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Application Number: **10378956**

Document Date: **01/21/2009**

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Form Revision Date: December 8, 2006

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875					Application or Docket Number 10/378,956		Filing Date 03/03/2003		☐ To be Mailed	
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APPLICATION AS FILED – PART I						OTHER THAN SMALL ENTITY			
(Column 1)		(Column 2)		SMALL ENTITY ☒		OR		SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)	RATE (\$)	FEE (\$)	RATE (\$)	FEE (\$)	
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A		N/A		N/A		
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A		N/A		N/A		
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A		N/A		N/A		
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X \$ =		OR	X \$ =			
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X \$ =		OR	X \$ =			
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))			If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$250 (\$125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))									
			TOTAL		TOTAL				

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

APPLICATION AS AMENDED – PART II						OTHER THAN SMALL ENTITY					
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OR		SMALL ENTITY	
AMENDMENT	01/21/2009	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	RATE (\$)	ADDITIONAL FEE (\$)			
Total (37 CFR 1.16(i))	*	5	Minus	** 36	=	0	OR	X \$ =			
Independent (37 CFR 1.16(h))	*	2	Minus	***9	=	0	OR	X \$ =			
☐ Application Size Fee (37 CFR 1.16(s))											
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))											
						TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE		

(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OR		SMALL ENTITY	
AMENDMENT	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	RATE (\$)	ADDITIONAL FEE (\$)				
Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =	OR	X \$ =				
Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =	OR	X \$ =				
☐ Application Size Fee (37 CFR 1.16(s))											
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))											
						TOTAL ADD'L FEE	OR	TOTAL ADD'L 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.

This collection of information is required by 37 CFR 1.16. 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: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Legal Instrument Examiner:
/FLORENCE R. PATTERSON/

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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 10/05/2009 SALIWANCHIK LLOYD & SALIWANCHIK A PROFESSIONAL ASSOCIATION PO Box 142950 GAINESVILLE, FL 32614			EXAMINER JAVANMARD, SAHAR	
			ART UNIT	PAPER NUMBER
			1617	
			NOTIFICATION DATE	DELIVERY MODE
			10/05/2009	ELECTRONIC

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.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

DETAILED ACTION

Status of the Application

This Office Action is in response to Applicant's arguments filed on January 21, 2009. Claim(s) 25, 27, 28, 37, and 38 are pending and examined herein.

Response to Arguments

In view of Applicant's arguments and/or amendments, all the rejections of the previous office action have been fully considered and are withdrawn. The following new rejections are set forth in the office action below.

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 negated 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 25, 27, 28, and 38 rejected under 35 U.S.C. 102(b) as being 103(a) as being unpatentable over Homeyer et al. (US 2,665,277).

Homeyer describes a method of making morphine phosphate hemihydrate. The said crystal contains a salt of an active agent (morphine phosphate) and a guest (water). The method (column 2 line 50 - column 3, line 7) described in Homeyer involves: selecting a salt of an active agent (morphine phosphate), selecting a guest (water), preparing a solution (morphine phosphate is mixed with water), performing crystallization (the mixture is cooled), forming a crystal (column 3, lines 6-7).

Homeyer does not specifically teach the concept of identifying and evaluating the structures for their chemical functionalities.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have known that based on the teachings of Homeyer that one would necessarily identify and evaluate the structures in order to access whether or not said components are have the capability of forming supramolecular synthons.

Thus is in view of the foregoing arguments, the instant claims are deemed unpatentable over Homeyer.

Claims 25, 27, 37, and 38 rejected under 35 U.S.C. 103(a) as being unpatentable over Ammar (Egypt J. Pharmacol. Sci., 1994) in view of Desiraju (Angew. Int. Ed. Engl., 1995) of record.

Ammar teaches the water solubility of carbamazepine in the presence of nicotinamide (page 210, last sentence of first paragraph and figure 1). It is taught that there are spectral changes occurring between the interaction which may give an indication of a molecular interaction between carbamazepine and the compounds tested, including nicotinamide, which forms a complex-formation between carbamazepine and the compounds. Ammar teaches that carbamazepine forms a 2:1 complex with nicotinamide (page 217, first paragraph).

Ammar does not specifically recite Applicant's steps as set forth in claim 25.

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 teachings of Ammar wherein the active pharmaceutical ingredient (carbamazepine) is evaluated and determined to have the capability of forming supramolecular synthons with itself, and that the chemical functionalities (i.e. H-bonding) are present in order to non-covalently bond to a second supramolecular synthon (nicotinamide). Furthermore, as taught by Desiraju, teaches that in fact that

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), in the absence of unexpected results.

Thus in view of the foregoing arguments, the instant claims are deemed unpatentable over Ammar in view of Desiraju.

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).

Art Unit: 1617

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-2,665,277	01-1954	HOMMEYER AUGUST H et al.	546/44
	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	Ammar et al., "Effects of Aromatic Hydrotropes on the Solubility of Carbamazepine. Part II: Effect of Nicotinamide, Sodium Salts of Benzoic, Naphthoic and Nicotinic Acids", Egypt J. Pharmacol. Sci., 1994, 35, No. 1-6, pp 209-223.
	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.

<i>Index of Claims</i> 	Application/Control No. 10378956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.
	Examiner SAHAR JAVANMARD	Art Unit 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	09/28/2009						
	1	-	-						
	2	-	-						
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	32	-	-						
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	36	-	-						

<i>Index of Claims</i> 	Application/Control No. 10378956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.
	Examiner SAHAR JAVANMARD	Art Unit 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	09/28/2009						
	37	✓	✓						
	38	✓	✓						

Search Notes 	Application/Control No. 10378956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.
	Examiner SAHAR JAVANMARD	Art Unit 1617

SEARCHED			
Class	Subclass	Date	Examiner
424	400 (update 8/31/09)	9/30/2008	

SEARCH NOTES		
Search Notes	Date	Examiner
EAST (searched each inventor name)	8/31/2009	SJ
EAST (keyword search)	8/31/2009	SJ
Pubmed	8/31/2009	SJ
Google	8/31/2009	SJ

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

/S. J./ Examiner.Art Unit 1617	
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Effect of Aromatic Hydrotropes on the Solubility of Carbamazepine. Part II: Effect of Nicotinamide, Sodium Salts of Benzoic, Naphthoic and Nicotinic Acids

H. O. Ammar and S. M. Omar

Department of Pharmaceutical Sciences, National Research Centre, Dokki, Cairo, Egypt.

THE EFFECT of nicotinamide and sodium benzoate, naphthoate and nicotinate on the solubility of carbamazepine in water was studied. The investigated hydrotropes were found to increase the solubility of carbamazepine. The solubilizing power of these hydrotropes was shown to be highly dependent on their chemical structure. The replacement of benzene ring by a naphthalene or pyridine ring enhances solubilization. Molecular interaction of carbamazepine with the investigated solubilizers were depicted via differential ultraviolet spectrophotometric measurements. Applying the continuous variation method revealed formation of 1:1 complex with sodium nicotinate, 2:1 complex with nicotinamide and sodium naphthoate and a mixture of 2:1 and 1:2 complexes with sodium benzoate. An apparent correlation seems to exist between the solubilizing power of these hydrotropic agents and the stability constant of their respective complexes. Calculating the amount of drug solubilized in free as well as complexed forms revealed that complex-formation as well as the decrease in activity coefficient of the drug are the two factors governing the hydrotropic behaviour of these compounds towards carbamazepine.

In the preceding communication, sodium salts of hydroxy and amino derivatives of benzoic acid have been shown to exhibit solubilizing properties towards carbamazepine which have been attributed to both complex-formation as well as to the decrease in the activity coefficient of the

drug. This motivated investigating the influence of other hydrotropes towards the solubility of carbamazepine in water. Thus, the present contribution deals with evaluating and elucidating both the solubilizing behaviour as well as the mechanism of solubilization of nicotinamide, sodium salts of benzoic, naphthoic and nicotinic acids towards carbamazepine.

Experimental

Materials

Carbamazepine (Egyptian International Pharmaceutical Industries Co.). Pharmaceutical grade of benzoic acid, naphthoic acid, nicotinic acid, nicotinamide and sodium biocarbonate.

Solubility Measurements

Solubility measurements were carried out according to the method of Higuchi and Zuck ⁽¹⁾ as previously described ⁽²⁾.

Results and Discussion

Figures 1-3 reveal that the apparent water solubility of carbamazepine is increased in presence of sodium benzoate, naphthoate, nicotinate and nicotinamide as a function of their concentrations. A linear relationship exists between the maximum additive concentration of the drug and sodium nicotinate concentration.

The solubilizing power of these hydrotropic agents towards carbamazepine calculated as mole drug solubilized by one mole of hydrotrope seems to be highly dependent on their concentration, with the exception of sodium nicotinate, whereby its solubilizing power is more or less independent of its concentration (Table 1). On the other hand, the solubilizing power of sodium benzoate, naphthoate or nicotinamide increases with increasing their concentration. It is also evident from the table that the solubilizing power of sodium naphthoate is higher than that of sodium benzoate. Thus, expansion of ring system from benzenoid to the naphthoate structure leads to augmenting the solubilizing efficiency. This result agrees with the results previously reported regarding the higher solubilizing power of sodium naphthoate towards chlorothiazide, hydrochlorothiazide and allopurinol compared to sodium benzoate ^(3,4).

