations, a finite number of structural isomers can be calculated if all nodes must lie in the same plane. However, a larger number of possibilities might exist when that limitation is relaxed. It is therefore perhaps ironic that two of the simplest examples of predictable networks are exemplified by 3D networks generated via self-assembly of tetrahedral or octahedral nodes.

Tetrahedral nodes are predisposed to generate diamond-like (diamondoid) architectures, whereas octahedral nodes are expected to afford octahedral networks. These architectures can be obtained for both organic (typically hydrogen bonded) and metal–organic (i.e., coordination polymer) systems. Interpenetration can occur in these compounds, thereby mitigating against enclathration and porosity. However, interpenetration can also be exploited as a potentially important design paradigm for rational transformation of some of the 2D networks described earlier into 3D frameworks. This principle is discussed in a later section with respect to interpenetration of identical networks (homocatenation) and

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interpenetration of different networks (heterocatenation).

1. Diamondoid Networks

The diversity of components that are available for crystal engineering of diamondoid networks and the means by which they self-assemble spans the full range of chemistry. The breadth of chemical moieties that might be used for crystal engineering is particularly well illustrated by the range of diamondoid networks that have been reported in recent years. Diamondoid architectures using a tetrahedral metal (Zn or Cd) as the node and cyanide ligands (CN^-) as the spacer represent prototypal examples of diamondoid coordination polymers. $Zn(CN)_2$ and $Cd(CN)_2$ form diamondoid networks with 2-fold interpenetration.[71,73−75] However, $Cd(CN)_2$ can also be obtained as a single network with CCl_4 filling the cavity.[71] This result illustrates two principles that have broad implications for crystal engineering: (1) Interpenetration can be avoided in the presence of an appropriate template or guest molecule; (2) Such compounds might be regarded as catenated and noncatenated supramolecular isomers of each other.

A diamondoid architecture also results when $Zn(CN)_4^{2-}$ is reacted with Cu(I). The resulting anionic network might be viewed as consisting of tetrahedral zinc nodes that are linked to tetrahedral copper nodes by cyanide spacers. However, the nature of coordination at the copper and zinc ions remains ambiguous. Analysis of the structural data indicated that it is most appropriate to consider the coordination of the copper as 100% organometallic (Cu−C) and the coordination of the zinc 100% metal−organic (Zn−N). The ionic nature of this particular framework means that the presence of a counterion in the resulting cavities is required. $N(CH_3)_4^+$ fits comfortably inside the adamantoid cavity and precludes interpenetration.

A report[226] on the crystal structure and properties of [Cu(2,5-dimethylpyrazine)$_2$(PF_6)] represents one of the first examples of a metal−organic diamondoid structure, and the related compound [Cu(4,4′-bipy)$_2$](PF_6)] was reported shortly thereafter.[218] Both structures exemplify the modular assembly design strategy and contain anions in the cavities generated by the diamondoid structure. In the case of the latter, the intermetallic separations are 11.16 Å and result in cavities that are sufficiently large to facilitate 4-fold interpenetration as well as inclusion of the counterions. A diamondoid architecture propagated by silver(I) and bipy, [Ag(4,4′-bipy)$_2$](CF_3SO_3), was reported[227] shortly thereafter, and it also exhibits 4-fold interpenetration with anions in cavities. The Ag−Ag separations are 11.6 Å. The 4-cyanopyridine analogue was reported in the same article and exhibits metal−metal separations of 9.93 Å. Despite the variations observed in the dimensions of these networks, both exhibit 4-fold levels of interpenetration.

Subsequent studies resulted in a plethora of diamondoid metal−organic structures and 2-, 3-, 4-, 5-, 7-, and 9-fold levels of interpenetration.[228−231] It should be noted that although interpenetration reduces or eliminates porosity, there are at least two important properties that can be addressed with such structures. (1) They are predisposed to form acentric networks since there is no inherent center of inversion at a tetrahedral node. An odd level of interpenetration and an unsymmetrical ligand will definitely generate a structure that exhibits polarity.[90] (2) These structures could be useful for selective anion exchange.

In the context of the former, a series of neutral diamondoid architectures have been prepared with bridging ligands of varying size.[74,218,228,231−233] These compounds are of general formula ML_2 (M = T_d metal; L = bridging anionic ligand), and it follows that a neutral network will be generated if a +2 metal is coordinated to two −1 anionic ligands. Zn(isonicotinate)$_2$ and Cd(*trans*-4-pyridylacrylate)$_2$ exhibit 3- and 5-fold degrees of interpenetration, respectively, and possess interesting properties in the context of polarity.[228] In the former compound, the Zn−Zn distance is ca. 8.8 Å. This is consistent with the previous structures that exhibit 4-fold interpenetration. The Cd−Cd distance is ca. 11.5 Å, similar to the intermetallic distances observed in the 4-fold interpenetrated structures that also contain counterions.

2. Octahedral Networks

Prototypal examples of octahedral networks are exemplified by iron cyano compounds. Such compounds are very well documented, and they have been used for centuries as pigments. An early X-ray study[234] of Berlin Green, $[Fe^{III}Fe^{III}(CN)_6]$, Prussian Blue, $[KFe^{II}Fe^{III}(CN)_6]$, and Turnbull's Blue, $[K_2Fe^{II}Fe^{II}(CN)_6]$, demonstrated that the iron cations act as the node in octahedral arrays in which they are linked by linear cyano ligands. These compounds form isostructural networks that vary only in the degree of potassium inclusion and the oxidation states of the iron atoms. Berlin Green can therefore be regarded as being the prototypal example of an open framework octahedral network; however, the limited length and lack of chemical versatility of the cyano ligand means that it has little relevance in the context of porosity.

Synthetic metal−organic octahedral networks were first reported in 1995. [Ag(pyrazine)$_3$](SbF_6)[235] is sustained by octahedral Ag(I) cations and relatively short pyrazine ligands. The framework is necessarily cationic and is illustrated in Figure 6a. A neutral analogue is exemplified by [Zn(bipy)$_2$(SiF_6)].[195] In this structure (Figure 6b), the SiF_6^{2-} counterions cross-link the square grids that are formed by Zn and bipy to form a rigid octahedral polymer. The structure cannot interpenetrate because the walls of the channels are blocked by bipy ligands. The resulting channels have an effective cross-section 8 × 8 Å and represent ca. 50% of the volume of the crystal. Solvent molecules are readily eliminated but the framework collapses irreversibly upon loss of solvent. Perhaps the most salient feature of this structure is that the structure is entirely predictable in terms of both shape and dimensions. [Zn(bipy)$_2$(SiF_6)] crystallizes in space group $P4/mmm$ with $Z = 1$. In other words, the point group at Zn, D_{4h}, is propagated into

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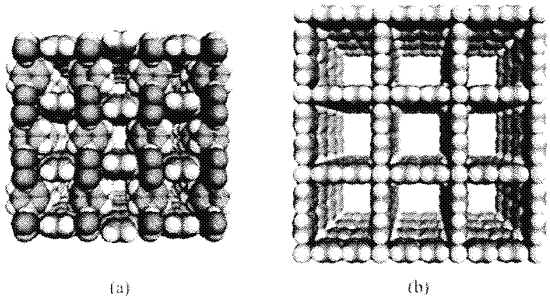


Figure 6. Space-filling models of two octahedral coordination polymers: (a) $[Ag(pyrazine)_3](SbF_6)$; (b) $[Zn(4,4'\text{-bipyridine})_2(SbF_6)](DMF)_x$.

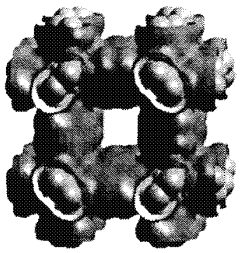


Figure 7. Space-filling illustration of $Zn_4O(BDC)_3$: an octahedral coordination polymer generated from a tetrahedral node (SBU). The structure is octahedral because the six edges of the tetrahedral SBU are linked by spacer ligands. The area outside the shaded surface represents the accessible surface area, approximately 60% of the total cell volume.

space group symmetry. Furthermore, the cell parameters are determined by the intermetallic separations. The Cu analogue of $[Zn(bipy)_2(SiF_6)]$ is isostructural and is of particular relevance since it has a higher capacity for methane adsorption than any previously studied porous material and is stable to loss of guest.[76] Octahedral coordination polymers remain much less common than their diamondoid counterparts, but a recent report revealed a novel metal−organic coordination polymer, $Zn_4O(BDC)_3$ (BDC = 1,3-benzenedicarboxylate), that suggests an exciting future for such compounds.[81] $Zn_4O(BDC)_3$ is a relatively simple and inexpensive material to prepare and is remarkably stable after loss or exchange of guest, remaining crystalline at temperatures above 300 °C. The key feature that makes $Zn_4O(BDC)_3$ special is that it exhibits a relative degree of porosity that is hitherto unprecedented in crystalline solids.

As revealed by Figure 7, the octahedral framework exhibits a large amount of surface area that remains accessible to guest molecules because it contains pores and cavities that are large enough to accommodate and release organic molecules such as chlorobenzene and dimethylformamide. Calculations and experimental data indicate that ca. 60% of the structure is available and accessible. This compares to the typical value of ca. 30% seen in zeolites. [128]

3. Other 3D Networks

In addition to the obvious, i.e., diamondoid and octahedral networks, there are numerous examples

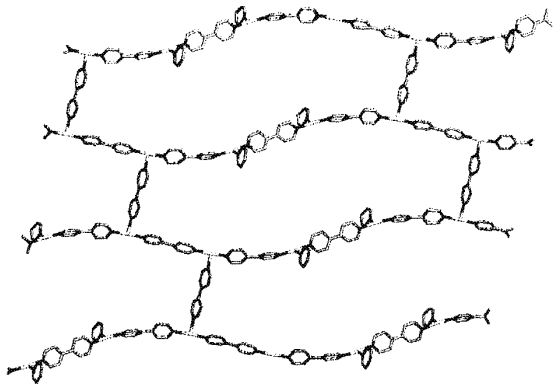
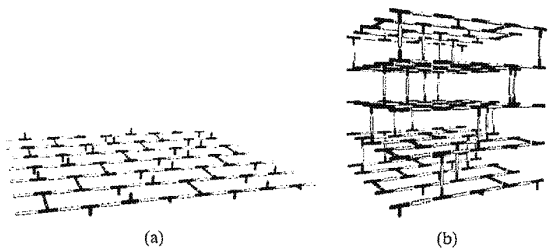


Figure 8. Illustration of the cross-section of a single network of $[Co(bipy)_{1.5}(NO_3)_2]\cdot 1.5$benzene; effective dimensions of the cavity are ca. 8 × 40 Å.

Scheme 6. Schematic Representation of the 3D-Frame Architecture: (a) Single Layer Illustrating the Large Cavities and the Relative Orientations of Adjacent T-Shaped Nodes and (b) Perspective View of the 3D Structure



of novel 3D networks that have been observed in recent years. Many can be described as supramolecular isomers of low-dimensional structures. Two such structures are supramolecular isomers formed by self-assembly of T-shaped nodes. As discussed earlier, such self-assembly can afford 3D architectures that have not been seen in naturally occurring compounds. Scheme 6 reveals one of these structures: $[Co(bipy)_{1.5}(NO_3)_2]_n\cdot 1.5$benzene.[177]

The cavities are revealed in Figure 8, and they are exceptionally large, having an effective cross-section of 8 × 40 Å. These large cavities are capable of sustaining both 3-fold interpenetration and inclusion of guest molecules in channels (Figure 9). Although the networks are inherently centrosymmetric, the crystal is polar because the guest molecules align in such a manner that their supramolecular structure cannot contain a center of inversion.

$[Ag(bipy)(NO_3)]_n$ generates another type of supramolecular isomer for self-assembly of T-shaped components. It self-assembles into linear Ag−bipy chains that cross-link via Ag−Ag bonds. This particular 3D structure has been described as a "Lincoln Log"-type structure and exhibits a 3-fold level of interpenetration that is open enough to facilitate ion exchange of the loosely bound nitrate anions.[236,237]

4. Hybrid Structures

An alternate approach to building 3D structures that seems to offer considerable potential is manipu-

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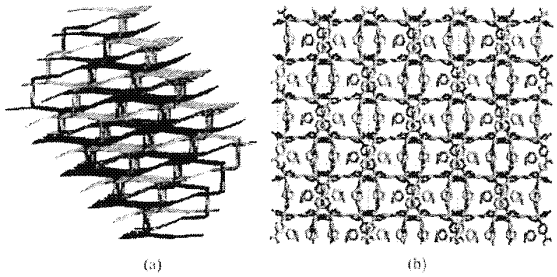
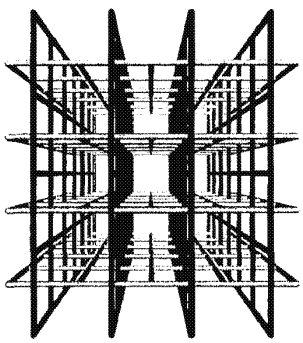


Figure 9. Crystal structure of $[Co(bipy)_{1.5}(NO_3)_2]\cdot 1.5$-benzene: (a) view illustrating the interpenetration of three networks and (b) illustration of the microchannels running parallel to the crystallographic z-axis. Polar 1D aggregates of benzene molecules are sustained by the channels.

Scheme 7. Schematic Illustrating How Porosity Can Be Generated by Inclined Interpenetration of Square Grid Networks



lation of existing 2D structures. There are two relatively simple strategies in this context: cross-linking of 2D structures and interpenetration of identical or different 2D networks.

Cross-linking becomes feasible if one selects an appropriate 2D structure that has functionality in the axial direction. Such an approach has been widely used by clay chemists, and hence, the term "pillaring" might be applied to describe such a process. $[Zn(bipy)_2(SiF_6)]$ could be used as a prototype in the context of coordination polymers since it can be regarded as having been generated from square grid coordination polymers that are cross-linked by μ-SiF_6 anions. In the context of hydrogen-bonded structures, guanidinium sulfonates represent a class of compounds that have been cross-linked in a rational manner so as to generate infinite 3D structures.[45,176,238-240]

Interpenetration is a widely encountered phenomenon that mitigates against the existence of frameworks with very large cavities. However, Scheme 7 reveals that there are situations in which interpenetration can occur, generate porosity, and afford 3D structures. Square grid polymers that are based upon longer spacer ligands such as 1,2-bis(4-pyridyl)ethane (bipy-eta) or 1,2-bis(4-pyridyl)ethylene (bipy-ete) can interpenetrate in such a fashion.[58] However, an even more intriguing situation that could have important implications for design of new hybrid materials is exemplified by the crystal structure of the square grid coordination polymer $\{[Ni(bipy)_2(NO_3)_2]\cdot 2pyrene\}_n$.[241]

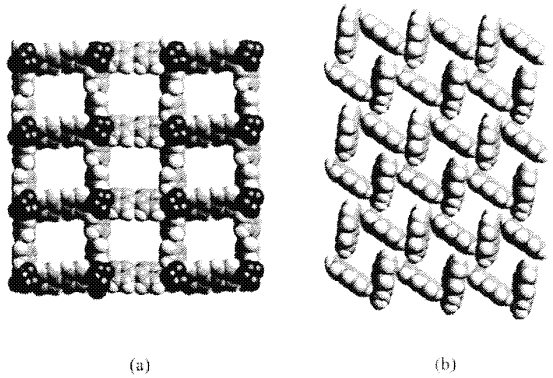


Figure 10. Space-filling illustrations of the two independent networks in $[Ni(bipy)_2(NO_3)_2]\cdot 2C_{10}H_8$: (a) metal–organic coordination polymer square grid and (b) noncovalent aromatic (4,4)-net.

Careful examination of the crystal packing in this compound reveals that the pyrene molecules form an independent noncovalent network that is complementary from a topological perspective with the square grid. The resulting crystal represents a compound in which two very different types of 2D net interpenetrate. The square grid coordination networks (Figure 10a) possess inner cavities of ca. 8 × 8 Å and stack in such a manner that they lie parallel to one another with an interlayer separation of ca. 7.9 Å. The pyrene nets (Figure 10b) are sustained by edge-to-face interactions and contain cavities of ca. dimensions 6.5 × 3.5 Å. The planes of the neighboring molecules intersect at an angle of ca. 60°, and there are no face-to-face stacking interactions between the molecules. The pyrene nets can be regarded as distorted (4,4) nets if the node is the point in space at which the vectors of the four pyrene planes intersect. An alternate interpretation is that nodes exist at the point of the edge-to-face interactions. The pyrene net could then be regarded as a distorted brick wall form of a (6,3) net. It is important to note that either a (4,4) or a (6,3) planar net is complementary from a topological sense with the (4,4) coordination polymer net and ensures that the coordination polymer nets must pack in a staggered manner. Given that cavity size within the pyrene nets is complementary with the width and height of a single aromatic ring, it should be unsurprising that the pyrene nets thread orthogonally with the bipy ligands of the coordination polymer via face-to-face and edge-to-face interactions and that the calculated volumes of the two nets are similar. This is to be expected based upon the observation that bipy square grids are self-complementary as they can interpenetrate in a 2-fold fashion.[196] The interpretation of this crystal structure as interpenetrating covalent and noncovalent nets is potentially important in the context of understanding the structure and stoichiometry of compounds that are based upon interpenetrated covalent and noncovalent nets. The structure also illustrates how polarity in crystals can be generated from subtle packing of achiral components, since the pyrene molecules form chiral nets.

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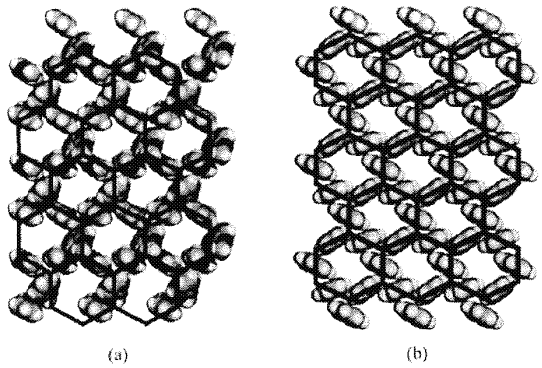
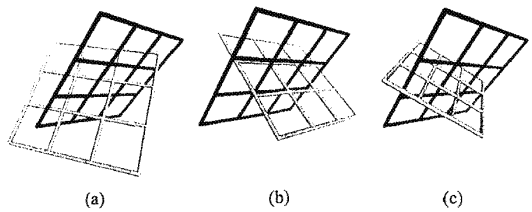


Figure 11. Space-filling illustrations of two hexagonal (6,3)-networks formed by (a) naphthalene and (b) veratrole in the intepentrated structures $[Ni(bipy)_2(NO_3)_2]\cdot$aromatic.

Scheme 8. Schematic Illustrating the Three Modes of Inclined Interpenetration Observed for Square Grid Networks: (a) Diagonal/Diagonal, (b) Parallel/Parallel, and (c) Parallel/Diagonal



It should be noted that this type of packing is not found uniquely in $\{[Ni(bipy)_2(NO_3)_2]\cdot 2pyrene\}_n$. Its naphthalene analogue, $\{[Ni(bipy)_2(NO_3)_2]\cdot 3naphthalene\}_n$, can be interpreted as being the result of interpenetration of hexagonal and square nets,[242] and a study of a series of more than 20 related compounds has revealed the presence of noncovalent nets in every one of these compounds.[243] The noncovalent hexagonal nets formed by anisole and veratrole are illustrated in Figure 11.

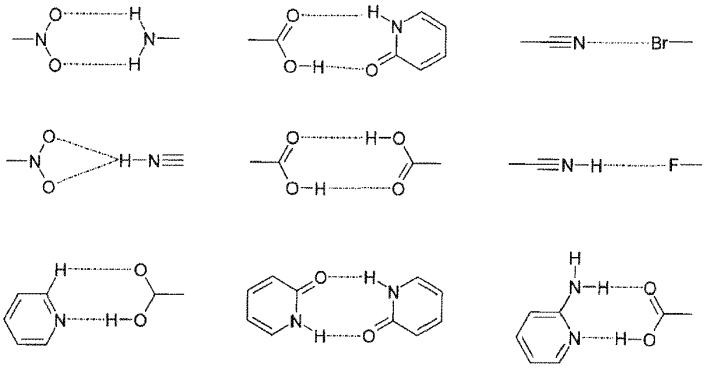
That interpenetration can vary and be influenced by subtle effects are exemplified by this class of compound. It has been reported that for coordination polymers in which (4,4) networks that are planar and identical interpenetrate, two types of interpenetration are typically observed, both of which are examples of *inclined interpenetration*.[58] The most commonly encountered form might be described as *diagonal/diagonal inclined interpenetration*[243] and was observed in the prototypal $[M(bipy)_2X_2]_n$ compound, $[Zn(bipy)_2(H_2O)_2]SiF_6$.[196] The other mode of interpenetration might be described as *parallel/parallel inclined interpenetration*.[208,244] These types of interpenetration are illustrated in parts a and b of Scheme 8, respectively, and differ in how the networks orient and cut through each other. *Parallel* refers to the structure in which a "spacer" ligand from one network threads through the cavity of the other; *diagonal* refers to the structure in which a "node" from one network (e.g., the metal moiety) is within the cavity of the other. One would anticipate that the structure that is adapted by a particular compound would be influenced by several geometric factors: the relative size of the cavity, the distance between adjacent nodes within a network, the thickness of the layers and how this limits the interlayer separation of adjacent networks, and the steric bulk of the node. In this context, it is important to note that with all other things equal, the diagonal/diagonal mode of interpenetration facilitates an interlayer separation that is 41.4% greater than that of the parallel/parallel mode. Furthermore, the diagonal/diagonal mode ensures a staggered orientation of parallel layers, whereas an eclipsed orientation is necessary if the parallel/parallel structure is present. Therefore, in terms of steric considerations, the diagonal/diagonal mode would appear most likely to be favored. However, circumstances where the interlayer separation would ideally be shorter or where the metal atoms in adjacent layers would be eclipsed (e.g., to maximize interlayer interactions) could favor the parallel/parallel mode.

The structures we have studied that are based upon complementary covalent and noncovalent networks exhibit a new mode of inclined interpenetration that is a hybrid of the modes described above: *parallel/diagonal inclined interpenetration*.[243] The noncovalent (4,4) arene networks exhibit parallel inclined interpenetration with respect to the (4,4) metal−organic coordination networks, whereas the covalent coordination networks demonstrate diagonal inclined interpenetration with respect to the arene networks (Scheme 8c). This salient structural feature means that the nitrate groups of adjacent parallel coordination polymer grids are staggered and that the interlayer separation is a consequence of the size of the arene network. It should therefore be unsurprising that type A grids result when templated by the smallest arenes (benzene and derivatives) as they exhibit smaller interlayer separations than types B and C packing. Grid types B and C occur in the presence of larger or more arenes.

Given that cavity size within the aromatic networks is complementary with the width and height of a single aromatic ring, the self-assembly of aromatic molecules in the compounds reported herein is readily sustained by edge-to-face and face-to-face interactions with the hydrocarbon portion of the bipy moieties. These interactions are presumably a primary driving force for the clathration of the guests and a mitigating factor against interpenetration. Interpenetration was not encountered in the square grid coordination polymer networks described above, and stacking interactions are seen in all compounds. It is also interesting to note that only three packing modes are observed in 13 compounds of similar composition. However, a question that cannot yet be answered with certainty concerns whether the noncovalent networks of aromatic molecules can exist in the absence of the coordination polymers. In this context, the existence of a 1:1 binary compound between ferrocene and pyrene[245] represents an important prototype since pairs of ferrocene molecules are stacked inside a pyrene 2D network that is sustained by noncovalent C−H···π interactions.

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Scheme 9. Representative Examples of Supramolecular Sythons



III. Hydrogen-Bonded Networks

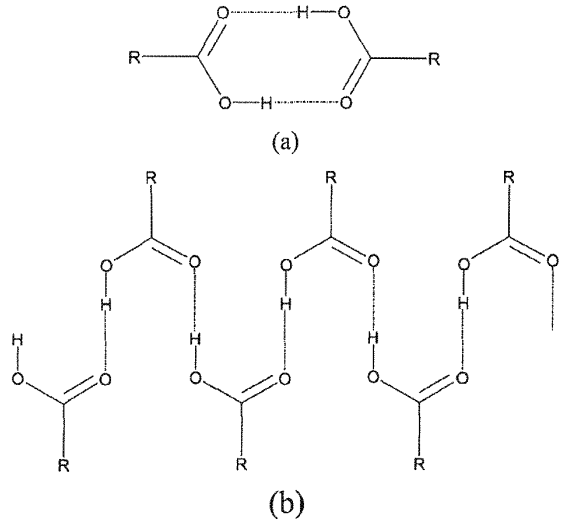
It would be inappropriate to attempt to present an exhaustive overview of crystal engineering of organic solids in this contribution. However, we feel that it is appropriate to highlight the analogies that can be drawn between hydrogen-bonded networks and coordination polymers. In particular, for hydrogen-bonded networks, the donor (i.e., a protic hydrogen atom) and the acceptor (i.e., a region of electron density) can be compared with metal atoms and ligands, respectively. Furthermore, as noted by Etter,[25] in cases where there are multiple hydrogen-bonding sites, there is a fair degree of predictability concerning which donors and acceptors will engage. Therefore, the "node and spacer" approach can be employed equally well with hydrogen bonds as with coordinate covalent bonds. Indeed, it is now realized that weak hydrogen bonds,[246-251] stacking interactions,[20,252,253] and halogen−halogen interactions[254-256] can also play a significant and predictable structure-determining role. However, we shall emphasize structures that are sustained by so-called strong hydrogen bonds, including ionic hydrogen bonds. For a more rigorous evaluation of the broader perspectives of hydrogen-bonded networks in the context of crystal engineering, one may consider looking at one of the many recent reviews on the subject.[22,90,257-264] In the context of this contribution, synthons that involve NH···O and/or OH···O hydrogen bonds, including those that exploit the carboxylic dimer or its deprotonated form, will be highlighted. They represent reliable and ubiquitous supramolecular synthons that already have been applied in a broad range of systems and have analogues in the context of coordination polymers.

It is only natural to analyze existing crystal structures by breaking them down, at least as far as is reasonably possible, into discrete aggregates or 1D, 2D, or 3D networks. At the very least, rationalization of crystal structures then becomes greatly simplified since even the presence of a reliable 1D network, for example, for a given set of molecular recognition features or supramolecular synthons significantly restricts the number of possible packing modes. An exciting byproduct of this thought process is that design of new compositions and crystal structures can also be achieved by thinking in terms of network design. The concept of using this *supramolecular synthesis* approach to design new generations of infinite network structures offers enticing targets for both scientific and technological reasons. The greatest degree of predictability occurs if 2D and 3D architectures can be generated from first principles. In the case of the latter, the only degree of unpredictability would appear to relate to whether subtle conformational effects can affect structure or, in the case of open framework structures, as to whether interpenetration occurs. This approach to crystal engineering offers the intriguing concept of inherent control over the dimensions and molecular recognition features that are present in laminated or porous structures.

Scheme 9 illustrates some of the more common supramolecular synthons that have been exploited by crystal engineers to design and build organic molecular networks. The carboxylic acid moiety represents perhaps the most widely observed and exploited of these supramolecular synthons. This should be unsurprising since the carboxylic acid moiety is ubiquitous in organic chemistry. The carboxylic acid moiety also represents an ideal illustration of the problems associated with crystal structure prediction and design if one concentrates upon a molecular unit with a limited number of dimensions and molecular recognition sites. Monocarboxylic acids have been widely studied crystallographically, and it has been demonstrated[88] that there are two common motifs observed in the solid state for carboxylic acids. These supramolecular isomers, which profoundly influence the crystal packing and bulk properties, are illustrated in Scheme 10. As might be expected, the carboxylic dimer, A, is the most commonly observed supramolecular isomer and, being inherently centrosymmetric, tends to afford nonpolar crystals. However, since it is effectively a discrete 0D aggregate, there is little information that might be used in order to facilitate prediction of the overall crystal structure. The other motif, B, affords a 1D chain that is polar because it is the result of "head-to-tail" self-assembly. This simplifies to some extent the problem of crystal structure prediction, but it still does not address how these 1D chains pack. There is almost random choice of parallel or antiparallel packing of these chains in observed crystal struc-

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Scheme 10. Schematic Diagram Illustrating the Two Supramolecular Isomers for the Carboxylic Acid Supramolecular Synthon: (a) 0D Dimer and (b) 1D Head-to-Tail Chain



tures. This is a subtle but important distinction since, in the case of parallel packing of chains, there is no crystallographic center of inversion within the 2D layer and crystallization in polar space groups therefore occurs in approximately 50% of structures that have thus far been characterized, i.e., centers of inversion between layers appear to occur in a random fashion. A similar situation occurs in the case of benzenedicarboxylic acids such as terephthalic acid. That terephthalic acid is inherently predisposed to form infinite 1D chains is intuitive. However, one must still jump from chains to grids to frames in order to generate a crystal structure. Indeed, terephthalic acid exhibits two polymorphs that are based upon identical chains that pack in different orientations.[265,266] It is possible to summarize the situation in the context of monocarboxylic acids and 1D structures as follows. (1) A lot of information can be generated by analyzing the crystal packing in monocarboxylic acids, including confirmation that the presence of a centrosymmetric supramolecular synthon (i.e., the carboxylic acid dimer) strongly tends toward centrosymmetric crystals. (2) Unfortunately, we still have only really learned what not to do if one wishes to design polar crystals (i.e., one should avoid a centrosymmetric supramolecular isomer) rather than what one must aim for in order to ensure optimized bulk polarity. (3) It appears that multiple molecular recognition sites will be necessary in order to gain a greater degree of predictability over organic crystal structures. Furthermore, the orientation of these recognition sites should be suitable for generation of at least a 2D network.

For the above reasons, our primary focus in the context of hydrogen-bonded networks will be 2D and 3D networks, prefaced by a brief discussion of discrete aggregates and 1D polymers.

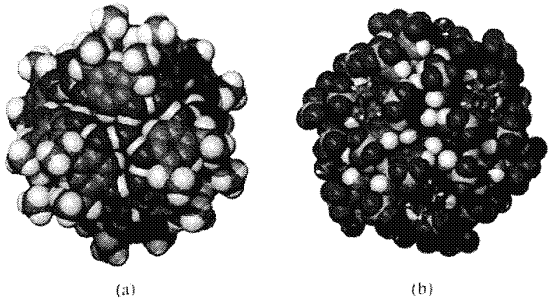


Figure 12. Space-filling representations of large self-assembled spherical assemblies: (a) [*C*-methylresorcin[4]-arene)$_6$(H_2O)$_8$], a snub cube, and (b) [(*p*-sulfonatocalix[4]-arene)$_7$], a great rhombicuboctahedron.

A. 0D (Discrete) Aggregates and 1D Networks

The structures that can result from self-assembly of a *cis*-octahedral or a *cis*-square planar metal and a linear "spacer" ligand have been previously discussed in section II in the context of coordination polymers. The important geometric constraint introduced by the *cis*-conformation is the 90° vector imposed by the coordination geometry, i.e., it represents an angular node which can direct self-assembly into either a 1D zigzag, 1D helical, or 0D discrete cyclic motif. A prototypal example of an angular "node" in the context of hydrogen-bonded networks is isophthalic acid, which subtends a 120° angle between its carboxylic acid moieties. Although the preferred solid-state structure of isophthalic acid is the zigzag motif,[267] it has been demonstrated that self-assembly of a discrete hexameric aggregate that also persists in solution can be invoked by the addition of a bulky substituent to the 5-position on the benzene core.[268,269]

The exploitation of bulky substituents to direct the formation of discrete aggregates over infinite structures has also been shown to be successful in binary hydrogen-bonded systems, as exemplified by a series of 1:1 complexes formed from cyanuric acid and disubstituted melamines.[270–275] The relative bulkiness of the melamine substituents determines whether the structure adopts a linear tape (1D), crinkled tape (1D), or rosette (0D) structure, in order of increasing steric contribution.

A different strategy that has recently been employed for the isolation and development of discrete structures is based upon generating molecular polyhedra by using geometric considerations as found in Platonic and Archimedean solids. A prototypal example of such a structure[121] is the self-assembled *snub cube*[276] that occurs when calix-*C*-methylresorcin-[4]arenes self-assemble with water molecules to form [*C*-methylresorcin[4]arene)$_6$(H_2O)$_8$]. The resulting structure forms a spheroid held together by hydrogen bonds, and it possesses a very large enclosed cavity, 1375 Å^3. A related structure[116] can be generated when *p*-sulfonatocalix[4]arenes self-assemble with pyridine-*N*-oxide, metal ions, and water. The resulting discrete structure is based upon a *rhombitruncated cuboctahedron*.[277] The two Archimedean structures are illustrated in Figure 12.

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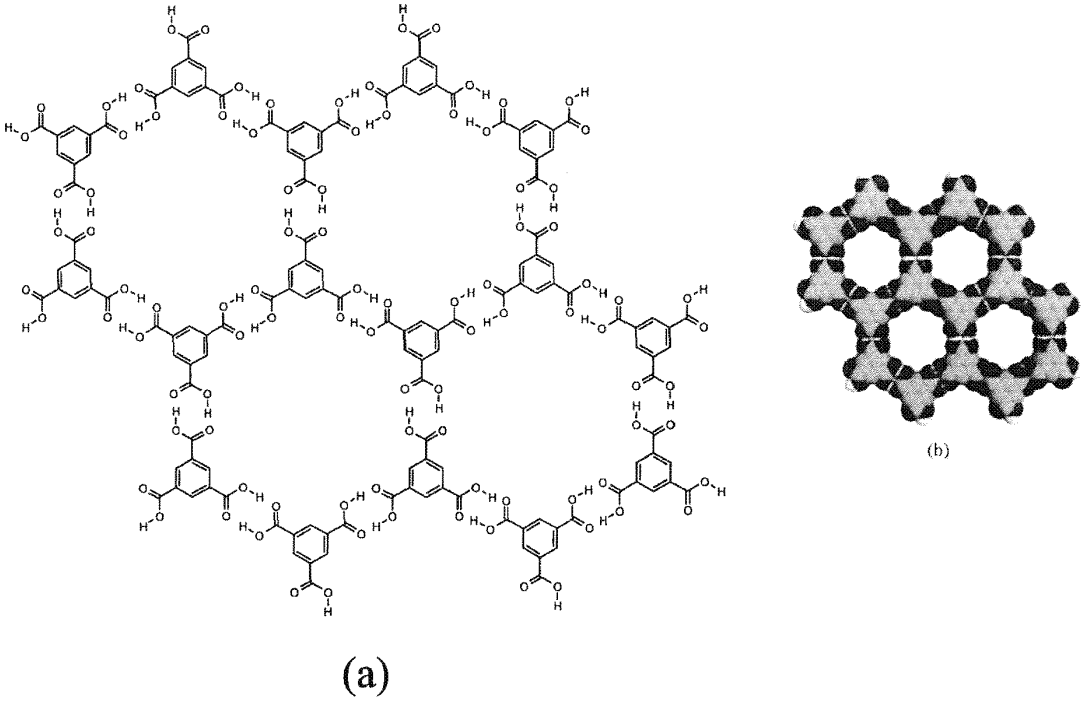


Figure 13. Honeycomb (6,3)-network observed for BTC (BTC = 1,3,5-benzenetricarboxylic acid): (a) schematic representation of the hydrogen-bonding pattern and (b) space-filling model illustrating the hexagonal channels that are formed.

Many viruses have an outer shell, or capsid, that can be described as a hydrogen-bonded polyhedron (icosahedron).[93] The above synthetic structures may provide chemists with insight as to how to design nanoscale polyhedra for application in biological systems. In this context, it should also be noted that Etter reported a series of discrete binary adducts between acyclic imides and a series of cocrystallization aids.[278] This work also represents an attempt to better understand and ultimately control the type of hydrogen-bonding interactions that play such an important role in molecular recognition of biological systems.[279] It seems reasonable to assert that the studies of hydrogen-bonding patterns in the systems described above might indeed eventually aid in the design of structures that will impact biological systems.

B. 2D Networks

Hydrogen-bonded 2D networks are exemplified by organic molecular networks that are constituted from organic moieties with multiple complementary terminal functional groups that necessarily assemble into 2D arrays because of their geometric disposition.

1. Derivatives of Trimesic Acid

The well-known structure of trimesic acid (1,3,5-benzene tricarboxylic acid, H_3TMA), a polyfunctional carboxylic acid that is inexpensive and chemically robust, has long intrigued crystal engineers and represents a more suitable prototype for crystal structure prediction and design than mono- or dicarboxylic acids. It possesses trigonal exodentate functionality that facilitates self-assembly into two dimensions. Figure 13 illustrates how the hydrogen-bonding pattern in the 2D networks formed by H_3TMA generates cavities of predictable size (approximately 14 Å diameter). In pure H_3TMA[280] the honeycomb grid is puckered and the cavities are filled by self-inclusion, or interpenetration, of other networks. However, subsequent reports revealed that there are methods for preparing a noninterpenetrated or open framework form of H_3TMA.[281,282] If crystallized in the presence of alkanes, H_3TMA forms open framework honeycomb layers that align in such a manner that adjacent sheets are almost eclipsed with respect to each other (Figure 14). The resulting architecture observed in the crystal structure is essentially identical to that depicted in Figure 13.

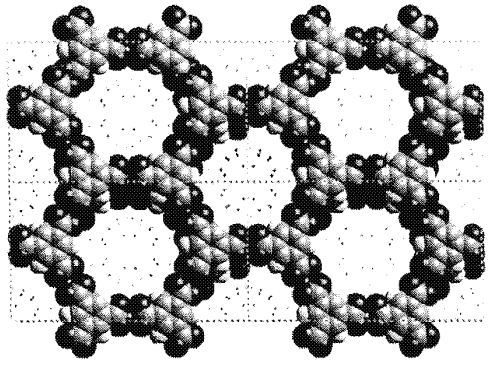
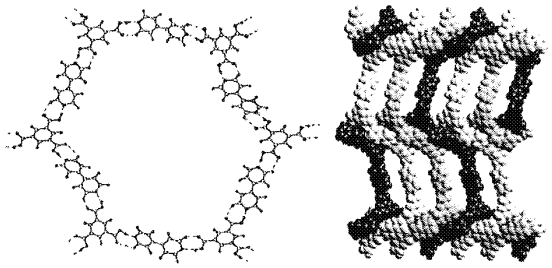


Figure 14. Space-filling illustration of the BTC·isooctane clathrate. The isooctane is disordered within the hexagonal channels.

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(a) (b)

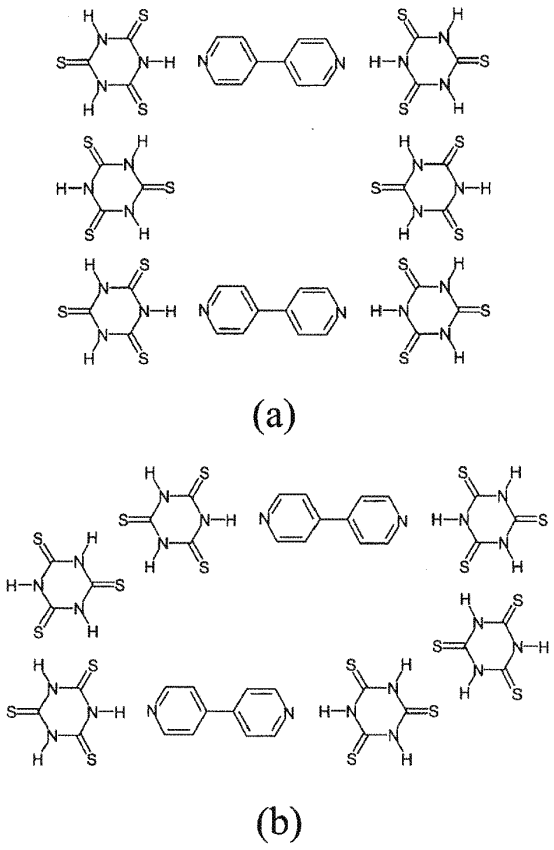
Figure 15.

H_3TMA represents an example of a motif that is the result of the assembly of a single component that is self-complementary. As discussed earlier, this means that there are limits in terms of supramolecular synthesis when compared to multiple-component modular systems. The H_3TMA network can be extended to generate larger holes and, therefore, larger channels and cavities by employing the modular self-assembly approach. The structure of $[H_3TMA][bipy]_{1.5}$ would be expected to exist as an expanded form of H_3TMA since the pyridine–carboxylic acid supramolecular synthon appears to be more stable than the carboxylic acid dimer itself.[283–285] As shown in Figure 15, the anticipated structure indeed occurs and the cavities are large (ca. 26 × 35 Å). However, these cavities are filled by the interpenetration of three independent networks (Figure 15b), thereby affording a close-packed structure with no cavities. This type of interpenetration, which can be termed parallel interpenetration,[10] resembles weaving and is facilitated by puckering of the pseudohexagons that form the network. The hexagons resemble the chair conformation of cyclohexane.

Rao et al. recently reported a related structure that is based upon modular self-assembly:[286] an organic network formed by trithiocyanuric acid (TCA) and bipy. Adjacent layers are aligned parallel to each other, but there is no interpenetration. The resulting open framework structure exhibits channels with an effective diameter of 10 Å. An interesting feature of this compound is that the cavities in the layers, and therefore the resulting channels, can vary in size depending on the solvent of crystallization that is used to template the modular self-assembly process. (Scheme 11). It should be noted that the two architectures that have thus been observed are not simply distorted or stretched variants of one another, they have distinct hydrogen-bonding patterns. Another salient feature is that there are sulfur atoms accessible in the cavities which could promote selective sorption or could facilitate desired chemical reactivity in the context of green chemistry.[287]

Network structures based upon metalloporphyrins with multiexodentate functionality (e.g., tetracarboxylic acid derivatives) have also yielded 2D networks sustained by hydrogen bonding.[288] An interesting feature of these structures is that the presence of a metal ion in the porphyrin ring can afford cross-linking of 2D layers by bidentate spacer ligands, thereby affording a 3D architecture.[288] Such an architecture is a hybrid form[289] of coordination polymer and organic network.