Egypt. J. Pharm. Sci. 35, No. 1-6 (1994)

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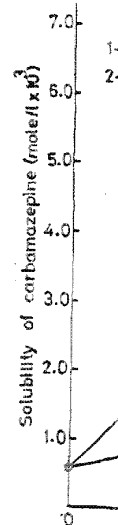


Fig. 1: Effect of sodium benzoate on the solubility of carbamazepine

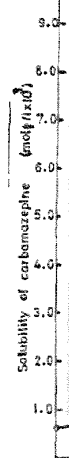


Fig. 2: Effect of sodium naphthoate on the solubility of carbamazepine at 25°C

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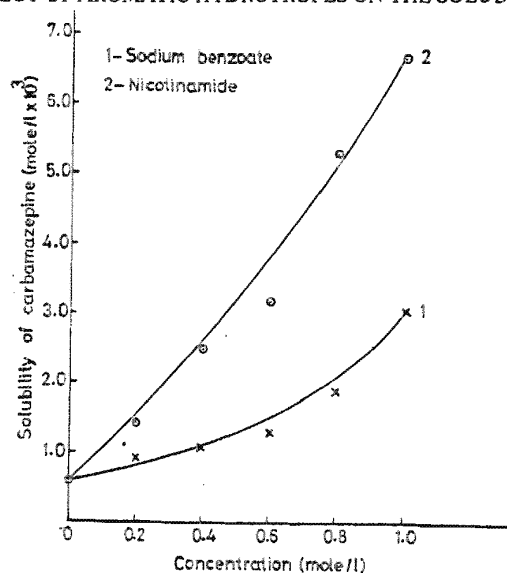


Fig. 1: Effect of sodium benzoate and nicotinamide on the water-solubility of carbamazepine at 25°

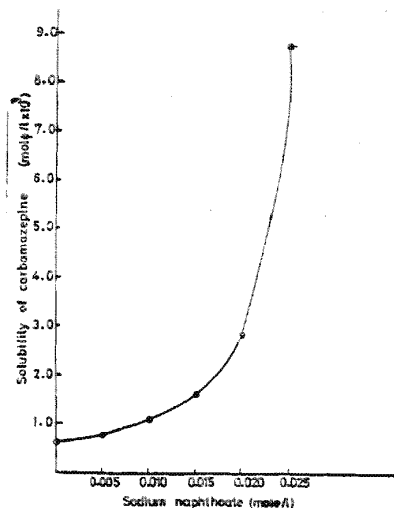


Fig. 2: Effect of sodium naphthoate on the water-solubility of carbamazepine at 25°

Egypt. J. Pharm. Sci. 35, No. 1-6 (1994)

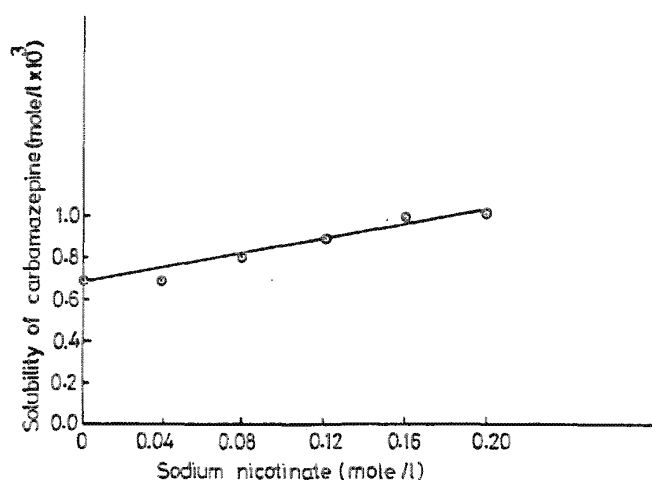


Fig. 3: Effect of sodium nicotinate on the water-solubility of carbamazepine at 25°

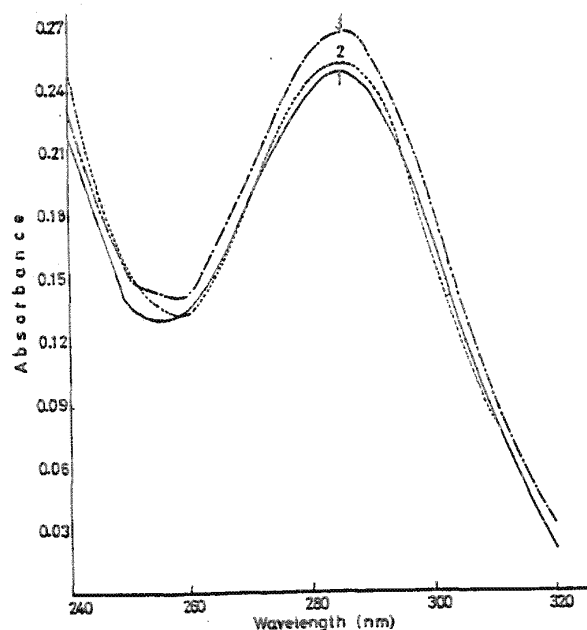


Fig. 4: Differential ultraviolet absorption spectrum of carbamazepine in presence of sodium benzoate (mmole/l) 1:0, 2:0.1, 3:0.4

Egypt. J. Pharm. Sci. 35, No. 1-6 (1994)

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TABLE 1. Effect of nicotinate on the water-solubility of carbamazepine at 25°.

Hydrotrope
Nicotinamide
Sodium benzoate
Sodium naphthoate
Sodium nicotinate

The possibility of an interaction between carbamazepine and these hydrotropes was studied by determining the differential ultraviolet absorption spectrum of carbamazepine (1 mmole/l.) in water and in the presence of sodium benzoate, sodium naphthoate, and sodium nicotinate (Fig. 4-7). The results showed that the presence of sodium benzoate, sodium naphthoate, and sodium nicotinate increased the water-solubility of carbamazepine. The wavelength of maximum absorption of carbamazepine was determined (Fig. 4-7). The presence of sodium benzoate, sodium naphthoate, and sodium nicotinate did not change the wavelength of maximum absorption of carbamazepine, while the presence of sodium nicotinate shifted the wavelength of maximum absorption of carbamazepine from 285 to 286 nm. The differential ultraviolet absorption spectrum of the drug in the presence of sodium benzoate, sodium naphthoate, and sodium nicotinate is shown in Fig. 4-7.

TABLE 1. Effect of nicotinamide and sodium benzoate, naphthoate and nicotinate on the solubility of carbamazepine in water at 25°.

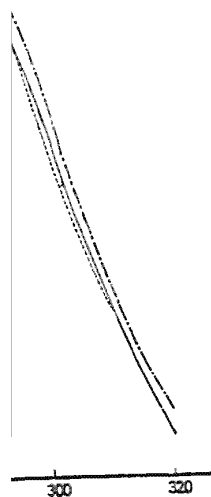
Hydrotrope	Concn (mole/l)	Solubilizing power
Nicotinamide	0.2	0.0036
	0.4	0.0044
	0.6	0.0044
	0.8	0.0058
	1.0	0.0060
Sodium benzoate	0.2	0.0011
	0.4	0.0010
	0.6	0.0014
	0.8	0.0015
	1.0	0.0025
Sodium naphthoate	0.005	0.0134
	0.010	0.0388
	0.015	0.0613
	0.020	0.1051
	0.025	0.3200
Sodium nicotinate	0.04	-
	0.08	0.0014
	0.12	0.0017
	0.16	0.0018
	0.20	0.0018

The possibility of an interaction taking place between carbamazepine and these hydrotropes was studied spectrophotometrically. The differential ultraviolet absorption spectrum of carbamazepine solution (2×10^{-5} mole/l.) in water and in presence of different concentrations of sodium benzoate, sodium naphthoate, sodium nicotinate and nicotinamide was determined (Fig. 4-7). The absorbance-value of the drug increases in presence of sodium benzoate or nicotinamide with increasing hydrotrope concentration, while the extinction of carbamazepine decreases in presence of sodium nicotinate. There is slight bathochromic shift in the wavelength of maximum absorbance of the drug in presence of nicotinamide from 285 to 286 nm. On the other hand, the ultraviolet absorption spectrum of the drug in presence of different concentrations of sodium

Egypt. J. Pharm. Sci. 35, No. 1-6 (1994)

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mmole/l) 1:0, 2:0.1, 3:0.4

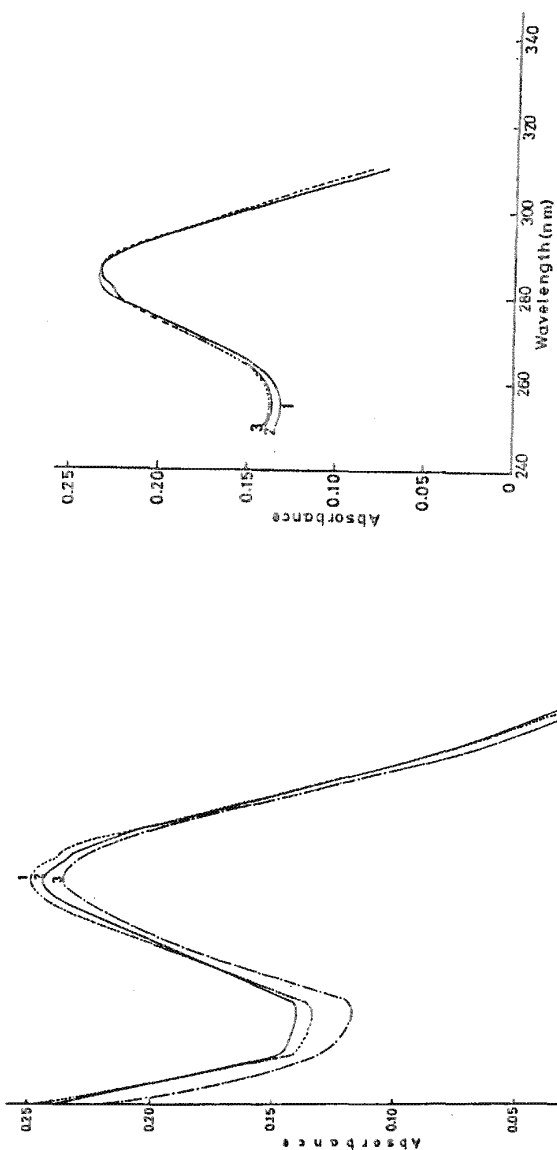


Fig. 5: Differential ultraviolet absorption spectrum of carbamazepine in presence of sodium naphthoate (m mole/l) 1:0.0, 2:0.06 3:0.08

Egypt. J. Pharm. Sci. 35, No. 1-6 (1994)

Wavelength (nm)

Absorbance

Fig. 6: Differential ultraviolet absorption spectrum of carbamazepine in presence of sodium nicotinate (m mole/l) 1:0.0, 2:0.05, 3:0.3

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TABLE 2. Stability complexes

Hydrotrope

Nicotinamide
Sodium benzoate

Sodium naphthoate
Sodium nicotinate

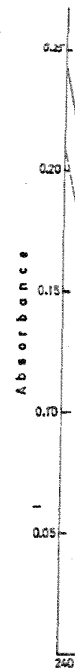


Fig. 7: Differential ultraviolet absorption spectrum of carbamazepine in presence of sodium naphthoate (m mole/l) 1:0.0, 2:0.06 3:0.08

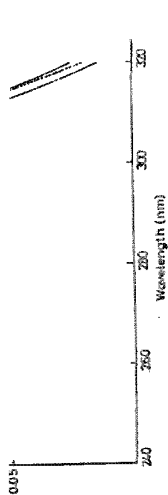


Fig. 5: Differential ultraviolet absorption spectrum of carbamazepine in presence of sodium naphthoate (m mole/l) 1) 1:0.0, 2:0.06 3:0.08

Fig. 6: Differential ultraviolet absorption spectrum of carbamazepine in presence of sodium nicotinate (m mole/l) 1:0.0, 2:0.05, 3:0.3

TABLE 2. Stability constant (K) of carbamazepine-hydrotrope complexes at 25°.

Hydrotrope	Stoichiometric ratio of complex	K (mole ⁻¹)
Nicotinamide	2: 1	1.225
Sodium benzoate	2: 1	0.454
	1: 2	1.143
Sodium naphthoate	2: 1	42.364
Sodium nicotinate	1: 1	1.549

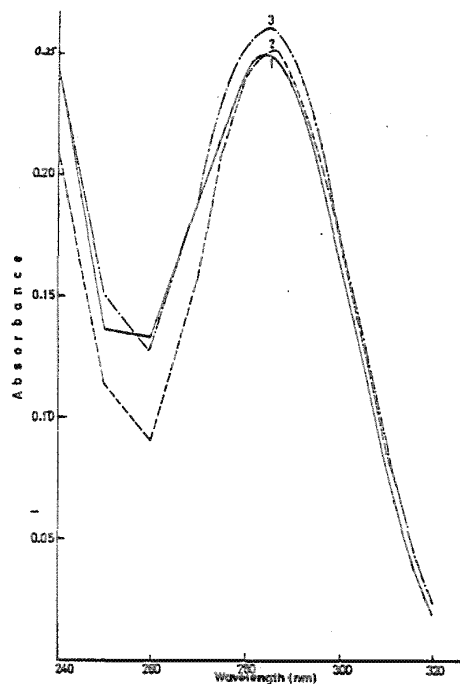


Fig. 7: Differential ultraviolet absorption spectrum of carbamazepine in presence of nicotinamide (m mole/l) 1:0.0, 2:0.4, 3:0.5

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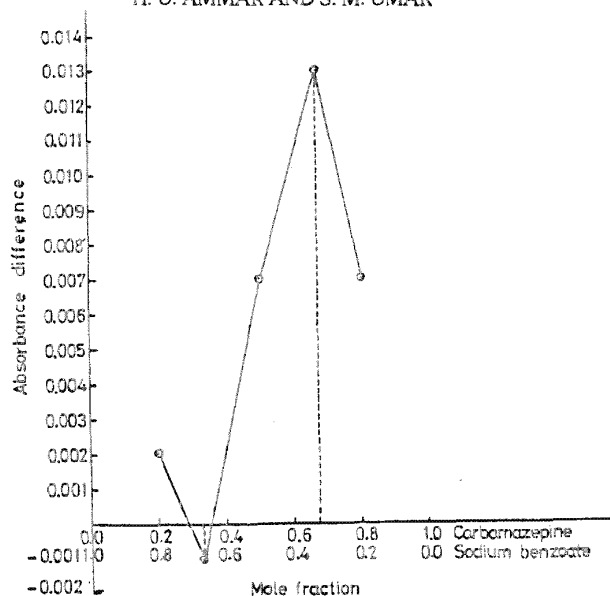


Fig. 8: Elucidation of the stoichiometric ratio of carbamazepine-sodium benzoate complex

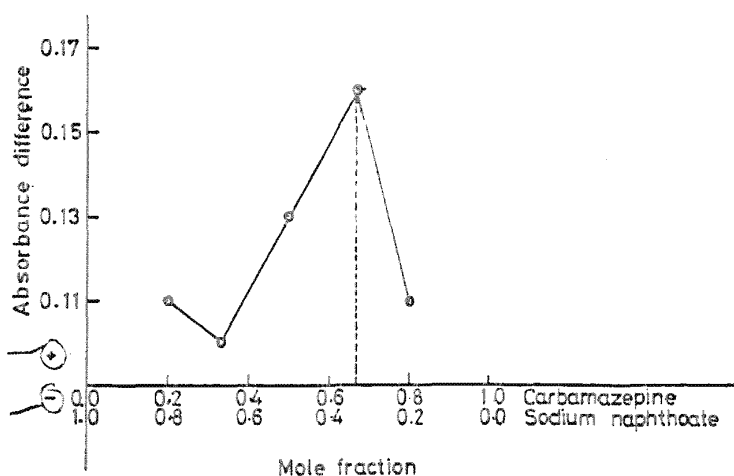


Fig. 9: Elucidation of the stoichiometric ratio of carbamazepine-sodium naphthoate.

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naphthoate exhibits two in nm (Fig. 5). The spect investigated hydrotropes interaction taking place b Also, the existence of is presence of sodium naph species of complexes in investigated through other variation method. The ab fractions of the drug an measured at 285 nm. The each solution was fixed a bance-values of all the in the summation of the abs nents. This gives eviden these compounds. The from the calculated values plotted against mole fract plots is shown in Fig. 8-1 two species of a complex, the point where the two s complex. It can be conclus nicotinate, 2:1 complex w mixture of 2:1 and 1:2 con

The stability constant spectrophotometrically. Th plexes with the investigate evident from the table that thoate complex is higher th zoate, sodium nicotinate an allel to a great extent with t

The amount of drug sol as in the free form (A) in t ing to the equation of Ben seen from the table that the

naphthoate exhibits two isosbestic points at wavelengths of 280 and 288 nm (Fig. 5). The spectral changes taking place in presence of all the investigated hydrotropes may give an indication of a sort of molecular interaction taking place between carbamazepine and these compounds. Also, the existence of isosbestic points in the spectrum of the drug in presence of sodium naphthoate might indicate the formation of a single species of complexes in this system. These interactions were further investigated through other spectral measurements utilizing the continuous variation method. The absorbance of solutions containing different mole fractions of the drug and each of the investigated hydrotropes was measured at 285 nm. The total concentration of CBZ and hydrotropes in each solution was fixed at a concentration of 0.06 mmole/l. The absorbance-values of all the investigated solutions were found to differ from the summation of the absorbance-values of their corresponding components. This gives evidence for complex-formation between CBZ and these compounds. The measured absorbance-values were subtracted from the calculated values and the resulting absorbance differences were plotted against mole fraction of each system. An illustration of such plots is shown in Fig. 8-11. Since for a constant total concentration of two species of a complex, the complex is at its greatest concentration at the point where the two species are combined in a ratio they occur in complex. It can be concluded that CBZ forms 1:1 complex with sodium nicotinate, 2:1 complex with nicotinamide and sodium naphthoate and a mixture of 2:1 and 1:2 complexes with sodium benzoate.

The stability constant of the formed complexes was determined spectrophotometrically. The values of the stability constant of CBZ complexes with the investigated hydrotropes are compiled in Table 2. It is evident from the table that the stability constant of CBZ-sodium naphthoate complex is higher than that of CBZ complexes with sodium benzoate, sodium nicotinate and nicotinamide. This result seems to run parallel to a great extent with their solubilizing power (Table 1).

The amount of drug solubilized in the form of complex (AB) as well as in the free form (A) in the investigated systems was calculated according to the equation of Benesi and Hildebrand (5) (Table 3). It can be seen from the table that the percentage concentration of complex formed

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1.0 Carbamazepine
0.0 Sodium benzoate

ratio of carbamazepine-

1.0 Carbamazepine
0.0 Sodium naphthoate

ratio of carbamazepine-

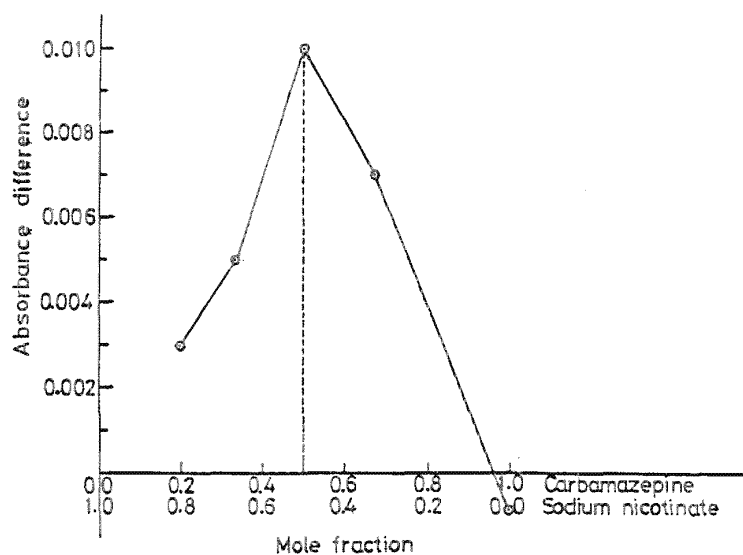


Fig. 10: Elucidation of the stoichiometric ratio of carbamazepine-sodium nicotinate complex.

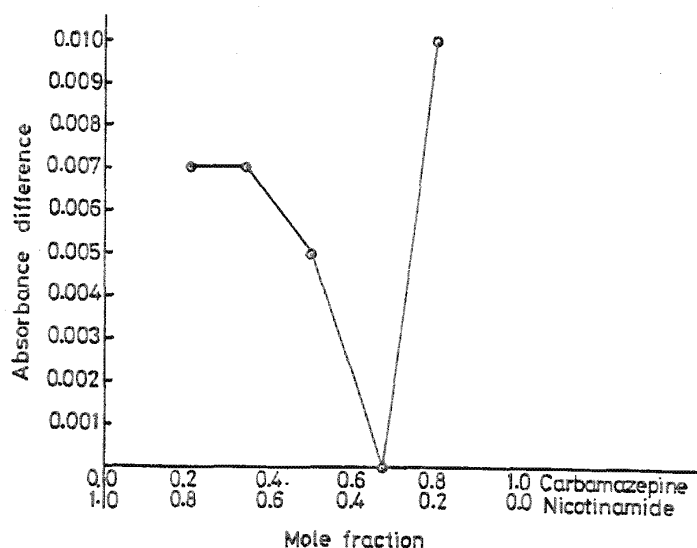


Fig. 11: Elucidation of the stoichiometric ratio of carbamazepine nicotinamide complex

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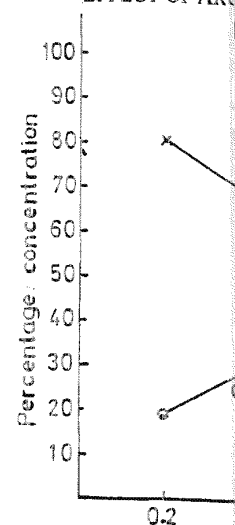