Scheme 11. Schematic of the Two Supramolecular Isomers Reported for the Modular Self-assembly of TCA and bipy



(a)

(b)

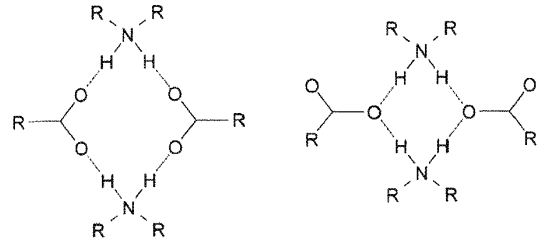
3. Hydrogen-Bonded Networks Sustained by Organic Ions

Salts that are based upon organic ions with complementary hydrogen-bonding sites represent an alternate approach to modular self-assembly of organic molecular components. H_3TMA also represents an appropriate precursor in this context, via formation of ammonium salts of the deprotonated forms of H_3TMA.[290–292] Although it might not at first be obvious how the ammonium moiety could extend anionic forms of H_3TMA into honeycomb networks, Scheme 12 illustrates two such motifs, the supramolecular isomers A and B, both of which facilitate linear propagation of carboxylate anions. In the case of TMA^{3-} and dicyclohexylammonium, supramolecular isomers A and B have both been observed to generate laminated structures. The generation of A or B appears to be solvent dependent. It has also been shown that self-assembly of the lamellar structure can occur at surfaces.[293]

An important feature of architectures that are sustained by A and B is that some of their components and features can be fine-tuned without destroying the basic architecture. For example, the

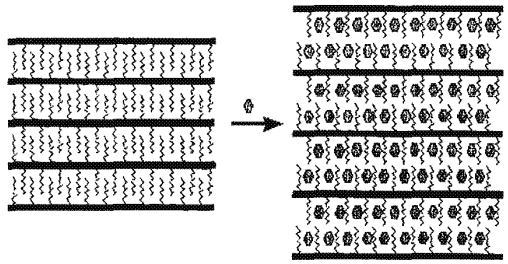
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Scheme 12. Schematic Illustration of Two Motifs that Can Occur through Self-assembly of Dialkylammonium and Carboxylate Moieties. Both Motifs Effect Linear Propagation



(a) (b)

Scheme 13. Schematic Illustration of the Interdigitation of the Alkyl Groups on Adjacent Layers in $[(BTC^{2-})(NH_2(alkyl)_2^+)_2]$ and the Possibility of Intercalation of Guest Molecules



ammonium cation substituents can be changed without influencing the basic molecular recognition properties in the context of motifs A and B. For secondary amines, organic substituents would extend above and below the network and in appropriate circumstances would preclude interpenetration. Depending upon the nature of the substituents, adjacent layers might interdigitate and/or adopt clay-like intercalates in the presence of appropriate guest molecules (Scheme 13). Both $HTMA^{2-}$ and TMA^{3-} can sustain laminar structures that result from crystallization of H_3TMA in the presence of primary and secondary amines (RNH_2 and R_2NH).

Related laminar architectures have also been synthesized using other polyfunctional carboxylic acids such as trimellitic and pyromellitic acids.[294] Stoichiometry has little influence over whether laminar structures are obtained, but it has a profound influence over the local hydrogen-bonding patterns and the molecular recognition features of the "organic clays" that are formed.

Stoichiometry 1:2 (H_3TMA:amine). The hydrogen-bond network within each sheet is hardly predictable, but it seems to be reproducible over a wide range of ammonium cations. The structure of the 2D network is illustrated in Figure 17, and it is composed entirely of ionic hydrogen bonds. If alkyl substituents are present on the ammonium cation, then the typical result is a laminated material with poor ability to adsorb molecules because of interdigitation of the alkyl substituents[291] (Figure 17). However, use of dibenzylamine (DBA), $[(PhCh_2)_2NH]$, mitigates against interdigitation and promotes reversible incorporation of aromatic guest molecules.[290] The resulting compounds are structurally related to clays, but they are inherently hydrophobic and have affinity for aromatic guests over alcohols or water. In this series of compounds, there is some variation in the geometry of the hydrogen-bond layer and in the manner in which guest molecules are incorporated. In general, the benzyl groups form a plethora of aromatic C−H···π interactions to the surrounding guest molecules. The unit cell lengths are typically multiples of ca. 12 × 17 × 21 Å (stacking axis, short axis, and long axis, respectively). The length of the stacking axis represents the interlayer separation, and a doubling of the length of the stacking axis occurs when adjacent layers are not related by translation. Multiples of short and long axes also occur because of differences in the arrangement of guest molecules between benzyl groups. In effect, guest molecules and/or benzyl groups do not necessarily repeat with the asymmetric unit of the H-bonded layer. The crystal structures might be classified based upon the stacking axis as being of one of two types: (a) identical packing of adjacent layers (i.e., related by translation) or (b) adjacent layers which are different from each other. The hydrogen-bonded sheets can be either flat or corrugated. In effect, the host matrix is a flexible, generic host material for aromatic molecules. A representative

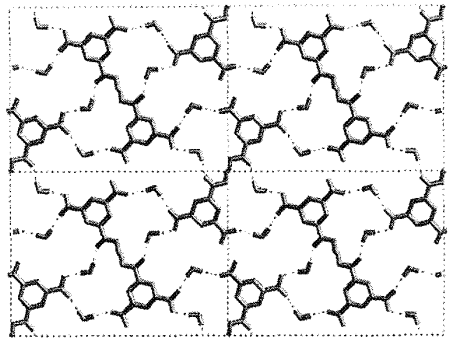
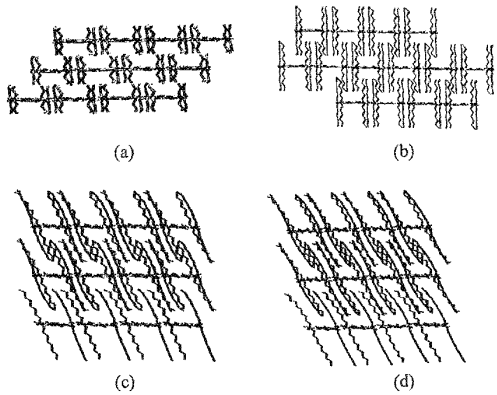


Figure 16. Illustration of the hydrogen-bonding pattern in $[(BTC^{2-})(NH_2(CH_2Ph)_2^+)_2]$; benzyl groups are omitted for clarity.



(a) (b) (c) (d)

Figure 17. Illustrations of the packing interactions of the hydrogen-bonded 2D networks in $[(BTC^{2-})(NH_2(alkyl)_2^+)_2]$, alkyl = (a) propyl, (b) hexyl, (c) octyl, and (d) decyl.

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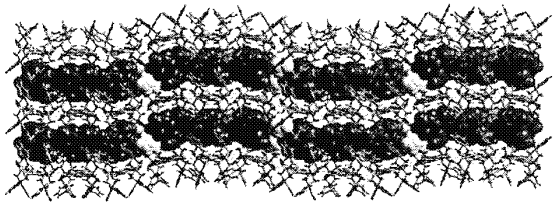


Figure 18. Illustrationof the crystal packing of the hydrogen-bonded 2D networks in $[(BTC^{2-})(NH_2(CH_2Ph)_2^+)_2]$. The benzyl moieties preclude interdigitation and facilitate reversible sorption of aromatic molecules.

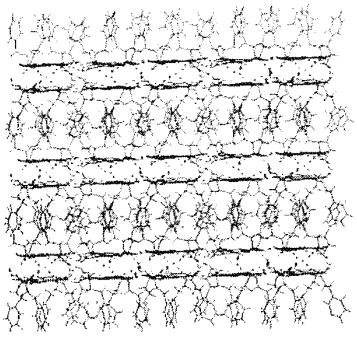


Figure 19. Illustration of the crystal packing in $[(BTC^{2-})(NH_3(CH_2Ph)^+)_2]$, a prototypal example of the network structures formed by BTC dianions and primary ammonium cations.

structure is illustrated in Figure 18, and as should be clear, there is no interdigitation of benzyl groups. The guest molecules interact with walls of the channels only, and the asymmetric unit is unusual: 3:3:1 for host:guest:solvent. In the presence of primary ammonium cations, similar structures are obtained but they are more appropriately termed bilayer architectures since there are alternating hydrophobic and hydrophilic regions. A typical structure is illustrated in Figure 19. Similar structures are obtained for both alkyl- and benzylammonium cations. It might be reasonable to describe such structures as being cytomimetic since there is a resemblance to the type of supramolecular synthons that exist in phospholipid membranes and in the solid phases of surfactants. The ancillary organic groups orient in the same direction and interdigitate with adjacent layers to generate hydrophobic regions. The hydrophilic faces of adjacent bilayers also face one another and can incorporate water molecules. The thickness of hydrophilic layers ranges from 3.2 to 3.4 Å, while the thickness of interdigitated layers increases with the size of the organic group.

Stoichiometry 1:3 (H_3TMA:amine). In principle, 1:3 stoichiometry offers the opportunity to generate honeycomb networks. As revealed by Figure 20a, motif A or B should be capable of propagating the trimesate anion into a honeycomb structure. Figure 20b reveals that the crystal structure of [TMA]-[dicylohexylammonium]$_3$ exists as the anticipated honeycomb array.[290] The cyclohexyl moieties, which are omitted for the sake of clarity, effectively prevent interpenetration by capping the 13 Å cavities that are present within the honeycomb structure. If the

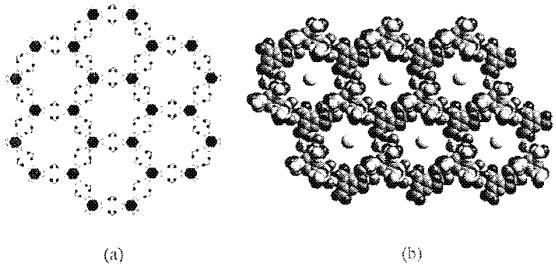


Figure 20. Modular honeycomb network sustained by BTC trianions and secondary alkylammonium cations: (a) schematic representation of the hydrogen-bonding pattern and (b) space-filling illustration of the crystal structure of $[(BTC^{2-})(NH_3(C_6H_{12})^+)_2]$.

solvent is changed, a honeycomb network based upon the other supramolecular synthon is generated,[293] and it has been reported that this form of the honeycomb network will self-assemble at the air–water interface. The modular nature of this structure permits replacement of the cyclohexyl moieties by other moieties. In this context, alkyl groups that are less sterically demanding (e.g., *n*-alkyl) have also been incorporated into the motif in Figure 20a. Interpenetration occurs in these structures.

Guanidinium Sulfonates. A series of related structures that are based upon two-dimensional layers resulting from hydrogen bonding of the trigonal guanidinium cation, $C(NH_2)_3^+$, and organic sulfonate ions RSO_3^- has been extensively studied by the Ward group[176,238,240,295–302] (Scheme 14).

Interdigitation of the organic substituent of the sulfonate ions on adjacent layers and ionic hydrogen-bonding predictably leads to a broad series of laminar architectures. It should be noted that there are several key differences between guanidinium sulfonates and alkylammonium trimesates. (1) There exists only one ancillary organic functional group per sulfonate ion compared to up to two ancillary functional groups per ammonium cation. (2) The anion is functionalized rather than the cation. (3) In one sense, the alkylsulfonates are more versatile since they can exhibit architectural (i.e., supramolecular) isomerism so as to generate either bilayer or clay-like architectures. To generate a clay-like architecture, organic groups must orient above and below each layer as illustrated by Scheme 15. The steric demands of the organic group appear to determine whether they orient in the same direction (i.e., a bilayer structure) or alternate above and below the layer (i.e., a clay-like structure).

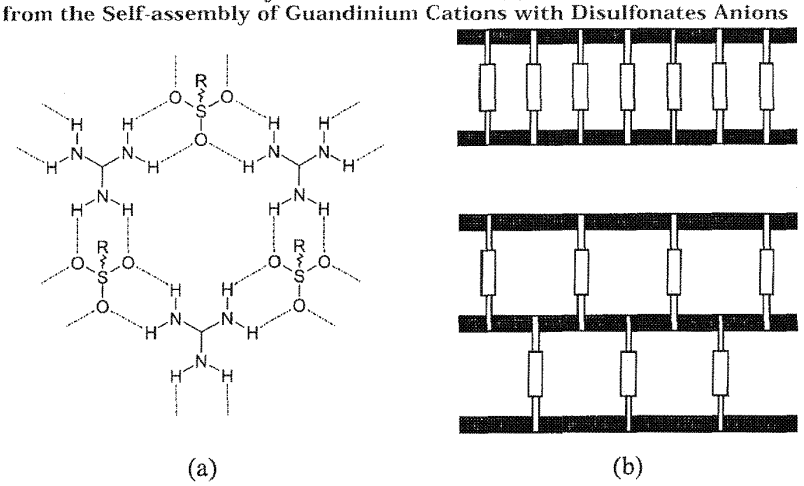
C. 3D Networks

1. Self-Assembled Hydrogen-Bonded Diamondoid Networks

A report by Ermer[86] on the structural characterization of adamantane-1,3,5,7-tetracarboxylic acid and its implications represented a watershed for crystal engineering. Ermer's study was followed by a flurry of activity into design from first principles of both organic diamondoid networks and metal–organic diamondoid coordination polymers. The carboxylic

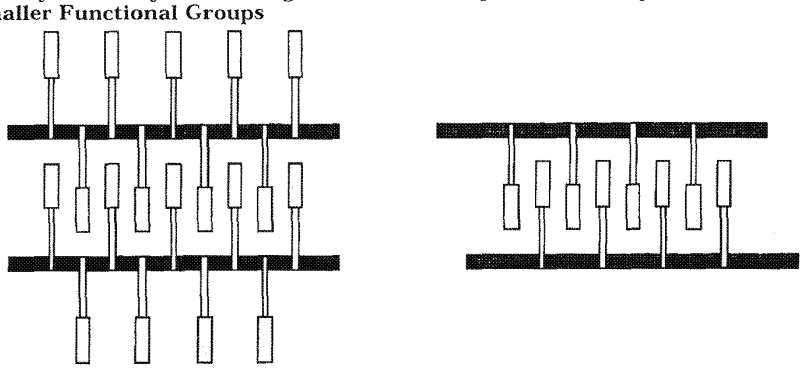
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Scheme 14. Schematic Illustration of the Key Structural Features of Guanidinium Sulfonates: (a) Hexagonal Channels that Form 2D Honeycomb Networks and (b) Two Extended Structures (2D and 3D) that Can Result from the Self-assembly of Guandinium Cations with Disulfonates Anions



(a) (b)

Scheme 15. Schematic Illustrating Two Possible Modes of Interdigitation for Guanidinium Sulfonates: (a) Clay-like, Induced by Sterically Demanding Functional Groups and (b) Bilayer Architecture, Typically Observed for Smaller Functional Groups



(a) (b)

acid groups of adamantane-1,3,5,7-tetracarboxylic acid are tetrahedrally oriented. It is therefore unsurprising that they self-assemble via the hydrogen-bonded carboxylic dimer supramolecular synthon to afford an infinite diamondoid network. Each network possesses cavities that could accommodate a large roughly spherical guest, or guest aggregate, of roughly 12 Å in diameter. However, these cavities are filled by five independent networks that interpenetrate in such a way that the crystal structure is densely packed, and consequently, guest inclusion is precluded. As subsequent studies have revealed, interpenetration is a widespread phenomenon in diamondoid networks and occurs in many other organic and metal−organic structures that would otherwise have large cavities or channels. An interpenetrated diamondoid architecture is also exhibited by methanetetraacetic acid, for which the cavities generated are approximately 10 Å in diameter.[87] As would be expected, methanetetraacetic acid exhibits a lower degree of interpenetration: 3-fold. 2,6-dimethylidineadamantane-1,3,5,7-tetracarboxylic acid also forms a hydrogen-bonded diamondoid structure, but it exhibits a much lower degree of interpenetration than its unsubstituted precursor. The 2-fold "double diamondoid" architecture is not as densely packed, and it can therefore act as a host and enclathrate guest molecules.[86]

Wuest demonstrated that the pyridone moiety also generates a hydrogen-bonded supramolecular synthon that is suitable for building extended arrays.[89,303,304] Remarkably, methanetetra(6-phenylethynyl-2-pyridone) exhibits a diamondoid network, 7-fold interpenetration, and cavities large enough to enclathrate butyric or valeric acid.[89] Wuest introduced the concept of "tectons" to describe molecules that inherently possess the molecular structure and intermolecular recognition features to predictably self-assemble into crystalline networks. This study was followed by studies that demonstrated that there are several other examples of diamondoid networks that can be sustained by the pyridone moiety.[305,306]

2. Modular Self-Assembly of Hydrogen-Bonded Diamondoid Networks

As discussed earlier, modular self-assembly relies upon two molecular components that are not individually capable of self-assembly and can be invoked

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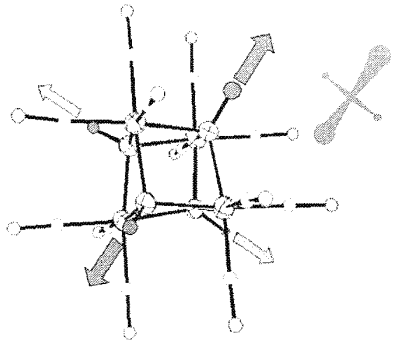
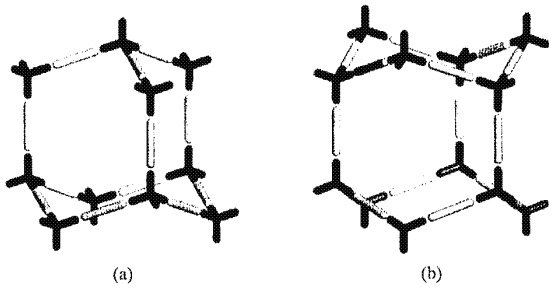


Figure 21. $[Mn(\mu_3\text{-}OH)(CO)_3]_4$: a cubane-like cluster possessing perfect T_d symmetry that represents a prototypal example of a tetrahedral hydrogen-bond donor.

Scheme 16. Schematic Illustration of the Two Types of Diamondoid Architecture: (a) Cubic and (b) Hexagonal



to understand coordination polymers or multiple-component hydrogen-bonded networks.[90] There are significant differences between the types of tetrahedral moiety that can sustain networks that have been self-assembled from a single component vs networks that have been self-assembled from multiple components. The most fundamental difference between the two types of structure is that the tetrahedral component that sustains single-component self-assembled architectures would not ordinarily be able to sustain modular architectures and vice versa. In the case of the former, the tetrahedral moieties must be self-complementary and there is only one component necessary for self-assembly to occur. This means, for example, that both hydrogen-bond donors and hydrogen-bond acceptors must be present in the same molecule. In the case of the latter, the tetrahedral node must be either an acceptor or a donor of hydrogen bonds and the linker or spacer must be complementary. Both components are necessary, and there must be a 1:2 ratio in order for the diamondoid architecture to self-assemble. Scheme 16 illustrates the difference between the two types of diamondoid networks.

An example of a node that is suitable for modular self-assembly is the cubane cluster $[Mn(\mu_3\text{-}OH)(CO)_3]_4$,[307] which possesses perfect T_d symmetry and has four strong hydrogen-bond donors and no strong hydrogen-bond acceptors (Figure 21). This tetrahedral hydrogen-bond donor forms diamondoid cocrystals with a wide range of obvious and, in some cases, not so obvious spacer molecules. A "not so obvious"

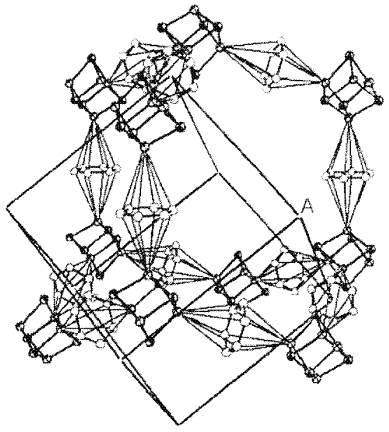


Figure 22. Illustration of the crystal structure and diamondoid cavity generated in $[Mn(\mu_3\text{-}OH)(CO)_3]_4$·2benzene.

structure is that formed when $[Mn(\mu_3\text{-}OH)(CO)_3]_4$ is cocrystallized with benzene.[308] A 2-fold diamondoid structure is sustained by OH···π hydrogen bonds, and the tetrahedral symmetry of the node is observed in the crystallographic sense since $[Mn(\mu_3\text{-}OH)(CO)_3]_4$·2benzene crystallizes in the cubic space group $Pn\text{-}3m$ with $z = 2$. As revealed by Figure 22, which illustrates an adamantoid portion of the structure, a large cavity is generated and this facilitates interpenetration of a second diamondoid network.

The use of transition metals or transition-metal clusters to act as nodes for the modular self-assembly of diamondoid networks that are sustained by coordinate covalent bonds is also well established. Such architectures are of more than aesthetic appeal, and they have resulted in a class of compounds with interesting bulk and functional properties. Metal–organic diamondoid structures in which the spacer moiety has no center of inversion are predisposed to generate polar networks since there would not be an inherent center of inversion. Pyridine-4-carboxylic acid, isonicotinic acid, is such a ligand, and bis(isonicotinato)zinc exists as a 3-fold diamondoid structure that is both thermally stable and inherently polar.[228] It exhibits SHG activity that is three times higher than the commercially relevant NLO material KDP.[309,310]

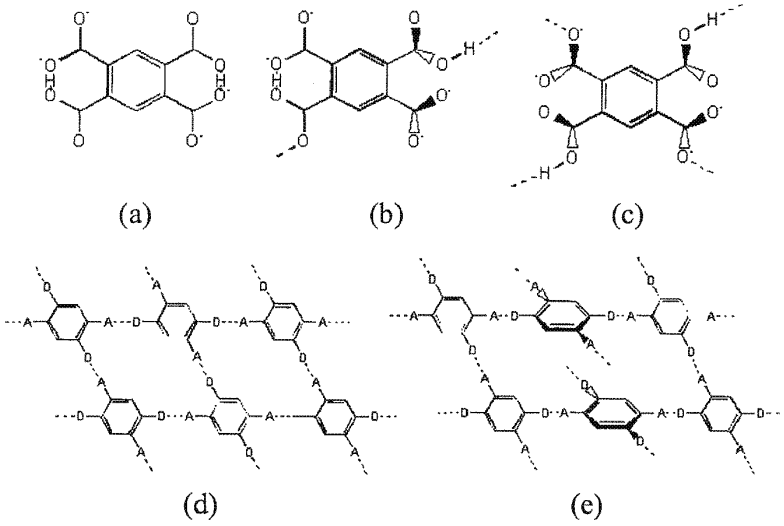
There are also supramolecular synthons that do not rely upon hydrogen bonds. In this context, N···Br interactions were exploited to propagate a diamondoid network in the cocrystal formed by carbon tetrabromide and hexamethylenetetraaamine. This structure also represents a different but equally effective form of the modular approach: two tetrahedral nodes with one possessing donor functionality and the other acceptor functionality only. The structure of the cocrystal formed by carbon tetrabromide and hexamethylenetetraaamine exhibits 2-fold interpenetration and does not enclathrate solvent or guest.[311]

3. Other 3D Hydrogen-Bonded Networks

Although there are many examples of organic crystals that can be defined as 3D networks, few of

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Scheme 17. Schematic Illustrating Five Supramolecular Synthons Possible for Pyromellitate Dianions



them are predictable or even rational in the same sense as diamondoid networks. Trimesic acid, H_3-TMA, is an interesting exception and was discussed earlier in the context of 2D structures. H_3TMA represents a prototypal molecule in the context of hydrogen bonding and generates extended structures when pure, partially deprotonated, in coordination polymers or in cocrystals. Anionic derivatives of H_3TMA self-assemble into honeycomb grids via O−H···O$^-$ hydrogen bonds.[280−282,312,313] Pyromellitic acid, 1,2,4,5-benzenetetracarboxylic acid, H_4PMA, has been less widely explored than H_3TMA. It has been utilized as a ligand in coordination polymer networks,[294] and very few organic structures containing H_4PMA or its derivatives are known. We anticipated that doubly deprotonated H_4PMA would self-assemble via dicarboxylate hydrogen bonds to form 0D (two intramolecular hydrogen bonds), 1D (one intramolecular and one intermolecular hydrogen bond), or 2D/3D (two intermolecular hydrogen bonds) networks (Scheme 17). H_2PMA^{2-} anions exhibit all four of these supramolecular isomers depending upon the polymorph or the counterion.[314] The 3D structure occurs because H_2PMA^{2-} moieties orient in such a manner that they form hydrogen bonds to the next layer. The network can be described as a framework built from square building blocks that alternate parallel and perpendicular with respect to one another. This network can therefore be regarded as an organic analogue of NbO.[66]

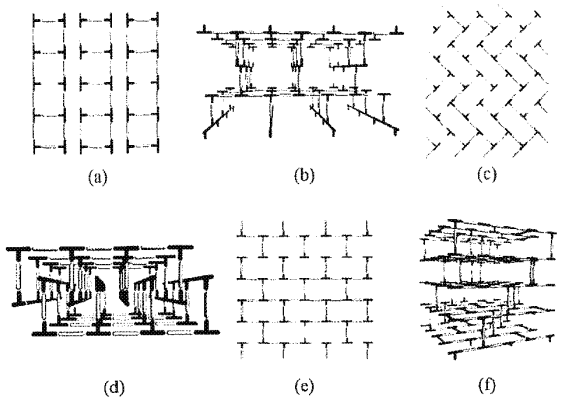
It should be obvious that all 2D networks must, in the absence of solvent or intercalated guest, engage in noncovalent interactions with the layers above and below. The possibility of exploiting a combination of molecular recognition modes represents a particularly attractive approach to control crystal packing since it places no restrictions in terms of the type of chemical components that can be rationally incorporated into crystalline phases. In this context, Fowler and Lauher[19,315−320] illustrated how it is possible to use hydrogen bonding to control interactions between 1D networks, or á-networks, and to thereby yield predictable 2D networks or α-networks. If the sheets are designed to be self-complementary in the third dimension, then a predictable 3D network or γ-network can result. Fowler and Lauher demonstrated not only that such a strategy is viable, but that it can offer a degree of control over stacking of layers such that the interlayer components are positioned within the limits of the topochemical principle. They were thereby able to effect solid-state reactions upon appropriate perturbation. When coupled with other advances in this context, including recent reports[17,19] that demonstrate how discrete aggregates may also afford components that are positioned within the topochemical boundaries, it should be clear that crystal engineering involving multiple types of molecular recognition offers significant implications for solid-state synthesis and solvent-free, green chemistry.

IV. Supramolecular Isomerism and Polymorphism

The existence of supramolecular isomerism might be seen as a problem from a design perspective since it necessarily implies that there will be superstructural diversity for a given molecular building block. However, there is another way to look at this matter. It is also possible to view supramolecular isomerism as an opportunity to gain a better fundamental understanding of the factors that influence crystal nucleation and growth. Such a linkage can be justified as follows. (1) If one invokes the concept of supramolecular isomerism, then it should become apparent that it represents a significant limitation on the number of possible superstructures (i.e., discrete structures or 1D, 2D, or 3D networks) that can occur for a given molecular building block. Therefore, one can invoke a study on supramolecular isomerism or polymorphism with the assumption that self-assembly means that there will only be a finite number of architectures that are feasible for a given molecular species. This assumption will be based upon crystals being the result of directional

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Scheme 18. Schematic Illustration of the Six Supramolecular Isomers Reported for T-Shaped Nodes Linked by Linear Bifunctional Exodentate Ligands: (a) 1D Ladder, (b) 3D Lincoln Logs, (c) 2D Herringbone, (d) 2D Bilayer, (e) 2D Brick Wall, and (f) 3D Frame



supramolecular synthons, the fundamental precept of crystal engineering. (2) The ability of the crystal engineer to design a molecular building block that is predisposed toward the formation of supramolecular isomers provides an ideal opportunity for design of supramolecular isomers and, perhaps more importantly, for learning how to control supramolecular isomers. At the very least, it will be possible to develop "recipes" that invoke crystallization conditions, templates, and/or solvents to favor or disfavor a particular supramolecular isomer.[321,322] (3) The concepts of self-assembly, crystal engineering, and networking provide clear implications for gaining a better fundamental understanding of polymorphism since polymorphism can be regarded as a subset of supramolecular isomerism. (4) It should be clear that to gain a better understanding of supramolecular isomerism and polymorphism, it is a requirement that full structural characterization of compounds be conducted. This means an in-depth analysis of crystal packing and intermolecular contacts as well as measurement of physical properties.

To illustrate the linkage between crystal engineering, supramolecular isomerism, and polymorphism, we shall consider three types of supramolecular isomerism and demonstrate how analogies can be readily drawn between coordination polymers and organic networks.

A. Structural Supramolecular Isomerism

That structural supramolecular isomerism can have profound implications for structure and properties is exemplified by the range of structures that has thus far been observed in coordination polymers that are generated by one of the simplest building blocks and stoichiometries: 1:1.5 stoichiometry, mer-metal, and linear spacer ligand. These building blocks can be regarded as being based upon self-assembly of T-shaped nodes. There already exists a surprisingly diverse range of structures that have been observed in this context. Scheme 18 illustrates the supramolecular isomers that have thus far been observed: ladder[91,178] (A), brick wall[204] (B), 3D frame or "Lincoln Logs"[236,237] (C), bilayer[213] (D), herringbone[210] (E),[78,211,212] and another version of a 3D frame[177] (F). Three of the isomers A,[178] D,[213] and F[177] have been observed for the same asymmetric unit for metal = $Co(NO_3)_2$ and ligand = bipy, and the other three have been seen in similar compounds which use bipy or extended analogues as "spacer ligands".

The following points should be noted about such structures. (1) These compounds are not true polymorphs since guest or solvent molecules are present in the lattice. However, neither are they solvates in the conventional sense. (2) The diversity of network structures and hence bulk properties is remarkable. (3) None of these architectures occurs naturally in minerals. (4) The network structures themselves are entirely predictable based upon simple structural considerations. (5) Some of these structures can occur from the same building blocks under almost identical crystallization conditions.

It is possible to draw direct analogies with polymorphism in organic crystals. For example, a similar approach based upon networks can be used to analyze the packing in organic compounds. A recent paper highlighted this situation in the context of 2-amino-5-nitropyrimidine, a compound that exhibits three readily available polymorphs, all of which have distinct hydrogen-bonded networks.[323] Etter's study concerning carboxylic acids[88] and how they can self-assemble to form either head-to-tail chains or centrosymmetric dimers also illustrates how one can rationalize polymorphism based upon supramolecular isomers and networks.

In summary, it seems likely that use of appropriate templates or guest molecules facilitates recipes that can be used to reliably generate all supramolecular isomers that are possible for a given node. Therefore, one might assert that there are a finite number of superstructures possible for a given molecular moiety and that it will eventually be possible to determine the crystallization conditions under which each one will occur.

B. Conformational Supramolecular Isomerism

Flexibility in ligands can lead to subtle or dramatic changes in architecture. For example, 1,2-bis(pyridyl)ethane, bipy-eta, can readily adapt *gauche*- or *anti*-conformations. In the case of $[Co(bipy\text{-}eta)_{1.5}(NO_3)_2]_n$, which contains a T-shaped node, infinite molecular ladders which contain six molecules of chloroform per cavity exist as the most commonly encountered architecture (Figure 23a).[186] In such a situation, all "spacer ligands" are necessarily *anti*. However, under certain crystallization conditions (e.g., solvent MeCN or dioxane), a bilayer architecture is obtained with two *anti*- and one *gauche*-spacer ligand per metal atom (Figure 23b).

The bilayer architecture can contain solvent molecules such as MeCN or can collapse on itself in the absence of solvent.[44] This more subtle form of supramolecular isomerism occurs if $[Co(bipy\text{-}eta)_{1.5}(NO_3)_2]_n$ is crystallized in the absence of a suitable guest or solvent.[217] Figure 24 reveals how [Co(bipy-

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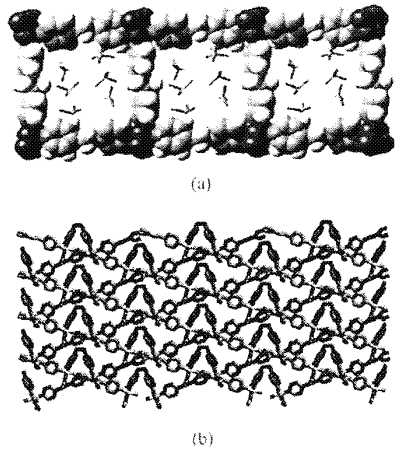


Figure 23. Illustrations of two structures observed for [Co(bipy-eta)$_{1.5}$(NO$_3$)$_2$]: (a) ladder in which all bipy-eta ligands adapt an *anti*-orientation and (b) bilayer in which bipy-eta ligands adapt *anti*- and *gauche*-orientations in a 2:1 ratio.

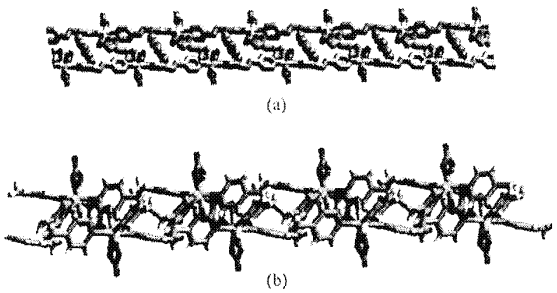


Figure 24. Illustrations of crystal structures of [Co(bipy-eta)$_{1.5}$(NO$_3$)$_2$] cocrystallized with (a) MeCN and (b) no solvent of crystallization. Note how the cavities collapse in the absence of the adsorbed solvent.

eta)$_{1.5}$(NO$_3$)$_2$]$_n$ collapses to close the cavity that exists when crystallized from MeCN.[44] Note the difference in torsion angles between the two compounds. A similar situation occurs in compounds based upon a longer bis-pyridyl ligand, 1,4-bis((4-pyridyl)methyl)-2,3,5,6-tetrafluorophenylene, **2**. When **2** is complexed to Cd to form compounds of formula [Cd(**2**)$_2$(NO$_3$)$_2$], three very different supramolecular isomers have been observed depending upon the nature of guests or templates: 1D chains, 2D sheets, and 3D diamondoid networks.[324]

A dramatic illustration of how conformational variability can influence crystal packing in organic compounds is illustrated by the compound 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitile. This compound exists in at least six polymorphic phases. The primary difference between the six phases lies with the torsion angle between the thiophene moiety and the *o*-nitroaniline fragment, which varies from 21.7° to 104.7°.[55]

C. Catenane Supramolecular Isomerism

The existence of independent interpenetrating networks is surprisingly common if relatively large

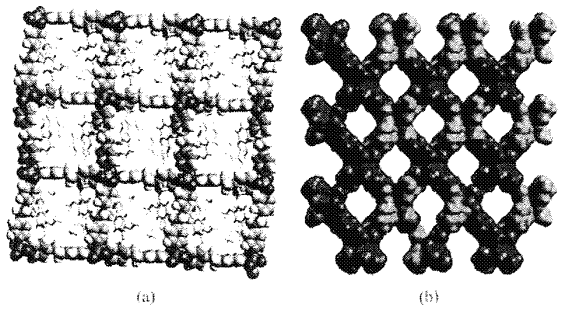


Figure 25. Illustrations of two crystal structures of the square grid coordination polymer [Ni(bipy-eta)$_2$(NO$_3$)$_2$]: (a) with included guest molecules and (b) interpenetrated networks.

cavities are generated within a network. A thorough review of this subject in the context of coordination polymers was recently published by Batten and Robson.[58] The existence of interpenetration has been regarded as a factor that mitigates strongly against the generation of stable open framework structures. However, it is becoming clear that appropriate use of templates can afford either open framework or interpenetrated structures for the same network. This is exemplified by the prototypal diamondoid and square grid networks Cd(CN)$_2$ and M(bipy)$_2$X$_2$. Both of these compounds have been prepared as interpenetrated and noninterpenetrated forms. Furthermore, some interpenetrated structures can also be regarded as open framework since if interpenetration will not necessarily afford close-packing. Interpenetrated structures can still contain channels large enough to hold, for example, aromatic guests. Such is the case for square grid networks based upon ligands such as bipy-eta. Figure 25 reveals how either open framework square grid or interpenetrated square grid structures can be readily generated for the same square grid network.[200] Both compounds contain square grids of formula [Ni(bipy-eta)$_2$(NO$_3$)]$_n$. As would be expected, the compound illustrated in Figure 25a, [Ni(bipy-eta)$_2$(NO$_3$)]$_n$, exhibits clay-like properties and can desorb and adsorb guests. Crystallinity is lost, but the square grid architecture retains its integrity below 220 °C. The interpenetrated analogue is illustrated in Figure 25b and is effectively a 3D architecture that is built by interpenetration of square grids. This compound has a more rigid structure than its noninterpenetrated form and behaves like a zeolitic solid rather than a clay-like solid. Both compounds are stable to loss of guest, but the former loses crystallinity upon loss of guest.

Organic networks are also capable of exhibiting interpenetration, and in this context H$_3$TMA represents a prototypal example. As discussed earlier, H$_3$TMA is predisposed to generate honeycomb sheets with large cavities. Three phases of H$_3$TMA have thus far been characterized. In two of these phases, one of which is pure H$_3$TMA, 3-fold interpenetration of the individual hexagonal cavities occurs.[282] In pure H$_3$TMA, the honeycomb networks are puckered in such a manner that small cavities are generated.[280] These cavities can hold small molecules, including

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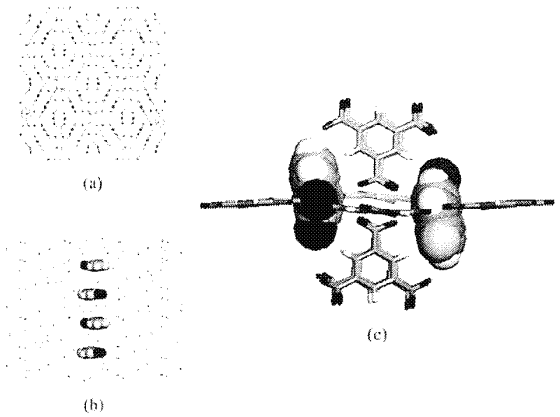


Figure 26. Illustration of the α-polymorph of BTC that illustrates how BTC can sustain the enclathration of *p*-nitroaniline: (a) view of the 10-fold interpenetrated puckered honeycomb networks, (b) view of a single BTC network with 3-fold interpenetration per cavity and incorporation of *p*-nitroaniline in "pockets", and (c) perspective view of two *p*-nitroanilines situated in a single cavity, surrounded by the three interpenetrating networks.

halogens[312] and *p*-nitroaniline.[325] The structure of the inclusion compound formed between H_3TMA and *p*-nitroaniline is illustrated in Figure 26. The other interpenetrated phase of H_3TMA contains flat sheets, and it therefore contains infinite 1D channels.[281] The noninterpenetrated phase of H_3TMA, illustrated in Figure 14, is formed when long-chain alkanes are used during the crystallization process.

A honeycomb network is also generated when H_3-TMA is cocrystallized with bipy. This structure exhibits interpenetration in 2D to form a novel carpet-like architecture.[283] However, the noninterpenetrated form remains to be isolated.

The results described above all suggest that interpenetration can be avoided if appropriate templates are used during the crystallization. It is therefore reasonable to see interpenetration as another example of supramolecular isomerism, one that can be controlled by use of guest or template molecules during crystallization.

V. Potential Applications

A considerable amount of research into understanding the nature and predictability of supramolecular synthons remains to be conducted. An enhanced database concerning supramolecular synthons in the broad context would also assist our fundamental understanding of solution chemistry and biochemistry. Nevertheless, it is clear that there are a number of applications of crystal engineering that could be realized in the short term. Several of these are summarized below. (1) From a supramolecular perspective, binary compounds represent an illustration of how one might exploit the modular approach to design new supermolecules, especially in the solid state. It is reasonable to assert that supramolecular synthesis of new classes of cocrystal and modular solid offers potential to increase the known range of crystalline materials by two or three orders of magnitude and to facilitate combinatorial approaches to materials science. For example, if one were to only consider cocrystals that are sustained by hydrogen bonding, a wide range of compositions exists that remain to be explored. It is perhaps sobering to realize that, at least in principle, molecules that are deficient in hydrogen-bond acceptors are inherently prone to form supermolecules with molecules that contain excess hydrogen-bond acceptors. Even if one considered only simple examples such as pyridines, there are many permutations for formation of binary compounds. If one were to study, for example, 20 pyridines and 20 carboxylic acids, then one would expect 400 new binary compounds with predictable composition and structure. Such a strategy could be important in the context of supramolecular derivatives of drugs and functional materials (i.e., modification of bulk properties without changing the molecular structure of the active species) or they could serve as precursors to covalent products, including polymers. Such an approach has already been effective in formulation of polaroid film.[326] There also exists the possibility of rationalizing certain types of host–guest structures as being based upon topologically complementary networks.[241,243] Such compounds are also based upon self-assembly and might be prototypal for large numbers of related structures. (2) It is already established that solvent-free synthesis, green chemistry, offers many potential advantages, including cost and environmental benefits.[13,14] Cocrystallization of substrates and subsequently conducting reactions in the solid state offers the opportunity for very careful control over regio- and stereochemistry. It is also possible that supramolecular arrays could act as precursors to new classes of 2D and 3D covalent polymers.[327] (3) New classes of adsorbent, "organic and metal–organic clays and zeolites" represent an area in which considerable progress has already been made. Such compounds offer clear potential for the following: efficient, cost-effective alternatives to current methods of enantiomeric separations, new materials for separation of gases, liquids, and solutes, new industrial heterogeneous catalysts, new drug delivery matrixes (e.g., matrix for oral delivery of otherwise unstable drugs), a new generation of chemical sensors, and new storage matrixes for gases such as methane. Recent results indicate that synthetic metal–organic polymers can offer high levels of thermal stability and can supersede zeolites in terms of surface area and capacity for small guest molecules.[76,81] (4) The rational design of polar materials for use in materials science also represents an aspect of crystal engineering that has already provided promising developments. Unfortunately, in most organic crystals, antiparallel architectures predominate, thereby canceling dipoles of highly polarizable molecules and mitigating against optimization of bulk polarity. Fortunately, there now exists an extended range of modular, open framework organic and metal–organic solids. Many of these compounds contain architectures (e.g., square grid, honeycomb, octahedral) that favor incorporation of polar strands into channels, thereby reducing the driving force for

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antiparallel alignment. Results obtained by the groups of Hollingsworth[328-332] and Hulliger et al.[333-340] suggest that such compounds, in particular channel-type inclusion compounds, hold considerable promise in the context of the design of solids that possess fine-tunable bulk polarity. Diamondoid networks also offer considerable potential in this context since tetrahedral nodes do not contain a center of inversion.[90] The recent results of Lin's group indicate that diamondoid networks can couple high thermal stability with high SHG activity.[228,229] (5) Metal−organic polymers offer considerable potential in the context of molecular magnetism, semiconductors, and conductors.[341-347] Once again, the possibility of design and fine-tuning becomes apparent when one develops structures with predictable architectures that are based upon paramagnetic metal ions. The presence of guest molecules can be a desirable feature as it would be expected to offer a degree of fine-tuning that is not inherently present in single-component compounds.

VI. Conclusions and Future Directions

"*The peasant who wants to harvest in his lifetime cannot wait for the ab initio theory of weather*", H. G. von Schnering (1981).

The fundamental precept of crystal engineering is that all information necessary for design of extended 1D, 2D, and 3D structures is already present at the molecular level in existing chemical species. Recent advances in our understanding of supramolecular chemistry and supramolecular synthons have been aided by the advent of CCD diffractometers coupled with ever more powerful visualization and analysis tools. It should therefore be unsurprising that control over supramolecular architectures, also known as molecular tectonics,[348] has advanced rapidly in recent years. That these tools are now routinely available means that an even more concerted and systematic approach to gaining an understanding of the subtle factors that control architectures in the solid state is feasible. The rational design of supramolecular structure necessarily relies upon invoking the concepts of self-assembly, in effect supramolecular synthesis, and exploits noncovalent forces as varied as the following: (1) hydrogen bonding, including both strong hydrogen bonding (e.g., O−H- - -O) and weak hydrogen bonding (e.g., C−H- - -O and even C−H- - -π), (2) coordinate covalent bonds (e.g., metal−organic polymers), (3) electrostatic and charge-transfer attractions, and (4) aromatic π-stacking interactions.

These principles of crystal engineering and supramolecular synthesis have thus far been used to design, isolate, and characterize a number of novel network structures that are prototypal because they are based upon modular components. However, these networks are typically based upon relatively small molecular components and the number and chemical type of components is typically restricted. It is in these two areas that there appears to be almost unlimited potential for supramolecular synthesis. In the context of coordination polymer networks, a recent review indicates how wide the range of chemical components and accessible network motifs has become.[215] However, the scale of these structures is such that cavities and channels are on the order of 10 Å and, to date, each cavity is identical. Careful selection of appropriate substrates or components and ever more control over crystal packing will offer the potential for rational design of an even more extensive array of modular (i.e., binary, ternary, or even higher order) structures than those that are currently available. In particular, judicious choice of secondary building units,[84] supermolecules, or biomolecules as templates and nodes should afford composite materials with nanoscale dimensions and cavities. The same is likely to be true concerning the rational development of structures that are based upon components that are at first glance incompatible. A number of examples of pure crystalline compounds that are based upon metal−organic polymers and metal oxide clusters have been reported in recent years.[197,289,349,350] Such composite materials would represent "uncharted territory", but they are a natural outgrowth of modular approaches to chemistry and now appear to be at hand. In essence, suprasupermolecular[351] synthesis in the solid state is likely to develop considerably further and, whereas prediction of crystal structures remains an elusive goal that will continue to be addressed, it does not preclude short-term applications of crystal engineering in a number of important areas. H. G. von Schnering's comments therefore seem particularly appropriate to summarize the current opportunities for crystal engineering and design.[352]

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Electronic Acknowledgement Receipt

EFS ID:	2044932
Application Number:	10378956
International Application Number:	
Confirmation Number:	4742
Title of Invention:	Multiple-component solid phases containing at least one active pharmaceutical ingredient
First Named Inventor/Applicant Name:	Michael J. Zaworotko
Customer Number:	23557
Filer:	Frank Christopher Eisenschenk/Sherry Loke
Filer Authorized By:	Frank Christopher Eisenschenk
Attorney Docket Number:	USF-106XC1
Receipt Date:	03-AUG-2007
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Time Stamp:	12:39:12
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1		Amd-RCE.pdf	1413541 db5ff9452323285a48e7b1a5176251305ea504aa	yes	28

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment Submitted/Entered with Filing of CPA/RCE	1	1
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	Applicant Arguments/Remarks Made in an Amendment	5	9
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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/378,956	03/03/2003	Michael J. Zaworotko	USF-106XC1	4742

23557 7590 08/10/2007
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EXAMINER	
WILLIAMS, LEONARD M	
ART UNIT	**PAPER NUMBER**
1617	

MAIL DATE	DELIVERY MODE
08/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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Office Action Summary	Application No.	Applicant(s)	
	10/378,956	ZAWOROTKO ET AL.	
	Examiner	Art Unit	
	Leonard M. Williams	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25,27 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25, 27 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

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Detailed Action

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/15/2007 has been entered.

Response to Arguments

Applicant's arguments filed 05/15/2007 have been fully considered but they are not persuasive. The applicant's have reiterated their position that the prior art is not appropriate for rejection under 102(e). This argument has been addressed in the last office action and the response and rejection of the last office action is included below.

Applicant's have amended claim 25 to include the phrase "is a crystal that". The examiner respectfully points out that the insertion of this phrase does not distinguish the claims over the prior art. The prior art clearly indicates that the solid includes crystal forms, polymorphs, etc... As such the 102(e) rejection of the last office action is not overcome and is maintained.

Response to Amendment

The applicant's have argued that the '293 patent is not prior art under 102(e) as the evidence set forth in the rejection is drawn from a provisional application later than applicant's. The examiner without agreeing to applicant's assertion, respectfully points out the following from pages 14-15 of provisional application No. 60/356764: "A further embodiment of the invention encompasses a method for treating or preventing cluster headache in a patient which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of a pharmaceutically acceptable salt of topiramate, or a polymorph, solvate, hydrate, dehydrate, anhydrous, or amorphous form thereof. Preferably, the pharmaceutically acceptable salt of topiramate is selected from the group consisting of topiramate sodium, topiramate lithium, and topiramate potassium, or a polymorph, solvate, hydrate, dehydrate, anhydrous, or amorphous form thereof.

Topiramate can be made using various methods known to those skilled in the art. For example, methods for the chemical synthesis of topiramate are described in U.S. Pat. No. 4,513,006, which is incorporated by reference herein in its entirety. Other methods well known in the art for preparing topiramate may also be used, including, for example, those disclosed in U.S. Pat. Nos. 6,319,903, 5,387,700; 5,258,402, 5,384,327, 5,242,942, 4,792,569, 2,554,816 and 2,980,679, all of which are incorporated by reference in their entirety.

The present invention involves the unexpected discovery that the sulfamate (-OSO2NH2) group of topiramate is slightly acidic and thus may be a handle for generation of salts. Salts are often associated with improved chemical stability and increased solubility of drugs leading to better delivery of drug to the body, by reducing unwanted degradation product exposure and increasing levels of drug in the body. Salt forms of drugs therefore constitute a useful set of options for development of drug formulations.

Pharmaceutically acceptable salts of topiramate can be prepared by treating topiramate with appropriate bases, such as organic or inorganic bases. Bases that can be used to prepare pharmaceutically acceptable salts of topiramate are those that form non-toxic base addition salts, i.e., salts containing pharmacologically acceptable cations, including, but not limited to, sodium, potassium, lithium, magnesium, calcium, aluminum, zinc, procaine, benzathine, chloroprocaine, choline, diethylamine, ethylenediamine, N-methylglucamine, benethamine, clemizole, diethylamine, piperazine, tromethamine, triethylamine, ethanolamine, triethanolamine, arginine, lysine, histidine, tributylamine, 2-amino-2-pentylpropanol, 2-amino-2-methyl-1,3-propanediol, tris(hydroxymethyl)aminomethane, benzylamine, 2-(dimethylamino)ethanol, barium or bismuth counter ions. Particularly preferred cations are sodium, lithium, and potassium. The most preferred cation is sodium.

Crystallization of pharmaceutically acceptable salts of topiramate can be accomplished by several means, as would be apparent to one skilled in the art. For instance, saturation of an aqueous solution of the salt can be increased by cooling, and

the cooling curve can be a determinant of the particle properties (e.g,. size, habit) that result from a crystallization process.

Alternatively, addition of an anti-solvent (or non-solvent), such as an alcohol or other water miscible solvent, can be used to increase saturation of the salt form in the medium and hence effect nucleation and growth of crystals. Examples of anti-solvents include, but are not limited to, iso-propanol, THF, and ethanol. Preferably, ethanol would be used, due to its azeotrope with water, anti-solvent quality with many salt forms and pharmaceutical acceptance."

The examiner respectfully points out that even in this provisional it is indicated that topiramate can be reacted with an organic or inorganic base to make a salt and that such a salt can be made via crystallization of the topiramate and the base. Included bases that can be crystallized with topiramate include compounds such as procaine, arginine, lysine, benzathine, etc... (all compounds that can generate their own crystal forms). Thus the basic requirements of the current claims are met even as their exist a active pharmaceutical agent (topiramate), chemical functionalities capable of forming supramolecular synthons with itself (topiramate crystals), other functionalities that can react with a second synthon via non-covalent bonding (topiramate's weak acidic properties and salt formation), and the formation of a multiple-component solid phase composition (recrystalized topiramate and the selected salt). The examiner asserts that this provisional disclosure provides basis for the 102(e) rejection as written and as this provisional has a date that is good for a 102(e) rejection, this patent constitutes appropriate prior art over the claims as presented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 25-28 are rejected under 35 U.S.C. 102(e) as being anticipated by Almarsson et al. (US Patent No. 6559293).

Almarsson et al., in the abstract, teach novel salts of topiramate, along with pharmaceutically acceptable polymorphs, solvates, hydrates, dehydrates, and co-crystals thereof as well as pharmaceutical compositions containing the same. The invention further encompasses novel co-crystals or complexes of topiramate and pharmaceutical compositions comprising them.

In col. 1 lines 15-65, Almarsson et al. teach that topiramate is a sulfamate-substituted monosaccharide which is a white crystalline powder. In col. 6 lines 1-12, Almarsson et al. teaches that specific co-crystals are complexes with caffeine. Almarsson et al. teach in col. 14 line 14 to col. 15 line 20 and example 7, methods of making a topiramate-caffeine co-crystal compositions. Almarrson et al. states:

"The present invention involves the unexpected discovery that the sulfamate (--OSO.sub.2 NH.sub.2) group of topiramate is slightly acidic and thus may be a handle

for generation of salts, co-crystals, and complexes with basic compounds such as, but not limited to, caffeine, N-methyl pyrrolidine, nicotine, nicotinamide, and ethers such as PEGs (examples include but are not limited to PEG 200 and PEG 300). Salts are often associated with improved chemical stability and increased solubility of drugs leading to better delivery of drug to the body, by reducing unwanted degradation product exposure and increasing levels of drug in the body. Salt forms of drugs therefore constitute a useful set of options for development of drug formulations."

Additional salts useful in the invention can be prepared by reaction of topiramate with organic and inorganic bases such as procaine, benzanthine, chloroprocaine etc...

Further in col. 14 Almarrson et al. state:

"Co-crystals and complexes of topiramate and other compounds can be prepared using conventional crystallization techniques, e.g., from solutions comprising topiramate and the other compounds. Without being limited by theory, it is believed that the compounds within co-crystals and complexes can interact via hydrogen bonding, ionic, or other interactions. Crystallization from melts of topiramate and other compounds may also be used to prepare co-crystals or complexes of topiramate. For example, a co-crystal or complex of topiramate and caffeine can be prepared by melting and recrystallizing caffeine, allowing such to cool, then contacting topiramate melt with the recrystallized caffeine, and allowing this to cool. In a particular method, caffeine is melted and recrystallized between a glass slide and glass cover slip on a hot-stage microscope (such as a Mettler-Toledo FP950tstage mounted on a Zeiss Axioplan II polarized light microscope). The hot-stage is allowed to cool to about 30.degree. C.

Topiramate is then placed on a glass slide in contact with the edge of the glass cover slip. The solid topiramate is melted and the melt is allowed to come into contact with the recrystallized caffeine. The temperature of the hotstage is lowered (e.g., to about 70.degree. C.) and held there overnight. During that time the melted topiramate recrystallizes and a co-crystalline phase crystallizes between the caffeine and topiramate regions. The slide can then be heated to determined the melting point of the caffeine:topiramate co-crystal."

Thus Almarsson et al. teach that topiramate has an acidic proton, the acidity can be exploited to make salts and/or co-crystals (such as when complexed with caffeine) and that such salts and/or co-crystals can be used to alter the structural and pharmaceutical properties of the salts and/or co-crystals. In example 7 the synthesis and characterization of the topiramate-caffeine co-crystal is detailed wherein caffeine was melted, recrystallized between a glass slide and a cover slip, allowed to cool and then topiramate was placed on the glass slide in contact with the cover slip and melted wherein the melt came into contact with the recrystallized caffeine. The melted topiramate was then recrystalized overnight and the interfacial region of the topiramate and caffeine was determined to be crystalline and showed a different morphology than the pure caffeine and pure topiramate phases. The absence of multiple melt regions (eutectics) between the topiramate and caffeine indicated only one pure topiramate-caffeine co-crystalline phase anticipating the "...method for identifying complementary chemical functionalities in order to form a desired supramolecular synthon, said method comprising: (a) evaluating the structure of an active pharmaceutical ingredient; (b)

determining whether the active pharmaceutical ingredient contains chemical functionalities capable of forming supramolecular synthons with itself; (c) identifying from a plurality of chemical functionalities that are known to form a supramolecular synthon at least one functionality that will form a further supramolecular synthon to the supramolecular synthon formed by the active pharmaceutical ingredient, wherein the identified chemical functionality is not capable of disrupting non-covalent bonding within the supramolecular synthon formed by the supramolecular synthon formed by the active pharmaceutical ingredient, and wherein the selected chemical functionality is capable of forming a noncovalent bond to the supramolecular synthon formed by the active pharmaceutical ingredient; (d) identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient and (e) preparing a multiple-component solid phase composition, wherein the multiple-component solid phase composition comprises the active pharmaceutical ingredient and at least one of the identified co-crystal formers" of claim 25, the "...method...wherein the at least one co-crystal former is selected from the group consisting of a different active pharmaceutical ingredient, a GRAS compound, a food additive, a low toxicity organic, and a metal-organic complex" of claim 27, and the "....method...wherein the multiple-component solid phase composition is formed by one or more methods selected from the group consisting of crystallization from solution, cooling the melt, sublimation, and grinding" of claim 28.

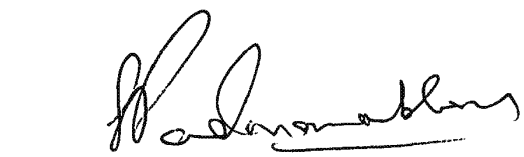
Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leonard M. Williams whose telephone number is 571-272-0685. The examiner can normally be reached on MF 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LMW



SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER

Substitute for form 1449B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	10/378,956
Filing Date	March 3, 2003
First Named Inventor	Michael J. Zaworotko
Group Art Unit	1617
Examiner Name	Leonard M. Williams
Attorney Docket Number	USF-106XC1

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article, (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
/LW/	R1	BALL, P. "Materials Chemistry - Scandal of Crystal Design ...", *Nature*, June 20, 1996, pp. 648-650, Vol. 381.	
/LW/	R2	BERNSTEIN, J. *et al.* "Concomitant Polymorphs", *Angew. Chem., Int. Ed.*, 1999, pp. 3440-3461, Vol. 38.	
/LW/	R3	BOUCHER, E. *et al.* "Use of Hydrogen-Bonds to Control Molecular Aggregation. Behavior of Dipyridones and Pyridone-Pyrimidones Designed to Form Cyclic Triplexes", *J. Org. Chem.*, 1995, pp. 1408-1412, Vol. 60.	
/LW/	R4	CHANG, Y. L. *et al.* "An Approach to the Design of Molecular-Solids. Strategies for Controlling the Assembly of Molecules Into Two-Dimensional Layered Structures", *J. Am. Chem. Soc.*, 1993, pp. 5991-6000, Vol. 115.	
/LW/	R5	DESIRAJU, G. R. "Crystal Gazing: Structure Prediction and Polymorphism", *Science*, October 17, 1997, pp. 404-405, Vol. 278, No 5337.	
/LW/	R6	FEYNMAN, R. "There's Plenty of Room at the Bottom", *Engineering and Science*, February 1960, pp. 22-36.	
/LW/	R7	MOULTON, B. *et al.* "From Molecules to Crystal Engineering: Supramolecular Isomerism and Polymorphism in Network Solids", *Chem. Rev.*, 2001, pp. 1629-1658, Vol. 101.	
/LW/	R8	ZAWOROTKO, M. J. "Crystal Engineering of Diamondoid Networks", *Chem. Soc. Rev.*, 1994, pp. 283-288, Vol. 23.	
	R9		
	R10		
	R11		
	R12		

Examiner Signature	/Leonard Williams/ (08/06/2007)	Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

TO-9199 (1-800-786-9199) and select option 2.

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Index of Claims

Application/Control No.	Applicant(s)/Patent under Reexamination
10/378,956	ZAWOROTKO ET AL.
Examiner	**Art Unit**
Leonard M. Williams	1617

R	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
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Claim		Date								
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Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination	
10/378,956	ZAWOROTKO ET AL.	
Examiner	**Art Unit**	
Leonard M. Williams	1617	

SEARCHED

Class	Subclass	Date	Examiner
424	401	3/9/2006	LMW
Updated 8/3/07 LMW			

INTERFERENCE SEARCHED

Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)

	DATE	EXMR
PALM MICHAEL J. ZAWOROTKO BRIAN MOULTON NAIR RODRIGUEZ-HORNEDO Updated 8/3/07 LMW	3/9/2006	LMW
EAST MICHAEL J. ZAWOROTKO BRIAN MOULTON NAIR RODRIGUEZ-HORNEDO Updated 8/3/07 LMW	3/9/2006	LMW

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/378,956	03/03/2003	Michael J. Zaworotko	USF-106XC1	4742

23557 7590 10/19/2007

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A PROFESSIONAL ASSOCIATION
PO BOX 142950
GAINESVILLE, FL 32614-2950

EXAMINER	
WILLIAMS, LEONARD M	
ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 10/19/2007

Please find below and/or attached an Office communication concerning this application or proceeding.

The request for deferral/suspension of action under 37 CFR 1.103 has been approved.

UM00014420
NOVARTIS EXHIBIT 1017
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UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/378,956	03/03/2003	Michael J. Zaworotko	USF-106XC1	4742

23557 7590 10/19/2007

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EXAMINER	
WILLIAMS, LEONARD M	
ART UNIT	**PAPER NUMBER**
1617	

MAIL DATE	DELIVERY MODE
10/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UM00014421
NOVARTIS EXHIBIT 1017
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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
10378956	3/3/03	ZAWOROTKO ET AL.	USF-106XC1

SALIWANCHIK LLOYD & SALIWANCHIK
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PO BOX 142950
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EXAMINER	
Leonard M. Williams	
ART UNIT	**PAPER**
1617	20071018

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

The Office Action of 08/10/2007 was inadvertantly sent on a suspended application and is hereby withdrawn.

/Padmanabhan/
SUPERVISORY PATENT EXAMINER

LMW

PTO-90C (Rev.04-03)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/378,956	03/03/2003	Michael J. Zaworotko	USF-106XC1	4742

23557 7590 10/14/2008

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EXAMINER	
JAVANMARD, SAHAR	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
10/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UM00014423
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Office Action Summary	Application No.	Applicant(s)	
	10/378,956	ZAWOROTKO ET AL.	
	Examiner	Art Unit	
	SAHAR JAVANMARD	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25,27,28,37 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25, 27, 28, 37, and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

This Office Action is in response to applicant's arguments filed on 08/03/2007. Claim(s) 25, 27, 28, 37, and 38 are pending and are examined herein.

Response to Arguments

In view of Applicant's affidavit, the Almarsson et al. reference (US Patent No. 6,559,293) is hereby being withdrawn as 102(e) art. The following new rejections are being made in the office action below.

Objection

Descriptions of figures 1 and 2 in the specification refers to color notations of the atoms, however such detail is not apparent from the drawings. Appropriate action is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is not clear what a “GRAS compound" is.

The rejection can be overcome by spelling out the abbreviation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 25, 27 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by DuRoss et al. (US Patent No. 5,023,092).

DuRoss teaches gamma sorbitol co-crystallized therewith mannitol in the gamma sorbitol polymorph. In particular, it is a co-crystalline product derived from a dehydrated aqueous solution of sorbitol containing mannitol. It is further directed to improved confections such as chewing gum, edible tablets and chocolates (column 1, lines 1-15). The co-crystallized product may further be characterized as having a melting point from 90°-100°C as determined by differential scanning calorimetry. DuRoss teaches that the curves generated in the apparatus indicates a single peaked

melting range unlike the double peak found for a synthetic blend made by pulverizing pure mannitol with pure sorbitol crystals into a uniform mixed powder or by blending a molten mixture of the two. This indicates that the product is a single crystal of sorbitol with mannitol included and not a mixture of pure crystals of mannitol and sorbitol (column 2, lines 35-45).

DuRoss teaches in carrying out the crystallization, the molten blend containing about 5-35 percent and more often, 7-16 percent mannitol (0.05 to less than 1.0% moisture) is held in a feed tank in a relatively dry atmosphere to inhibit moisture pickup such that the moisture content does not exceed about 0.75 percent by weight. This precaution becomes less a factor as the temperature of the molten mixture exceeds 100°C. In the operation of the mixing equipment the feed rate is adjusted such that as the cooling magma passes through the mixer, a molten blend having increasing concentrations of crystals is generated as the magma passes through from the feed to the discharge orifice. The rotating screws move the molten magma containing crystals from the center of the equipment to the outer cooled edge whereupon additional crystals are precipitated and remixed with additional molten material to act as a co-crystallized seed. As the temperature profile drops from molten feed temperature to discharge temperature the viscosity of the melt increases due to the formation of mannitol/sorbitol co-crystals in concentrations ranging from 35-80 percent by weight. The action of the rotating screws pushes the molten magma containing crystalline mass in the form of a rope or ribbon paste through the discharge orifice whereupon it is extruded as an elongated mass in the shape of a ribbon, circular rod, oval rod,

hexagonal rod, or star-shaped rod into the cold zone. It is cut into short lengths ranging from 1 to 4 inches and permitted to cool for several days at room temperature. If the temperature of the emitted extrudate is too hot the molten mass will not retain its shape and is difficult to handle. When such operating conditions take place, the product obtained is a mixture of crystals with glass. The problem can be corrected by decreasing the throughput time or jacket cooling temperature or a combination of both. Under ideal operating conditions, the extrudate crystalline paste develops a solid outer shell of crystalline product which is only slighted wetted on the interior side with molten magma. This material when permitted to stand will fully crystallize if allowed to cool slowly for a period of 6-96 hours for an extrudate having a cross-sectional dimension of about 5-20 millimeters. Longer periods may be required for extruded shapes having a cross-sectional dimension of greater than 20 millimeters. The manufacture of the co-crystallized mannitol/sorbitol product may be better understood with reference to the following example wherein all proportions expressed therein are by weight unless otherwise specified (column 3, line 61-column 4, line 43; also see examples 1 and A-D), thus meeting the limitations of claims 25, 27 and 28.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 37 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over DuRoss et al. (US Patent No. 5,023,092) as applied to claims 25, 27, 28 above in view of Desiraju (Angew. Int. Ed. Engl., 1995) of record.

DuRoss is discussed above.

DuRoss does not discuss the pharmaceutical agents as being aspirin, ibuprofen, flurbiprofen, carbamazepine, phenytoin, or acetaminophen.

Desiraju teaches that hydrogen bonding, the master key for molecular recognition, is the most reliable directional interaction in supramolecular construction, and its significance in crystal engineering can scarcely be underestimated.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have employed the co-crystallization method as taught by DuRoss and used aspirin, ibuprofen, flurbiprofen, carbamazepine, phenytoin, or acetaminophen. The motivation, provided by Desiraju, teaches that in fact these pharmaceutical molecules

are all capable of hydrogen bonding and would therefore obviously be capable of forming these supramolecular synthons. Thus, one in the art would expect, with a reasonable degree of certainty, that it would be possible to form co-crystals of the instant pharmaceutical agents as they possess all the prerequisites (ie, hydrogen bonding) inherently, in the absence of unexpected results.

Conclusion

Claims 25, 27, 28, 37, and 38 are not allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAHAR JAVANMARD whose telephone number is (571) 270-3280. The examiner can normally be reached on 8 AM-5 PM MON-FRI (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/S. J./

Examiner, Art Unit 1617

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617

Notice of References Cited	Application/Control No. 10/378,956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.	
	Examiner SAHAR JAVANMARD	Art Unit 1617	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-5,023,092	06-1991	DuRoss, James W.	426/3
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

UM00014432
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EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S2	2	("6559293").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2008/07/30 09:53
S3	1	aspirin cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/12 14:28
S4	1	almarrson	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/12 14:29
S5	246	almarsson	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/12 14:29
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S8	1303795	crystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/12 14:30
S9	102	S5 S8	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/12 14:30
S10	17	aspirin crystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/12 14:36

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S12	1	wo "0142222"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/12 14:59
S13	4182	supramolecul$2	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/12 15:00
S14	31445	aspirin	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/12 15:00
S15	157	S13 S14	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/12 15:00
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S17	2200	active pharmaceutical ingredient	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/12 15:02
S18	19	S13 S17	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/12 15:02
S19	2	heterosynthon	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/12 15:04
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S21	1329	co crystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/30 08:31
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S24	2	S22 and @pd<"20020301"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 08:45
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S26	18	S20 S25	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 08:48
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S31	543	Pharmaceutical (co adj crystal) composition drug	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 09:56
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S34	119	crystal engineering	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/30 10:03
S35	32	S34 and @pd<"20030303"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:03
S36	29	S34 drug	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:04
S37	4	S36 and @pd<"20030303"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:04
S38	228231	crystallization	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:26
S39	7179	S20 S38	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:26
S40	200	S20 S38	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	SAME	OFF	2008/09/30 10:26

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S41	132	S40 and @pd<"20030303"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:26
S42	106	S20 S38	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	WITH	OFF	2008/09/30 10:26
S43	64	S42 and @pd<"20030303"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:27
S44	472	cocrystallization	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:28
S45	41	S20 S44	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:28
S46	9	((MICHAEL) near2 (ZAWOROTKO)).INV.	US-PGPUB; USPAT	OR	OFF	2008/09/30 13:51
S47	5	((BRIAN) near2 (MOULTON)).INV.	US-PGPUB; USPAT	OR	OFF	2008/09/30 13:51
S48	5	((NAIR) near2 (RODRIGUEZ-HORNEDO)).INV.	US-PGPUB; USPAT	OR	OFF	2008/09/30 13:51
S49	77	(40/424).CCLS.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2008/09/30 14:23
S50	8	(400/424).CCLS.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2008/09/30 14:23

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NLM Catalog
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Query #15 deleted.

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- Search numbers may not be continuous; all searches are represented.
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- To combine searches use #search, e.g., #2 AND #3 or click query # for more options.

Search	Most Recent Queries	Time	Result
#14	Search **acetominophen cocrystal**	09:29:28	0
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#12	Search **carbamazepine cocrystal**	09:29:06	7
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#7	Search **aspirin cocrystal**	09:21:57	0
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#5	Search **ibuprofen cocrystal**	09:20:40	1
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#3	Search **api cocrystal**	09:19:38	6
#2	Search **carbamazepine-nicotinamide cocrystals**	09:19:24	3

Clear History

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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10378956	ZAWOROTKO ET AL.
	Examiner	Art Unit
	SAHAR JAVANMARD	1617

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	09/30/2008								
	1	-								
	2	-								
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NOVARTIS EXHIBIT 1017
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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10378956	ZAWOROTKO ET AL.
	Examiner	Art Unit
	SAHAR JAVANMARD	1617

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	09/30/2008								
	37	✓								
	38	✓								

UM00014440
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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10378956	ZAWOROTKO ET AL.
	Examiner	Art Unit
	SAHAR JAVANMARD	1617

SEARCHED			
Class	Subclass	Date	Examiner
424	400	9/30/2008	SJ

SEARCH NOTES		
Search Notes	Date	Examiner
EAST (searched each inventor name)		
EAST (keyword search)		
Pubmed (see search notes)		

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

/S. J./ Examiner.Art Unit 1617	

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1617

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313 on January 14, 2009.

Frank C. Eisenschenk

Frank C. Eisenschenk, Ph.D., Patent Attorney

PETITION UNDER 37 CFR 1.84(a)(2)
Patent Application
Docket No. USF.106XC1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Sahar Javanmard
Art Unit	:	1617
Applicants	:	Michael J. Zaworotko, Brian Moulton, Nair Rodriguez-Hornedo
Serial No.	:	10/378,956
Filed	:	March 3, 2003
Conf. No.	:	4742
For	:	Multiple-Component Solid Phases Containing at Least One Active Pharmaceutical Ingredient

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION UNDER 37 CFR 1.84(a)(2)
(USE OF COLOR PHOTOGRAPHS IN APPLICATION)

Sir:

Submitted herewith are three color copies of the formal drawing for Figures 2-12 and 14-23 (20 pages total). A color photograph is required because the color drawing is the best medium by which to disclose the subject matter of the drawing. It is hereby stated that no new matter has been incorporated into these figures.

Applicants petition herewith for permission to include these color figures in the application and for publication in the patent upon allowance and payment of the issue fee. A black and white photocopy of the color figure is also provided with an Amendment Under 37 C.F.R. §1.111 being simultaneously filed. The fee of $130.00, as required for this Petition, should be charged to Deposit Account No. 19-0065. The Commissioner is also authorized to charge any additional fees as

01/22/2009 SSANDARA 00000015 190065 10378956
01 FC:1464 130.00 DA

required by this paper to the above deposit account. Two copies of this Petition are attached for Deposit Account authorization.

Respectfully submitted,

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/sl
Attachments: Three color copies of Formal drawings for Figures 2-12 and 14-23

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JAN 21 2009
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IAP34

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Frank C. Eisenschenk

Frank C. Eisenschenk, Ph.D., Patent Attorney

PETITION UNDER 37 CFR 1.84(a)(2)
Patent Application
Docket No. USF.106XC1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Sahar Javanmard
Art Unit	:	1617
Applicants	:	Michael J. Zaworotko, Brian Moulton, Nair Rodriguez-Hornedo
Serial No.	:	10/378,956
Filed	:	March 3, 2003
Conf. No.	:	4742
For	:	Multiple-Component Solid Phases Containing at Least One Active Pharmaceutical Ingredient

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION UNDER 37 CFR 1.84(a)(2)
(USE OF COLOR PHOTOGRAPHS IN APPLICATION)

Sir:

Submitted herewith are three color copies of the formal drawing for Figures 2-12 and 14-23 (20 pages total). A color photograph is required because the color drawing is the best medium by which to disclose the subject matter of the drawing. It is hereby stated that no new matter has been incorporated into these figures.

Applicants petition herewith for permission to include these color figures in the application and for publication in the patent upon allowance and payment of the issue fee. A black and white photocopy of the color figure is also provided with an Amendment Under 37 C.F.R. §1.111 being simultaneously filed. The fee of $130.00, as required for this Petition, should be charged to Deposit Account No. 19-0065. The Commissioner is also authorized to charge any additional fees as

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required by this paper to the above deposit account. Two copies of this Petition are attached for Deposit Account authorization.

Respectfully submitted,

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/sl
Attachments: Three color copies of Formal drawings for Figures 2-12 and 14-23

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OIPE
JAN 21 2009
IAP34
PATENT & TRADEMARK OFFICE

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313 on January 14, 2009.

Frank C. Eisenschenk

Frank C. Eisenschenk, Ph.D., Patent Attorney

PETITION UNDER 37 CFR 1.84(a)(2)
Patent Application
Docket No. USF.106XC1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Sahar Javanmard
Art Unit	:	1617
Applicants	:	Michael J. Zaworotko, Brian Moulton, Nair Rodriguez-Hornedo
Serial No.	:	10/378,956
Filed	:	March 3, 2003
Conf. No.	:	4742
For	:	Multiple-Component Solid Phases Containing at Least One Active Pharmaceutical Ingredient

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION UNDER 37 CFR 1.84(a)(2)
(USE OF COLOR PHOTOGRAPHS IN APPLICATION)

Sir:

Submitted herewith are three color copies of the formal drawing for Figures 2-12 and 14-23 (20 pages total). A color photograph is required because the color drawing is the best medium by which to disclose the subject matter of the drawing. It is hereby stated that no new matter has been incorporated into these figures.

Applicants petition herewith for permission to include these color figures in the application and for publication in the patent upon allowance and payment of the issue fee. A black and white photocopy of the color figure is also provided with an Amendment Under 37 C.F.R. §1.111 being simultaneously filed. The fee of $130.00, as required for this Petition, should be charged to Deposit Account No. 19-0065. The Commissioner is also authorized to charge any additional fees as

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required by this paper to the above deposit account. Two copies of this Petition are attached for Deposit Account authorization.

Respectfully submitted,

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FCE/sl
Attachments: Three color copies of Formal drawings for Figures 2-12 and 14-23

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1AP34

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313 on January 14, 2009.

Frank C Eisenschenk

Frank C. Eisenschenk, Ph.D., Patent Attorney

AMENDMENT UNDER 37 C.F.R. § 1.111
Patent Application
Docket No. USF.106XC1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Sahar Javanmard
Art Unit	:	1617
Applicants	:	Michael J. Zaworotko, Brian Moulton, Nair Rodriguez-Hornedo
Serial No.	:	10/378,956
Filed	:	March 3, 2003
Conf. No.	:	4742
For	:	Multiple-Component Solid Phases Containing at Least One Active Pharmaceutical Ingredient

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

AMENDMENT UNDER 37 C.F.R. § 1.111

Sir:

In response to the Office Action dated October 14, 2008, please amend the above-identified patent application as follows:

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In the Specification

Please insert the following paragraph on page 6, following the "Brief Description of the Figures" heading and before paragraph [0014]:

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawings will be provided by the Patent Office upon request and payment of the necessary fee.

Please substitute the paragraph [0014] on page 6 as follows:

Figure 1 shows the chemical structure of ibuprofen. The external functionalities are an isopropyl group (encircled on the left~~, in cyan~~) and a carboxylic acid (encircled on the right~~, in magenta~~).

Please replace original Figures 1-12 and 14-23 with replacement pages attached herewith.

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In the Claims

1-24 (canceled).

25 (previously presented). A method for identifying complementary chemical functionalities in order to form a desired supramolecular synthon, said method comprising:

(a) evaluating the structure of an active pharmaceutical ingredient;

(b) determining whether the active pharmaceutical ingredient contains chemical functionalities capable of forming supramolecular synthons with itself (a first supramolecular synthon);

(c) identifying, from a plurality of chemical functionalities that are known to form a supramolecular synthon, at least one functionality that will form a second supramolecular synthon with the first supramolecular synthon formed by the active pharmaceutical ingredient, wherein the identified chemical functionality is not capable of disrupting non-covalent bonding within the supramolecular synthon formed by the active pharmaceutical ingredient, and wherein the selected chemical functionality is capable of forming a noncovalent bond to the supramolecular synthon formed by the active pharmaceutical ingredient;

(d) identifying co-crystal formers having at least one functionality identified in step (c); and

(e) preparing a multiple-component solid phase composition, wherein the multiple-component solid phase composition is a crystal that comprises the active pharmaceutical ingredient and at least one of the identified co-crystal formers.

26 (canceled).

27 (currently amended). The method of claim 25, wherein the at least one co-crystal former is selected from the group consisting of a different active pharmaceutical ingredient, a ~~GRAS~~ Generally Regarded as Safe (GRAS) compound, a food additive, a low toxicity organic, and a metal-organic complex.

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28 (previously presented). The method of claim 25, wherein the multiple-component solid phase composition is formed by one or more methods selected from the group consisting of crystallization from solution, cooling the melt, sublimation, and grinding.

29-36 (canceled).

37 (previously presented). The method according to claim 25, wherein said active pharmaceutical ingredient is selected from aspirin, ibuprofen, flurbiprofen, carbamazepine, phenytoin or acetaminophen.

38 (previously presented). A method for identifying complementary chemical functionalities in order to form a desired supramolecular synthon, said method comprising:

(a) selecting an active pharmaceutical ingredient and evaluating the structure of said active pharmaceutical ingredient;

(b) determining whether the active pharmaceutical ingredient contains chemical functionalities capable of forming supramolecular synthons with itself (a first supramolecular synthon);

(c) identifying, from a plurality of chemical functionalities that are known to form a supramolecular synthon, at least one functionality that will form a second supramolecular synthon with the first supramolecular synthon formed by the active pharmaceutical ingredient, wherein the identified chemical functionality is not capable of disrupting non-covalent bonding within the supramolecular synthon formed by the active pharmaceutical ingredient, and wherein the selected chemical functionality is capable of forming a noncovalent bond to the supramolecular synthon formed by the active pharmaceutical ingredient;

(d) identifying co-crystal formers having at least one functionality identified in step (c) and selecting said identified co-crystal formers for the preparation of a multiple component solid phase composition; and

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(e) preparing a multiple-component solid phase composition, wherein the multiple-component solid phase composition is a crystal that comprises the active pharmaceutical ingredient and at least one of the identified co-crystal formers.

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Remarks

Claims 25, 27, 28, 37 and 38 are pending in the subject application. By this Amendment, Applicants have amended claim 27. Support for the amendments can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 25, 27, 28, 37 and 38 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Applicants gratefully acknowledge the Examiner's withdrawal of the rejection 35 U.S.C. § 102(e) (over Almarsson *et al.*).

The Office Action indicates that the descriptions of Figures 1 and 2 in the specification refer to color notations of the atoms, however such detail is not apparent from the drawings. The brief description of Figure 1 has been amended to remove the indication of color as it is apparent that the isopropyl group is circled on the left and that the carboxylic acid is circled on the right. As indicated in the brief description of Figure 2, "The standard chemical color correlation appears in **all** the figures where color is utilized (*e.g.*, red = oxygen; white = oxygen; dark blue = nitrogen; light blue = fluorene; yellow = sulfur)." (emphasis added). Accordingly, Figures 1-12 and 14-23 are being replaced (to enlarge the figures) and are being submitted in color. The necessary paragraph has been inserted into the application. Applicants note that Figures 13A-C and 24 are unchanged and not provided herewith. Enclosed with this Amendment is a Petition Under 37 CFR 1.84(a)(2) (Use of Color Photographs in Application). Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claim 27 is rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The Office Action indicates that it is not clear what a "GRAS compound" is and that the rejection can be overcome by spelling out the abbreviation. By this Amendment, Applicants have replaced the acronym "GRAS" with "Generally Regarded as Safe by the Food and Drug Administration (FDA)" and then placed the acronym in parenthesis. Applicants respectfully assert that the claims as filed are definite and support for this amendment can be found, for example, in the last sentence of paragraph 51 of the as-filed specification). Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

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Claims 25, 27 and 28 are rejected under 35 U.S.C. § 102(b) as anticipated by DuRoss *et al.* (U.S. Patent No. 5,023,092). The Office Action indicates that DuRoss teaches gamma sorbitol co-crystallized therewith mannitol in the gamma sorbitol polymorph. In particular, it is a co-crystalline product derived from a dehydrated aqueous solution of sorbitol containing mannitol and is directed to improved confections such as chewing gum, edible tablets and chocolates. Applicants respectfully assert that the DuRoss *et al.* reference does not anticipate the claimed invention.

As stated by the Federal Circuit in *Net Moneyin, Inc. v. Verisign, Inc.*, No. 2007-1565, decided October 20, 2008):

> Section 102 embodies the concept of novelty—if a device or process has been previously invented (and disclosed to the public), then it is not new, and therefore the claimed invention is "anticipated" by the prior invention. As we have stated numerous times (language on which VeriSign relies), in order to demonstrate anticipation, the proponent must show "that the four corners of a single, prior art document describe every element of the claimed invention." *Xerox*, 458 F.3d at 1322 (quoting *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000)). This statement embodies the requirement in section 102 that the anticipating invention be "described in a printed publication," and is, of course, unimpeachable. But it does not tell the whole story. Because the hallmark of anticipation is prior invention, the prior art reference—in order to anticipate under 35 U.S.C. § 102—must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements "arranged as in the claim." *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983).
>
> The meaning of the expression "arranged as in the claim" is readily understood in relation to claims drawn to things such as ingredients mixed in some claimed order. In such instances, a reference that discloses all of the claimed ingredients, but not in the order claimed, would not anticipate, because the reference would be missing any disclosure of the limitations of the claimed invention "arranged as in the claim." But the "arranged as in the claim" requirement is not limited to such a narrow set of "order of limitations" claims. Rather, our precedent informs that the "arranged as in the claim" requirement applies to all claims and refers to the need for an anticipatory reference to show all of the limitations of the claims arranged or combined in the same way as recited in the claims, not merely in a particular order. The test is thus more accurately understood to mean "arranged or combined in the same way as in the claim."

In the case of the instantly claimed invention, Applicants respectfully submit that DuRoss fails to disclose all the elements of the claim and the reference also fails to teach the claimed elements

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"arranged or combined in the same way as in the claim." Particularly, Applicants note that DuRoss fails to teach:

> (a) evaluating the structure of an active pharmaceutical ingredient;
> (b) determining whether the active pharmaceutical ingredient contains chemical functionalities capable of forming supramolecular synthons with itself (a first supramolecular synthon);
> (c) identifying, from a plurality of chemical functionalities that are known to form a supramolecular synthon, at least one functionality that will form a second supramolecular synthon with the first supramolecular synthon formed by the active pharmaceutical ingredient, wherein the identified chemical functionality is not capable of disrupting non-covalent bonding within the supramolecular synthon formed by the active pharmaceutical ingredient, and wherein the selected chemical functionality is capable of forming a noncovalent bond to the supramolecular synthon formed by the active pharmaceutical ingredient;
> (d) identifying co-crystal formers having at least one functionality identified in step (c); and
> (e) preparing a multiple-component solid phase composition, wherein the multiple-component solid phase composition is a crystal that comprises the active pharmaceutical ingredient and at least one of the identified co-crystal formers.

Thus, each of the claimed elements is not taught by the cited reference in the same manner as "arranged or combined" in the claim.

It is also unclear what teaching of DuRoss is relied upon for the teaching of an "active pharmaceutical ingredient" as neither sorbitol or mannitol is asserted to be such an active pharmaceutical ingredient in the Office Action. In this regard, the Office Action indicates that DuRoss is directed to improved confections such as chewing gum, edible tablets and chocolates (Office Action at page 3). Applicants also submit that DuRoss indicates that the co-crystallized mannitol/sorbitol disclosed in the patent can also be used "as an excipient in combination with a medicinal agent such as vitamin C, aspirin or an antacid" (see column 5, lines 29-35); thus, it is clear that DuRoss does not contemplate mannitol or sorbitol as an active pharmaceutical ingredient as the co-crystallized form of mannitol/sorbitol is to be used as an excipient in the formulation of a medicinal agent. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(b) is respectfully requested.

Claims 37 and 38 are rejected under 35 U.S.C. § 103(a) as obvious over DuRoss *et al.* (U.S. Patent No. 5,023,092) as applied to claims 25, 27 and 28 above in view of Desiraju (1995). The

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Office Action states that Desiraju teaches that hydrogen bonding, the master key for molecular recognition, is the most reliable directional interaction in supramolecular construction, and its significance in crystal engineering can scarcely be underestimated. The Office Action indicates that it, thus, would have been obvious to one of ordinary skill in the art at the time of the invention to have employed the co-crystallization method as taught by DuRoss and used aspirin, ibuprofen, flurbiprofen, carbamazepine, phenytoin, or acetaminophen. Applicants respectfully assert that the claimed invention is not obvious over the cited reference and traverse the rejection of record.