Fig. 12: Free and complexed concentration of carbamazepine and sodium benzoate

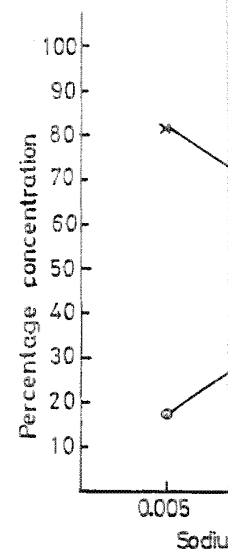


Fig. 13: Free and complexed concentration of carbamazepine and sodium naphthoate

1.0 Carbamazepine
0.0 Sodium nicotinate

ratio of carbamazepine-

1.0 Carbamazepine
0.0 Nicotinamide

ratio of carbamazepine nic-

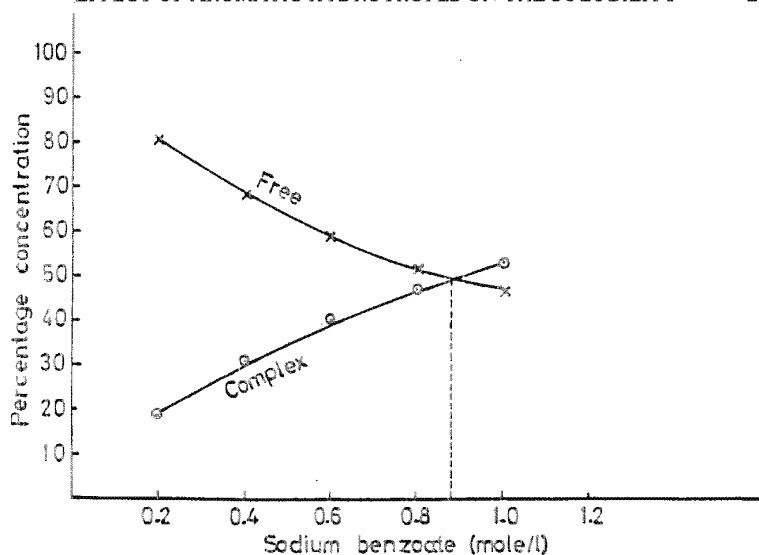


Fig. 12: Free and complexed forms of carbamazepine solubilized by sodium benzoate at 25°

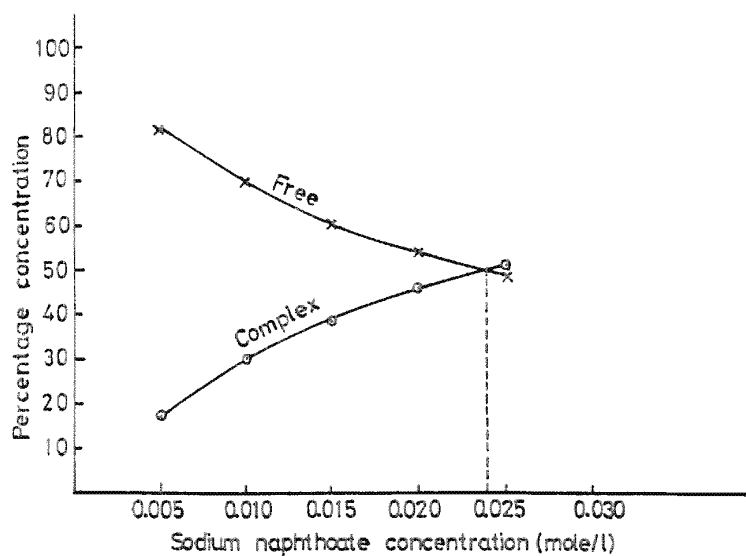


Fig. 13: Free and complexed forms of carbamazepine solubilized by sodium naphthoate at 25°

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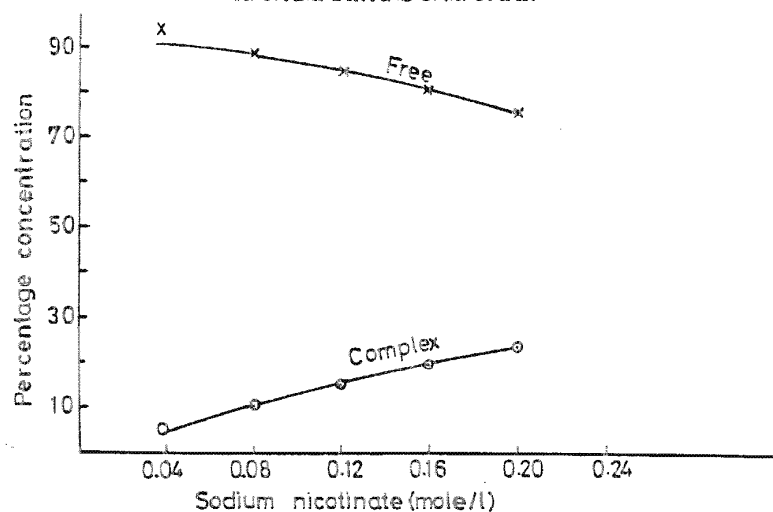


Fig. 14: Free and complexed forms of carbamazepine solubilized by sodium nicotinate at 25°

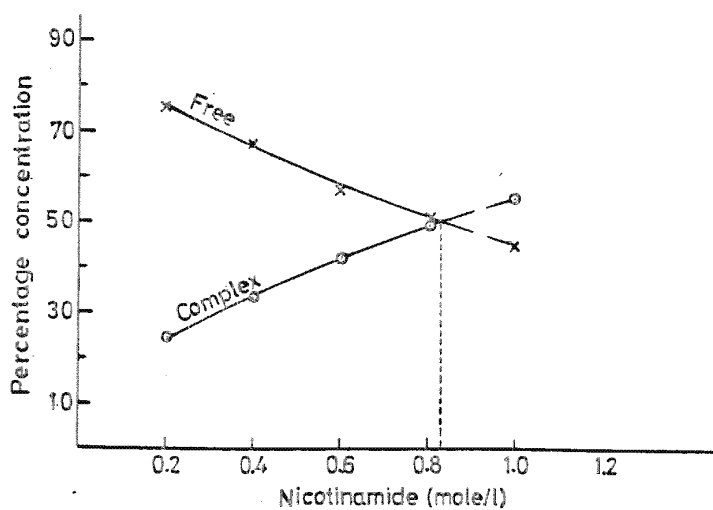


Fig. 15: Free and complexed forms of carbamazepine solubilized by nicotinamide at 25°

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TABLE 3. The carbamazepine

Solubilizer

Water
Nicotinamide

Sodium
benzoate

Sodium
naphthoate

Sodium
nicotinate

in the solubilization of carbamazepine. The concentration and of free form decrease with the concentration of hydrotrolic agents. The solubilization of CBZ in free and complexed forms by 0.88, 0.024 and 0.0024 mole/l nicotinamide, respectively, show that the in

TABLE 3. The calculated amounts of complexed and free forms of carbamazepine in solubilized systems.

Solubilizer	Concn (M)	S (M x 10 ³)	(AB) (M x 10 ³)	(A) (M x 10 ³)	A/So	(AB) %
Water	So =	0.694				
Nicotinamide	0.2	1.42	0.348	1.072	1.54	24.51
	0.4	2.45	0.806	1.644	2.37	32.90
	0.6	3.33	1.411	1.919	2.76	42.37
	0.8	5.30	2.623	2.677	3.86	49.49
	1.0	6.65	3.661	2.989	4.31	55.05
Sodium benzoate	0.2	0.907	0.169	0.738	1.06	18.63
	0.4	1.09	0.342	0.748	1.08	31.38
	0.6	1.32	0.537	0.783	1.13	40.68
	0.8	1.87	0.893	0.977	1.41	47.75
	1.0	3.19	1.701	1.489	2.15	53.32
Sodium naphthoate	0.005	0.761	0.133	0.628	0.90	17.48
	0.01	1.082	0.322	0.76	1.09	29.76
	0.015	1.614	0.627	0.987	1.42	38.85
	0.02	2.795	1.282	1.513	2.18	45.87
	0.025	8.73	4.49	4.24	6.11	51.43
Sodium nicotinate	0.04	0.68	0.04	0.640	0.92	5.88
	0.08	0.806	0.089	0.717	1.03	11.04
	0.12	0.898	0.141	0.757	1.09	15.70
	0.16	0.985	0.196	0.789	1.14	19.90
	0.2	1.044	0.247	0.797	1.15	23.66

in the solubilized systems increases with increasing the solubilizer concentration and consequently the percentage concentration of CBZ in the free form decreases. The graphical representation of the percentage concentration of CBZ solubilized in free and complexed forms as a function of hydrotrope concentration reveals that equimolar concentration of CBZ in free and complexed forms are solubilized at concentration of 0.88, 0.024 and 0.83 M for sodium benzoate, sodium naphthoate and nicotinamide, respectively (Fig. 12-15). The data presented in Table 3 show that the increased solubility of CBZ by sodium nicotinate is more

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or less entirely due to complex-formation between the drug and the hydrotrope, since the ratio of $(A)/S_0$ is about unity. On the other hand, there seems to exist another factor beside complex-formation promoting solubilization of the drug in presence of the other hydrotropes, since the ratio of the drug solubilized in free form to the solubility of the drug in water in these systems is higher than unity. This factor is most probably related to the decrease in the activity coefficient of the drug in presence of these hydrotropes (6). On the other hand, the data presented in Table 3 may explain to a great extent the lower solubilizing power of sodium nicotinate towards the drug relative to the other investigated compounds, since its solubilizing effect is only due to complex-formation.

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EFFECT OF ARC

وبان

ميد

ثوريك

قاهرة

اميد واملاح الصوديوم
والنيكوتينيك على ذوبان
المواد جميعا تزيد من ذوبان
هذه المواد وجد انها تعتمد
بمعنى ان استبدال حلقة
يزيد من قوة اذابة المادة

جزئية بين هذه المذيبات
الضوئي في المجال فوق
المواد مع الكاربامازين وقد
٢ : ١ مع النيكوتيناميد أو
مع نيكوتينات الصوديوم
الترافكات تتكون بين
٢ : ١ وايضا بنسبة ٢ : ١
كبات بطريقة الامتصاص
والاذابة لهذه المواد وعامل

في وجود هذه المواد يرجع
مستراكبات مع هذه المواد
سل النشاط للدواء في وجود

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unity. On the other hand,
mplex-formation promoting
other hydrotropes, since the
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Sci. Ed. 42, 138 (1953).

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(in Press).

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il, 119 (1952).

(Received 5/193; accepted 9/93)

تأثير المواد الأيدروتروبية على ذوبان الكارابامازيبين. الجزء الثاني : تأثير النيكوتيناميد وأملاح الصوديوم لأحماض البنزويك والثانثويك والنيكوتينيك .

حسين عثمان عمار ، سناء محمد مصطفى عمر

قسم العلوم الصيدلانية - المركز القومي للبحوث - الدقى - القاهرة

- مصر

يتناول البحث دراسة تأثير النيكوتيناميد وأملاح الصوديوم
لأحماض البنزويك - الثانثويك والنيكوتينيك على ذوبان
الكارابامازيبين فى الماء . وقد وجد أن هذه المواد جميعا تزيد من ذوبان
الكارابامازيبين وبحسب قوة الاذابة لهذه المواد وجد أنها تعتمد
اعتماداً كبيراً على شكلها الكيميائى بمعنى أن استبدال حلقة
البنزين بالنفثالين أو البردين يزيد من قوة اذابة المادة
الايدروتروبية.