As the Patent Office is aware, all the claim limitations must be taught or suggested by the prior art in order to establish the *prima facie* obviousness of a claimed invention (*CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) citing *In re Royka*, 490 F.2d 981, 985 (C.C.P.A. 1974)). As noted above, DuRoss *et al.* fail to teach many of the limitations recited in the presently pending claims. For example, the reference fails to teach:

> (a) evaluating the structure of an active pharmaceutical ingredient;
>
> (b) determining whether the active pharmaceutical ingredient contains chemical functionalities capable of forming supramolecular synthons with itself (a first supramolecular synthon);
>
> (c) identifying, from a plurality of chemical functionalities that are known to form a supramolecular synthon, at least one functionality that will form a second supramolecular synthon with the first supramolecular synthon formed by the active pharmaceutical ingredient, wherein the identified chemical functionality is not capable of disrupting non-covalent bonding within the supramolecular synthon formed by the active pharmaceutical ingredient, and wherein the selected chemical functionality is capable of forming a noncovalent bond to the supramolecular synthon formed by the active pharmaceutical ingredient;
>
> (d) identifying co-crystal formers having at least one functionality identified in step (c); and
>
> (e) preparing a multiple-component solid phase composition, wherein the multiple-component solid phase composition is a crystal that comprises the active pharmaceutical ingredient and at least one of the identified co-crystal formers.

Applicants respectfully submit that the teachings of Desiraju (*Angew. Int. Ed. Engl.*, 1995) fail to remedy the defects noted in the teachings of DuRoss and the combination of references fails to render the claimed invention *prima facie* obvious as all of the claim limitations are not taught or suggested by the combination of references. Indeed, the cited references fail to teach any of aspirin, ibuprofen, flurbiprofen, carbamazepine, phenytoin or acetaminophen as pharmaceutical molecules

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(active pharmaceutical ingredients) and no discussion or teaching of co-crystal formers that are to be used to construct a crystal comprising an active pharmaceutical ingredient and one of the co-crystal formers identified in the method steps is identified in the Office Action. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested as the Office Action fails to establish that the claimed invention is *prima facie* obvious.

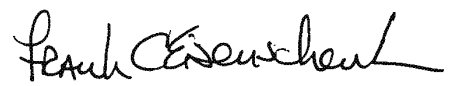
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/jb/sl
Attachments: Replacement Figures 1-12 and 14-23
Petition Under 37 CFR 1.84(a)(2) (Use of Color Photographs in Application)

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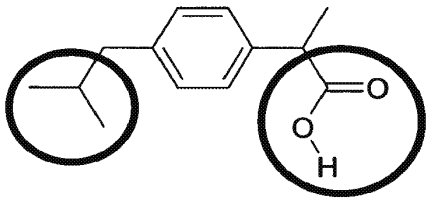


FIG. 1

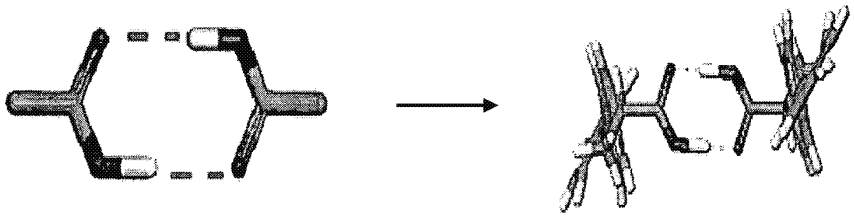


FIG. 2

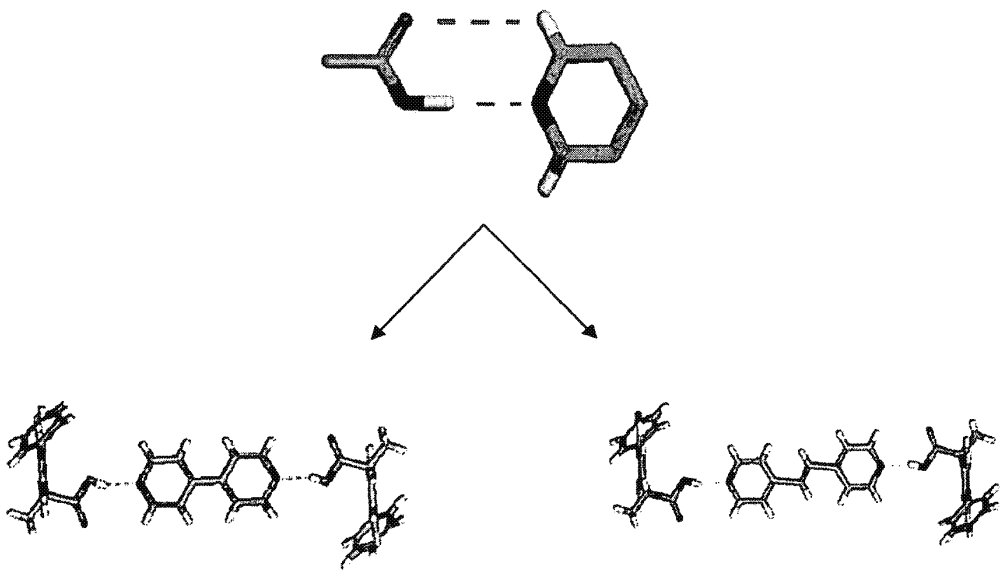


FIG. 3

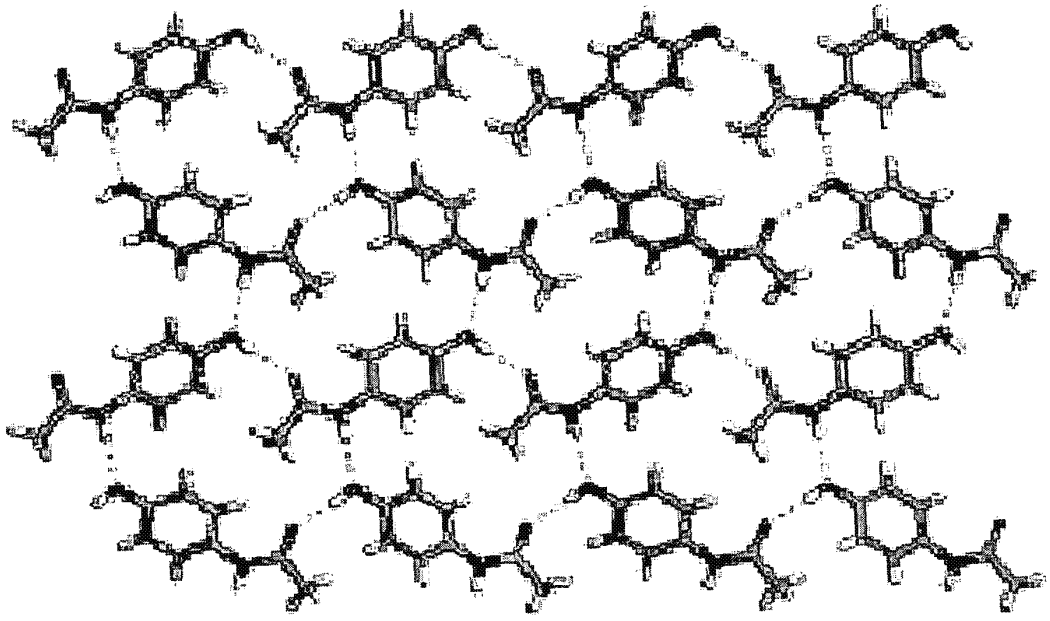


FIG. 4A

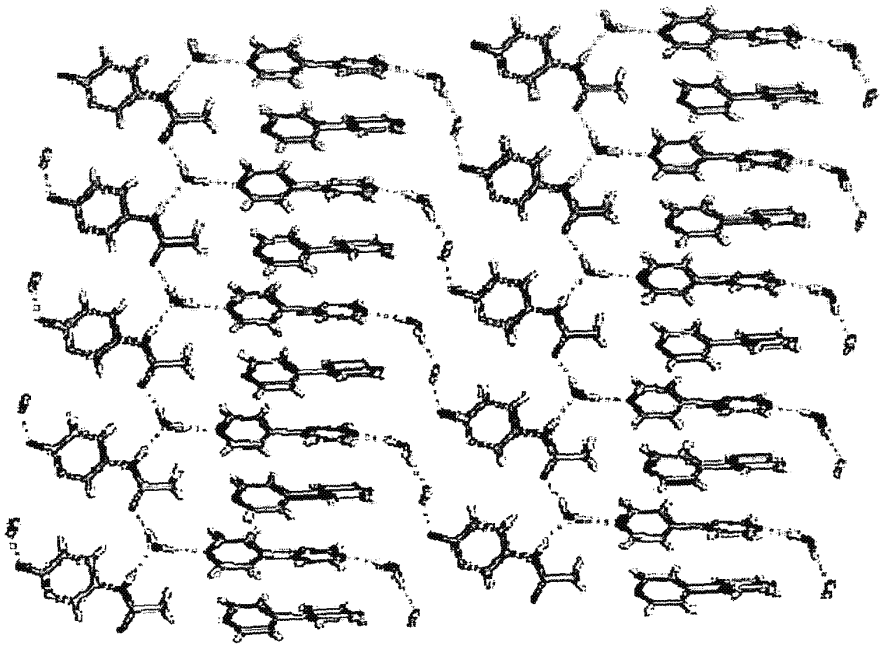


FIG. 4B

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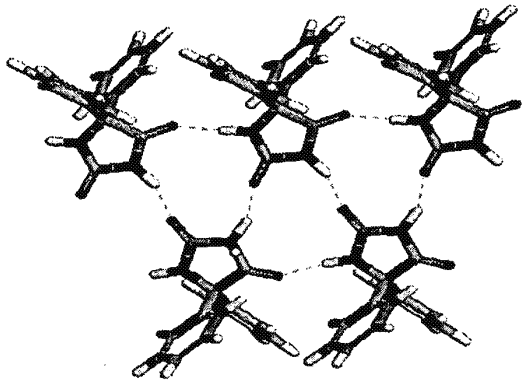


FIG. 5A

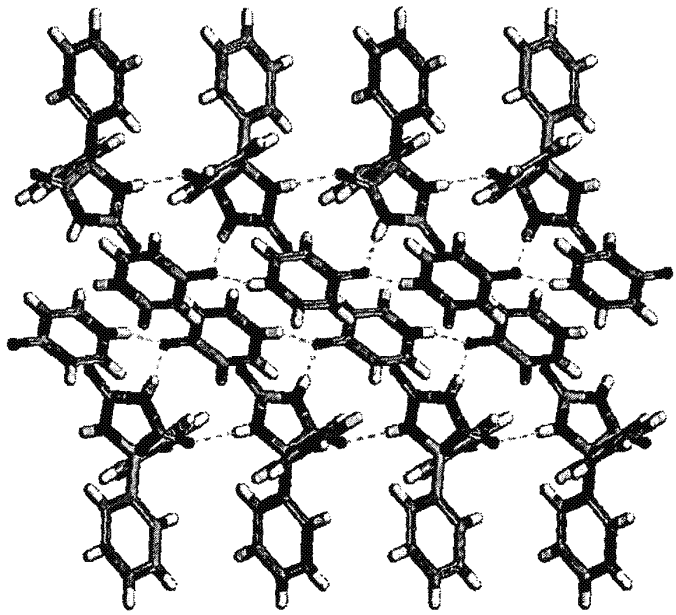


FIG. 5B

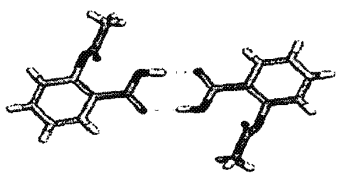


FIG. 6A

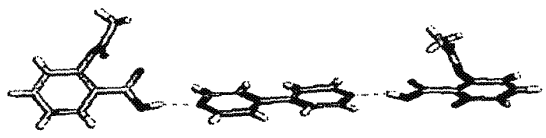


FIG. 6C

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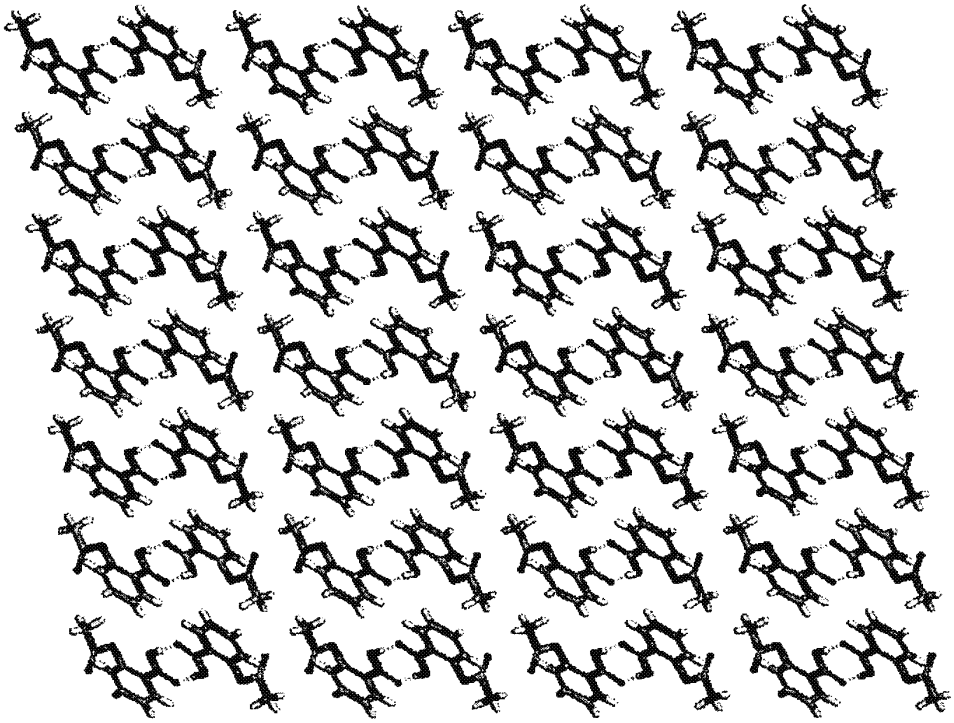


FIG. 6B

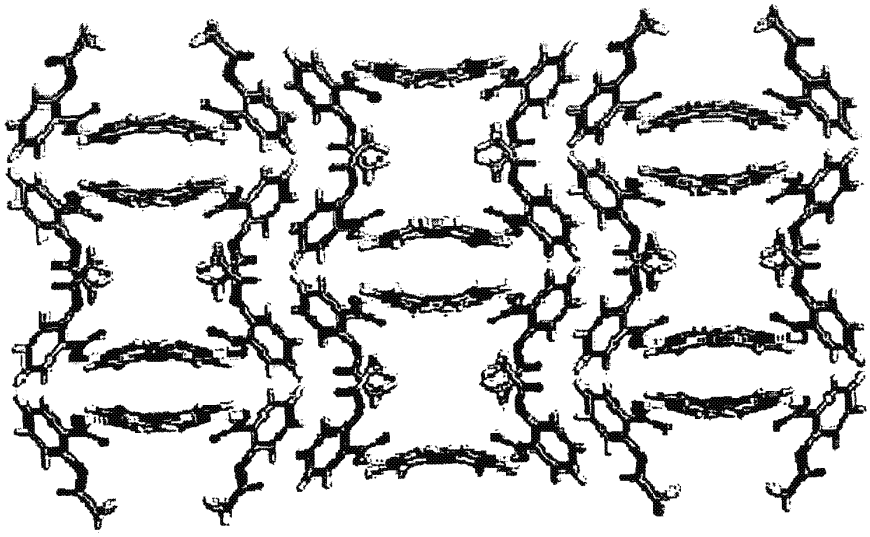


FIG. 6D

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FIG. 7A

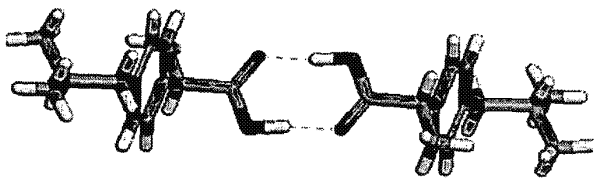
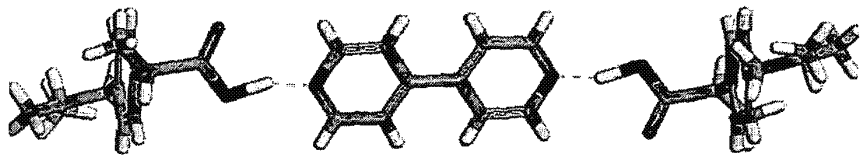


FIG. 7C



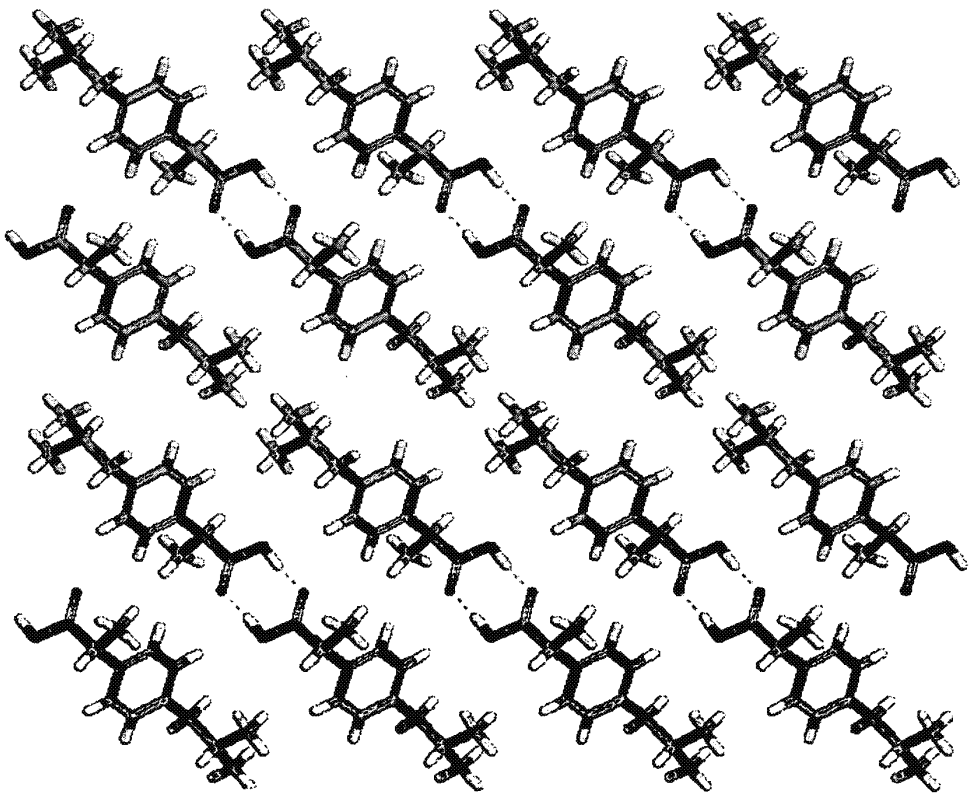


FIG. 7B

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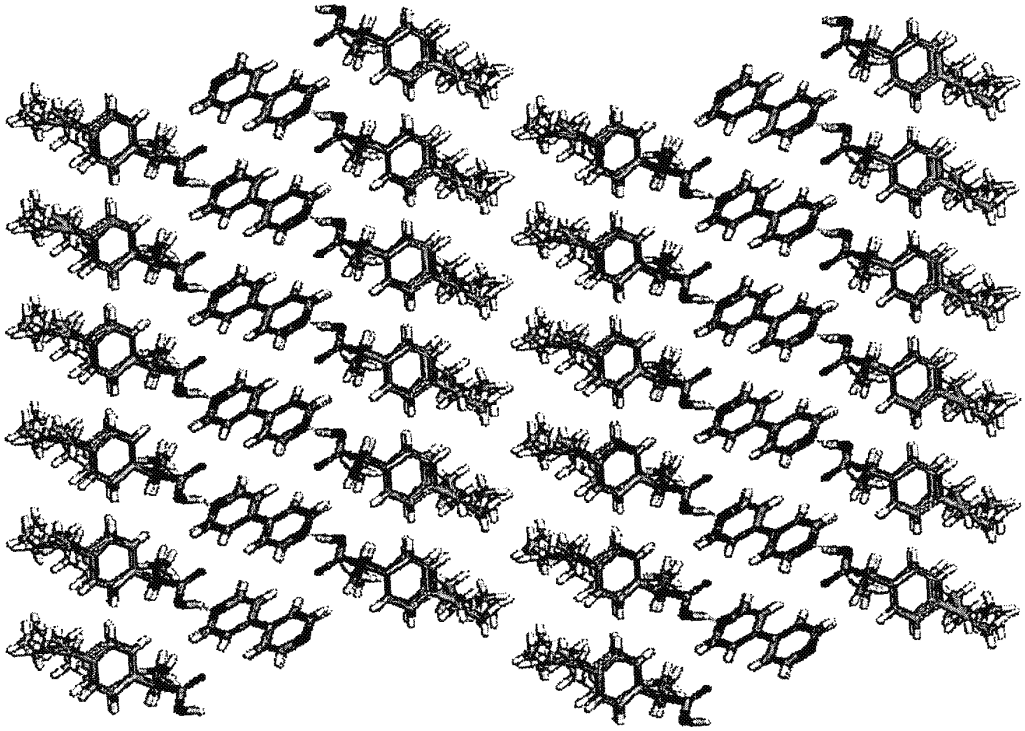


FIG. 7D

FIG. 8A

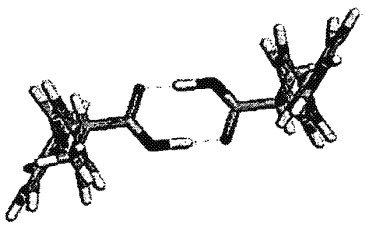
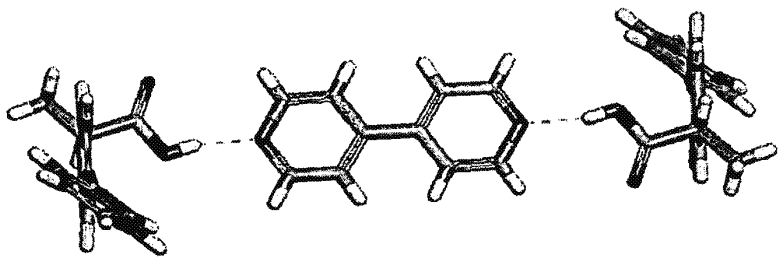


FIG. 8C



NOVARTIS EXHIBIT 1017
Novartis v. Regents, IPR2023-01346
Page 3202 of 4460

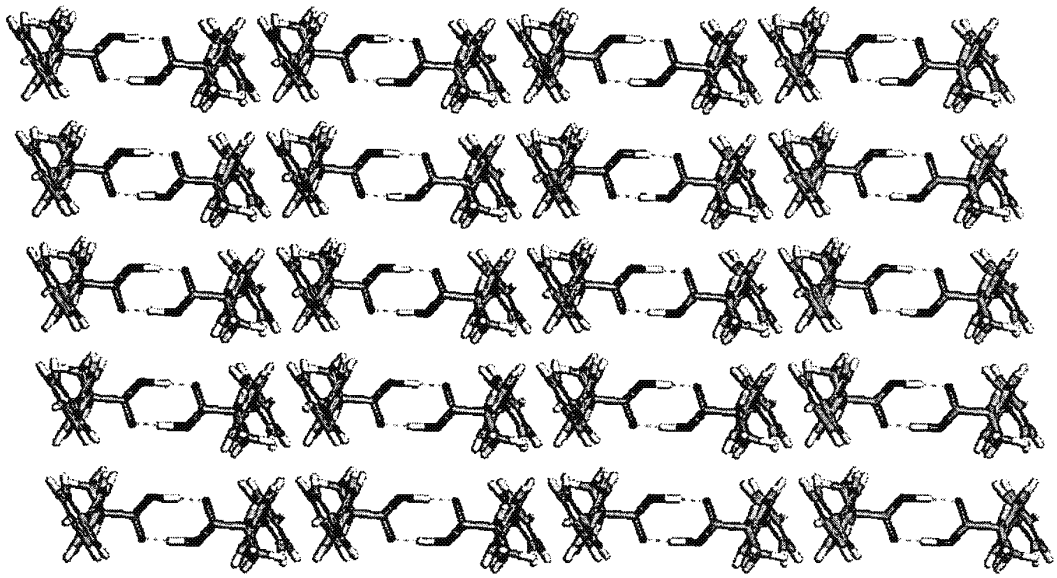


FIG. 8B

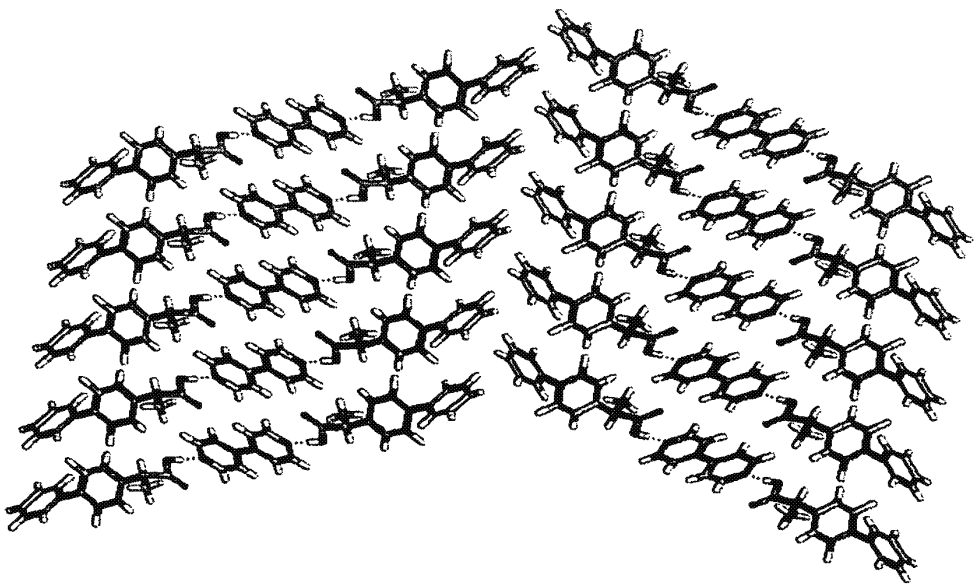


FIG. 8D

NOVARTIS EXHIBIT 1017
Novartis v. Regents, IPR2023-01346
Page 3203 of 4460

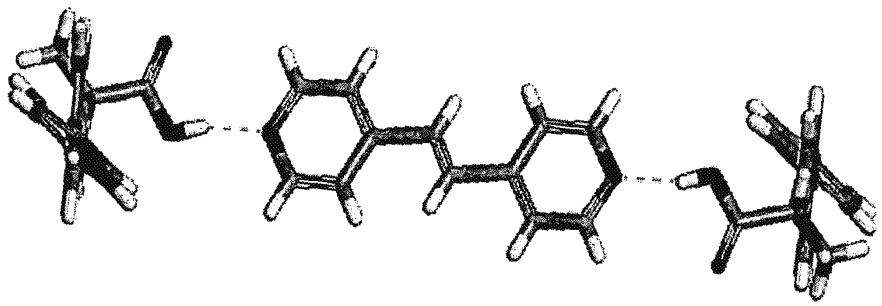


FIG. 9A

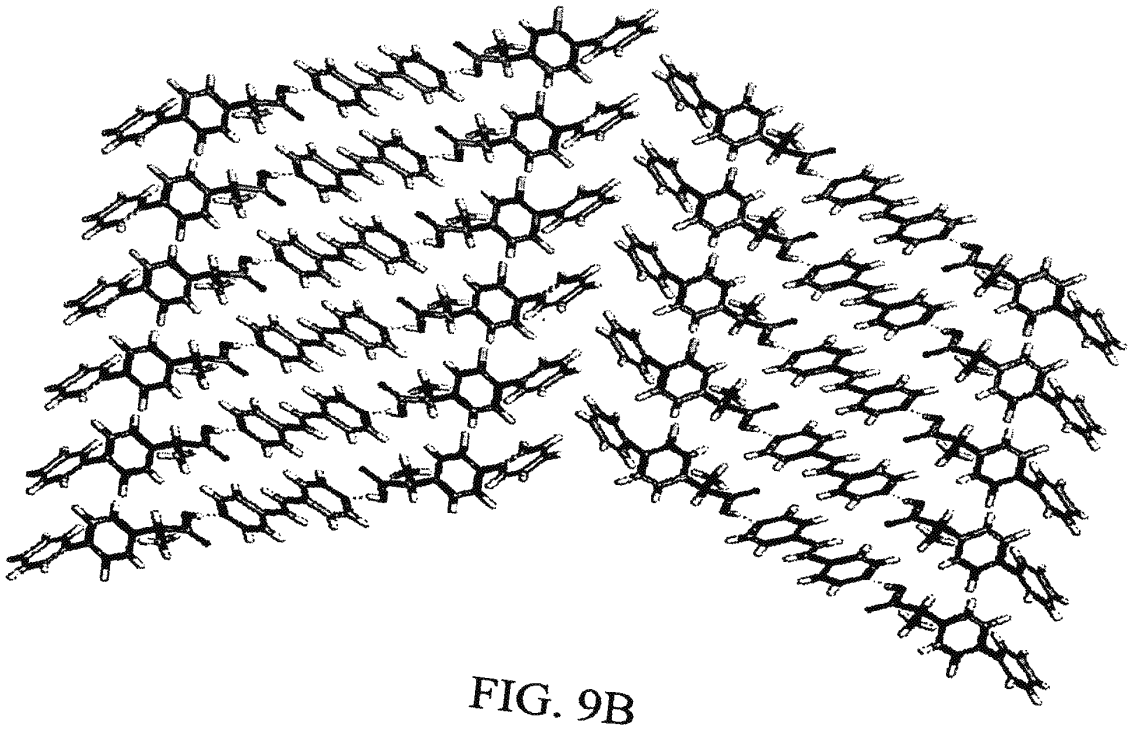


FIG. 9B

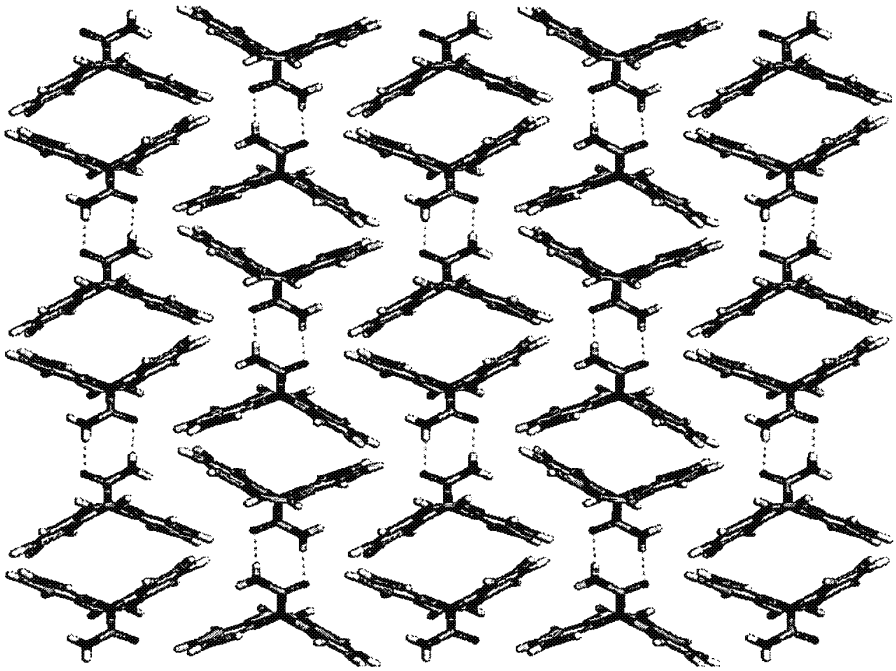


FIG. 10A

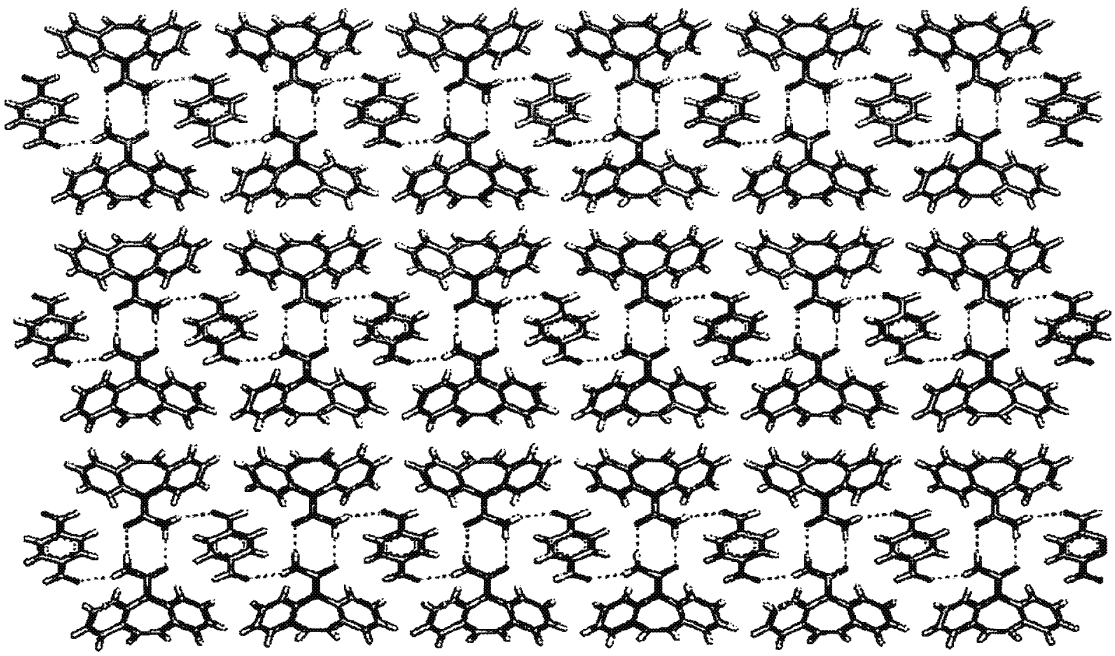


FIG. 10B

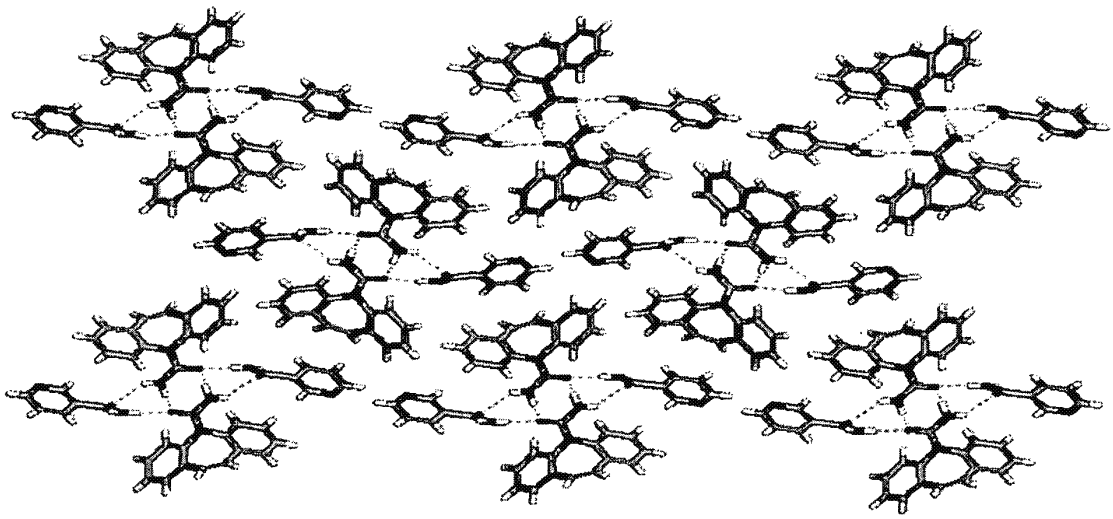


FIG. 11

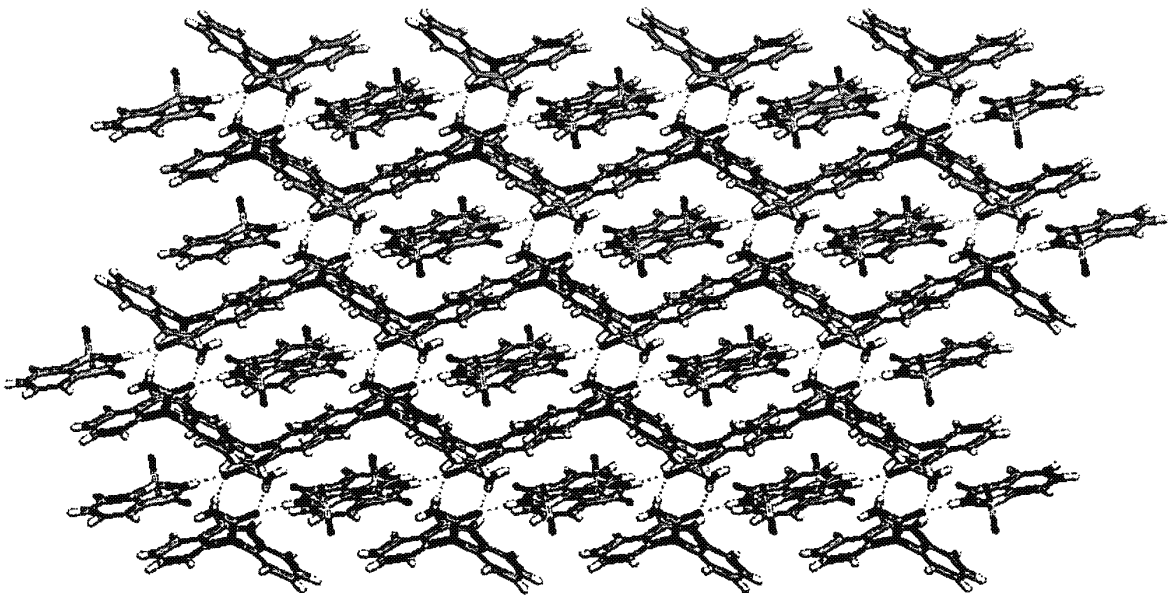


FIG. 12

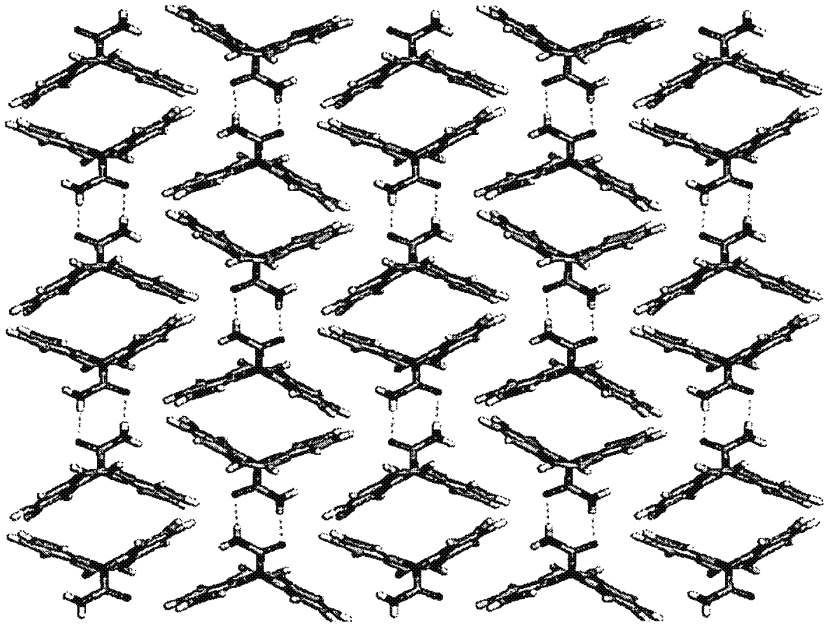


FIG. 14A

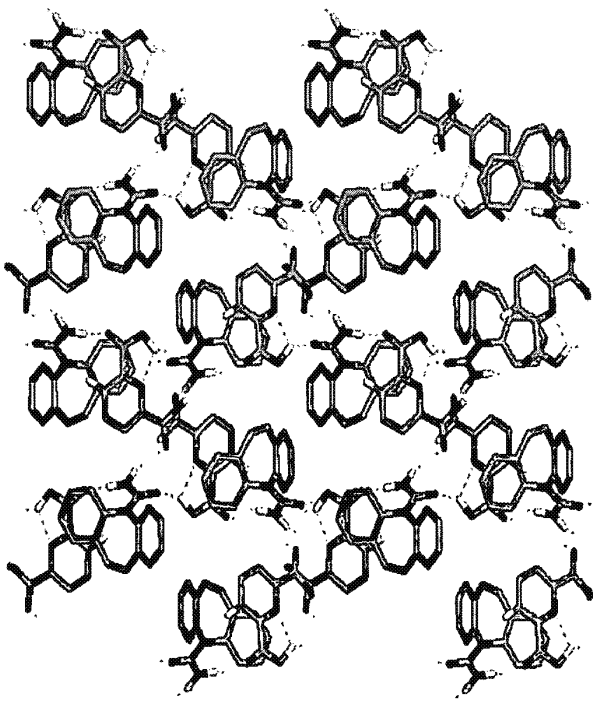


FIG. 14B

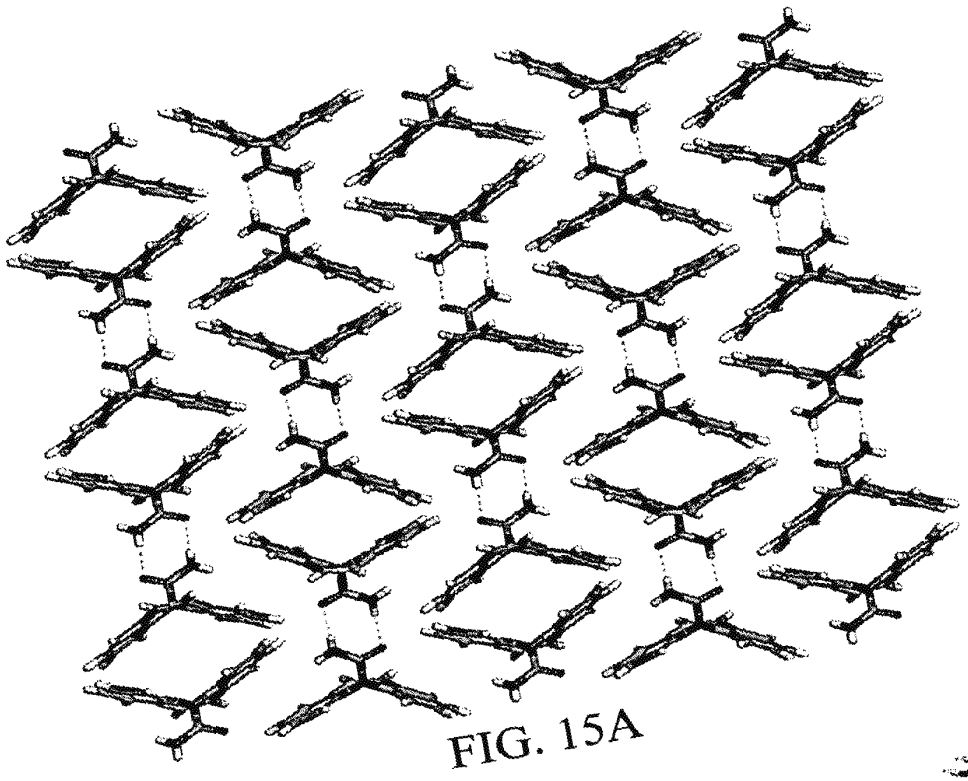


FIG. 15A

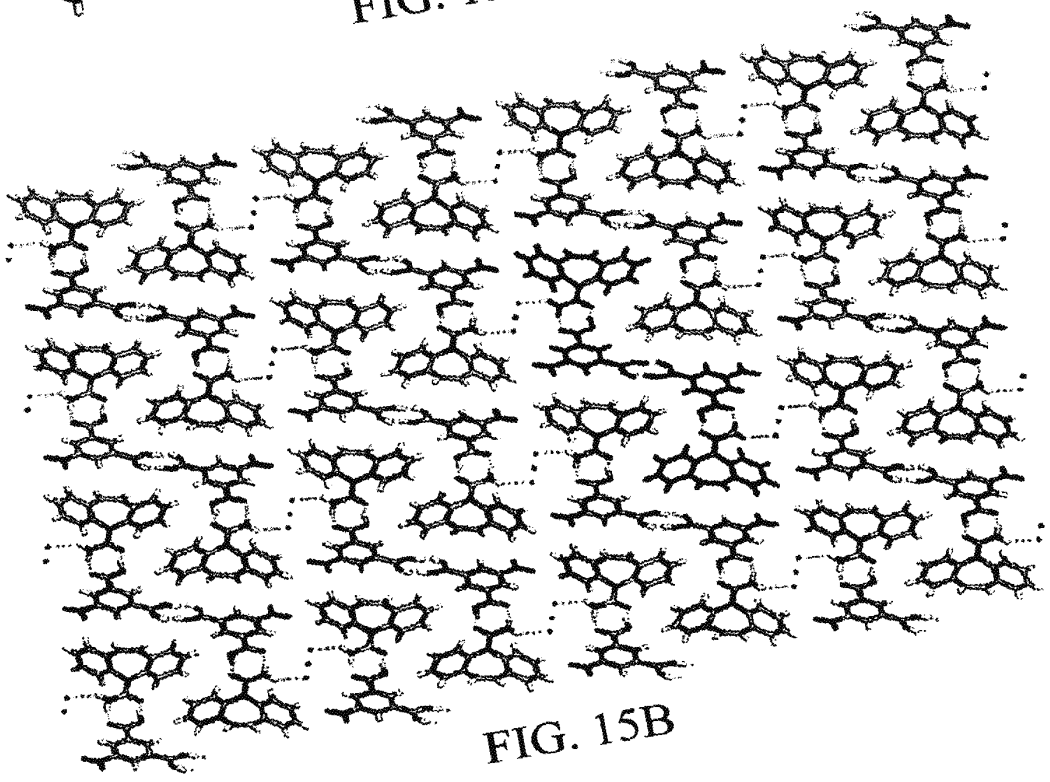


FIG. 15B

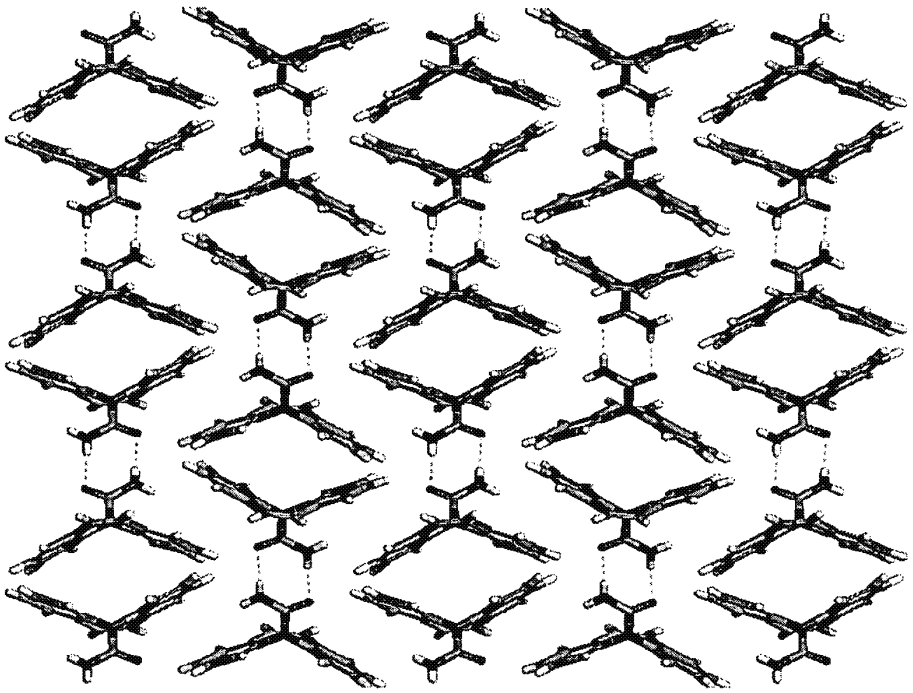


FIG. 16A

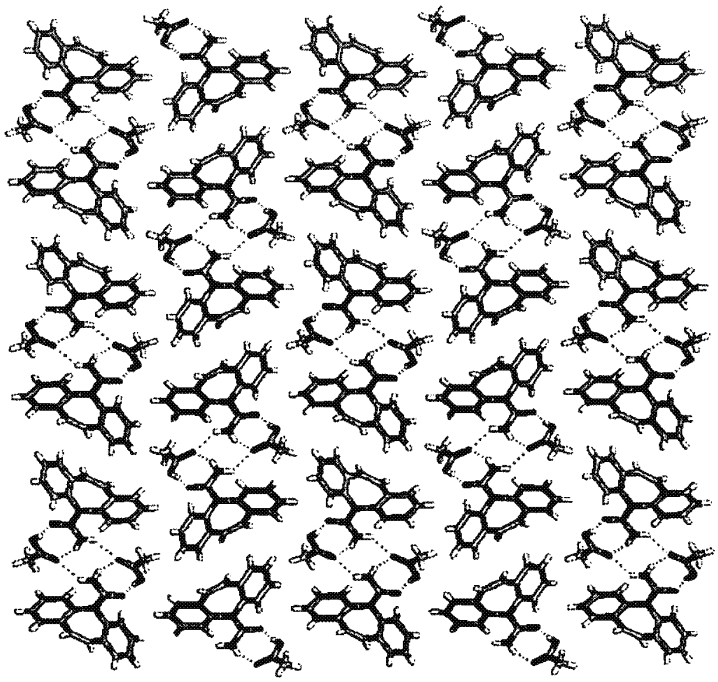


FIG. 16B

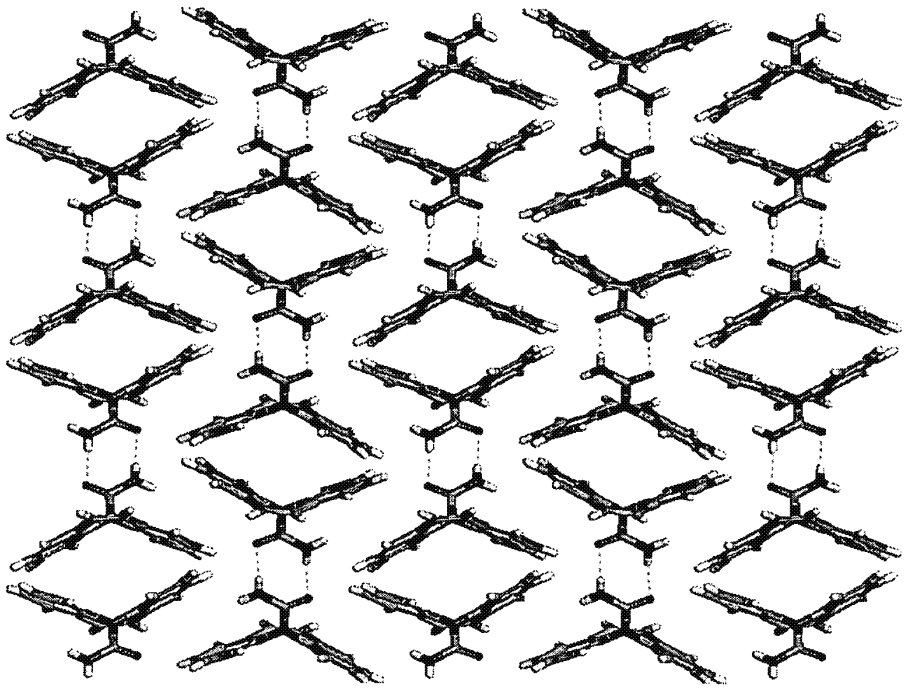


FIG. 17A

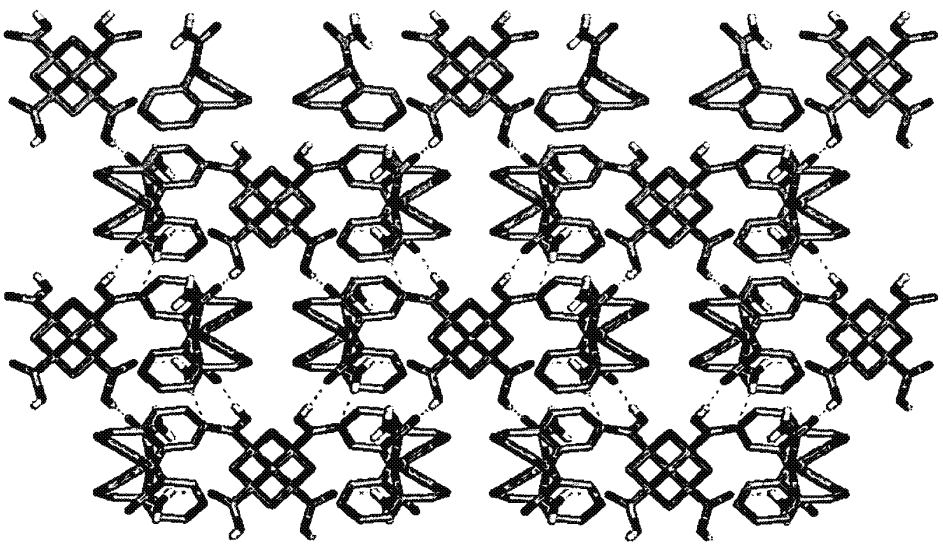


FIG. 17B

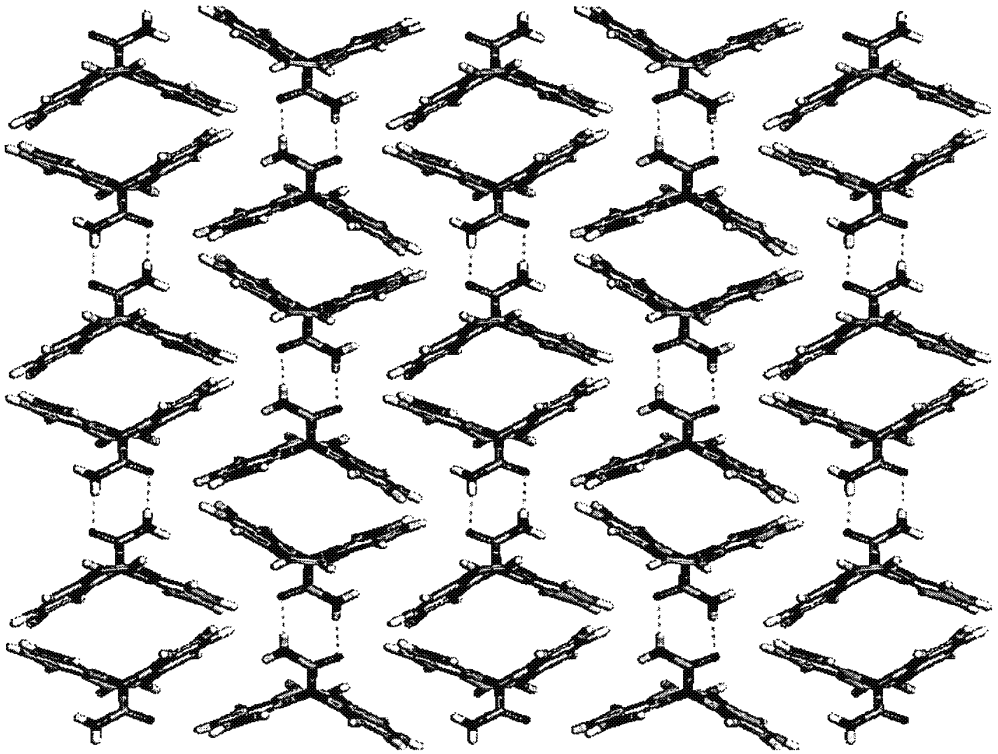


FIG. 18A

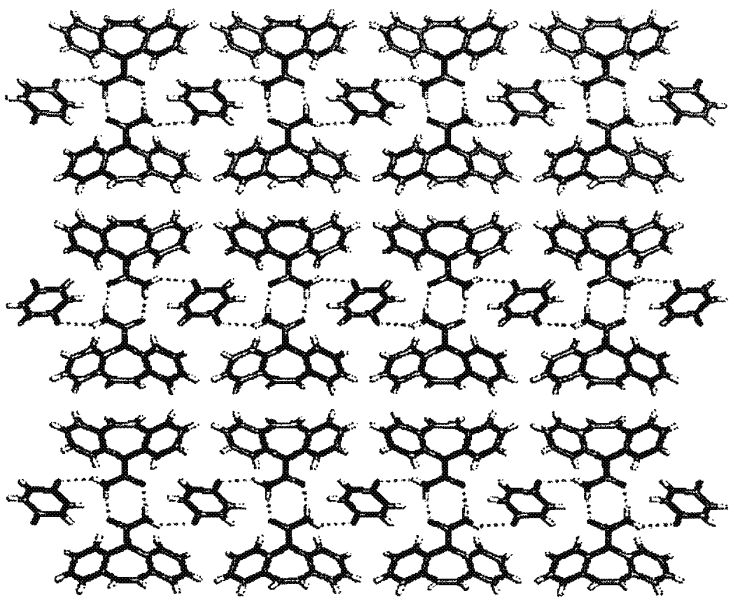


FIG. 18B

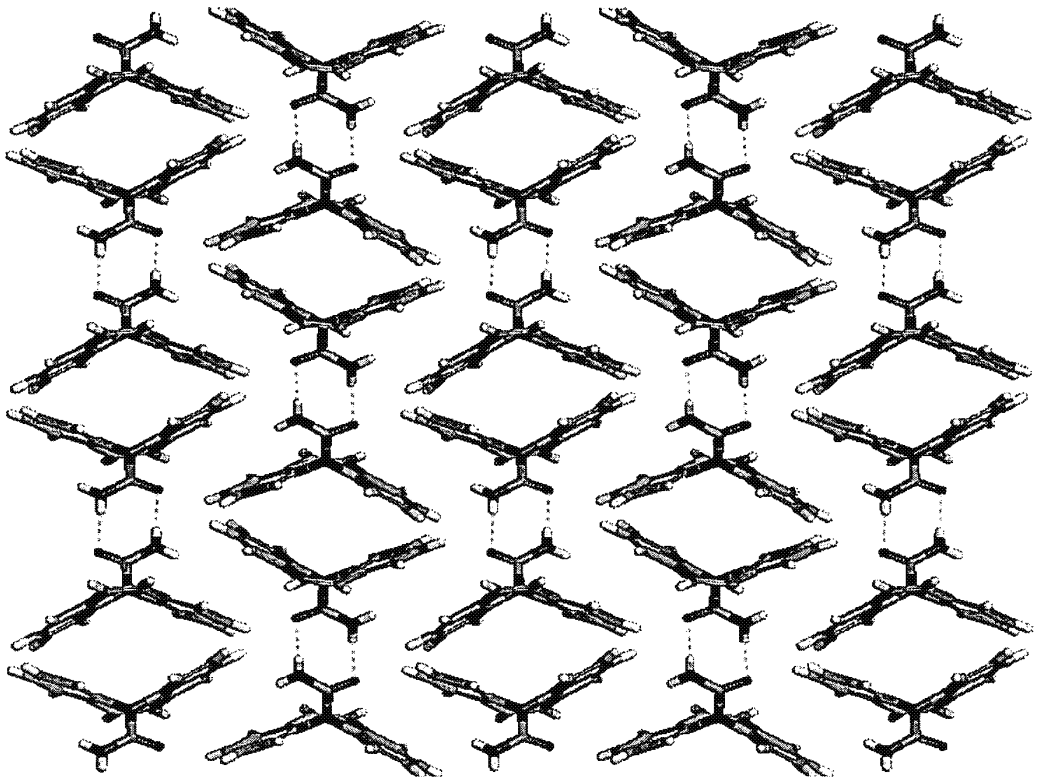


FIG. 19A

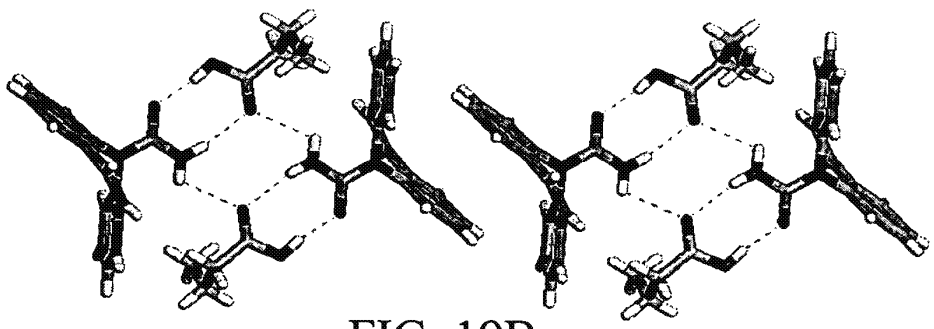


FIG. 19B

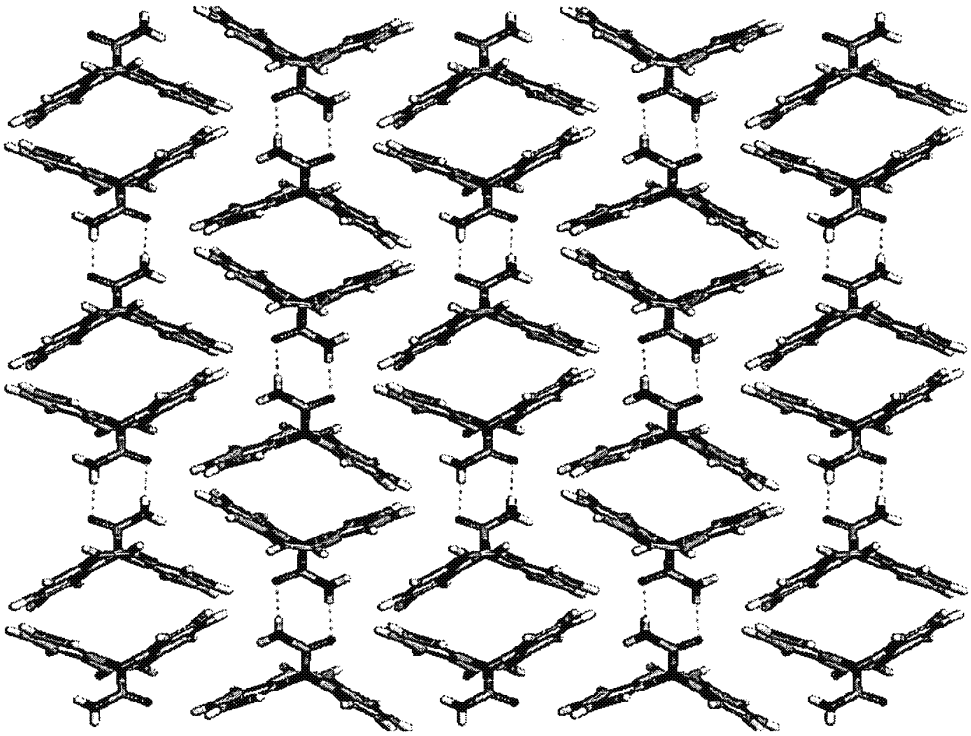


FIG. 20A

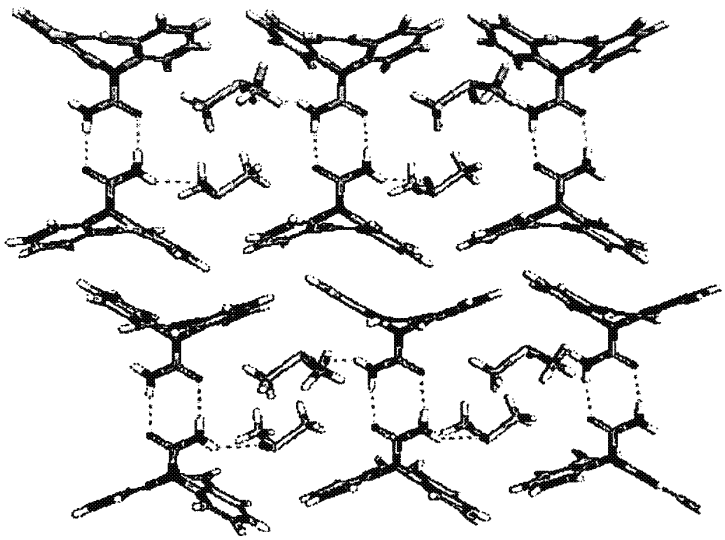


FIG. 20B

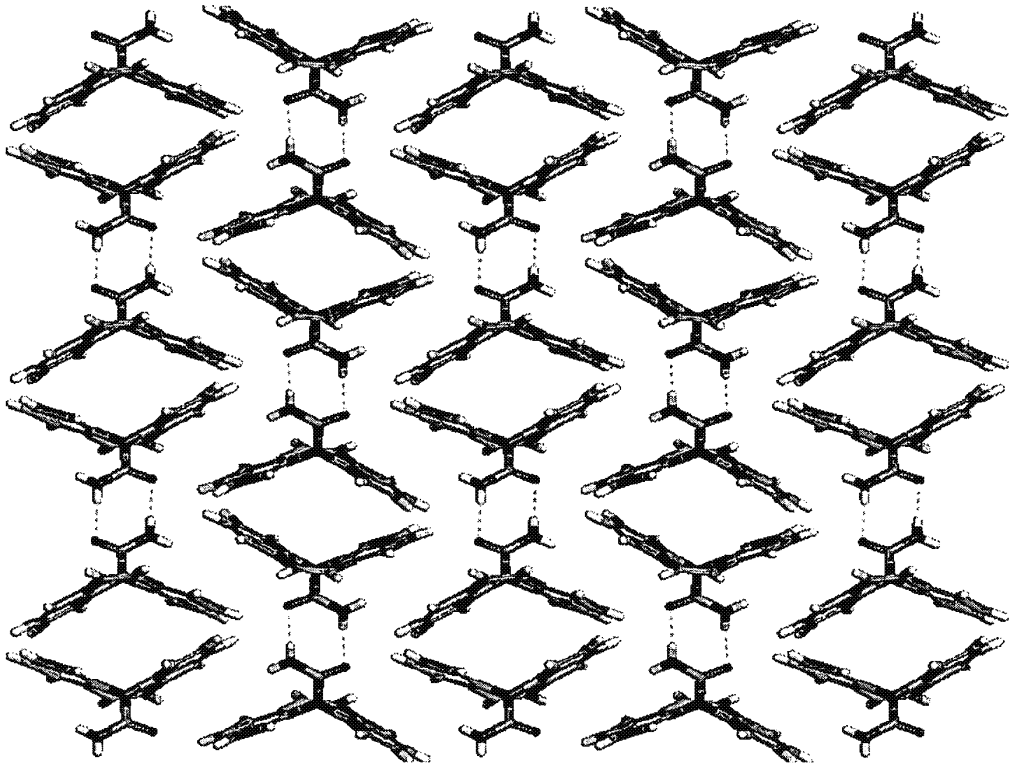


FIG. 21A

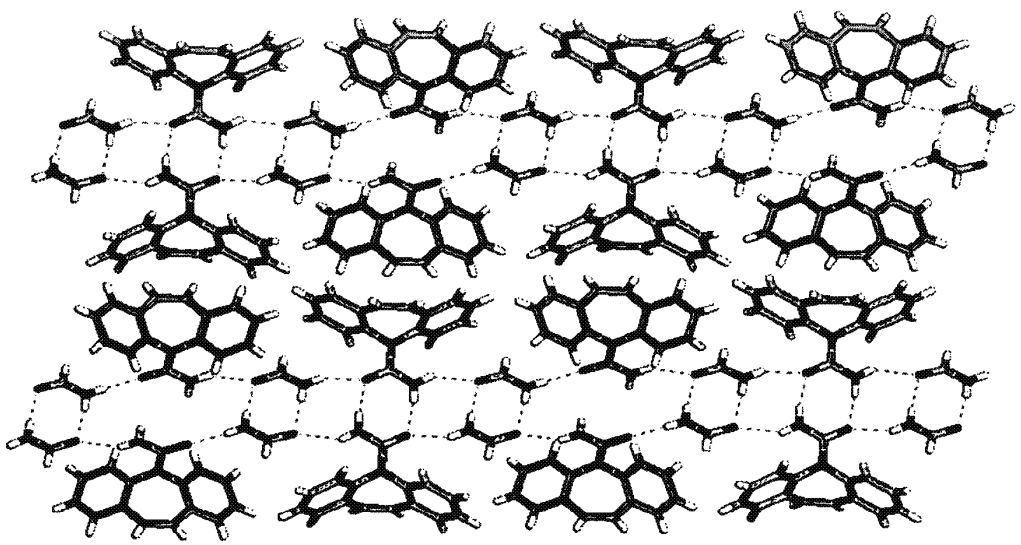


FIG. 21B

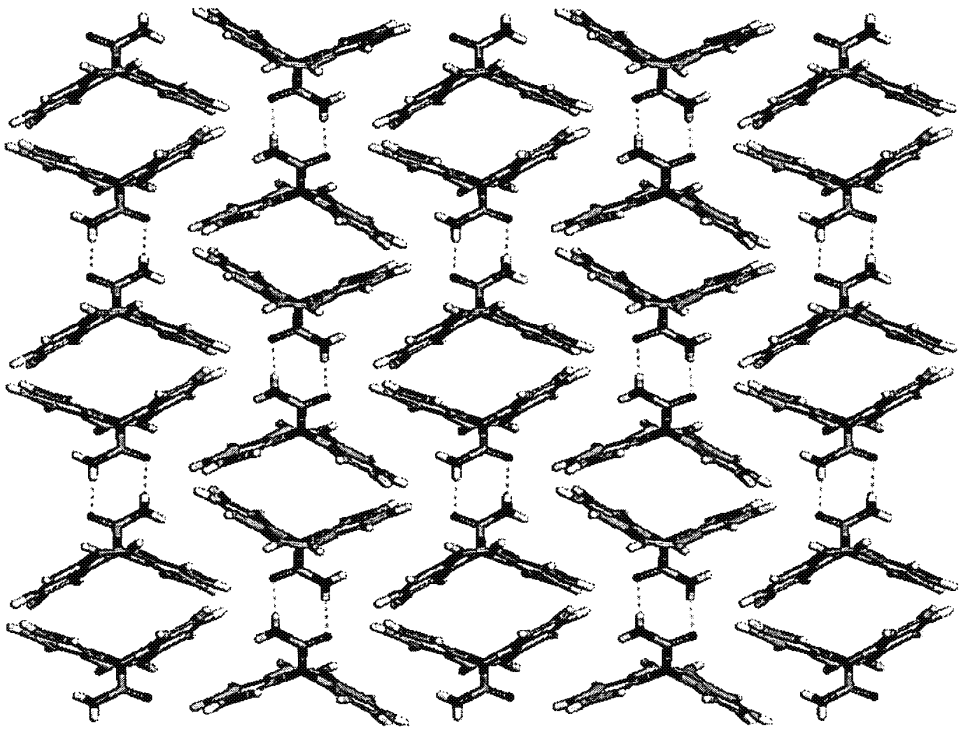


FIG. 22A

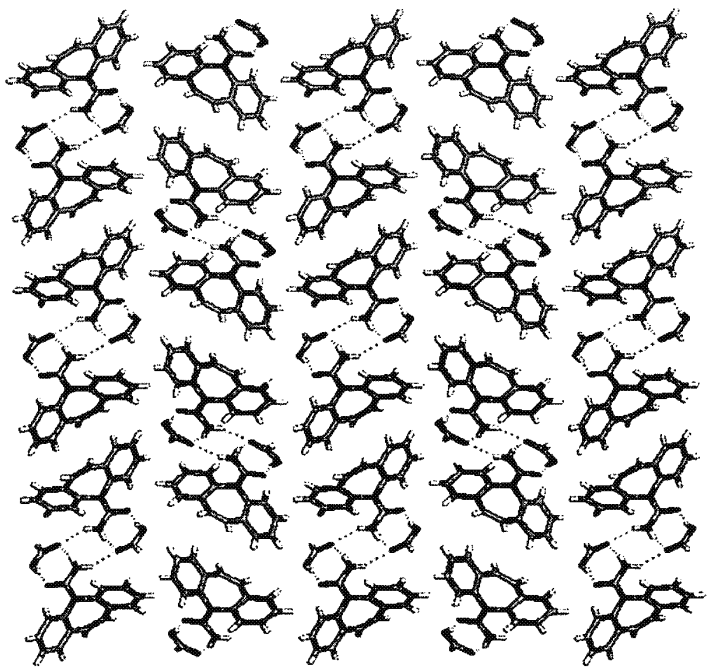


FIG. 22B

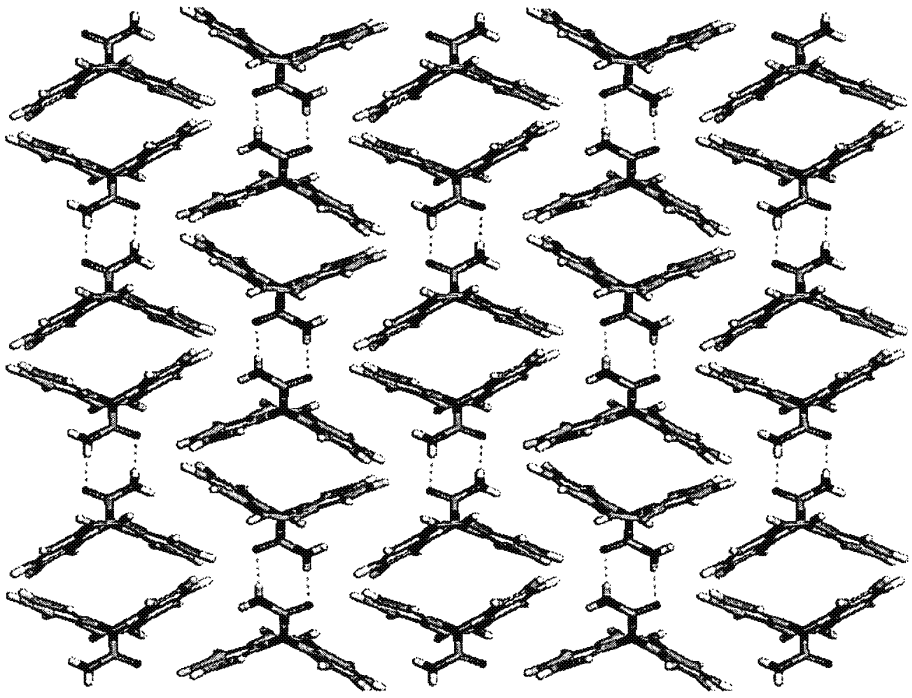


FIG. 23A

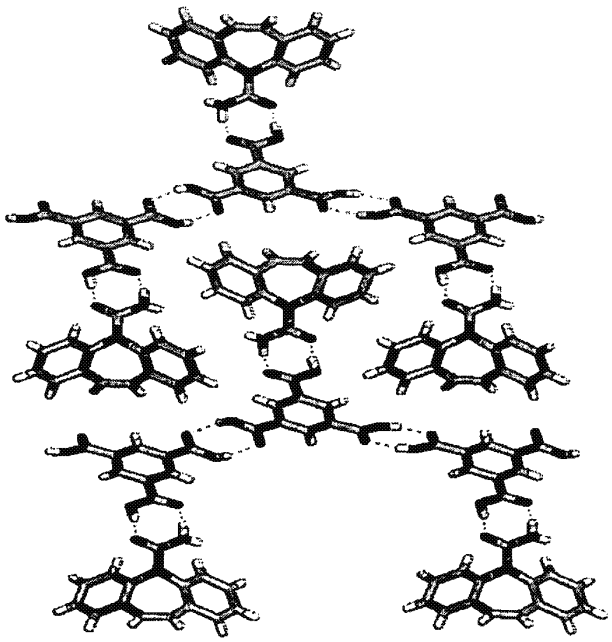
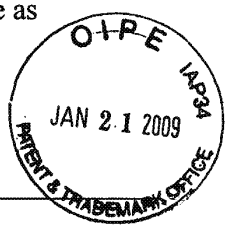


FIG. 23B

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Frank C. Eisenschenk

Frank C. Eisenschenk, Ph.D., Patent Attorney



SUPPLEMENTAL INFORMATION
DISCLOSURE STATEMENT
Examining Group 1617
Patent Application
Docket No. USF.106XC1
Serial No. 10/378,956

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Art Unit	:	1617
Applicants	:	Michael J. Zaworotko, Brian Moulton, Nair Rodriguez-Hornedo
Serial No.	:	10/378,956
Filed	:	March 3, 2003
Conf. No.	:	4742
For	:	Multiple-Component Solid Phases Containing at Least One Active Pharmaceutical Ingredient

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR §§1.97 AND 1.98

Sir:

In accordance with 37 CFR §1.56, the references listed on the attached form PTO/SB/08 are being brought to the attention of the Examiner for consideration in connection with the examination of the above-identified patent application. A copy of each cited reference is enclosed.

However, Applicants have not submitted copies of the U.S. patents cited on attached Form PTO/SB/08 pursuant to 37 CFR 1.98(a)(2)(ii).

01/22/2009 SSESHE1 00000076 190065 10378956
01 FC:1806 180.00 DA

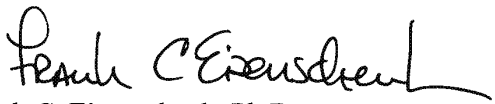
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It is respectfully requested that the references cited on the attached form PTO/SB/08 be considered in the examination of the subject application and that their consideration be made of record.

Applicants respectfully assert that the substantive provisions of 37 CFR §§1.97 and 1.98 are met by the foregoing statements.

Respectfully submitted,



Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/jb
Attachments: Form PTO/SB/08; copies of references cited therein.

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Frank C. Eisenschenk

Frank C. Eisenschenk, Ph.D., Patent Attorney

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT
Examining Group 1617
Patent Application
Docket No. USF.106XC1
Serial No. 10/378,956

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Serial No.	:	10/378,956
Filed	:	March 3, 2003
Conf. No.	:	4742
For	:	Multiple-Component Solid Phases Containing at Least One Active Pharmaceutical Ingredient

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

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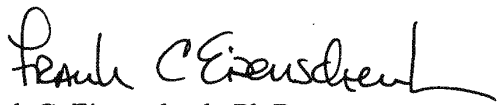
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Patent Attorney
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Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

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Examining Group 1617
Patent Application
Docket No. USF.106XC1
Serial No. 10/378,956

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Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

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Attachments: Form PTO/SB/08; copies of references cited therein.

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Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	10/378,956
Filing Date	March 3, 2003
First Named Inventor	Michael J. Zaworotko
Art Unit	1617
Examiner Name	Sahar Javanmard
Attorney Docket Number	USF.106XC1

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number - Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	U1	US-7,452,555	11-18-2008	Childs	All
	U2	US-7,446,107	11-04-2008	Remenar *et al.*	All
	U3	US-7,205,413	04-17-2007	Morissette *et al.*	All
	U4	US-7,078,526	07-18-2006	Remenar *et al.*	All
	U5	US-			
	U6	US-			
	U7	US-			
	U8	US-			
	U9	US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] - Number[4] - Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	F1					
	F2					
	F3					
	F4					
	F5					
	F6					
	F7					

Examiner Signature		Date Considered	

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This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	10/378,956
Filing Date	March 3, 2003
First Named Inventor	Michael J. Zaworotko
Art Unit	1617
Examiner Name	Sahar Javanmard
Attorney Docket Number	USF.106XC1

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article, (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	R1	SHATTOCK, T. R. *et al.* "Hierarchy of Supramolecular Synthons: Persistent Carboxylic Acid ··· Pyridine Hydrogen Bonds in Cocrystals that also contain a Hydroxyl Moiety" *Crystal Growth 7 Design*, 2008, pp. 4533-4545, Vol. 8, No. 12.	
	R2		
	R3		
	R4		
	R5		
	R6		
	R7		
	R8		
	R9		
	R10		
	R11		
	R12		

Examiner Signature		Date Considered	

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Hierarchy of Supramolecular Synthons: Persistent Carboxylic Acid···Pyridine Hydrogen Bonds in Cocrystals That also Contain a Hydroxyl Moiety

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ABSTRACT: A Cambridge Structural Database (CSD) analysis was conducted in order to evaluate the hierarchy of supramolecular heterosynthons that involve two of the most relevant functional groups in the context of active pharmaceutical ingredients, carboxylic acids and alcohols, in competitive environments. The study revealed that 34% of the 5690 molecular carboxylic acid entries and 26% of the 25 035 molecular alcohol entries form supramolecular homosynthons, whereas the remaining entries form supramolecular heterosynthons with other functional groups, in particular N_{arom}, $CONH_2$, C−O−C, C=O, and chloride anions. Further refinement of this raw data revealed the following: 98% occurrence of the COOH···N_{arom} supramolecular heterosynthon in the 126 crystal structures that contain acid and pyridine moieties in the absence of other hydrogen bond donors or acceptors; and 78% occurrence of the OH···N_{arom} supramolecular heterosynthon in 228 crystal structures that contain hydroxyl and pyridine moieties (excluding intramolecular hydrogen bonding). Such high frequencies indicate that these supramolecular heterosynthons are strongly favored over their respective COOH···COOH and OH···OH supramolecular homosynthons. However, the CSD does not contain enough information to evaluate the predictability of even common supramolecular heterosynthons in the presence of competing hydrogen bonding moieties; for example, there are only 15 entries when -COOH, -OH, and N_{arom} moieties are present exclusively (no other hydrogen bond donors and acceptors groups) in a molecule. We have addressed the competition between the COOH···N_{arom} and the OH···N_{arom} supramolecular heterosynthons by analyzing these 15 entries in CSD and characterizing 15 new compounds (cocrystals **1**−**13**; salts **14** and **15**) that are composed of cocrystal formers which contain a permutation of -COOH, -OH and N_{arom} functional groups. Analysis of this group of compounds reveals that supramolecular heterosynthons are favored over the respective supramolecular homosynthons. We also address the methodologies that can be used to prepare **1**−**15** in the context of solvent evaporation, solvent-drop grinding, and slurrying.

1. Introduction

Crystal engineering,[1] a term coined by R. Pepinsky[2] in 1955 and subsequently implemented by G. M. J. Schmidt[3] in 1971 in the context of topochemical reactions has matured into a paradigm for the preparation or supramolecular synthesis[4] of new compounds with tailor-made properties. Crystal engineered materials can be exploited for many purposes such as host−guest compounds, nonlinear optical materials, organic conductors, or coordination polymers.[5−9] However, given that active pharmaceutical ingredients (APIs) represent perhaps the most valuable substances known, it is unsurprising that pharmaceutical cocrystals are attracting considerable attention from both industrial and academic researchers.[10−15]

In general, a detailed understanding of the supramolecular chemistry of functional groups is a prerequisite for the rational design (supramolecular synthesis) of novel cocrystals and for understanding the structure−property relationships in such compounds. Cocrystals[16−21] represent a class of compound that could reasonably be described as long known but little studied. Indeed, to our knowledge the term cocrystal was not coined until 1967[22] and it was not popularized in the context of small molecules until Etter used the term extensively in the 1980s.[23] Furthermore, even today the term cocrystal is poorly defined and represents ambiguity or even controversy.[24] For the purposes of this manuscript we define a cocrystal as the following: a multiple component crystalline solid formed in a stoichiometric ratio between two compounds that are crystalline solids under ambient conditions. At least one of these compounds is molecular (the cocrystal former) and forms supramolecular synthons(s) with the remaining component(s). If one uses this definition then the first cocrystals were reported in the 1800s,[25] and they have had various terms applied to them: addition compounds, organic molecular compounds, complexes and heteromolecular crystals.[26−33] Cocrystals are also distinct from solvates,[34] salts,[35] and inclusion compounds[36] if one employs this definition. APIs are a natural target for cocrystals since the solid state chemistry of APIs represents an area of scientific, commercial, regulatory and legal interest.[37] Furthermore, in terms of crystal engineering, the inherent nature of APIs means that they contain exterior functional group(s) that can engage in molecular recognition events with biological targets. These same functional group(s) are responsible for the well-documented "promiscuity" of APIs in the context of polymorphs,[38] solvates,[34] and cocrystals.[10−12] Nevertheless, the term pharmaceutical cocrystal, that is, a cocrystal between an API and a molecular cocrystal former, was not widely used until recent years. Pharmaceutical cocrystals have been known since at least the 1930s, yet it is only in recent years that their diversity in terms of crystal form and physical properties has been fully recognized in the context of preformulation and formulation of APIs. The number of cocrystals in the Cambridge Structural Database (CSD)[39] remains remarkably low (1951 entries, ca. 1% of all organic entries) although, as revealed by Figure 1, the number of entries is growing steadily.

The key to understanding and designing cocrystals lies with supramolecular synthons. Supramolecular synthons exist in two distinct categories: supramolecular homosynthons that are composed of identical complementary functional groups, also

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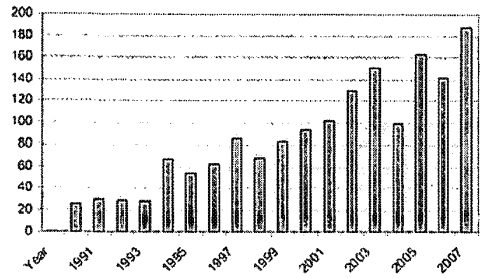
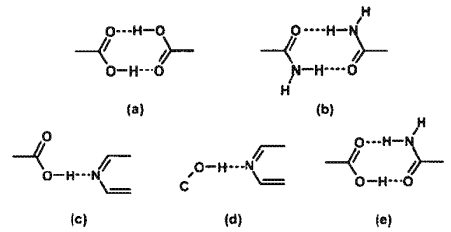


Figure 1. Hydrogen-bonded co-crystals in the CSD from 1990−2007.