وقد تم أيضاً دراسة التفاعلات الجزيئية بين هذه المذيبات
والكارابامازيبين بواسطة الامتصاص الضوئى فى المجال فوق
البنفسجى . كما تم دراسة تراكبات هذه المواد مع الكارابامازيبين وقد
وجد أن الكارابامازيبين يتراكم بنسبة ٢ : ١ مع النيكوتيناميد أو
ثانثوينات الصوديوم وكذلك بنسبة ١ : ١ مع نيكوتينات الصوديوم
ومن جهة أخرى هناك نوعين من التراكبات تتكون بين
الكارابامازيبين وبنزوات الصوديوم بنسبة ١ : ٢ وايضا بنسبة ٢ : ١
وقد تم تعيين عامل الثبات لهذه التراكبات بطريقة الامتصاص
الضوئى وقد ظهر علاقة وثيقة بين قوة الاذابة لهذه المواد وعامل
الثبات لتراكباتها مع الكارابامازيبين .

وقد تبين أن الزيادة فى ذوبان العقار فى وجود هذه المواد يرجع
الى عاملين أساسيين وهما تكوين متراكبات مع هذه المواد
الايدروتروبية بالإضافة الى نقصان معامل النشاط للدواء فى وجود
هذه المركبات.

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EAST Search History

EAST Search History (Prior Art)

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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

S51	9	("7452555") or ("7446107") or ("7205413") or ("7078526")).PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2009/08/31 06:23
S52	4	("2003/0224006").URPN.	USPAT	OR	OFF	2009/08/31 06:38
S53	3	("2665277").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2009/08/31 07:13
S54	2904	active pharmaceutical ingredient	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/08/31 07:18
S55	53594	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetaminophen	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2009/08/31 07:18
S56	607	S54 S55	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 07:18
S57	335	cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2009/08/31 07:19
S58	13	S56 S57	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 07:19
S59	27058	hydrogen bond	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/08/31 07:20
S60	28	S56 S59	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 07:20
S61	58	co-crystal former	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/08/31 07:21

S62	14	S55 S61	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 07:22
S63	2904	active pharmaceutical ingredient	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/08/31 08:44
S64	791	S63 crystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 08:44
S65	20	S63 cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 08:44
S66	2904	active pharmaceutical ingredient	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/08/31 08:58
S67	53594	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetaminophen	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2009/08/31 08:58
S68	607	S67 S66	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 08:58
S69	210	S68 CRYSTAL	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 08:58
S70	4	("7452555") or ("7446106") or ("7205413") or ("7078526").PN.	USPAT	OR	OFF	2009/09/28 10:26
S71	95	phosphate hemihydrate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/09/28 14:42

S72	54110	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetaminophen	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2009/09/28 14:42
S73	5	S72 S71	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/09/28 14:42
S74	2	(("3028420") or ("5521207")).PN.	USPAT	OR	OFF	2009/09/28 14:52
S75	19	API cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/09/28 15:02
S76	0	ep "0548028"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/09/28 15:46

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		Application Number	10/378,956		
		Filing Date	March 3, 2003		
		First Named Inventor	Michael J. Zaworotko		
		Art Unit	1617		
		Examiner Name	Sahar Javanmard		
Sheet	1	of	2	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 <i>et al.</i>	All
	U3	US-7,205,413	04-17-2007	Morissette <i>et al.</i>	All
	U4	US-7,078,526	07-18-2006	Remenar <i>et al.</i>	All
	U5	US-			
	U6	US-			
	U7	US-			
	U8	US-			
	U9	US-			

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document		Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Country Code ³	Number ⁴ - Kind Code ⁵ (if known)			
	F1					
	F2					
	F3					
	F4					
	F5					
	F6					
	F7					

Examiner Signature	/Sahar Javanmard/	Date Considered	09/28/2009
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		Application Number	10/378,956		
		Filing Date	March 3, 2003		
		First Named Inventor	Michael J. Zaworotko		
		Art Unit	1617		
		Examiner Name	Sahar Javanmard		
Sheet	2	of	2	Attorney Docket Number	USF.106XC1

NON PATENT LITERATURE DOCUMENTS			
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	R1	SHATTOCK, T. R. <i>et al.</i> "Hierarchy of Supramolecular Synthons: Persistent Carboxylic Acid ... Pyridine Hydrogen Bonds in Cocrystals that also contain a Hydroxyl Moiety" <i>Crystal Growth & Design</i> , 2008, pp. 4533-4545, Vol. 8, No. 12.	
	R2		
	R3		
	R4		
	R5		
	R6		
	R7		
	R8		
	R9		
	R10		
	R11		
	R12		

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10378956	CTNF	10/05/2009	USF-106XC1
	892	10/05/2009	USF-106XC1
	1449	10/05/2009	USF-106XC1

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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 10/01/2009 SALIWANCHIK LLOYD & SALIWANCHIK A PROFESSIONAL ASSOCIATION PO Box 142950 GAINESVILLE, FL 32614			EXAMINER JAVANMARD, SAHAR	
			ART UNIT 1617	PAPER NUMBER
			NOTIFICATION DATE 10/01/2009	DELIVERY MODE ELECTRONIC

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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
10378956	3/3/2003	ZAWOROTKO ET AL.	USF-106XC1

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EXAMINER

SAHAR JAVANMARD

ART UNIT	PAPER
1617	20090830

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Commissioner for Patents

This is a decision on the PETITION FOR ACCEPTANCE OF COLOR DRAWINGS UNDER 37CFR1.83(a)(2). The petition was filed January 21, 2009. Entry of color drawings requires: 1) three sets of the color drawings, 2) a proper amendment to the specification indicating color photographs or drawings are present in the file, and 3) the required fee under 37 CFR 1.17(h).

A review of the application record indicates that the petition meets all of the requirements for acceptance of color drawings. This should not be construed that all of the drawings are accepted, only that the color drawings are acceptable.

The petition is GRANTED.

Should there be any questions with respect to this decision, please contact Sreeni Padmanabhan, by telephone at 571-272-0629.

Sreeni Padmanabhan
Supervisory Patent Examiner, Art Unit 1617

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1617

/S. J./
Examiner, Art Unit 1617



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10378956	3/3/2003	ZAWOROTKO ET AL.	USF-106XC1

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EXAMINER

SAHAR JAVANMARD

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Sreeni Padmanabhan
Supervisory Patent Examiner, Art Unit 1617

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1617

/S. J./
Examiner, Art Unit 1617

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10378956	PETDEC	10/01/2009	USF.106XC1

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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 11/09/2009 SALIWANCHIK LLOYD & SALIWANCHIK A PROFESSIONAL ASSOCIATION PO Box 142950 GAINESVILLE, FL 32614			EXAMINER JAVANMARD, SAHAR	
			ART UNIT 1627	PAPER NUMBER
			NOTIFICATION DATE 11/09/2009	DELIVERY MODE ELECTRONIC

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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
10378956	3/3/2003	ZAWOROTKO ET AL.	USF-106XC1

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ART UNIT	PAPER
1617	20090830

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Sreeni Padmanabhan
Supervisory Patent Examiner, Art Unit 1617

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1617

/S. J./
Examiner, Art Unit 1617

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10378956	M327	11/09/2009	USF.106XC1

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			Application Number	10/378,956	
			Filing Date	March 3, 2003	
			First Named Inventor	Sahar Javanmard	
			Art Unit	1617	
			Examiner Name	Michael J. Zaworotko	
Sheet	1	of	2	Attorney Docket Number	USF.106XC1

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Examiner Initials*	Cite No. ¹	Document Number Number - Kind Code* (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
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	F1	JP-B 46-33588	10-01-1971	Sanzu Inc.	All	
	F2					
	F3					
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		First Named Inventor	Sahar Javanmard
		Group Art Unit	1617
		Examiner Name	Michael J. Zaworotko
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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	WUNDERLICH, H. F. <i>et al.</i> "The Derivatives of carbamazepine with ammonium halogenides and formamide" <i>Pharmazie</i> , 1991, pp. 507-509, Vol. 46, No. 7.	
	R2	EL-NAHHAS, S. A. "Physico-chemical characteristics of carbamazepine- β -cyclodextrin inclusion compounds and carbamazepine-PEG solid dispersions" <i>Pharmazie</i> , 1996, pp. 960-963, Vol. 51, No. 12.	
	R3	REYNOLDS, J. E. F. (ed). Martindale, The Extra Pharmacopoeia, 1993, The Pharmaceutical Press, London, England, 13 th edition, p. 1610.	
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	R5	ZAMAN, M. B. <i>et al.</i> "Crystal Engineering Using Anilic Acids and Dipyriddy Compounds through a New Supramolecular Synthon" <i>J. Org. Chem.</i> , 2001, pp. 5987-5995, Vol. 66,.	
	R6	Japanese Notice of Reasons for Rejection dated October 8, 2009, Japanese Application No. 2003-572946.	x
	R7		
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	R12		

Examiner Signature		Date Considered	
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$C_{10}H_{10}IN_4$ (394.3)
Ber.: N 14.21
Gel.: N 13.93

3.3.3. 1-(N-Phenylamidino)pyrazolidin-hydrochlorid (3r)

Ausbeute: 52%. Farblose Nadeln. Schmb. 185–187.5 °C (o-C₆H₅OH). UV
[CH₃OH, nm (lg ε)]: λ_{max} = 222 (4.44). IR (KBr, cm⁻¹): ν = 3380, 3280, 3130, 1630
(C=N), 1580 (NH), 1240 (C-N). ¹H-NMR (DMSO-d₆, ppm): δ = 2.10 (t, 2H, -CH₂-); 2.92 (dt, 2H, -CH₂-); 3.48 (t, 2H, -CH₂-); 7.17–7.44 (m, 5H, Ar-H); 7.54 (s, 4H, NH).
 $C_{10}H_{10}IN_4$ (313.2)
Ber.: N 13.61
Gel.: N 16.64

3.3.4. 1-(N-(4-Methylphenyl)amidino)pyrazolidin-hydrochlorid (3f)

Ausbeute: 47%. Farblose Nadeln. Schmb. 152–154 °C (o-C₆H₅OH). UV
[CH₃OH, nm (lg ε)]: λ_{max} = 231 (4.31). IR (KBr, cm⁻¹): ν = 3370, 3100, 2970, 1620
(C=N), 1583 (NH), 1570, 1230 (C-N). ¹H-NMR (DMSO-d₆, ppm): δ = 2.10 (t, 2H, -CH₂-); 2.29 (s, 3H, -CH₃); 2.89 (dt, 2H, -CH₂-); 3.43 (t, 2H, -CH₂-); 7.05 (d, 2H, Ar-H); 7.20 (d, 2H, Ar-H); 7.41 (s, 4H, NH).
 $C_{11}H_{11}IN_4$ (332.2)
Ber.: N 16.87
Gel.: N 17.32