Scheme 1. (a, b) Supramolecular Homosynthons and (c, d, and e) Supramolecular Heterosynthons



referred to as self-association motifs (dimers, chains, etc.), for example, carboxylic acid dimers,[40] amide dimers[41] (Scheme 1a,b), pyrazoles and oximes;[42] supramolecular heterosynthons composed of different but complementary functional groups such as acid-aromatic nitrogen,[43] acid-amide,[44] hydroxyl-aromatic nitrogen[45] etc. (Scheme 1c−e). It is quite well documented that some of these supramolecular heterosynthons are reliable for the preparation of cocrystals (i.e., they form preferentially over supramolecular homosynthons)[46] and there are several CSD statistical studies that address hydrogen bonding motifs. However, studies related to the occurrence of a particular supramolecular heterosynthon in a more competitive environment are limited in quantity and scope.[47]

Infantes et al. studied the probabilities of formation of intermolecular hydrogen bonds between chemical groups containing at least one strong hydrogen bond donor group. It was demonstrated that carboxylic acid supramolecular homosynthons can be broken when there are other chemical groups present; however, amide supramolecular homosynthons are relatively robust. The relative strength of supramolecular homosynthons is amides > acids > alcohols functional groups. The study of supramolecular heterosynthons in competitive environments would provide valuable insight for crystal engineering of cocrystals of even more complex APIs and vice versa since the modular nature of cocrystals makes them ideally suited to study the competition between different supramolecular heterosynthons and by their very nature they must be composed of two or more components. This contribution is part of our continuing effort to explore pharmaceutical cocrystals and combines a systematic CSD study with a synthetic and structural study. More specifically, we focus herein upon the ability of carboxylic acids and alcohols to form reliable supramolecular heterosynthons that persist in the presence of competing functionalities. These functional groups were chosen since carboxylic acids and alcohols are overexpressed in APIs when compared to organic compounds in general. As revealed by Table 1, alcohols and carboxylic acids represent 21% and 6% of the organic entries in the CSD, respectively, but they are present in 33 and 25 of the top 100 prescribed drugs, respectively.[48] Furthermore, they

Table 1. Cocrystal Design: % Occurrence of Functional Groups in APIs[a]

groups	CSD only organics	biological activity	pharmacological	prescription
ether	29	40	37	41
alcohol	21	39	36	**33**
ester	17	24	18	12
2° amide	9	18	22	14
carbonyl	14	22	16	28
2° amine	5	8	8	17
3° amine	7	12	13	43
C−Cl	9	13	16	21
$N_{aromatic}$	7	10	13	16
carboxylic acid	6	9	11	**25**
Cl-	3	8	9	16
sulfonamide	0.11	0.65	1.4	9

[a] CSD Conquest 1.10 (January 2008 update) 436 384 total entries. Search parameter: organics only 187 025 entries. Biological activity 11 046 entries. CSD All Text Search: Activity, Agent, Biological, Drug, Inhibitor, Pharmaceutical, Pharmacological.

are frequently encountered in pharmaceutical excipients and salt formers and are therefore highly relevant as cocrystal formers in pharmaceutical cocrystals.[49]

We also report herein X-ray crystal structures of 15 compounds (**1**−**13** are cocrystals; **14** and **15** are salts) and discuss their relevance in the context of delineation of hydrogen bonding hierarchy among -COOH, and -OH functional moieties in the presence of N_{arom} functional groups (including entries from CSD). The reliability of a particular supramolecular heterosynthon involving carboxylic acids (-COOH) or alcohols (-OH) is also evaluated in a competitive environment using CSD statistics. Finally, we address synthetic methodologies and their potential to afford polymorphism in the starting materials or cocrystal products.

2. Experimental Section

Cocrystal formers that contain permutations of COOH, OH, and N_{arom} moieties were used in this study (Chart 1). Cocrystal formers were selected in order to facilitate the study of three groups of cocrystal as follows: cocrystal formers containing N_{arom} moieties only were crystallized in the presence of cocrystal formers containing both COOH and OH moieties; cocrystal formers containing COOH moieties only were crystallized in the presence of cocrystal formers containing both N_{arom} and OH moieties; cocrystal formers containing OH moieties only were crystallized in the presence of cocrystal formers containing both N_{arom} and COOH moieties. Cocrystals **1**−**13** and salts **14** and **15**[21b,50] were obtained as single crystals via slow evaporation. However, slow evaporation of 5-hydroxyquinoline, 5HQL, with benzoic acid, isophthalic acid, trimesic acid, glutaric acid and sorbic acid and 3-hydroxypyridine, 3HP, with trimesic acid, glutaric acid and sorbic acid produced powders rather than single crystals. The powders obtained by solvent-drop grinding experiments of 5-hydroxyisoquinoline and 3-hydroxypyridine were characterized by powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC) and IR spectroscopy. We were not able to harvest single crystals from the solution mediated technique, however the PXRD, DSC and IR on the bulk sample clearly showed the formation of new phase rather than starting materials. The details of these techniques are described in the Experimental Section. Nicotinic acid (NA) and iso-nicotinic acid (INA) produced mixtures of starting materials rather than new crystal forms. These observations are salient and will be discussed later.

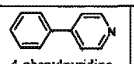
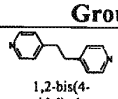
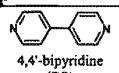
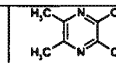
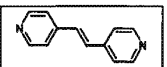
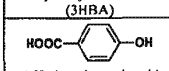
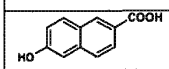
Synthesis. All reagents used in this study were obtained from commercial suppliers and used as such without further purification. HPLC grade solvents were used for the crystallization experiments. Single crystals of compounds **1**−**15** were obtained via slow evaporation of stoichiometric amounts of starting materials in an appropriate solvent and were isolated from solution before complete evaporation of their mother liquor in all cases except **15**.

Cocrystallization via Grinding. Stoichiometric amounts of the starting materials listed in Chart 1 were ground with a mortar and pestle

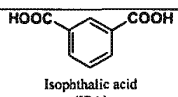
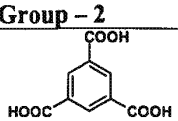
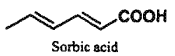
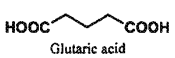
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Chart 1. Molecular Structures of Cocrystal Formers Used in Crystallization Experiments

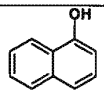
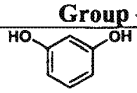
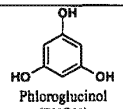
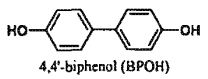
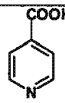
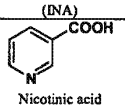
Group – 1

	 Pyrazine (PYZ)	 4-phenylpyridine (4PP)	 1,2-bis(4-pyridyl)ethane (BPEA)	 4,4'-bipyridine (BP)	 Quinoxaline (QXL)	 Tetramethylpyrazine (TMP)	 *trans*-1,2-bis(4-pyridyl)ethane (BPEE)
 3-Hydroxybenzoic acid (3HBA)	**Cocrystal – 1**	**Cocrystal – 6**	**Cocrystal – 7**	**Cocrystal – 8**	**Cocrystal – 9**	**Cocrystal – 10**	**Cocrystal – 13**
 4-Hydroxybenzoic acid (4HBA)	**Cocrystal – 4**	**Cocrystal – 3**	**Cocrystal – 2**			**Cocrystal – 5 acetonitrile solvate**	**Cocrystal – 12**
 6-Hydroxy-2-naphthoic acid (HNA)							**Cocrystal – 11**

Group – 2

	 Benzoic acid (BA)	 Isophthalic acid (IPA)	 Trimesic acid (TMA)	 Sorbic acid (SA)	 Glutaric acid (GA)
 3-hydroxypyridine (3HP)	**Salt – 14**	**Salt – 15**	**New phase**	**New phase**	**New phase**
 5-hydroxyisoquinoline (5HQL)	**New phase**	**New phase**	**New phase**	**New phase**	**New phase**

Group – 3

	 1-Naphthol (NPOH)	 Resorcinol (RESOH)	 Phloroglucinol (PHOH)	 4,4'-biphenol (BPOH)
 Isonicotinic acid (INA)	**No reaction**	**No reaction**	**No reaction**	**No reaction**
 Nicotinic acid (NA)	**No reaction**	**No reaction**	**No reaction**	**No reaction**

for ca. 4 min, and the resulting powders were analyzed by diffuse reflectance IR spectroscopy and X-ray powder diffraction.

Cocrystallization via Solvent-Drop Grinding.[51] Stoichiometric amounts of the starting materials listed in Chart 1 were ground with a mortar and pestle for ca. 4 min following addition of solvent (10 μL of solvent per 50 mg of starting materials). The resulting powders were analyzed by diffuse reflectance IR spectroscopy and X-ray powder diffraction.

Cocrystallization via Solvent Evaporation. Synthesis of cocrystals was carried out by dissolving the reactants in appropriate solvents, either at room temperature or by warming on a hot plate and subsequent slow-evaporation (See Table 2). For a typical crystallization, in a 10 mL glass vial, 0.031 g (0.13 mmol) of 3-hydroxybenzoic acid (**3HBA**) and 0.020 g (0.13 mmol) of 4,4′-bipyridine (**BP**) were dissolved in methanol. The solution was left undisturbed to evaporate under ambient conditions. Yellow needle-like single crystals of **9** (mp = 176−179 °C) were obtained within 12 days and were used for single-crystal X-ray crystallography.

FT-IR, PXRD and Melting Point Determinations. All samples were characterized by IR spectroscopy using a Nicolet Avatar 320 FT-IR instrument. The bulk samples were analyzed by X-ray powder diffraction. To perform PXRD analysis a Rigaku Miniflex diffractometer was used. Experimental conditions: Cu Kα radiation (λ = 1.54056 Å); 40 kV and 30 mA. Scanning interval: 3−40° 2 θ; time per step: 0.5 s. Melting points of **1**−**15** were determined on a MEL-TEMP apparatus and are presented in Table 3.

Differential Scanning Calorimetry (DSC). Thermal analysis was carried out employing a TA instruments DSC 2920 differential scanning calorimeter. Aluminum pans were used for the experiment for all the samples. Temperature calibrations were made using indium as the standard. An empty pan, sealed in the same way as the sample, was used as a reference. The thermograms were run at a scanning of 5 °C/

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Table 2. Details about the Reactants and Solvents Used for Crystallization and Stoichiometric Ratios of the Molecular Complexes (1−15)

molecular complexes	reactants	solvent of crystallization	composition (including solvent molecules)
1	3HBA + PYZ	chloroform	2:1
2	4HBA + BPEE	methanol	2:1
3	4HBA + 4PP	acetone/ethyl acetate (1:1)	1:1
4	4HBA + PYZ	acetonitrile	2:1
5	4HBA + TMP	acetonitrile	2:1
6	3HBA + 4PP	acetone/ethyl acetate (1:1)	1:2
7	3HBA + BPEA	acetone	1:1
8	3HBA + BP	methanol	1:1
9	3HBA + QXL	ethanol	2:2 (1:1)
10	3HBA + TMP	acetonitrile	2:3
11	HNA + BPEE	methanol	1:1
12	4HBA + BPEE	methanol	1:1
13	3HBA + BPEE	ethanol	1:1
14	3HP + BA	methanol/ethanol (1:1)	1:1
15	3HP + IPA	dimethylsulfoxide	1:1

Table 3. Melting Point Comparisons between the Starting Materials and 1−15

	melting point (°C) compounds	melting point (°C) cocrystal former 1	melting point (°C) cocrystal former 2
1	178	199−203	52−55
2	194−198	214−217	107−110
3	90−96	214−217	69−73
4	160−164	214−217	52−55
5	178−182	214−217	84−86
6	115−118	199−203	69−73
7	180−184	199−203	107−110
8	176−179	199−203	111−114
9	100−104	199−203	29−32
10	139−142	199−203	84−86
11	184−187	237−241	150−153
12	184−186	214−217	150−153
13	180−184	199−203	150−153
14	82−85	125−128	121−125
15	161−163	125−128	341−343

min or 10 °C/min from 30 °C to the required temperature on 5−10 mg powdered sample.

Single-Crystal X-ray Data Collection and Structure Determinations. Single crystals of **1−15** were examined under a microscope and suitable crystals were selected for single crystal X-ray crystallography. Single crystal X-ray diffraction data were collected on a Bruker-AXS SMART APEX CCD diffractometer with monochromatized Mo Kα radiation (λ = 0.71073 Å) connected to a KRYO-FLEX low temperature device. Data for **1−15** were collected at 100 K. Lattice parameters were determined from least-squares analysis and reflection data were integrated using the program SAINT.[52] Lorentz and polarization corrections were applied for diffracted reflections. In addition, the data was corrected for absorption using SADABS.[53] Structures were solved by direct methods and refined by full matrix least-squares based on F^2 using SHELXTL.[54] Non-hydrogen atoms were refined with anisotropic displacement parameters. All H-atoms bonded to carbon atoms, except methyl groups, were placed geometrically and refined with an isotropic displacement parameter fixed at 1.2 times U_q of the atoms to which they are attached. N or O bonded protons and H-atoms of methyl groups were located from difference Fourier map inspection and refined isotropically with thermal parameters based upon the corresponding N, O or C atom (U(H) = $1.2U_q$(N, O)). Selected bond distances are listed in Table 4 and crystallographic data for **1−15** are presented in Table 5.

CSD Analysis.[55] CSD surveys of carboxylic acids and alcohols with complementary functional groups, X, that can serve as components of supramolecular heterosynthons were conducted (X = aromatic nitrogen moieties, N_{arom}, primary amides, carbonyl, esters, ethers, water, chloride, amines, cyano, nitro). The CSD searches afforded information regarding the following: (i) the total number of structures containing both X and carboxylic acid/alcohol moieties regardless of their mutual recognition and what other functional groups are present; (ii) the number of structures that form a supramolecular heterosynthon between X and a carboxylic acid/alcohol moiety; (iii) the occurrence of supramolecular homosynthons for either carboxylic acids/alcohols or X; (iv) the distance range and the mean length of the interactions. The parameters used to define the searches were as follows: 3D-coordinates present, no ions, only organics and $R \leq 7.5\%$. Contact limits for each interaction were subsequently determined from distance distribution plots based on visual inspection of the resulting histogram and structural analysis of selected entries. Histograms for O−H···O hydrogen bonds for carboxylic acids are presented in Figure 2. All searches were conducted in two categories: (1) "raw" and (2) "refined". The raw searches addressed the occurrence of a particular functional group or supramolecular synthon in the presence of all other functional groups that could partake in hydrogen bonding. The refined searches addressed the occurrence of a particular functional group or supramolecular heterosynthon in the absence of competing functional groups. The accuracy of the refined searches were confirmed by manually checking each entry in the search list. In the present context, reliability is defined as the consistency of occurrence of a particular supramolecular synthon based on CSD statistics and persistency is defined as continued existence or occurrence despite the presence of competing moieties.

3. Results and Discussion

3.1. CSD Analysis of Carboxylic Acid (COOH) Functional Group. It is well documented that carboxylic acids tend to exhibit two primary motifs for self-organization and formation of supramolecular homosynthons: dimer **I** or catemer **II** (Scheme 2).[56] A CSD analysis of all crystal structures of molecular organic compounds containing a carboxylic acid moiety was conducted in order to interpret the statistics of supramolecular

Table 4. Hydrogen Bond Distances and Parameters for 1−15

	hydrogen bond	*d* (H···A) /Å	*D*(D···A)/Å	*θ*/°		hydrogen bond	*d* (H···A) /Å	*D*(D···A)/Å	*θ*/°
1	O−H···N	1.74	2.675(2)	169.0	8	O−H····N	1.76	2.6881(19)	168.0
	O−H···O	1.82	2.7540(19)	176.5		O−H····N	1.81	2.7898(19)	175.0
2	O−H···N	1.54	2.590(2)	173.5	9	O−H····N	1.85	2.720(2)	170.0
	O−H···O	1.81	2.6455(19)	167.8		O−H····N	1.89	2.782(2)	170.6
	O−H····N	1.72	2.546(2)	177.6		O−H····N	1.77	2.699(2)	169.5
	O−H···O	1.90	2.7411(19)	171.6		O−H····N	1.86	2.762(2)	163.1
	N−H···O	1.59	2.546(2)	177.8	10	O−H····N	1.77	2.673(2)	177.2
3	O−H···O	1.59	2.630(3)	170.4		O−H····N	1.81	2.755(2)	162.2
	O−H···N	1.79	2.703(3)	167.0	11	O−H····N	1.70	2.756(3)	176.7
4	O−H···N	1.87	2.7739(17)	169.9		O−H····N	1.71	2.640(2)	172.5
	O−H···O	1.76	2.6282(15)	169.6	12	O−H····N	1.54	2.617(4)	168.8
5	O−H···N	1.92	2.739(2)	163.7		O−H····N	1.79	2.756(4)	163.8
	O−H···O	1.78	2.617(2)	175.4	13	O−H····N	1.64	2.6482(16)	168.6
6	O−H···N	1.64	2.596(2)	166.6	14	O−H····N	1.80	2.7358(16)	174.8
	O−H···N	1.74	2.685(2)	169.3		N−H····O	1.43	2.559(10)	176.1
7	O−H···N	1.48	2.590(4)	172.4	15	O−H····O	1.74	2.569(9)	169.0
	O−H···N	1.66	2.663(4)	167.8		N−H····O	2.41	3.065(10)	115.1
						O−H····O	1.76	2.662(3)	165.8

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Table 5. Crystallographic Data and Structure Refinement Parameters for Compounds 1–15

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
formula	$C_6H_6NO_2$	$C_{26}H_{24}N_2O_6$	$C_{18}H_{15}NO_2$	$C_9H_8NO_2$	$C_{13}H_{15}N_2O_2$	$C_{26}H_{24}N_2O_2$	$C_{19}H_{18}N_2O_2$	$C_{12}H_{14}N_2O_2$	$C_{15}H_{12}N_2O_2$	$C_{19}H_{24}N_2O_2$	$C_{23}H_{18}N_2O_2$	$C_{19}H_{16}N_2O_2$	$C_{19}H_{16}N_2O_2$	$C_{12}H_{11}NO_2$	$C_{13}H_{11}NO_2$
MW	178.16	460.47	293.31	178.16	247.27	448.50	322.35	294.30	268.27	342.41	370.39	320.34	320.34	217.22	261.23
crystal system	monoclinic	monoclinic	monoclinic	triclinic	monoclinic	monoclinic	triclinic	triclinic	triclinic	monoclinic	triclinic	triclinic	triclinic	monoclinic	monoclinic
space group	$P2_1/n$	$P2_1/c$	$C2/c$	$P\bar{1}$	$P2_1/c$	$P2_1/n$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P2_1/c$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	Pc	$P2_1/n$
a (Å)	5.2006(11)	7.3666(3)	26.780(4)	5.9424(9)	11.693(4)	9.2032(16)	7.9810(15)	8.1965(12)	7.2850(9)	9.4609(14)	5.9682(8)	6.1928(19)	7.9011(13)	5.038(4)	10.218(5)
b (Å)	14.568(3)	23.716(3)	7.4445(13)	6.8175(10)	8.694(3)	20.819(4)	8.9312(17)	8.8828(12)	12.1470(15)	17.807(3)	8.7387(12)	6.957(2)	10.3101(16)	10.012(8)	11.001(6)
c (Å)	10.994(3)	12.5523(15)	19.471(3)	10.6376(16)	12.732(4)	11.827(2)	11.209(2)	10.3613(15)	14.4319(18)	11.0809(17)	17.938(3)	18.499(5)	10.8629(17)	10.362(8)	10.412(5)
α (deg)	90	90	90	102.963(3)	90	90	97.585(3)	72.213(3)	87.837(2)	90	78.473(2)	95.046(6)	114.081(2)	90	90
β (deg)	100.450(5)	103.033(2)	131.101(2)	97.383(2)	94.920(7)	93.487(3)	90.745(4)	72.213(2)	85.937(2)	92.184(3)	82.090(3)	94.058(7)	103.883(3)	100.33(2)	99.983(9)
γ (deg)	90	90	90	100.057(3)	90	90	90.665(4)	86.773(3)	80.916(2)	90	88.921(3)	103.928(6)	93.041(3)	90	90
V /Å^3	819.1(3)	2136.5(4)	2925.1(8)	407.16(11)	1288.5(7)	2261.9(7)	791.9(3) [3]	685.25(17)	1257.4(3)	1865.5(5)	907.9(2)	767.1(4)	772.8(2)	514.2(7)	1152.6(10)
D_c/g cm^{-3}	1.235	1.432	1.332	1.453	1.275	1.317	1.352	1.426	1.417	1.219	1.355	1.387	1.377	1.430	1.505
Z	4	4	8	2	4	4	2	2	4	4	2	2	2	2	4
2θ range	4.70–50.04	3.44–52.74	4.04–50.14	4.00–52.74	3.50–50.14	3.92 – 52.74	4.60–56.48	4.82–49.42	2.84–52.74	4.88–52.74	2.34–56.36	2.22–50.18	4.40–49.42	5.74 – 50.16	5.48–52.74
Nref/Npara.	1417/118	4356/307	2477/199	1635/118	2198/163	4628/307	3126/217	2311/199	5006/361	3804/229	3632/253	2508/217	2591/217	961/145	2340/172
T /K	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)
R_1 [$I > 2\sigma(I)$]	0.0418	0.0472	0.0495	0.0456	0.0461	0.0534	0.0810	0.0442	0.0498	0.0576	0.0564	0.0682	0.0416	0.0597	0.0566
wR_2	0.1007	0.1082	0.1222	0.1213	0.1110	0.1085	0.2240	0.1109	0.1194	0.1303	0.1282	0.1366	0.1112	0.1370	0.1359
GOF	1.066	1.032	1.020	1.068	1.037	1.047	1.186	1.092	1.058	1.033	1.040	0.999	1.088	1.088	1.038
abs coef	0.110	0.103	0.091	0.111	0.092	0.086	0.093	0.100	0.101	0.084	0.091	0.095	0.095	0.102	0.117

Scheme 2. Carboxylic Acid Dimer I and Catemer II

synthons formed by carboxylic acids. The search furnishes the % occurrence and structural parameters of supramolecular homosynthons and supramolecular heterosynthons involving carboxylic acid moieties.

The CSD data reveals 5690 entries in which at least one carboxylic acid moiety is present. 1787 (31%) compounds exhibit the dimer motif I (O···O range 2.50−3.00 Å, average O···O distance of 2.650 (3) Å) and 149 exhibit the catemer motif II (3%). At the very least this data indicates that supramolecular homosynthons are not dominant in the solid state. However, this represents a raw set of data and a more refined search was conducted to evaluate the occurrence of the supramolecular homosynthon in the absence of competing hydrogen bond donors and/or acceptors. There are 474 crystal structures that contain a carboxylic acid moiety in the absence of other hydrogen bond donor or acceptor groups. 439 (93%) of these structures exhibit dimer motif **I** and 42 (9%) exhibit catemer motif **II**, suggesting **I** is favored over **II** in the absence of competition. It would therefore be fair to say that supramolecular homosynthons are indeed dominant in the absence of competition. Now we shall address the competitive aspect of carboxylic acids and its relevance to cocrystals.

Given that only 34% of carboxylic acids form supramolecular homosynthons in crystalline solids the following question arises: what other functional groups are responsible for the supramolecular heterosynthons that presumably exist in the remaining 66% of carboxylic acid crystal structures? The following functional groups are all complementary and relevant in this context: basic nitrogen atoms that are part of a delocalized or conjugated system, N_{arom}, chloride anions, primary amides, carbonyls, and alcohols. The detail analysis of the remaining crystal structures containing a COOH moiety and a complementary functional group is listed in Table 6. (See Supporting Information for detailed description of CSD analysis of COOH acid moiety with complementary functional groups.) The COOH···N_{arom} supramolecular heterosynthon (Scheme 3a) reveals 98% occurrence when competing hydrogen bond donor and/or acceptor groups are absent. The carboxylic acid-chloride ion supramolecular heterosynthon (Scheme 3b) is a charge-assisted hydrogen bond that has already been exploited in the context of pharmaceutical cocrystals.[12c] Interactions involving the COOH···$CONH_2$ supramolecular heterosynthon (Scheme 3c) have been utilized in the formation of numerous supramolecular structures, including pharmaceutical cocrystals. The carbonyl moiety is present in 28 of the top 100 prescription drugs and there are numerous APIs with both carbonyl and carboxylic acid functional groups (Scheme 3d).[57] Alcohol moieties can act as a hydrogen bond donor and/or an acceptor and they interact with carboxylic acids to form either of two supramolecular heterosynthons as shown in Scheme 3e−f.

In summary, both the raw and the refined analyses presented herein address the competitiveness of supramolecular heterosynthons vs their competing supramolecular homosynthons. The COOH···N_{arom} supramolecular heterosynthon exhibits the highest % occurrence (98%) in the absence of any other hydrogen bond donor and acceptor groups. The COOH···N_{arom} supramolecular heterosynthon exhibits the highest persistence (77%) in

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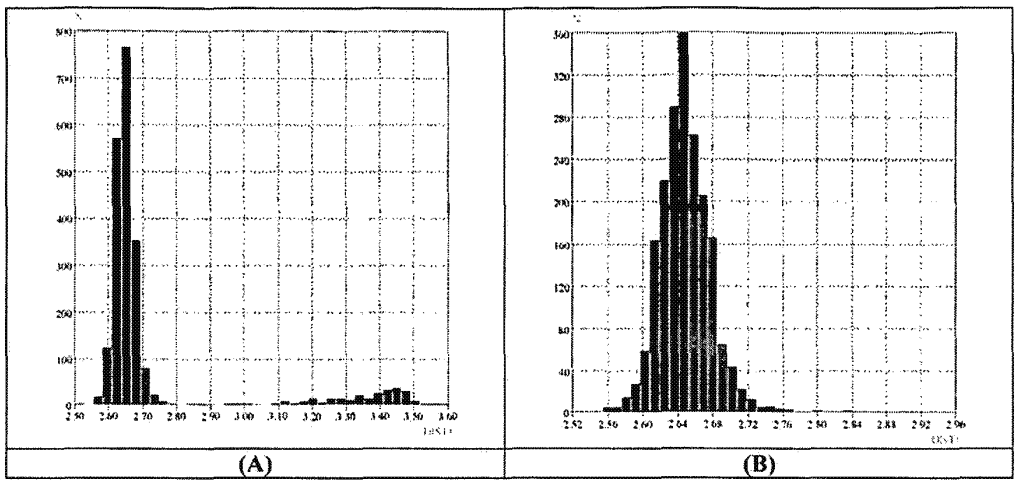


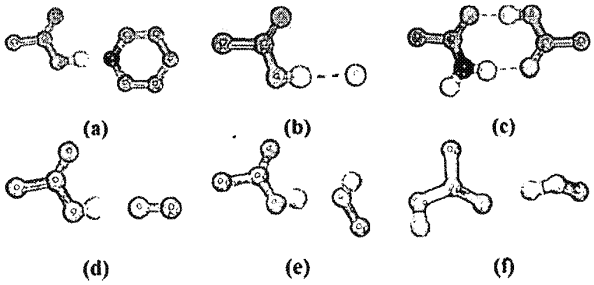
Figure 2. (A) and (B) Histograms of O−H···O hydrogen bond lengths in carboxylic acid dimers retrieved from CSD.

Table 6. A Summary of the CSD Data As It Relates to Carboxylic Acid Moieties and Their Tendency to Form Supramolecular Homosynthons vs. Supramolecular Heterosynthons

functional groups present	raw data			refined data				
	no. of structures	homosynthons	heterosynthons	no. of structures	homosynthons	heterosynthons	range (Å)	mean σ (Å)
COOH	5690	1787 (31%) COOH dimer 149 (3%) COOH catemer		474	439 (93%) COOH dimer 42 (9%) COOH catemer		2.50−3.00	2.650(3)
COOH and N_{arom}	607	45 (7%) COOH···COOH	468 (77%) COOH···N_{arom}	126	9 (7%) COOH···COOH	123 (98%) COOH···N_{arom}	2.50−3.00	2.652(2)
COOH and Cl^-	267	3 (1%) COOH···COOH	172 (64%) COOH···Cl^-	51	0 (0%) COOH···COOH	51 (100%) COOH··· Cl^{-a}	2.70−3.25	2.999(4)
COOH and $CONH_2$	177	52 (29%) $CONH_2$···$CONH_2$ 8 (5%) COOH···COOH	101 (57%) COOH···$CONH_2$	19	2 (11%) $CONH_2$···$CONH_2$ 1 (5%) COOH···COOH	16 (84%) COOH···$CONH_2$	2.50−2.80 2.80−3.25	2.583(3)2.958(9)
COOH and O=C	597	167 (28%) COOH···COOH	161 (27%) COOH···O=C	178	111 (62%) COOH···COOH	85 (48%) COOH···O=C	2.40−2.90	2.698(6)
COOH and OH	1176	235 (20%) COOH···COOH 314(26%) OH···OH	540 (46%) (OH)C=O···OH 502 (43%) COOH···OH	276	82 (30%) COOH···COOH 107 (39%) OH···OH	191 (69%) (OH)C=O···OH 191 (69%) COOH···OH	2.40−3.00 2.60−3.00	2.659(3)2.792(3)

[a] Cation exclusively on hydrocarbon skeleton.

Scheme 3. (a) COOH···N_{arom} Supramolecular Heterosynthon, (b) COOH···Cl^- Supramolecular Heterosynthon, (c) COOH···$CONH_2$ Supramolecular Heterosynthon, (d) COOH···O=C Supramolecular Heterosynthon, (e and f) COOH ···OH Supramolecular Heterosynthons



the presence of competing functional groups. The other persistent supramolecular heterosynthon is the COOH···Cl^- charge assisted hydrogen bond which shows 100% and 64% occurrence in the absence or presence of other hydrogen bonding groups, respectively. The analysis of carboxylic acids and amides indicates that the COOH···$CONH_2$ supramolecular heterosynthon shows 57% reliability of occurrence in the presence of other competing groups whereas the percentage increases to 84% in the absence of other hydrogen bonding groups, however, the total number of entries for the refined data is limited to 19 entries. The COOH···OH supramolecular heterosynthons exhibit ca. 46% reliability of occurrence in the presence of competing groups whereas it increase to 69% if competing functional groups are absent. The OH···OH supramolecular homosynthon is slightly preferred (26% and 39%) vs the carboxylic acid supramolecular homosynthon (20% and 30%) in the presence or absence of other competing functional groups, respectively.

CSD Analysis of Alcohol (OH) Functional Group. Alcohols are the second largest functional group in the CSD after ethers and third in the list of top 100 prescription drugs (Table 1).[48] A CSD analyses of all molecular organic crystal structures containing an alcohol moiety was conducted in order to evaluate supramolecular synthons formed by alcohols. Alcohols are similar to carboxylic acids in that they can serve as both a hydrogen bond donor and a hydrogen bond acceptor. They are therefore self-complementary and can also interact with comple-

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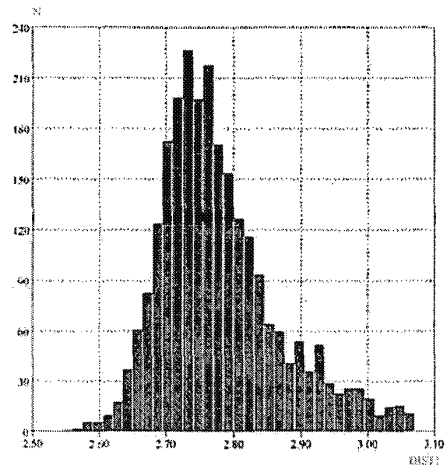


Figure 3. Histogram of O−H···O hydrogen bond lengths in alcohols retrieved from CSD.

mentary functional groups such as N_{arom}, primary amides, carbonyl, esters, ethers, water, chloride, amines, cyano, nitro, etc. to form supramolecular heterosynthons.

The CSD data reveals 25 035 entries containing at least one OH moiety and 6584 (26%) exhibit the OH···OH supramolecular homosynthon. The raw data reveals a similar trend to that seen in the survey of carboxylic acids, that is, the persistent nature of supramolecular heterosynthons. The refined analysis reveals that there are 1316 entries containing an OH moiety and 1006 (76%) exhibit the OH···OH supramolecular homosynthon. However, the remaining 74% of crystal structures in the raw data are dominated by supramolecular heterosynthons with complementary functional groups such as basic nitrogen atoms that are part of a delocalized or conjugated system, N_{arom}, chloride anions, primary amides, carbonyls, and carboxylic acids. A summary of the results of this analysis is presented in Table 7 and the histogram for O−H···O hydrogen bond in alcohols is presented in Figure 3.

In summary, both the raw and the refined analyses presented herein for alcohols reveal that supramolecular heterosynthons dominate vs their competing supramolecular homosynthons. The CSD analysis reveals ca. 50% reliability for supramolecular heterosynthon formation between alcohols and functional groups such as N_{arom} and $CONH_2$ even in the presence of other competing functional groups and in the absence of other hydrogen bond donor or acceptor groups the percentages for OH···N_{arom} supramolecular heterosynthons increase to 78% and that of primary amides to 90%. The analysis of alcohols with amides indicates that the OH···OH supramolecular homosynthon (31% raw, 76% refined) occurs more commonly than the $CONH_2$···$CONH_2$ supramolecular homosynthon (19% raw, 10% refined). This observation is different from that seen in carboxylic acids, for which the amide supramolecular homosynthon is favored over the carboxylic acid supramolecular homosynthon. The OH···Cl^- supramolecular heterosynthon persists in 73% of structures in which both functional groups are present although there is no refined data since there are no crystal structures in the CSD with chloride anions and counter cations exclusively on hydrocarbon skeletons. The % occurrence of the OH···O=C supramolecular heterosynthon is found to be 43% when other competing functional groups are present whereas it increases to 65% when both these groups are exclusively present on the hydrocarbon skeleton.

Competitive Study between Carboxylic Acid (COOH) and Alcohol/Hydroxyl (OH) Functional Groups. The CSD statistics concerning carboxylic acids and alcohols indicate that, in general, both of these functional groups favor supramolecular heterosynthons over supramolecular homosynthons. Our interest herein is 2-fold: the competitive behavior of these two functional groups in the presence of a specific additional moiety is relevant in the context of most APIs; the information gathered herein is relevant in the general context of crystal engineering protocols and especially for crystal structure prediction and cocrystal design. The analysis of the competitive hydrogen bonding ability of carboxylic acids and alcohols is summarized in Table 8. It indicates that there are only 15 entries[58] having -COOH, -OH and N_{arom} groups present without other hydrogen bond donors or acceptors, and all of these crystal structures contain COOH···N_{arom} and/or OH···N_{arom} supramolecular heterosynthons rather than COOH···COOH or OH···OH supramolecular homosynthons. Similar trends are observed with other functional groups such as the chloride ion, which exhibits 90% or 80% probability of COOH···Cl^- and OH···Cl^- supramolecular heterosynthons, respectively, in the absence of other hydrogen bond donors or acceptors. There is only 1 CSD entry (ZZZR-JG01) having COOH, OH and $CONH_2$ moieties present in the absence of other hydrogen bond donors and acceptors. The constraints applied for these searches were identical to those of the carboxylic acid and alcohol searches; contact limits for each interaction were determined from histograms of contact distances well beyond the sum of the van der Waals radii of the acceptor and the donor atoms.

The CSD analysis concerning the competitive nature of carboxylic acid and alcohol functional groups reveals limited information about the reliability and hierarchy of a particular

Table 7. A Summary of the CSD Data As It Relates to Alcohol Moieties and Their Tendency to Form Supramolecular Homosynthons vs. Supramolecular Heterosynthons

functional groups present	raw data			refined data				
	no. of structures	homosynthons	heterosynthons	no. of structures	homosynthons	heterosynthons	range (Å)	mean σ (Å)
OH	25035	6584 (26%) OH···OH		1316	1006 (76%) OH···OH		2.50−3.07	2.780(3)
OH and N_{arom}	1477	283 (19%) OH···OH	782 (53%) OH···N_{arom}	228	60 (26%) OH···OH	178 (78%) OH···N_{arom}	2.50−3.10	2.776(3)
OH and Cl^-	804	97 (12%) OH···OH	590 (73%) OH···Cl^-	0[a]			2.80−3.50	3.101(3)
OH and $CONH_2$	329	63 (19%) $CONH_2$···$CONH_2$ 102 (31%) OH···OH	166 (50%) OH···$CONH_2$ 173 (53%) OH···NH_2CO	58	6 (10%) $CONH_2$···$CONH_2$ 44 (76%) OH···OH	52 (90%) OH···$CONH_2$ 52 (90%) OH···NH_2CO	2.50−3.00 2.70−3.20	2.750(5) 2.998(6)
OH and O=C	5436	948 (17%) OH···OH	2348 (43%) OH···O=C	1133	252 (22%) OH···OH	735 (65%) OH···O=C	2.40−3.10	2.814(2)

[a] Cation exclusively on hydrocarbon skeleton.

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Table 8. A Summary of the CSD Data As It Relates to Competition between Carboxylic Acid and Alcohol Moieties and Their Tendency to Form Supramolecular Synthons

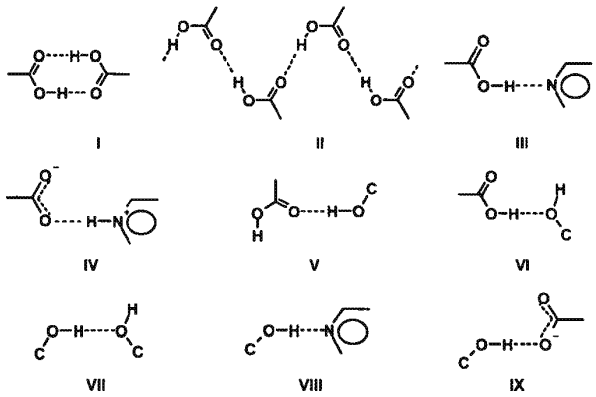
functional groups present	raw data			refined data				
	no. of structures	homosynthons	heterosynthons	no. of structures	homosynthons	heterosynthons	range (Å)	mean σ (Å)
COOH, OH and N_{arom}	58	4 (7%) COOH···COOH 4 (7%) OH···OH	35 (60%) COOH···N_{arom} 22 (38%) OH···N_{arom}	15	3 (20%) COOH···COOH 2 (13%) OH···OH	11 (73%) COOH···N_{arom} 8 (53%) OH···N_{arom}	2.50−3.00 2.50−3.00 2.50−3.07 2.50−3.10	2.650(3) 2.652(2) 2.780(3) 2.776(3)
COOH, OH and Cl^-	46	2 (4%) COOH···COOH 2 (4%) OH···OH	25 (54%) COOH···Cl^- 34 (74%) OH···Cl^- 4 (9%) COOH···OH 5 (11%) (OH)C=O···OH	20	1 (5%) COOH···COOH 1 (5%) OH···OH	18 (90%) COOH···Cl^- 16 (80%) OH···Cl^-	2.70−3.25 2.80−3.50	2.999(4) 3.101(3)
COOH, OH and $CONH_2$	28	0 COOH···COOH 0 OH···OH 5 (18%) $CONH_2$···$CONH_2$	14 (50%) COOH···$CONH_2$ 9 (32%) OH···NH_2CO 5 (18%) OH···$CONH_2$	1		$OH···CONH_2$ OH···COOH	2.50−2.80 2.80−3.25 2.50−3.00 2.70−3.20	2.583(3) 2.958(9) 2.750(5) 2.998(6)
COOH, OH and O=C	166	26 (16%) COOH···COOH 38 (23%) OH···OH	24 (14%) COOH···O=C 41 (25%) OH···O=C	73	25 (34%) COOH···COOH 11 (15%) OH···OH	14 (19%) COOH···O=C 22 (30%) OH···O=C	2.40−2.90 2.40−3.10	2.698(6) 2.814(2)

supramolecular synthon in the presence of other hydrogen bond donors or acceptors as the number of structures found in CSD is so low. We have therefore conducted a series of experiments to collect additional data and these experimental results are now detailed herein.

3.2. Description of Crystal Structures of Compounds 1−15. Herein we report the crystal structures of 15 multiple component crystals that contain COOH, OH and N_{arom} functional groups. The selection of cocrystal formers possessing permutations of COOH, OH and N_{arom} moieties was based upon several criteria: they should contain moieties that are sterically accessible; there should be no intramolecular hydrogen bonding interactions in either solution or the solid state; they should be free of competing hydrogen bond donors and acceptors. The COOH, OH and N_{arom} moieties were dispersed among pairs of cocrystal formers and were cocrystallized in three sets: COOH/OH with N_{arom}; COOH/N_{arom} with OH; OH/N_{arom} with COOH (Chart 1). The resulting cocrystals were characterized through the following techniques: melting point, differential scanning calorimetry, infrared spectrometry, and powder and single-crystal X-ray diffraction. Various permutations and combinations of supramolecular synthons are possible when all these moieties (COOH, OH, and N_{arom}) exist within the same crystal structure (Scheme 4). The crystal structures of **1−15** (see Supporting Information) are analyzed to evaluate the hierarchy of their supramolecular synthons and are discussed individually.

Failed Cocrystallization Experiments. Solution and solvent drop grinding methodologies were used in attempts to cocrystallize isonicotinic acid and nicotinic acid with a series of alcohols (See Chart 1). These experiments failed as instead they resulted in physical mixtures of starting materials as determined by analysis of X-ray powder diffraction patterns. These observations can be readily explained if supramolecular heterosynthon **III** is dominant over competing supramolecular heterosynthons. Indeed, the crystal structures of isonicotinic acid[59] and nicotinic acid[60] are sustained by supramolecular heterosynthon **III** and generate extended tapes as shown in Figure 4. Furthermore, an analysis of the CSD yielded no examples of cocrystals containing isonicotinic acid. However, there are five examples of organic salts involving the isonicotinate ion in the CSD[61] (Refcodes: AJECAT, FETXIM, REFFIS, XECDUF and YERXUP). The counterions in the compounds are derived from molecules that are either more basic or acidic than isonicotinic acid. A similar observation is made in the case of nicotinic acid. Nicotinic acid forms several organic salts[62] and cocrystals with 4-aminobenzoic acid (SESLIM)[63] and 3,5-dinitrobenzoic acid (AWUDEB).[64] These observations collectively support that supramolecular heterosynthon **III** observed in the crystal structures of isonicotinic acid and nicotinic acid is stronger than the OH···N_{arom} supramolecular heterosynthon that would be expected if a cocrystal were to form.