3.3.5. 1-[N-(4-Chlorphenyl)amidino]pyrazolidin-hydrochlorid (3g)

Ausbeute: 43%. Farblose Kristalle. Schmb. 169–171.5 °C (o-C₆H₅OH). UV
[CH₃OH, nm (lg ε)]: λ_{max} = 223 (4.37), 245 (sh 4.17). IR (KBr, cm⁻¹): ν = 3420,
3310, 3100, 1640 (C=N), 1595 (NH), 1560, 1490, 1230 (C-N). ¹H-NMR
(DMSO-d₆, ppm): δ = 2.07 (t, 2H, -CH₂-); 2.88 (dt, 2H, -CH₂-); 3.41
(t, 2H, -CH₂-); 7.15 (d, 2H, Ar-H); 7.42 (d, 2H, Ar-H); 7.55 (s, 4H, NH).
 $C_{10}H_9ClIN_4$ (352.6)
Ber.: N 13.89
Gel.: N 16.04

3.3.6. 1-[N-(4-Bromphenyl)amidino]pyrazolidin-hydrochlorid (3h)

Ausbeute: 51%. Farblose Kristalle. Schmb. 179–182.5 °C (CH₃OH). UV
[CH₃OH, nm (lg ε)]: λ_{max} = 233 (4.51), 264 (sh 3.89). IR (KBr, cm⁻¹): ν = 3390,
3180, 1630 (C=N), 1583 (NH), 1530, 1470, 1220 (C-N). ¹H-NMR (DMSO-d₆, ppm): δ = 2.15 (t, 2H, -CH₂-); 2.91 (dt, 2H, -CH₂-); 3.45 (t, 2H, -CH₂-); 7.15 (d, 2H, Ar-H); 7.56 (d, 2H, Ar-H); 7.70 (s, 4H, NH).
 $C_{10}H_9BrIN_4$ (397.1)
Ber.: N 14.11
Gel.: N 14.24

3.3.7. 1-(N-Naphth-1-ylamidino)pyrazolidin-hydrochlorid (3i)

Ausbeute: 48%. Farblose Kristalle. Schmb. 219–223 °C (o-C₆H₅OH). UV
[CH₃OH, nm (lg ε)]: λ_{max} = 273 (sh 3.87), 283 (3.95), 294 (sh 3.87). IR (KBr, cm⁻¹): ν = 3390,
3360, 3100, 1610 (C=N), 1590 (NH), 1390, 1250 (C-N). ¹H-NMR (DMSO-d₆, ppm): δ = 2.16 (t, 2H, -CH₂-); 2.98 (dt, 2H, -CH₂-); 3.52 (t, 2H, -CH₂-); 7.30 (s, 4H, NH); 7.35–8.02 (m, 7H, Ar-H).
 $C_{14}H_{12}IN_4$ (368.2)
Ber.: N 15.21
Gel.: N 15.23

Wir danken Herrn T. Nagel, Berlin-Chemie, für die Unterstützung bei der Aufnahme und Diskussion der ¹H-NMR-Spektren.

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連番 0004

Arzneimittelwerk Dresden GmbH, Geschäftsbereich Forschung und Entwicklung

Untersuchungen über Additionsverbindungen von Carbamazepin

H. WUNDERLICH, L. ZENKER, H. USBECK, A. STARK, D. LOHMANN und W. THIEL

Es werden Additionsverbindungen von Carbamazepin mit Ammoniumchlorid, Ammoniumbromid und Formamid dargestellt und charakterisiert (IR-Spektren, Verhalten gegenüber Wasser, Löslichkeit).

Derivatives of carbamazepine with ammonium halogenides and formamide

The reaction of carbamazepine with ammonium chloride, ammonium bromide, and formamide is described. The products were characterized by means of IR spectra, the reaction with water and their solubility.

1. Einleitung

Das Antiepileptikum Carbamazepin (Finlepsin® AWD; 1) bildet Additionsverbindungen, die in der Literatur schon mehrfach Erwähnung fanden. So beschrieben Föhlmann et al. [1] die Anlagerung von Wasser unter Bildung von Carbamazepindihydrat. Von japanischen Autoren wurde über ein Monoaceton-Addukt ausführlich berichtet [2]. In einer DDR-Patentschrift [3] sind Additionsverbindungen aus 1 und anorganischen oder organischen Säuren mitgeteilt worden. Im Rahmen unserer Arbeiten zur technischen Herstellung und Reinigung von 1 konnten wir feststellen, daß dieses auch mit Ammoniumhalogeniden und Formamid Addukte bildet.

Pharmazie 46 (1991), H. 7

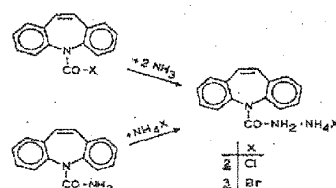
2. Untersuchungen und Ergebnisse

2.1. Additionsverbindungen aus Carbamazepin und Ammoniumhalogeniden

2.1.1. Herstellung

Bei der Reaktion von 5-Chlorcarbonyl-5H-dibenz[b,f]azepin (4, X=Cl) mit gasförmigem Ammoniak in siedendem Chloroform wird ein farbloses, in Chloroform schwer lösliches Kristallisat erhalten, dessen Schmelzverhalten von dem des 1 verschieden ist. In gleicher Weise verläuft die Reaktion in Alkoholen, Butylacetat, Benzen oder Toluol. Aus der Elementaranalyse folgt, daß die Substanz stöchiometrisch aus 1 und Ammoniumchlorid im Verhältnis 1:1 zusammengesetzt ist. Geht man von 1 aus, so lassen sich in geeigneten organischen Lösungsmitteln durch Zusatz von Ammoniumhalogeniden ebenfalls die bislang nicht bekannten Addukte isolieren (vgl. 3.1.). Die Bildungsweise der Addukte ist im Schema 1 dargestellt.

Schema 1



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Die Additionsverbindungen 2 und 3 sind an der Luft stabil und lassen sich in niedrigen Alkoholen unzersetzt umkristallisieren. Um die neuen Verbindungen genauer zu charakterisieren, wurden neben spektroskopischen und Löslichkeitsuntersuchungen auch umfassende elektrochemische und röntgenstrukturanalytische Untersuchungen eingeleitet, über deren Ergebnisse gesondert berichtet wird [4, 5].

2.1.2. IR-Spektren

Die IR-Spektren (in KBr) der beiden Addukte 2 und 3 sind einander sehr ähnlich (Tabelle 1). Unterschiede gegenüber 1 zeigen sich an einer doppelt auftretenden Carbonylbande bei 1650 und 1660 cm^{-1} , an der verschobenen Bandengruppe für vNH-Schwingungen und an der breiten, intensiven Bande bei 1435 cm^{-1} , die wir einer verschobenen δNH -Schwingung zuordnen. Daraus läßt sich ein stärkerer Einfluß des ionischen Partners im Kristallgitter auf die Carbamoylgruppe ableiten. Das NH_4^+ -Kation in 2 und 3 zeigt eine sehr intensive, breite Bande bei 2960 cm^{-1} .

Tabelle 1 IR-Absorptionsbanden [cm^{-1}] der Ammoniumhalogenid-Addukte im Vergleich zu repräsentativen Kristallmodifikationen des Carbamazepins (I_a , I_b)

2	3	I_a	I_b	Schwingung
770	765	750		γCH (out-of-plane)
1435	1435	1375	1385	δNH
1480	1480	1480		$\nu\text{C}=\text{C}$
1575	1575	1585		(aromatisch)
1595	1595	1595		
1650	1650	1665	1685	$\nu\text{C}=\text{O}$
1660	1660	—	—	
3243	3250	3270		vNH
3310	3315	3335		
3400	3395	3460	3475	

Die IR-Spektren berechtigen zu der Annahme, daß es sich um definierte Additionsverbindungen und nicht nur um Gemische handelt.

2.1.3. Verhalten gegenüber Wasser

Die Zerlegung der $1\text{-NH}_4\text{X}$ -Addukte in Wasser läuft vor allem bei nicht ausreichender Wassermenge unvollständig ab. Ein bloßes Auswaschen des Reaktionsproduktes mit Wasser führt nicht zu reinem 1. Offenbar war Schindler [6] bei der Erstbeschreibung der Synthese von 1 aus 5-Chlorcarboxyl-5H-dibenz[b,f]azepin und Ammoniak diesem Irrtum unterlegen, als er nach wiederholtem Umkristallisieren den Schmb. mit 204–206 °C anstatt mit dem zutreffenden von 190–192 °C angab.

Die Herstellung von $1\text{-NH}_4\text{X}$ -Addukten ist nach Schema 1 in organischen Lösungsmitteln auch in Gegenwart von begrenzten Mengen Wasser möglich und gestattet z.B. die Anwendung von konz. Ammoniaklösung. So liefert die Reaktion zwischen 4 (X=Cl) und 25% wäßriger Ammoniaklösung in Butylacetat als Finalprodukt das $1\text{-NH}_4\text{Cl}$ -Addukt in guter Ausbeute [7]. Dies ist bei der technischen Herstellung von 1 und für die weiteren Reinigungsoperationen von Bedeutung, denn 10-Bromcarbamazepin oder 10,11-Dihydrocarbamazepin bilden mit Ammoniumchlorid unter vergleichbaren Bedingungen keine Addukte.

Zur Ermittlung der Löslichkeit wurden 20 mg Substanz (Variante A) bzw. 100 mg Substanz (Variante B) mit einem Zusatz von 25,0 ml Wasser im verschlossenen Erlenmeyer-Kolben mittels Thermovibrator bei 25 °C geschüttelt. Zum Vergleich wurde eine äquimolare Mischung von 23,6 mg Carbamazepin- β -modifikation (I_a) und 5,3 mg Ammonium-

chlorid mit einem Zusatz von 25 ml destilliertem Wasser untersucht.

Nach der in Tabelle 2 angegebenen Zeit wurden Proben der klaren, wäßrigen Lösung genommen und ihr Gehalt an Carbamazepin UV-spektroskopisch bestimmt. Die Ergebnisse sind in Tabelle 3 zusammengestellt.

Tabelle 2 Löslichkeiten (mg/100 ml Lösung) von 2, 3, I_a und einem äquimolaren Gemisch $I_a + \text{NH}_4\text{Cl}$ bei 25 °C

Zeit [h]	2	3	I_a	$I_a + \text{NH}_4\text{Cl}$
1	14,6	29,3	11,8	14,3
3	14,1	27,9	12,1	13,4
7	13,9	23,8	12,2	12,9
24	15,2	17,2	13,6	12,8
48	—	15,6	14,6	12,5

Unter vergleichbaren Bedingungen zeigen alle Substanzen ähnliche Löslichkeitswerte. Geringfügige Unterschiede lassen sich durch Abweichungen in den Korngrößen- und Phasenverteilungen erklären. Der Einfluß des anwesenden Ammoniumhalogenids auf die Löslichkeit ist unerheblich.