Scheme 4. Supramolecular Synthons That Are Likely to Be Formed When COOH, OH and N_{arom} Functional Groups Are Present in the Same Crystal Structure



The Relevance of pK_a as a Predictor of Cocrystals vs Salts. In the pharmaceutical industry, it is generally accepted that the reaction of an acid and a base will afford a salt if the ΔpK_a [pK_a (base) − pK_a (acid)] is greater than 2 or 3, and this criterion is often used to guide selection of counterions during salt selection.[65] With respect to neutral COOH···N_{arom} vs charge-assisted N^+-H···$^-$O hydrogen bonds, Johnson and Rumon[66] have suggested that a ΔpK_a < 3.75 affords neutral COOH···N interactions, whereas ΔpK_a > 3.75 results in proton transfer. However, more recently it has been reported that, even though ΔpK_a values tend to be reliable indicators of salt formation when ΔpK_a > 3, there is ambiguity in the ΔpK_a range

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Table 9. pK_a and ΔpK_a Values for the Cocrystal Formers of Cocrystals 1−13 and Salts 14−15

cocrystal/salts no.	pK_a[a] acid	pK_a[a] base	ΔpK_a[b]
1	4.08 ± 0.10	1.00 ± 0.30	−3.08
2	4.57 ± 0.10	6.13 ± 0.10	1.56
3	4.57 ± 0.10	5.44 ± 0.10	0.87
4	4.57 ± 0.10	1.00 ± 0.30	−3.57
5	4.57 ± 0.10	2.88 ± 0.50	1.56
6	4.08 ± 0.10	5.44 ± 0.10	1.36
7	4.08 ± 0.10	6.13 ± 0.10	2.05
8	4.08 ± 0.10	3.27 ± 0.26	0.81
9	4.08 ± 0.10	0.59 ± 0.28	−3.49
10	4.08 ± 0.10	2.88 ± 0.50	1.20
11	4.34 ± 0.30	5.50 ± 0.26	1.16
12	4.57 ± 0.10	5.50 ± 0.26	0.93
13	4.08 ± 0.10	5.50 ± 0.26	1.42
14	8.51 ± 0.10	4.2	4.31
	4.86 ± 0.10	4.2	0.66
15	8.51 ± 0.10	3.53	4.98
	4.86 ± 0.10	3.53	1.33

[a] The listed pka values for the starting materials were obtained from Scifinder Scholar. [b] $\Delta pK_a = pK_a$ (conjugated acid of the base) − pK_a (acid).

of 0 to 3. Specifically, cocrystal formation is only expected when $\Delta pK_a < 0$ but a salt-cocrystal continuum can exist between 0 to 3.[67] The ΔpK_a values for **1**−**15** are presented in Table 9 and can be summarized as follows: **1**, **4** and **9** exhibit $\Delta pK_a < 0$ and form cocrystals as expected; **2**, **3**, **5**, **6**, **7**, **8**, **10**, **11**, **12** and **13** exhibit ΔpK_a values ranging from 0.86 to 2.05 and all form cocrystals although **2** is a cocrystal of a salt and **5** is a solvated cocrystal; **14** and **15** exhibit $\Delta p\ K_a$ values of 4.31 and 4.98, respectively, and exist as salts. Thus, $\Delta p\ K_a$ values are fully consistent with the structural results obtained herein.

General Observations Concerning the Crystal Structures of 1−15. The diversity of supramolecular interactions in the new crystal structures reported herein is also manifested in the polymorphic behavior of 3-hydroxybenzoic acid (**3HBA**)[68] and 4-hydroxybenzoic acid (**4HBA**).[69] **3HBA** exhibits two polymorphic modifications (BIDLOP and BIDLOP01): form I exhibits supramolecular homosynthons **I** and **VII** (Figure 5A). However, form II exhibits supramolecular 1-point synthons **V** and **VI** and generates supramolecular tapes (Figure 5B).

There are also two types of supramolecular tape observed in the crystal structures for which **3HBA** is a cocrystal former: **6**, **7**, **8**, **9**, **10** and **13**. **6**, **7**, **8** and **9** could be described as having been generated by inserting an aromatic nitrogen moiety between synthon **VI** in form II of **3HBA** to create tapes with alternating arrangements of supramolecular heterosynthons **III** and **VIII**. In a similar manner, one could envision the insertion of aromatic nitrogen moieties between supramolecular homosynthons **I** and **VII** in form I of **3HBA** to account for the supramolecular tapes observed in **10** and **13** (Figure 6).

Interestingly, **4HBA** is also polymorphic, although only one form has been deposited in the CSD. The crystal structure of form II of **4HBA** was determined by exploiting synchrotron X-ray microcrystal diffraction techniques. The crystal structure of **4HBA** form I exhibits supramolecular homosynthons **I** and **VI** (Figure 7A), and, in a manner similar to that seen in form I of **3HBA**, the hydroxyl groups sustain chains that extend through the crystal. The crystal structure of form II of **4HBA** also contains **I**; however, there is no interaction between adjacent hydroxyl groups as seen in form I. Rather, the hydroxyl group in form II is involved in the formation of supramolecular heterosynthon **V**, which serves to link adjacent dimers and thereby generates a supramolecular sheet as shown in Figure 7B.

There are three types of tapes observed in the crystal structures for which **4HBA** is a cocrystal former (**2**, **3**, **4**, **5** and **12**). The structural features of **3**, **4**, and **5** could be described as having been generated by inserting aromatic nitrogen moieties between supramolecular homosynthon **VII** in form I of **4HBA** to create tapes with alternating arrangement of supramolecular synthons **I** and **VIII**. Similarly the insertion of aromatic nitrogen moieties between supramolecular homosynthon **I** in form I of **4HBA** could account for the arrangement of tapes observed in **2**, whereas the insertion of aromatic nitrogen moieties between supramolecular homosynthons **I** and **VII** in form I of **4HBA** would facilitate the formation of the supramolecular tapes found in **12**.

In summary, the cocrystal structures reported herein and the data retrieved from the CSD reveal the following (Table 10): 12 of 30 related crystal structures (**6**, **7**, **8**, **9**, **10**, **11**, **12**, **13**, **BEQWAV**, **IDUBUF**, **VEFVEI** and **XIFQEJ**) exhibit the presence of supramolecular heterosynthons **III** and **VIII**; 4 crystal structures (**GEHROB**, **SOFHIE**, **XAPMAC** and **DEXTOQ**) exclusively form supramolecular heterosynthon **III**; 6 crystal structures (**3**, **4**, **5**, **HAKVEV**, **GUTSAP** and **ODOBIT**) exhibit supramolecular homosynthon **I** and supramolecular heterosynthon **VIII** although **GUTSAP** also forms supramolecular heterosynthon **VI**; 6 crystal structures (**1**, **2**, **MOBZUY**, **VEFVIM**, **WEPDIF** and **ODOBIT01**) exhibit supramolecular heterosynthons **III** and **V** although **2** also forms **IV** and **IX**; **VEFVIM** forms supramolecular heterosynthon **VIII**.

Overall, out of 30 structures, 24 (80% with **14** and **15** forming a charge assisted ionic version of **III**) exhibit supramolecular

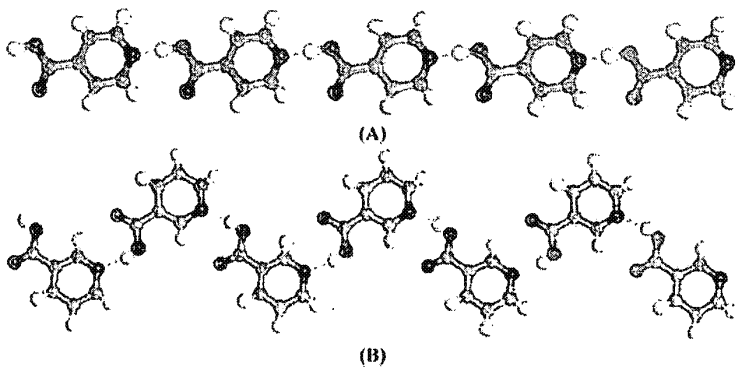


Figure 4. (A) Crystal structure of isonicotinic acid showing the formation of supramolecular heterosynthon **III** and the resulting linear tapes. (B) Crystal structure of nicotinic acid showing the formation of supramolecular heterosynthon **III** and the resulting *zigzag* tapes.

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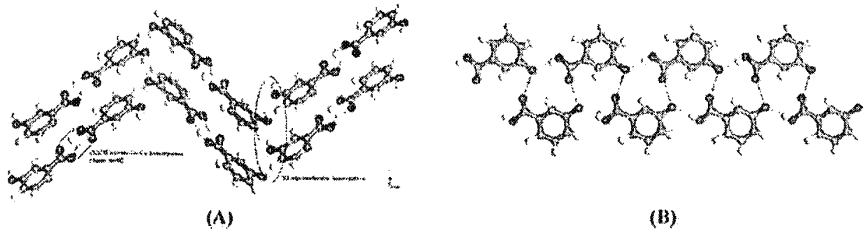


Figure 5. (A) Crystal structure of form I of **3HBA** showing the occurrence of supramolecular homosynthons **I** and **VII**. (B) Crystal structure of form II of **3HBA** illustrating the occurrence of supramolecular heterosynthons **V** and **VI**.

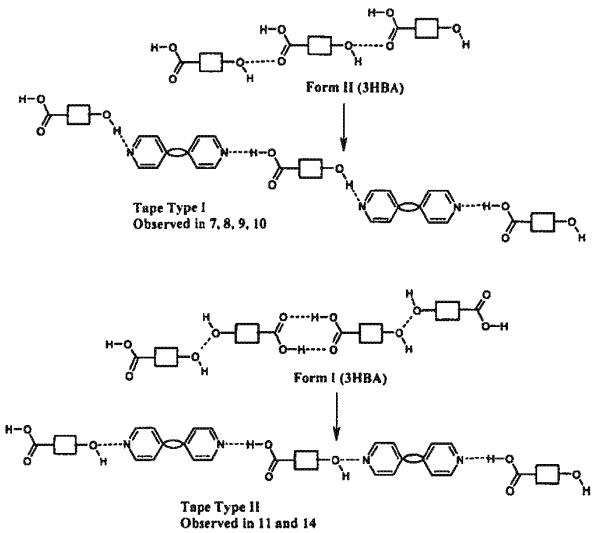


Figure 6. Schematic representation showing the formation of type I and II tapes generated from form II and form I of **3HBA**.

heterosynthon **III**, whereas 19 (63%) exhibit supramolecular heterosynthon **VIII**. Seven (23%) structures exhibit supramolecular homosynthon **I**, whereas there are no structures that form supramolecular homosynthon **VII**. The persistent nature of supramolecular heterosynthon **III** in the presence of competing supramolecular synthons is apparent from this combined CSD and experimental study.

4. Conclusions

A goal of our research program is to study supramolecular synthons in the context of cocrystals. In this contribution, we have demonstrated the ability of carboxylic acid and hydroxyl functional groups to exhibit a variety of hydrogen bonding motifs, and it is apparent there is some degree of predictability concerning supramolecular heterosynthons that involve these

Table 10. Summary of Supramolecular Synthons Present in 1−15 and Those Observed in Related Compounds Archived in the CSD

compound and ratio	I	II	III	IV	V	VI	VII	VIII	IX
1 (2:1)			√		√				
2 (2:1)			√	√	√				√
3 (1:1)	√							√	
4 (2:1)	√							√	
5 (2:1)	√							√	
6 (1:2)			√					√	
7 (1:1)			√					√	
8 (1:1)			√					√	
9 (2:2)			√					√	
10 (2:3)			√					√	
11 (1:1)			√					√	
12 (1:1)			√					√	
13 (1:1)			√					√	
14 (1:1)				√					√
15 (1:1)	√			√					√
GEHROB			√						
SOFHIE			√						
XAPMAC			√						
DEXTOQ			√						
MOBZUY			√		√				
HAKVEV	√							√	
GUTSAP	√					√		√	
BEQWAV			√					√	
IDUBUF			√					√	
VEFVEI			√					√	
VEFVIM			√		√			√	
WEPDIF			√		√				
XIFQEJ			√					√	
ODOBIT	√							√	
ODOBIT01			√		√				

two groups even in the presence of competing hydrogen bond donors and acceptors. CSD statistics indicate that supramolecular heterosynthons **III** and **VIII** are both strongly favored over the corresponding supramolecular homosynthons **I** and **VII**. However, there is insufficient archival data with respect to the hierarchy of these supramolecular homosynthons versus supramolecular heterosynthons when COOH, OH and N_{arom} moieties are present in the same crystal structure. The series of model cocrystals presented herein complements the limited information within the CSD related to the frequency of

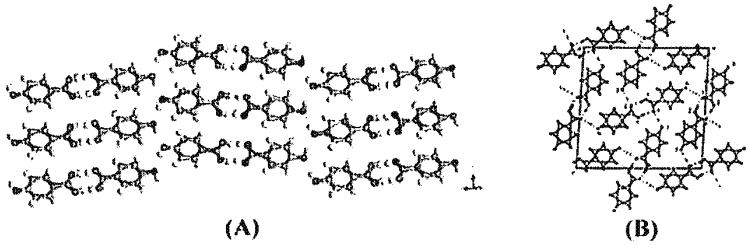


Figure 7. (A) Crystal structure of form I of **4HBA** showing the occurrence of supramolecular homosynthons **I** and **VII**. (B) Crystal structure of form II of **4HBA** showing the occurrence of supramolecular homosynthons I and supramolecular heterosynthon **V**.

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occurrence of supramolecular heterosynthon **III** in the presence of the competing alcohol moieties. That both **III** and **VIII** occur when an acid, an alcohol, and an aromatic nitrogen are cocrystallized suggests that the COOH···N_{arom} **III** hydrogen bond is comparable to the O−H···N_{arom} hydrogen bond **VIII**. We also note that the cocrystal structures obtained herein may be rationalized based upon the supramolecular synthons that exist in the pure cocrystal formers. The negative results obtained involving isonicotinic acid and nicotinic acid with alcohols are particularly salient since, when they are coupled with the positive results obtained involving OH/N_{arom} with COOH, they suggest that the formation of supramolecular heterosynthon **III** is favored over supramolecular heterosynthon **VIII**. Single crystals of 3-hydroxypyridinium benzoate, **14** and 3-hydroxypyridinium isophthalate, **15**, are outliers in that they exhibit proton transfer between the carboxylic acid cocrystal formers and aromatic nitrogen moieties and they are therefore sustained by charge assisted interactions **IV** and **IX**. These conclusions are salient in the context of pharmaceutical cocrystals, which frequently contain OH and/or COOH moieties.

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Supporting Information Available: Detailed CSD analysis of carboxylic acid and alcohol with other complementary functional groups, structural description of **1**−**15**, crystallographic information (.cif files), DSC, SDG, IR and PXRD patterns for **1**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Indicate quantity of a single type of artifact received but not scanned. Create individual artifact folder/box and artifact number for each Artifact Type.

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- computer program listing ☐ — Doc Code: Computer — Artifact Type Code: P
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March 8, 2004

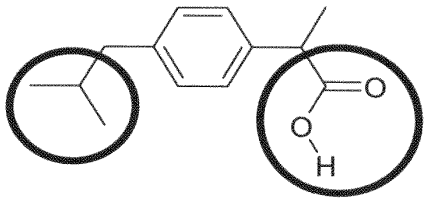


FIG. 1

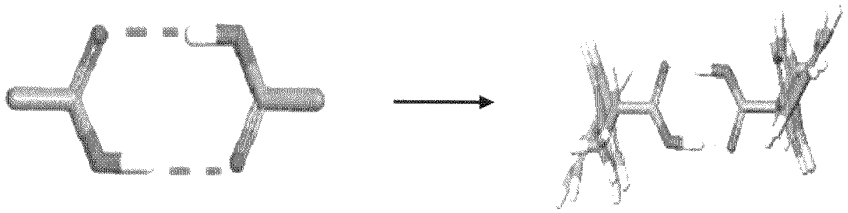


FIG. 2

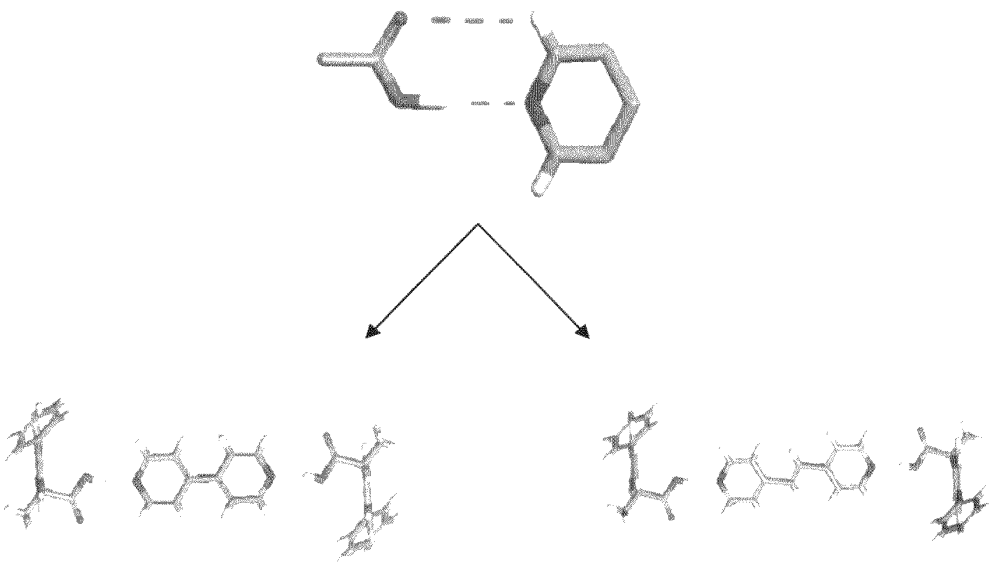


FIG. 3

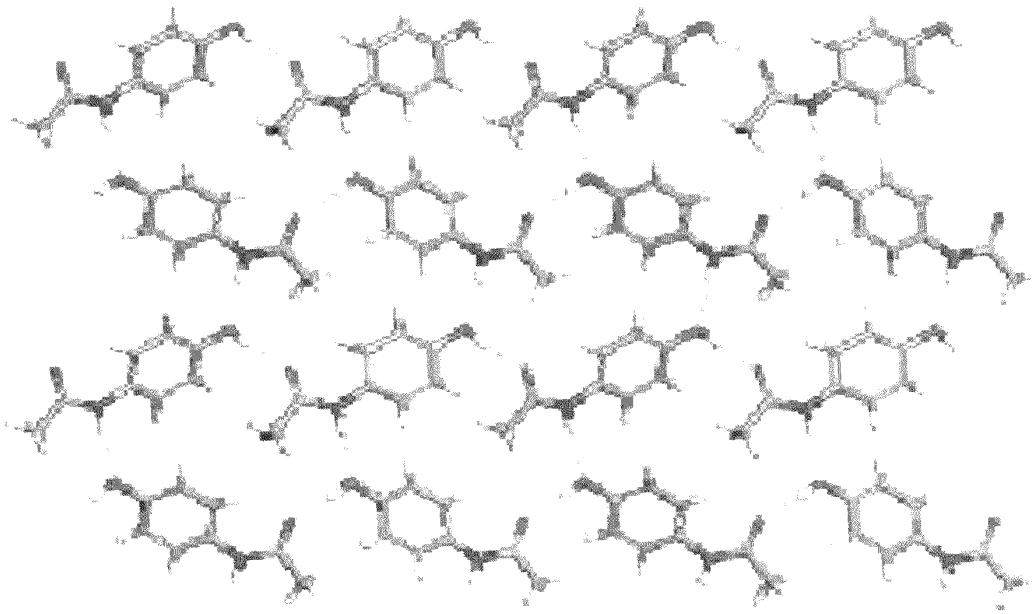


FIG. 4A

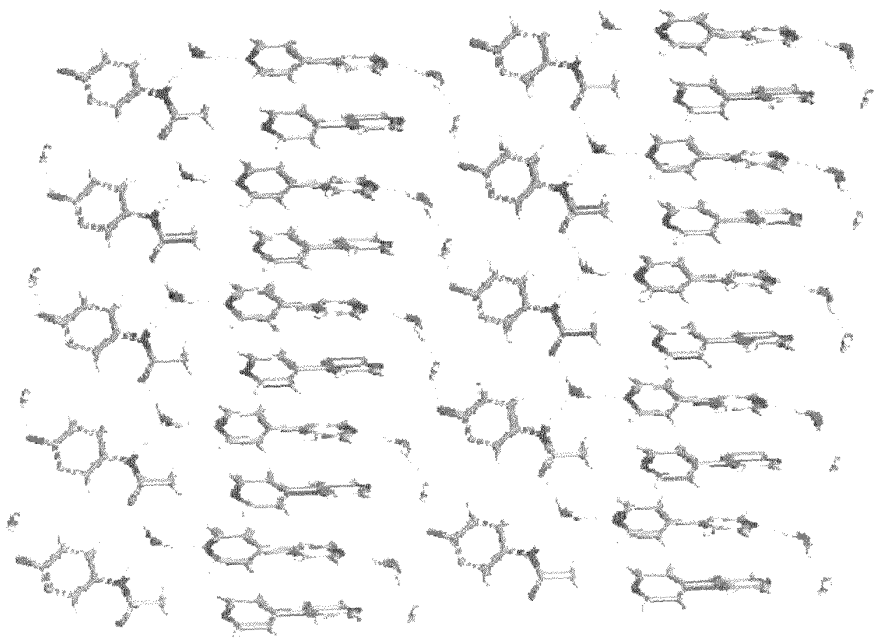


FIG. 4B

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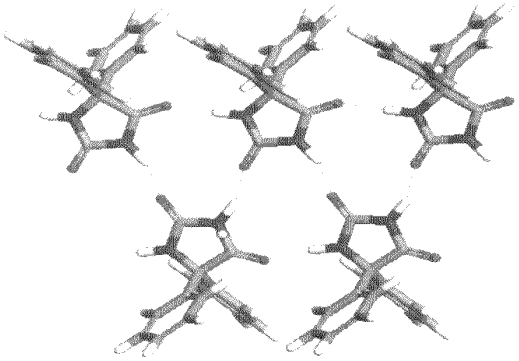


FIG. 5A

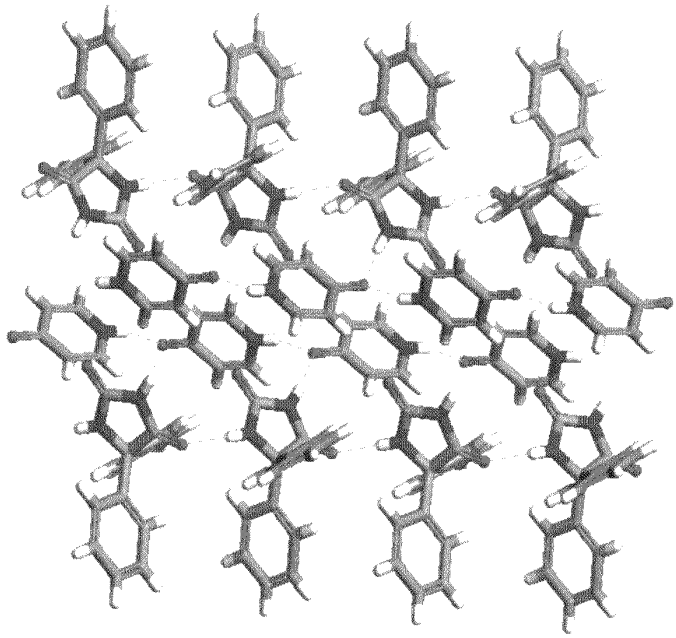


FIG. 5B

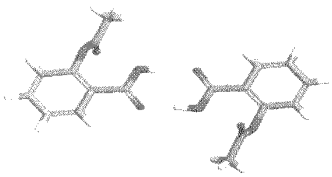


FIG. 6A

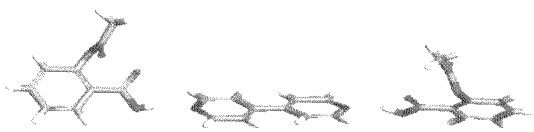


FIG. 6C

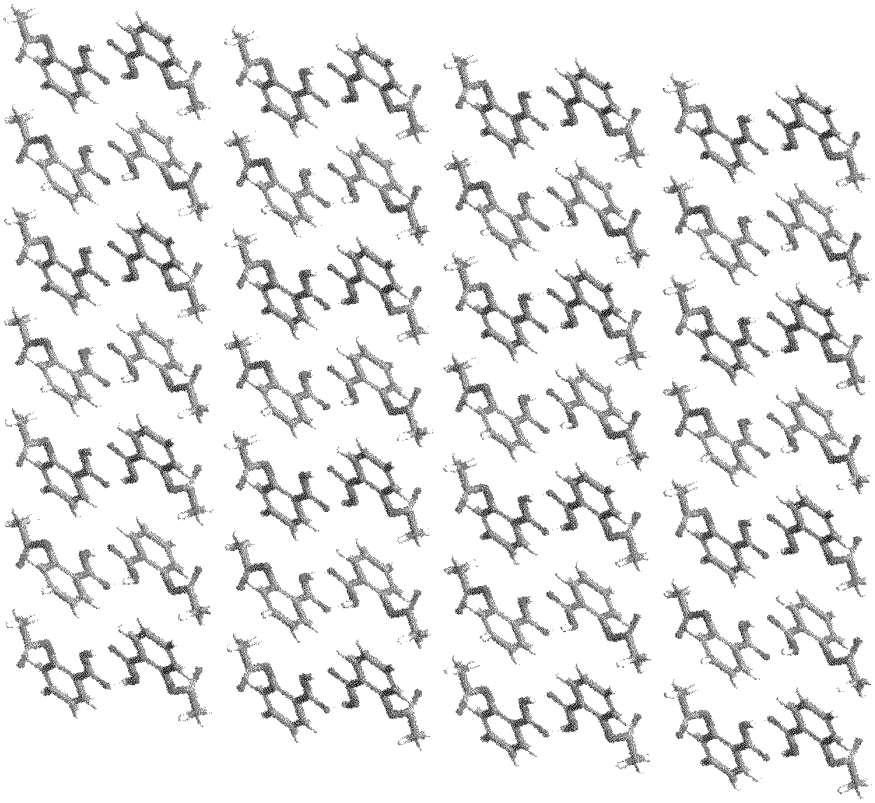


FIG. 6B

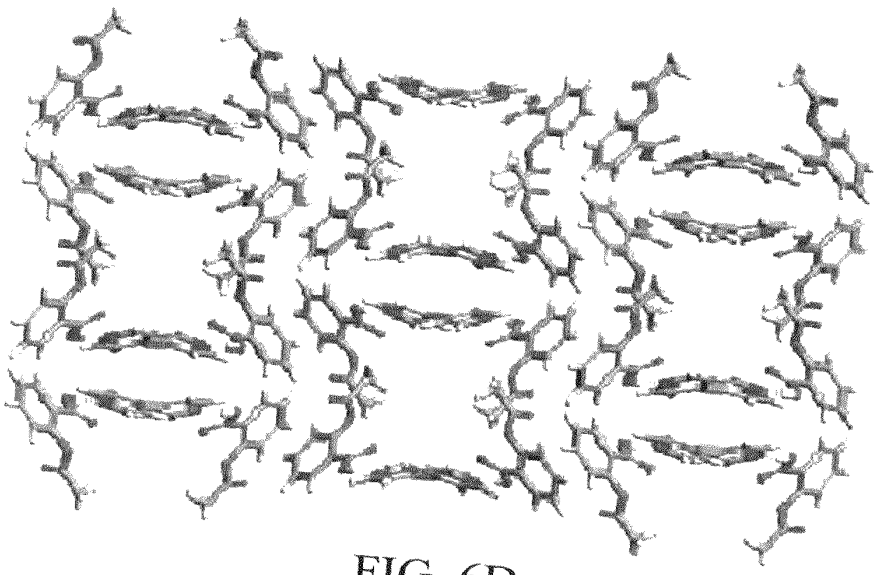


FIG. 6D

FIG. 7A

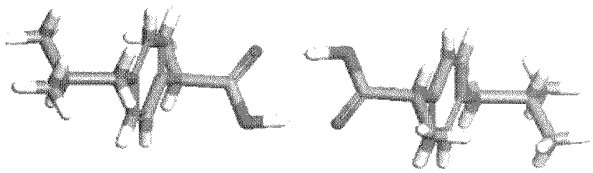
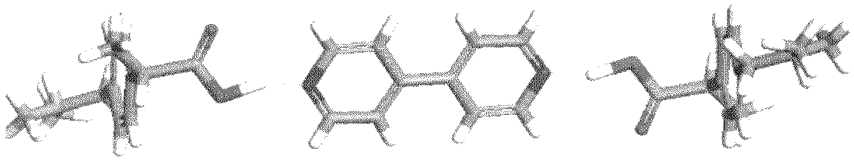


FIG. 7C



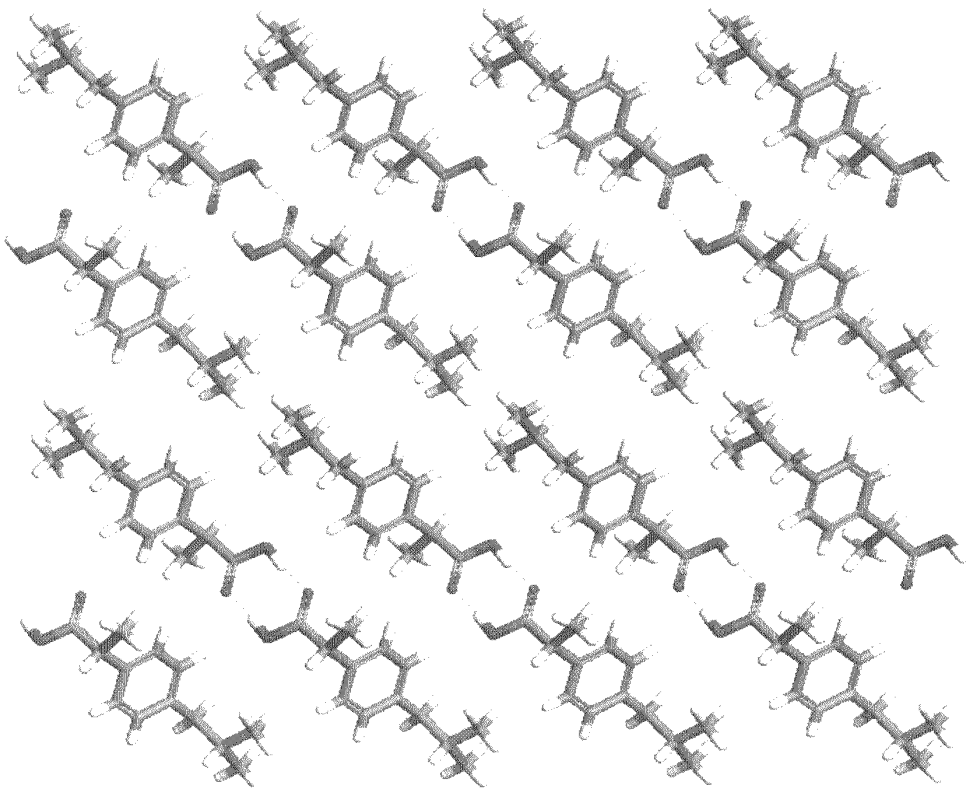


FIG. 7B

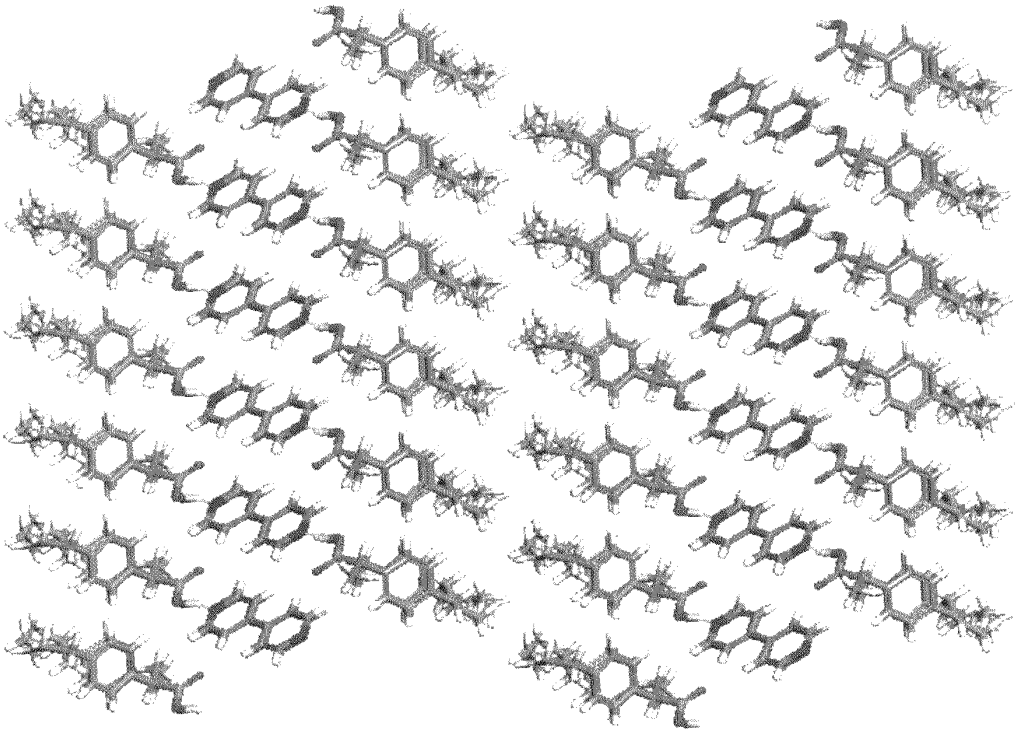


FIG. 7D

FIG. 8A

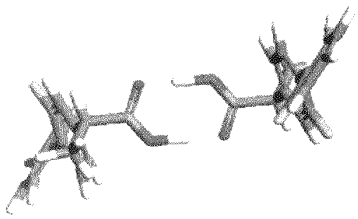
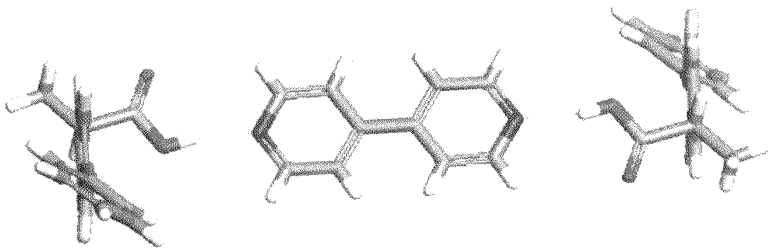


FIG. 8C



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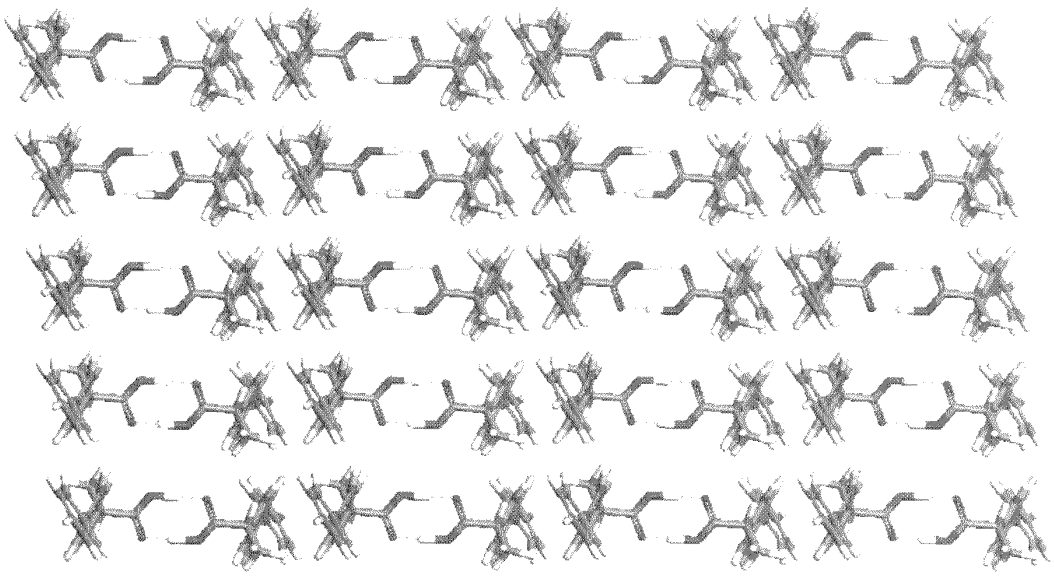


FIG. 8B

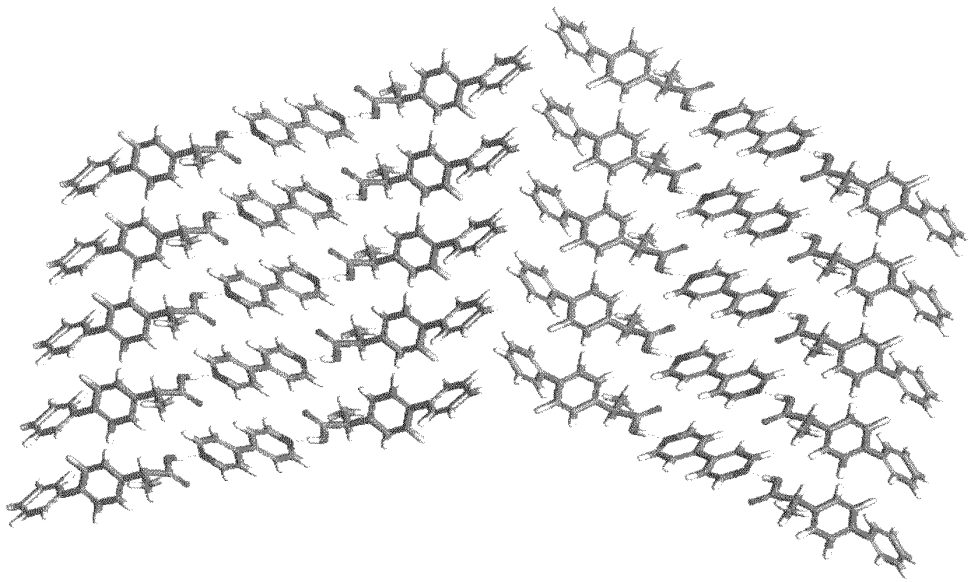


FIG. 8D



FIG. 9A

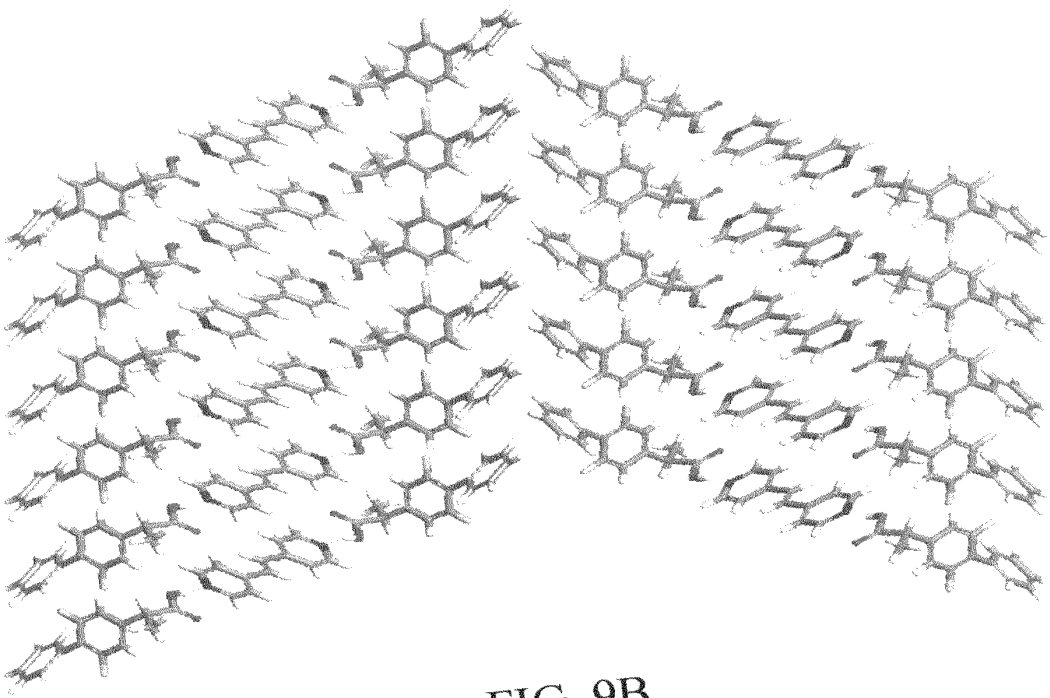


FIG. 9B

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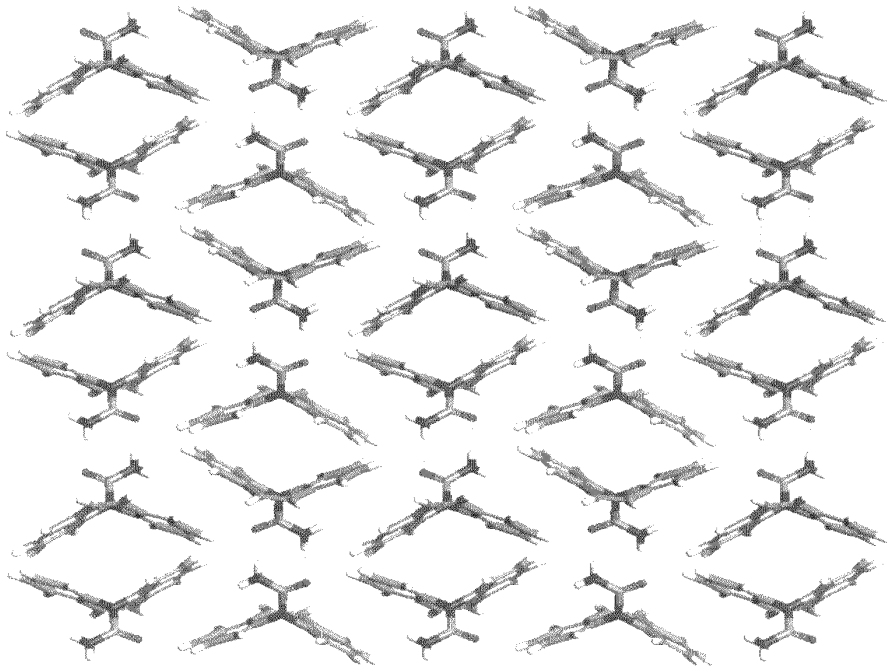