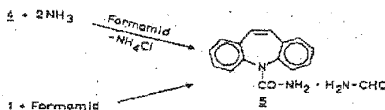
Eine nach 1 h zusätzlich vorgenommene argentometrische Chloridbestimmung in der wäßrigen Lösung der Probe 2 (B) ergab bereits den auf die Einwaage berechneten vollen Chloridwert. Diese Ergebnisse zeigen, daß nach 1 h nur noch 1 (heterogen) neben freiem Ammoniumchlorid in homogener Lösung vorliegt. Die beträchtlich erhöhte Anfangslöslichkeit bestätigt das Vorliegen eines Addukthabitus. Der schnell fortschreitende Übergang in einen anderen Habitus ist begleitet von einer Übersättigung der wäßrigen Phase, die sich langsam zum normalen Löslichkeitsgleichgewicht von 1 hin abbaut (Tabelle 2, Spalte 2). Die IR-Spektren der luftgetrockneten Adduktrückstände und von I_a aus den Ansätzen der Löslichkeitsbestimmungen enthalten die charakteristischen Banden des Einsatzstoffes nicht mehr. Es liegen Mischphasen von I_a und $1 \cdot 2\text{H}_2\text{O}$ vor.

Das Löslichkeitsverhalten deutet auf eine nur lockere Bindung des Ammoniumchlorids im Kristallgefüge.

2.2. Additionsverbindung aus Carbamazepin und Formamid

Verwendet man zur Beschleunigung der Reaktion von 4 (X=Cl) mit konz. wäßrigen Ammoniak als zusätzliche Lösungskomponente Formamid, so erhält man überraschenderweise anstelle von 1 ein im verwendeten Lösungsmittelgemisch schwer lösliches Addukt aus 1 und Formamid. Die Bildung dieses Adduktes 5 ist in Chloroform ebenfalls direkt aus 1 und Formamid möglich (Schema 2).

Schema 2



Die elementaranalytische Untersuchung ergab für 5 wiederum eine Zusammensetzung im Molverhältnis 1:1. Durch Wasser und wäßrige alkalische Lösungen wird es in seine Komponenten zerlegt.

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5 ist aus wasserfreien Alkoholen (Methanol, Ethanol) in Gegenwart von 1 bis 5% Formamid unzerlegt umkristallisierbar. Bei Anwendung von wäßrigen Alkoholen erfolgt eine vollständige Zerlegung des Adduktes. Aus der warmen Mutterlauge kristallisiert reines 1 aus, das bei Raumtemperatur völlig klar in Chloroform löslich ist. Das Addukt ist im Unterschied dazu in Chloroform schwer löslich.
Formamid verdrängt offenbar auf Grund seiner stärkeren Affinität zu 1 Ammoniumchlorid. Bei Anwendung von Methyl- oder Dimethylformamid anstelle von Formamid ist dies nicht der Fall, vielmehr wird hierbei 2 isoliert.

3. Experimenteller Teil

Die IR-Spektren wurden mit einem Spektralphotometer Specord 75 IR (Carl Zeiss JENA) aufgenommen, die Schmelz- und Siedepunkte mit einem Heitzschperit nach Hofmann sowie dem Thermosystem FP5 (Mettler) bestimmt, wobei Überstimmung erzielt wurde.

3.1. 5-Carbamoyl-5H-dibenz[b,f]azepin (1)-NH₄Cl-Addukt (2)

3.1.1. 47,2 g (0,2 mol) 1 werden unter Erwärmen in 500 ml 96%

C₂H₅OH gelöst. Dann wird eine filtrierte Lösung von 10,7 g (0,2 mol) NH₄Cl in 50 ml H₂O zugegeben. Man erwärmt die Mischung 15 min zum Sieden, kühlt sie auf 15 °C und setzt den entstandenen Niederschlag nach 24 h ab. Dieser wird mit wenig C₂H₅OH gewaschen und bei 100 °C getrocknet. Nach Umkristallisation aus der 20fachen Menge C₂H₅OH erhält man Nadeln. Schmelzpunkt: 195,5–199 °C. C₁₅H₁₃ClN₂O (289,9)

Ber.:	C	62,17	H	5,57	N	14,50	Cl	12,24
Gef.:	C	61,93	H	5,54	N	14,40	Cl	12,02
		62,21		5,63		14,43		12,17

3.1.2. 12,8 g (0,05 mol) 3-Chloracetyl-5H-dibenz[b,f]azepin werden in 45 ml Butylacetat verflüchtigt. Man erwärmt auf 80 °C, tropft in die entsprechende Lösung 15 ml einer 25% wäßrigen NH₃-Lösung und rührt 1 h bei 80 °C. Anschließend werden über einen Wasserabscheider ca. 10 ml H₂O abdestilliert. Der Ansatz wird dann auf 12 °C gekühlt, das Kristallfäll über eine Filterutsche abgeseigt und zweimal mit je 10 ml Butylacetat gewaschen. Es wird bei 100 °C getrocknet und aus 50% wäßriger 1-C₂H₅OH umkristallisiert.

3.2. 1-NH₄Br-Addukt (3)

47,2 g (0,2 mol) 1 werden im siedenden Wasserbad in 200 ml Butylacetat gelöst. Man tropft eine Lösung von 20 g (0,224 mol) NH₄Br in 10 ml H₂O zu, erwärmt 0,5 h, kühlt die Mischung auf 15 °C und filtriert den ausgefallenen Niederschlag.

ab. Dieser wird mit Butylacetat gewaschen und bei 100 °C getrocknet. Durch Umkristallisation aus C₂H₅OH erhält man das 1:1-Addukt als farblose, verflüchtigte Nadeln. Schmelzpunkt: 119–201 °C. C₁₆H₁₄BrN₂O (334,2)

Ber.:	C	53,89	H	4,82	N	12,56	Br	23,93
Gef.:	C	52,69	H	4,84	N	12,50	Br	25,10
		52,46		4,86		12,50		25,11

3.3. 1-Formamid-Addukt (5)

25,6 g (0,1 mol) 1 werden bei Raumtemperatur in 100 ml CHCl₃ unter Rühren gelöst. In die klare Lösung werden unter Rühren 5,6 g (0,125 mol) NH₃·CHO zugegeben. Die Lösung beginnt sich einzutrüben und in wenigen min erfolgt die Kristallisation. Nach 2–3 h Kühlen im fließenden Wasserbad wird das Kristallfäll abgeseigt und mit gekühltem CHCl₃, das 1% NH₃·CHO enthält, gewaschen. Der farblose Filterkuchen wird im Trockenschrank bei ca. 70 °C getrocknet. Man erhält 23 g (81,7%) 5. Schmelzpunkt: 189–192 °C (bei 142–145 °C erfolgt eine deutliche Kristallumwandlung). C₁₆H₁₃N₂O₂ (281,3)

Ber.:	C	68,31	H	5,37	N	14,94
Gef.:	C	68,33	H	5,36	N	15,10

3.4. Bestimmung der Löslichkeit von 2 und 3

Substanzmengen von ca. 20 mg und 25 ml dest. H₂O (A) bzw. 100 mg und 25 ml dest. H₂O (B) werden in je einem 100 ml-Schüttel-Friesmeyer gegeben. Die verschlossenen Kolben werden bei 25 °C 125 rotierenden Schüttelbewegungen je min ausgesetzt. Das Klarfiltrat einer Probeaufnahme wird 1:10 mit dest. H₂O verdünnt und die UV-Absorption in einer 10 mm Küvette bei 286 nm gegen dest. H₂O gemessen. Für die analog auszuführende Eichmessung werden ca. 8 mg Einwaage 1 in 100 ml dest. H₂O durch leichtes Erwärmen und ggf. mit Ultraschall klar gelöst.

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Kristallstrukturen der Addukte Carbamazepin-Ammoniumchlorid und Carbamazepin-Ammoniumbromid sowie deren Umwandlung in Carbamazepin-Dihydrat

G. RECK¹ und W. THIEL²

Die Addukte Carbamazepin-Ammoniumchlorid und Carbamazepin-Ammoniumbromid haben isomorphe Kristallstrukturen. In ihnen gibt es stabile Schichten, in denen die Wirkstoffmoleküle, Ammonium- und Chlorid- bzw. Bromidionen über 6 symmetrieunabhängige Wasserstoffbrücken miteinander verknüpft sind. In Wasser werden die Addukte durch eine topotaktische Reaktion vollständig in Carbamazepin-Dihydrat umgewandelt.

Crystal structures of the adducts carbamazepine-ammonium chloride and carbamazepine-ammonium bromide and their transformation in carbamazepine dihydrate

The adducts carbamazepine ammonium chloride and carbamazepine ammonium bromide have isomorphous

crystal structures. Drug molecules, ammonium, and chloride (bromide) ions are connected by 6 symmetry independent hydrogen bonds forming stable layers in the crystal. In water the adducts are transformed completely to carbamazepine dihydrate by a topotactic reaction.

1. Einleitung

Der antiepileptische Wirkstoff 5H-Dibenz[b,f]azepin-5-carboxamid (Carbamazepin, 1) bildet mit Ammoniumchlorid beim Umkristallisieren in Ethanol ein Addukt (2), das über 200 °C schmilzt und damit eine wesentlich höhere Schmelztemperatur als der reine Wirkstoff (189–193 °C) besitzt. Das IR-Spektrum zeigt eine deutliche Veränderung einiger Banden [1].

記事 0005
通番

ORIGINAL ARTICLES

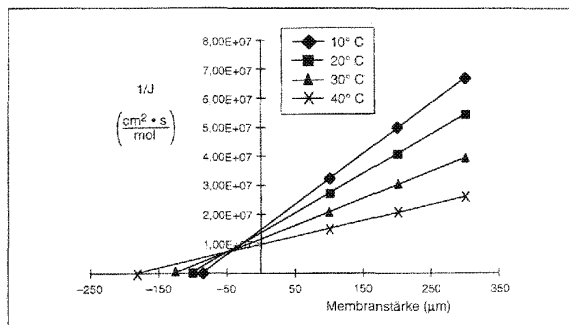


Abb. 7: Darstellung des reziproken Flusses gegen die Membranstärke für das Modell Kaliumchlorid/Wasser

tionswiderstands erfolgte aus den reziproken Diffusionsflüssen für die Schichtdicke $x = 0$ (Abb. 7). Die errechneten Permeationsgrößen sind in Tabelle 2 aufgelistet.