FIG. 10A

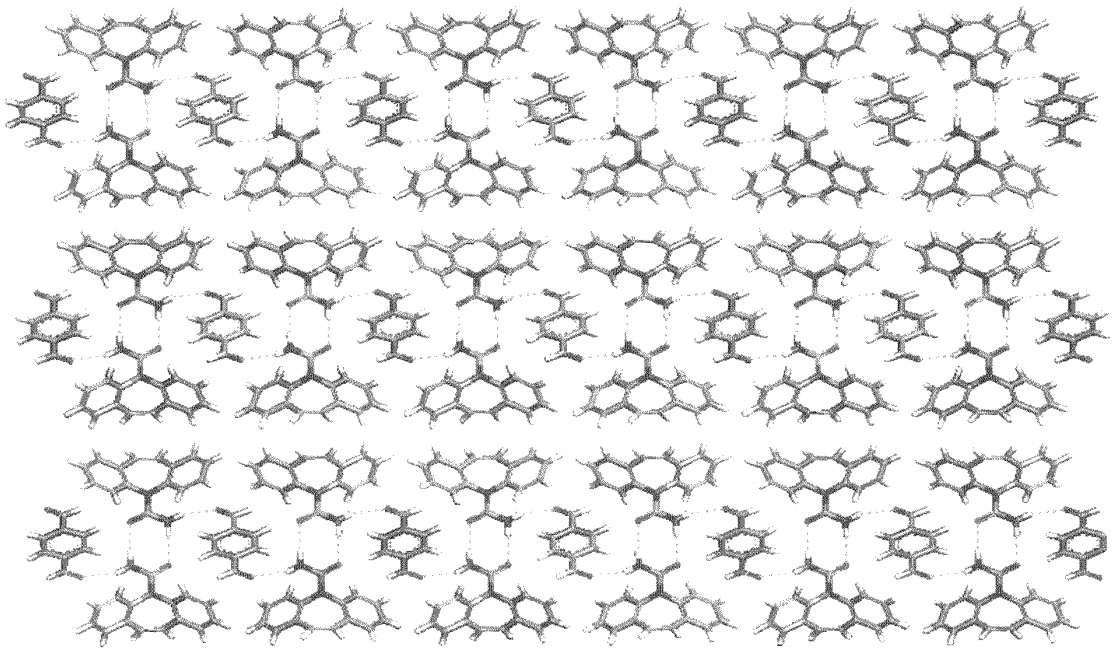


FIG. 10B

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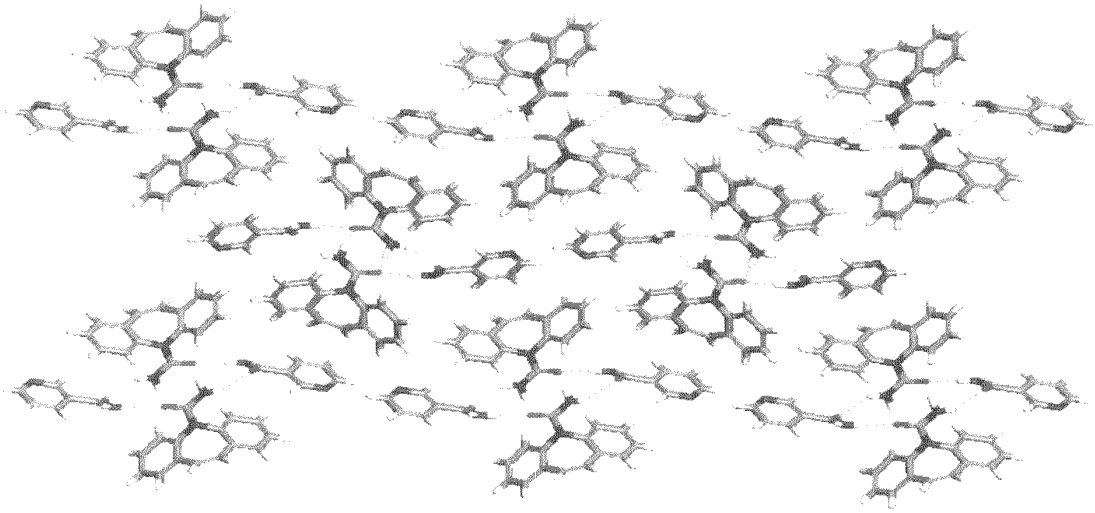


FIG. 11

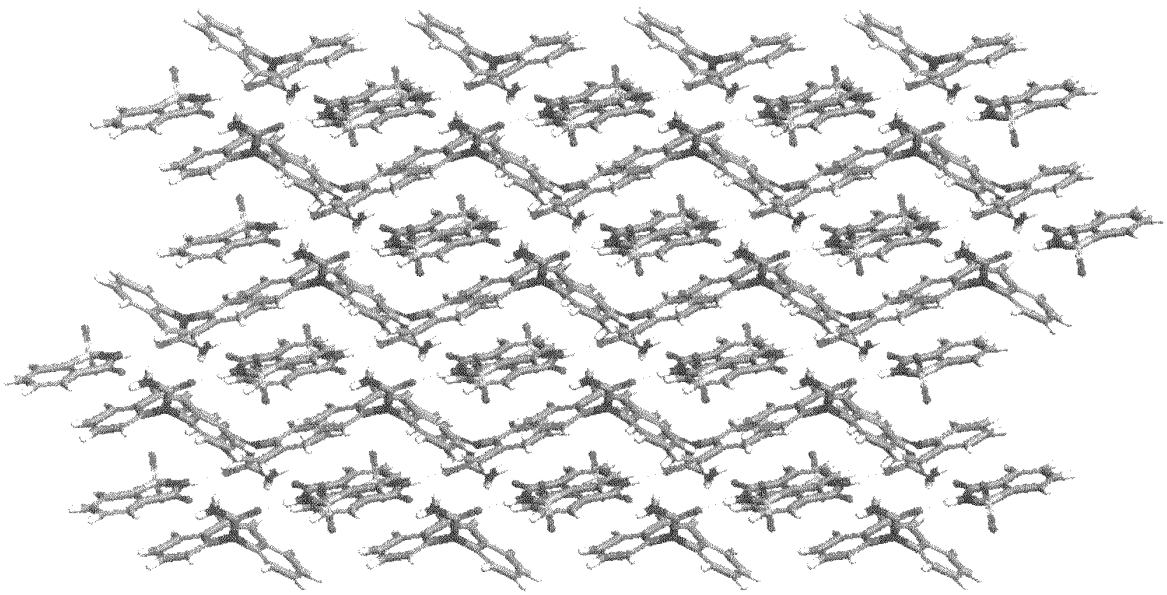


FIG. 12

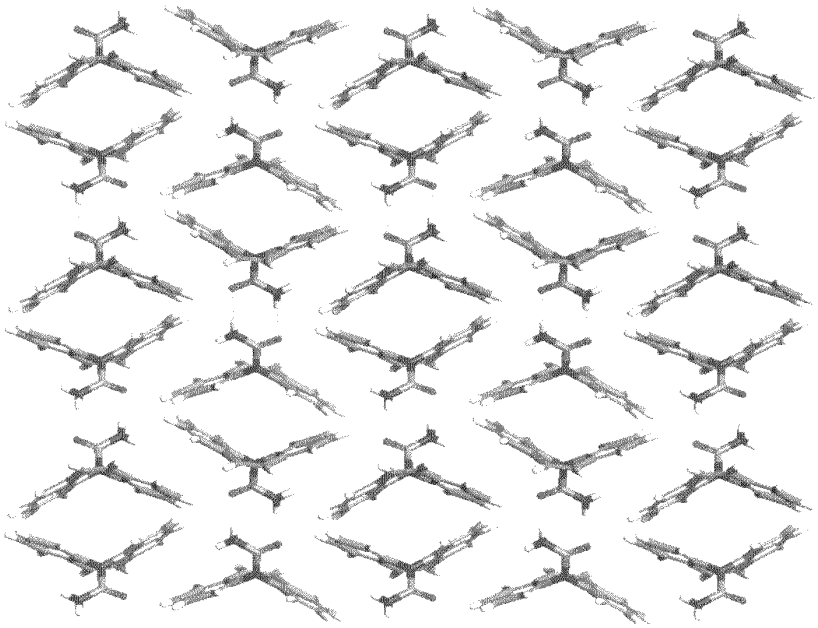


FIG. 14A

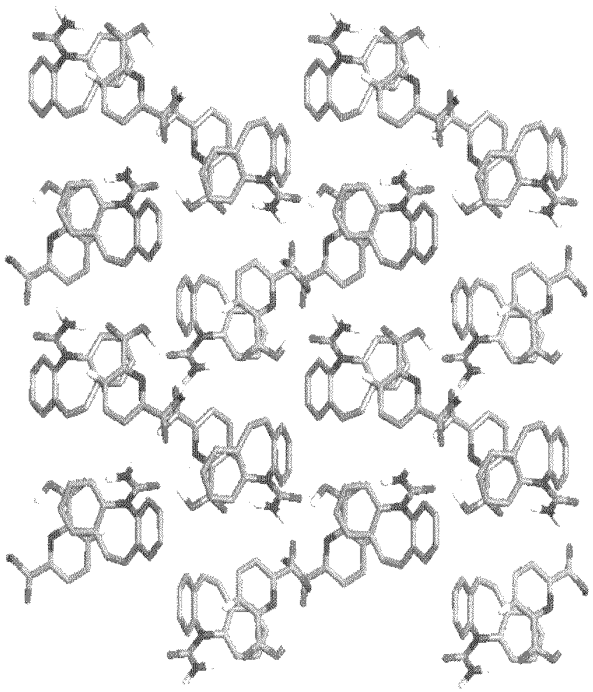


FIG. 14B

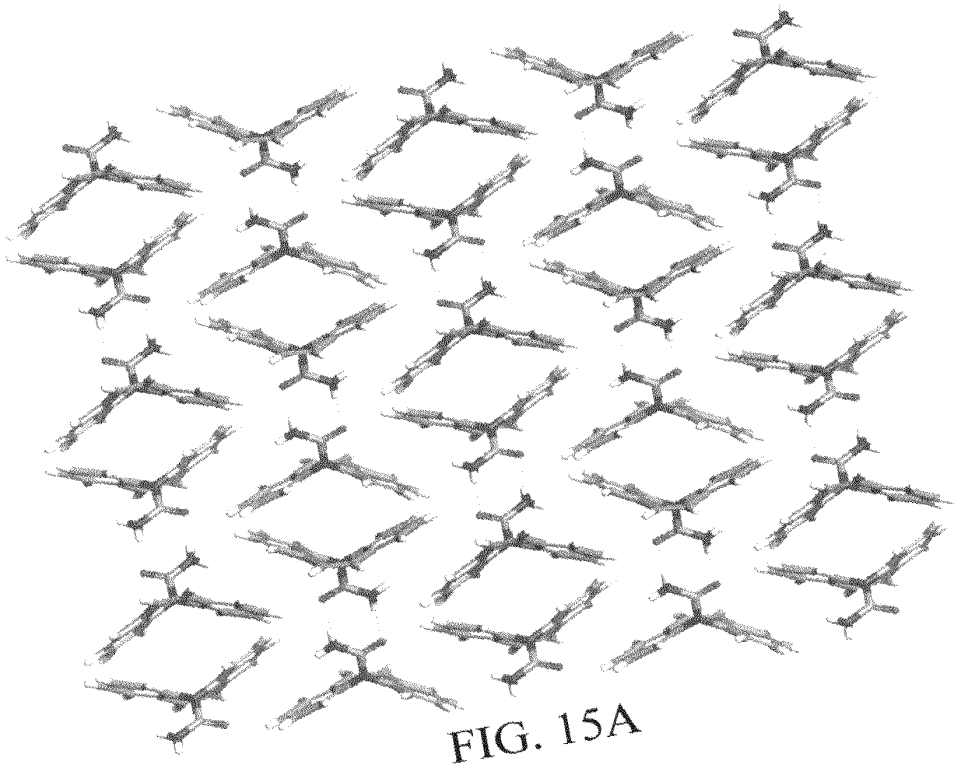


FIG. 15A

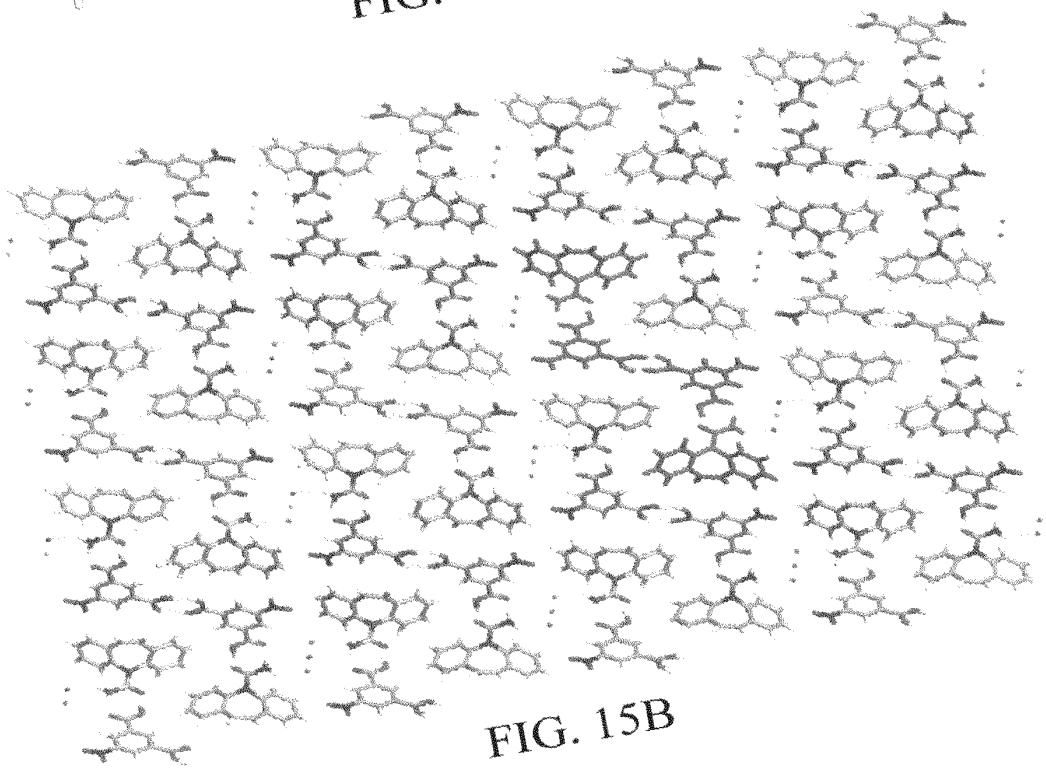


FIG. 15B

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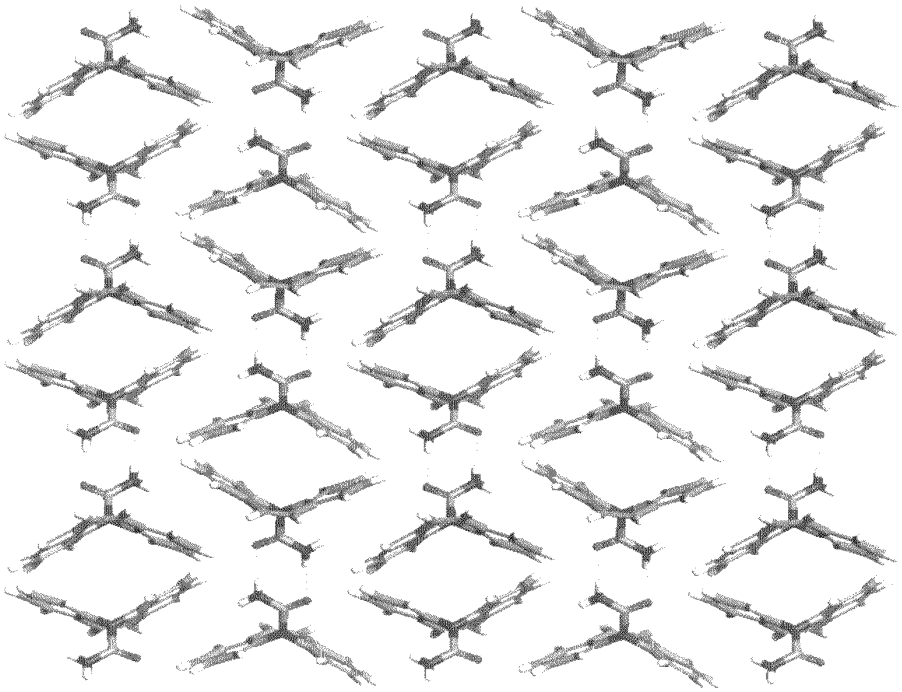


FIG. 16A

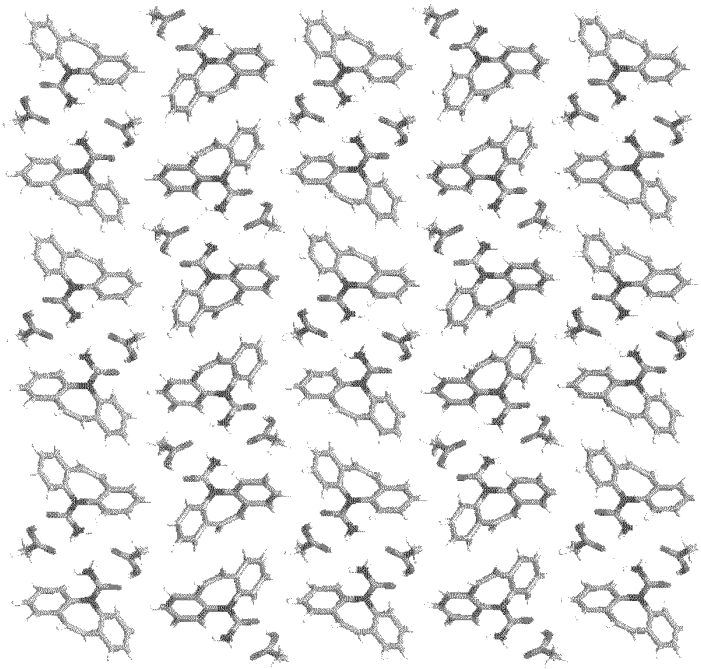


FIG. 16B

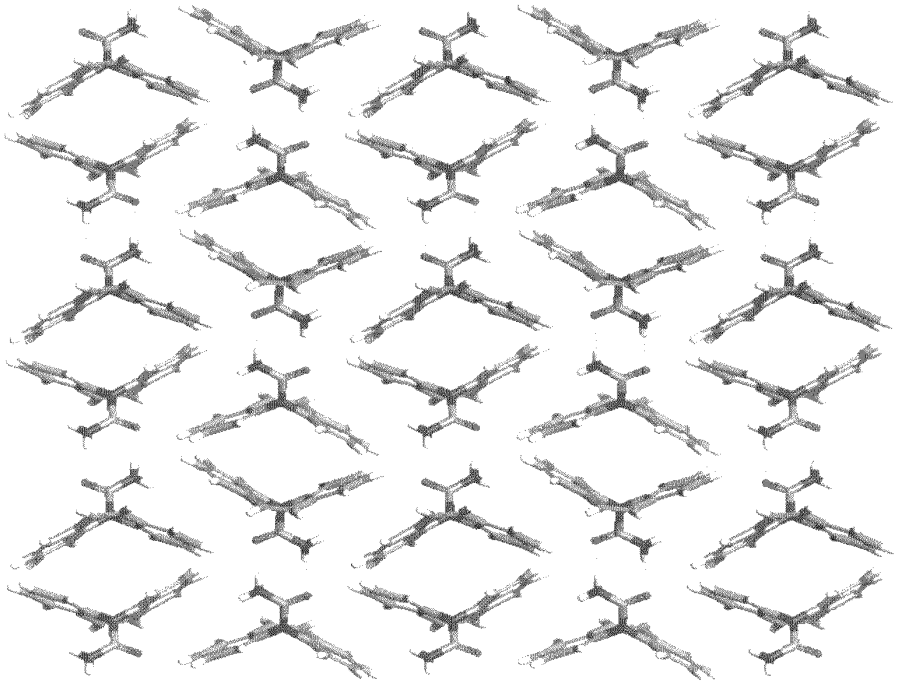


FIG. 17A

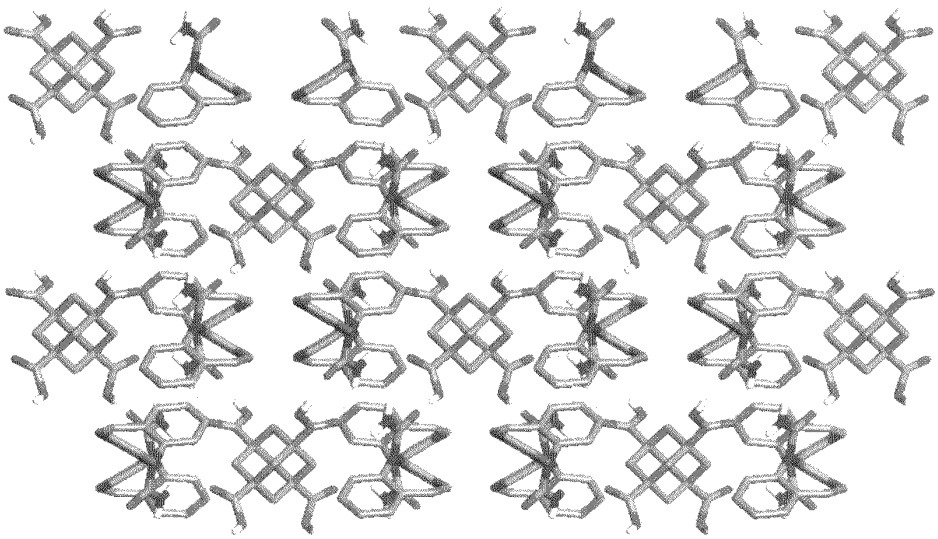


FIG. 17B

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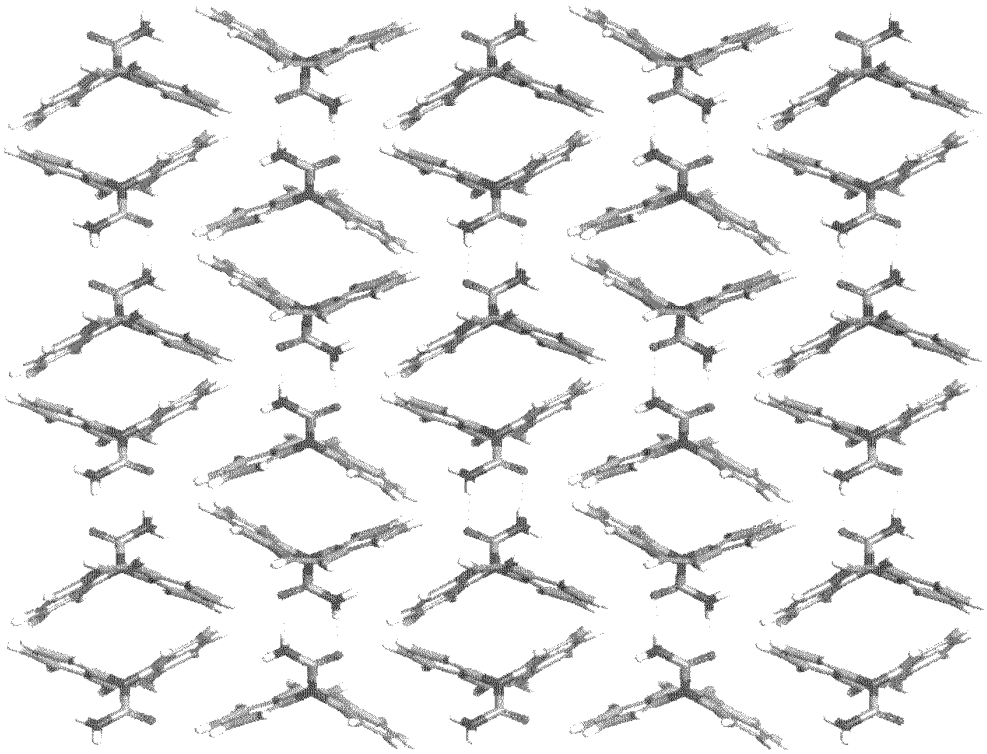


FIG. 18A

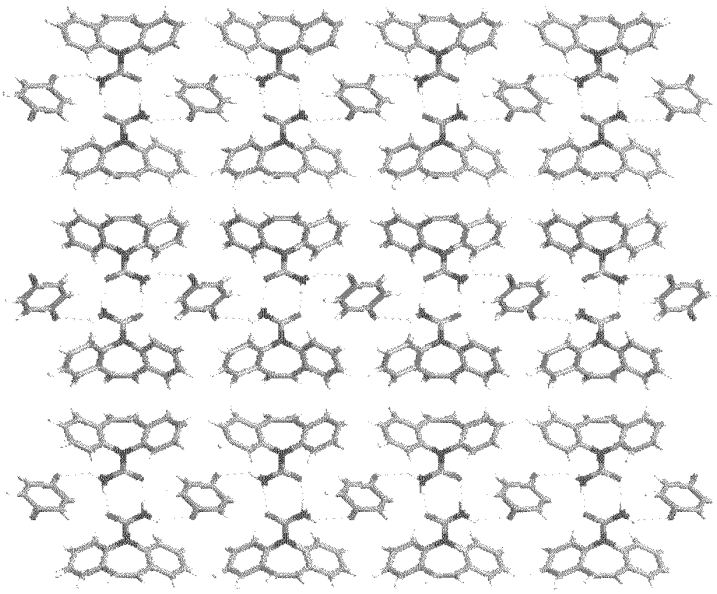


FIG. 18B

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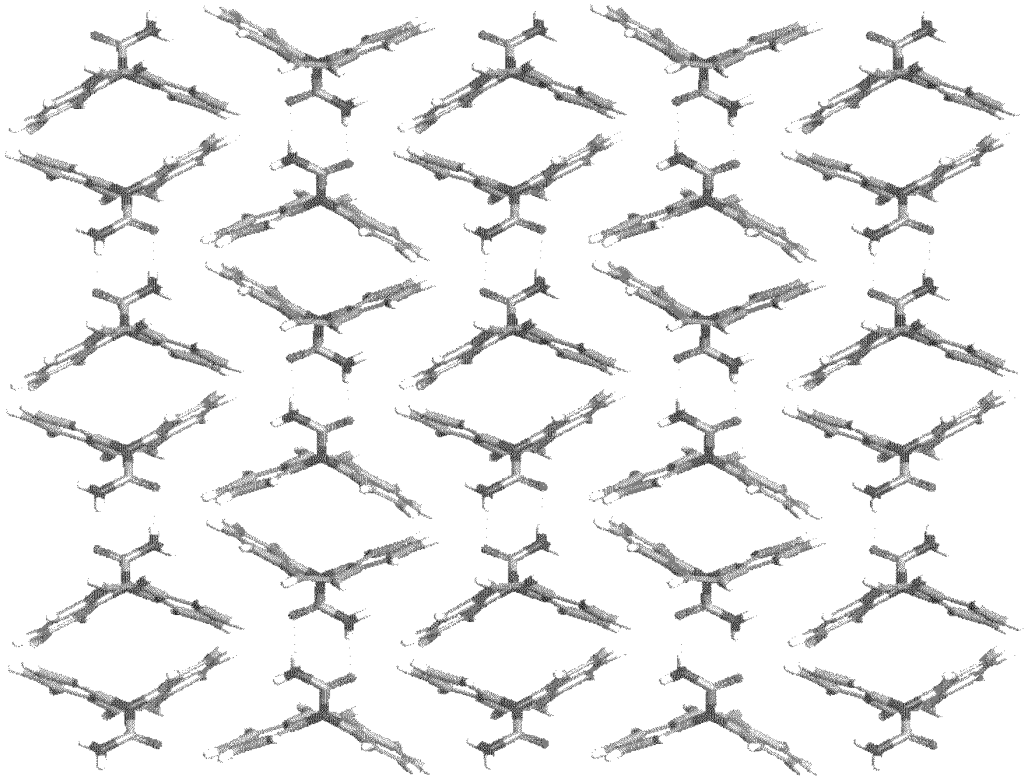


FIG. 19A

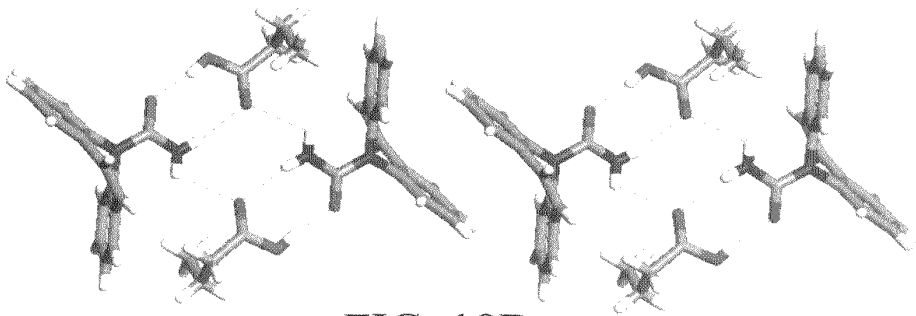


FIG. 19B

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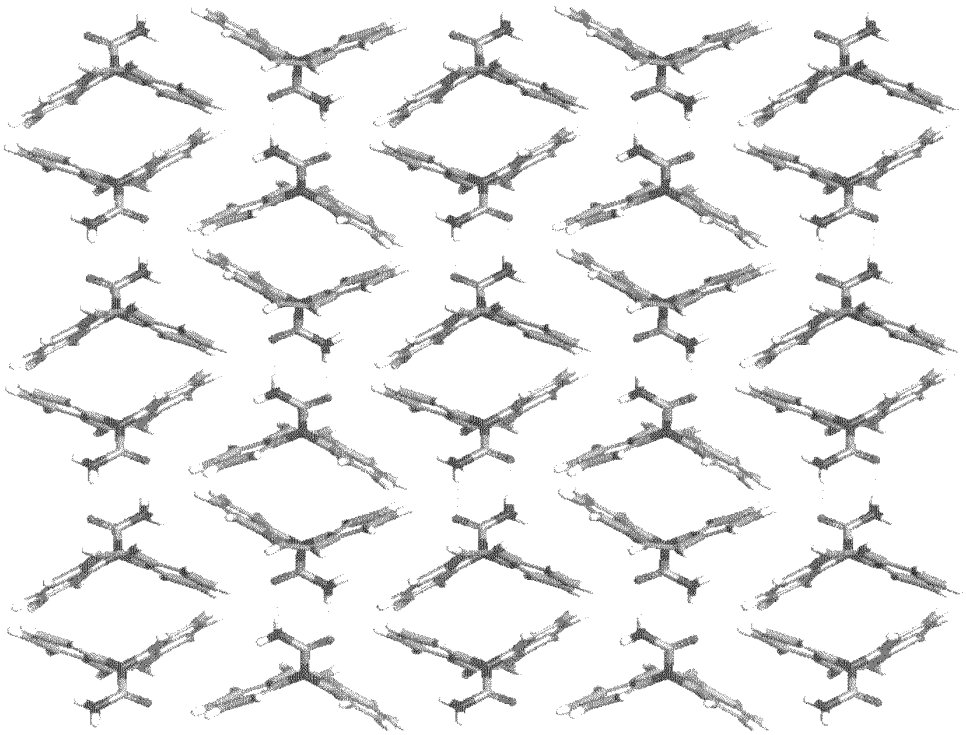


FIG. 20A

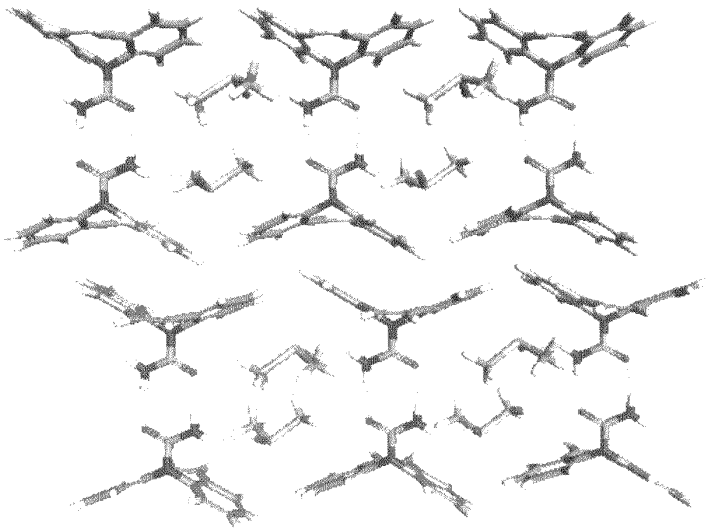


FIG. 20B

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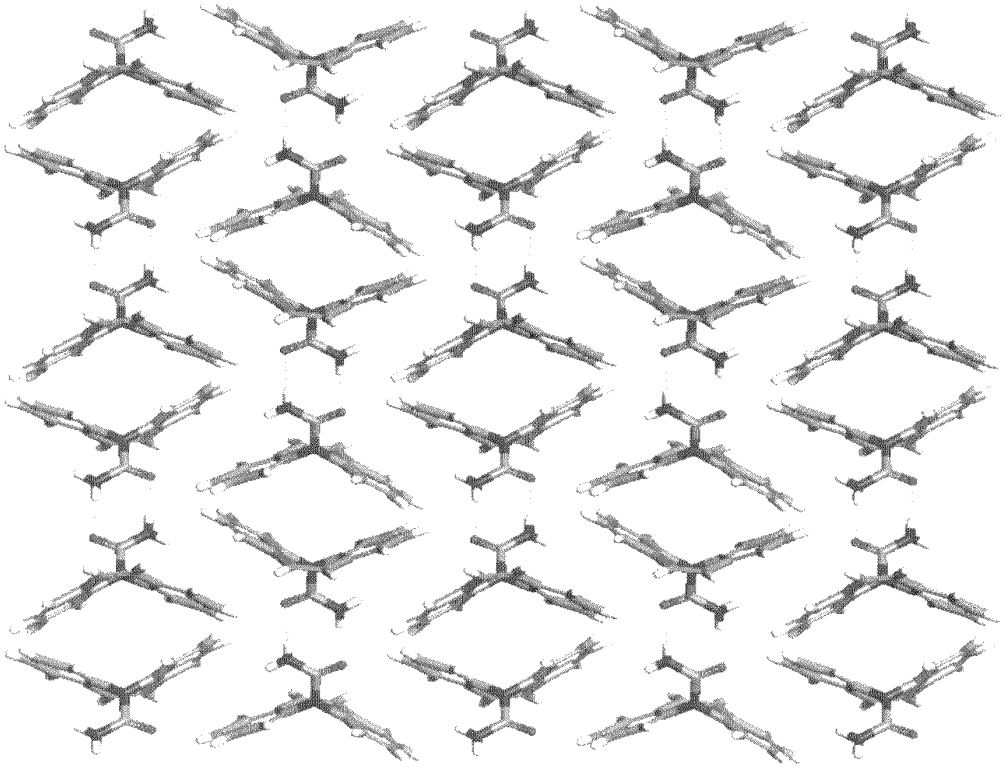


FIG. 21A

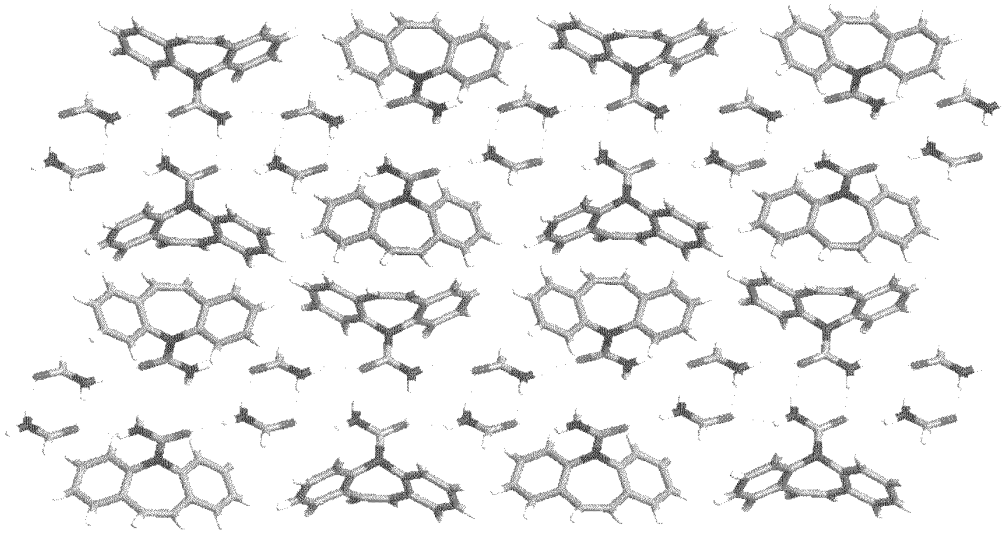


FIG. 21B

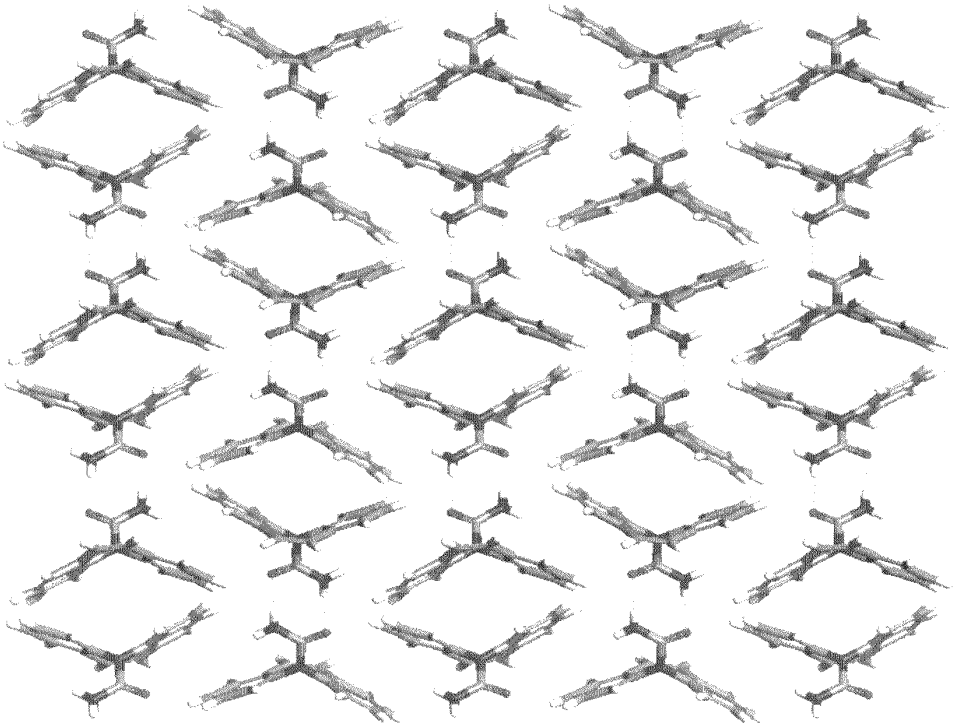


FIG. 22A

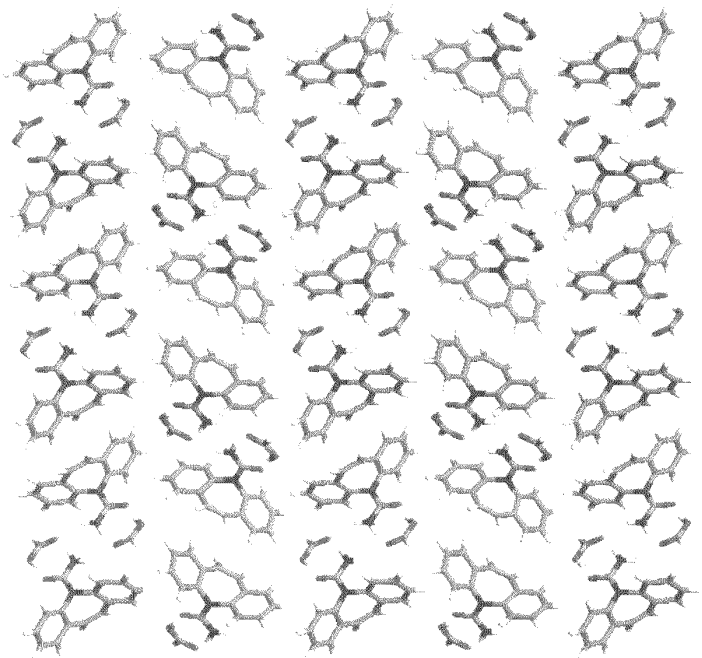


FIG. 22B

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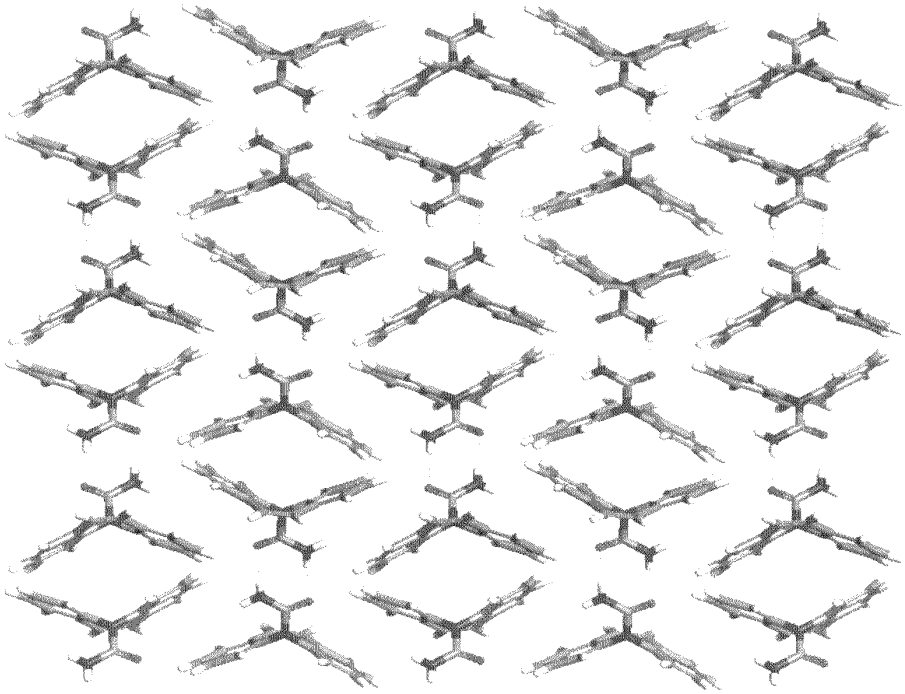


FIG. 23A

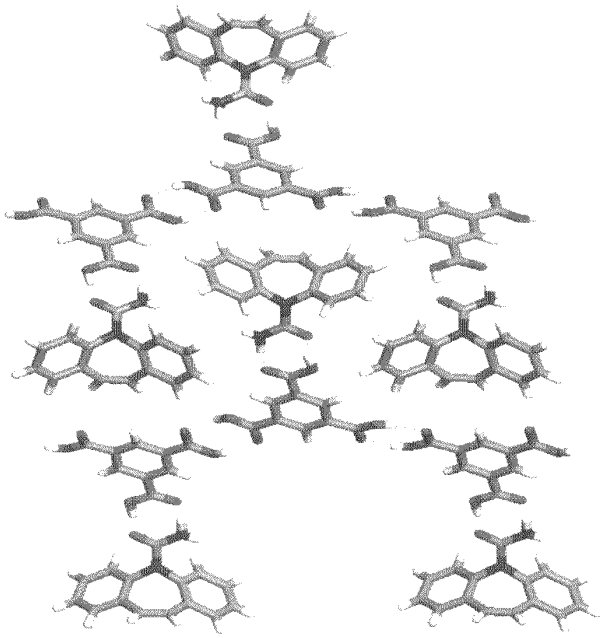


FIG. 23B