Tabelle 2: Permeationswerte für die ungerührten Schichten im KCl-Modell

Temperatur (°C)	$1/J$ ($10^{-7} \text{ cm}^2 \cdot \text{s/mol}$)	J ($10^{-8} \text{ mol/cm}^2 \cdot \text{s}$)	P (10^{-4} cm/s)	R (s/cm)
10	1,49	6,71	6,71	1490
20	1,35	7,40	7,40	1350
30	1,15	8,69	8,69	1150
40	0,965	10,36	10,36	965

Der Anteil der ungerührten Schichten am Gesamtpermeationswiderstand bei den Untersuchungen mit den amphiphilen Netzwerken lag je nach Temperatur, Membrandicke und Permeabilität zwischen 0,1% und 3%.

3. Diskussion

Die vorgestellte Diffusionszelle hat sich in der Praxis bewährt. Dies beruht auf der einfachen Variation von einzelnen Faktoren wie beispielsweise Akzeptor/Donatorvolumina, Rührbedingungen, Einsatz verschiedener Medien und Membranmaterialien sowie an dem relativ geringen apparativen Aufwand.

Untersuchungen mit unterschiedlichen Medien haben gezeigt, daß der Anteil der ungerührten Schichten am Gesamt-widerstand bei der verwendeten Apparatur erheb-

liche Ausmaße (bis zu 15%, je nach Versuchsbedingungen) annehmen kann. Aufgrund der Abhängigkeit des Permeationswiderstandes dieser „Bereiche ohne Konvektion“ von der Temperatur, vom Medium, vom untersuchten Stoff, von den Rührbedingungen und von der Geometrie der Diffusionszelle können Abschätzungen nicht zu befriedigenden Ergebnissen führen. Es muß daher grundsätzlich die Bestimmung des Widerstandes der ungerührten Schichten im Rahmen von Diffusionsexperimenten empfohlen werden.

4. Experimenteller Teil

Die Rührgeschwindigkeiten für alle Diffusionsmodelle und Versuche waren gleich und wurden konstant gehalten (100 U/min). Es wurden jeweils Rührstäbe der gleichen Größe und Geometrie eingesetzt.

4.1. Bestimmung der ungerührten Schichten

Für die Bestimmung wurde Dialysierschlauch mit Schichtdicken von 0,1 mm, 0,2 mm und 0,3 mm verwendet. Es wurden Messungen bei vier unterschiedlichen Temperaturen (10 °C, 20 °C, 30 °C, 40 °C) durchgeführt. Der Diffusionsfluß wurde über einen Zeitraum von mindestens 3 h gemessen. Jede Messung wurde mindestens dreimal wiederholt.

4.2. Flavon-Modell

Die Meßdauer für einen Temperaturwert betrug 3 h. Akzeptor: 100 ml Paraffin. Donator: ca. 5 ml Paraffin. Donatorkonzentration: 0,1 mmol/l Flavon. Die Ermittlung der Konzentration erfolgte diskontinuierlich im Abstand von etwa 20 min UV-spektrometrisch bei $\lambda = 252 \text{ nm}$.

4.3. KCl-Modell

Die Volumina betrugen 600 ml für den Akzeptor und ca. 8 ml für den Donator. Die eingesetzte Donator-Konzentration war 0,1 M KCl. Die Bestimmung des Diffusionsflusses erfolgte durch kontinuierliche Messung der Leitfähigkeitsänderung im Donatorkompartiment. Dazu wurde eine WTW LTA-100-Leitfähigkeitsmeßzelle eingesetzt. Die Meßdauer für einen Temperaturwert betrug mindestens 3 h.

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Physico-chemical characteristics of carbamazepine- β -cyclodextrin inclusion compounds and carbamazepine-PEG solid dispersions

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Carbamazepine (CBZ) was found to form an inclusion complex with β -cyclodextrin (β -CD). The solubility of CBZ increased on addition of β -CD displaying a linear relationship. A stability constant of 404 mol^{-1} was calculated. The complex obtained had a stoichiometry of 1:1. A comparison of the complex was carried out with polyethylene glycol 6000 solid dispersion prepared by either the comelting or coevaporate method using IR spectrophotometry and differential thermal analysis. Dissolution profiles in 0.1 N HCl medium of CBZ-comelt, coevaporate and inclusion complex

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NOVARTIS EXHIBIT 1517

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Physikochemische Charakteristiken von β -Cyclodextrin-Einschlußverbindungen und festen Polyethylenglycol-Dispersionen des Carbamazepins

Carbamazepin (CBZ) bildet einen 1:1-Einschlußkomplex mit β -Cyclodextrin (β -CD). Die Löslichkeit von CBZ wächst linear mit der Zugabe von β -CD. Für den Komplex wurde eine Stabilitätskonstante von 404 mol^{-1} ermittelt. Die IR- und DTA-Befunde des Komplexes wurden mit denen von CBZ-Polyethylenglycol(PEG)-6000-Dispersionen, hergestellt durch Schmelz- oder Coevaporationsverfahren, verglichen. Die Dissolution in 0,1 HCl verläuft beim β -CD-Komplex schneller als bei den PEG-Dispersionen.

1. Introduction

Since the first description of a solid dispersion in order to increase the dissolution and oral absorption of poorly water soluble drugs by Sekiguchi et al. [1], the tremendous amount of research carried out in this field led only to a very limited range of patented products on the world market. More recently, complexation with cyclodextrin has been extensively applied to improve the solubility, stability and bioavailability of various drugs [2–4].

The objective of the present study was to investigate the potentiality of interaction of carbamazepine (CBZ), a practically insoluble drug with β -cyclodextrin (β -CD) and to assess the implication of such an interaction on improving certain pharmaceutical properties of the drug. On the other hand, comparing the results with those achieved via dispersing the drug with polyethylene glycol (PEG 6000) in the form of a comelt or a coevaporate was a major objective.

2. Investigations, results and discussion

2.1. Potentiality of interaction of carbamazepine with β -cyclodextrin

A differential UV absorption spectrum of CBZ solution was monitored in presence of different concentrations of β -CD. The extinction of the drug is remarkably increased as a function of the β -CD concentration. Also, there is a bathochromic shift in the λ_{max} of the drug in presence of

β -CD from 285 to 288 nm. These spectral changes most probably reflect a sort of molecular interaction between the drug and β -CD.

The absorbance of a solution of a fixed total concentration (0.03 mmol/l) and different mole fractions of CBZ and β -CD was measured at 285 nm. The difference between the measured absorbance values and those expected if no complexation takes place, as a function of the mole fraction is illustrated in Fig. 1. Since for a constant total concentrations of the two species of a complex, the complex is at its high concentration at the point which they occur in the complex, it can be concluded that CBZ forms an 1:1 complex with β -CD.

2.2. Phase solubility

The graphical representation of the amount of CBZ dissolved as a function of β -CD concentration reveals enhancement of water-solubility of the drug in presence of β -CD (Fig. 2). The solubility increased with an increasing β -CD concentration, whereby a linear relationship exists between the maximum additive concentration of the drug and β -CD concentration. The stability constant of the

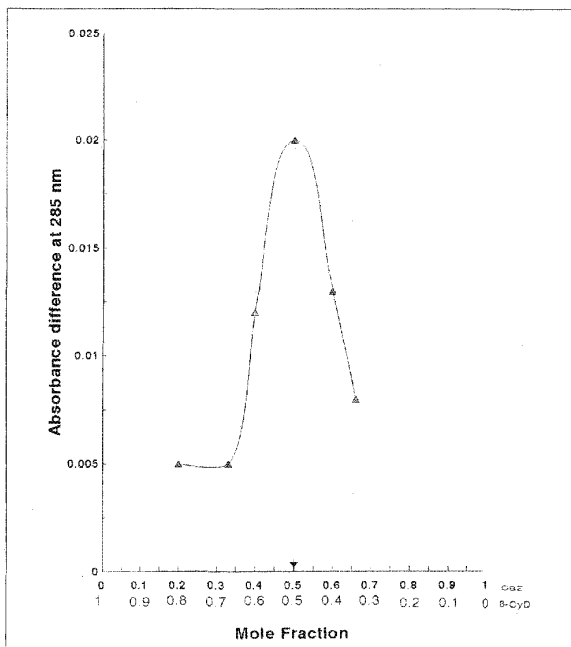


Fig. 1: Elucidation of the stoichiometric ratio of carbamazepine- β -cy-

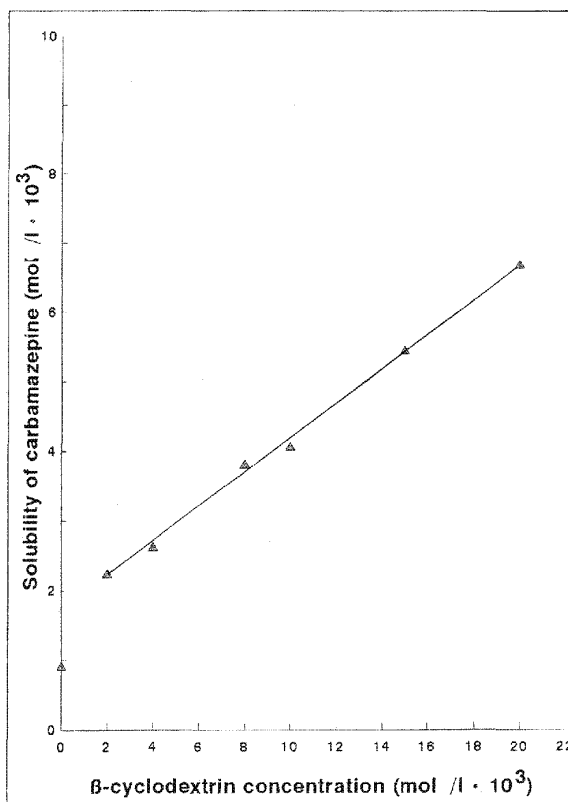


Fig. 2: Effect of β -cyclodextrin on the solubility of carbamazepine in water

Table: IR spectra of the carbamazepine/ β -cyclodextrin inclusion complex and the carbamazepine/PEG 6000 coevaporate or comelt

System	I	II	III	IV	V	VI	VII	VIII	IX	X
CBZ	765		1245	1305	1390		1490	1590	1690	3450
β -CD	1020	1150							1670	3350
CBZ/ β -CD complex	1020	1150							1690	3350
CBZ/PEG coevaporate		1110	1240	1280	1390		1490	1590	1700	3450
CBZ/PEG comelt		1105	1240	1280	1360	1470	1490	1590	1695	3450

CBZ/ β -CD complex was determined from the slope of this linear relationship according to the equation of Higuchi et al. [5].

$$K = \text{slope}/S_0(1 - \text{slope})$$

where S_0 is the solubility of the drug in water.

The stability constant of CBZ/ β -CD complex was found to be 404 mol^{-1} .

2.3. Infrared spectra

The IR spectra of the inclusion complex of the drug in β -CD as well as its comelt and coevaporate with PEG 6000 generally appeared to be the consequence of the superposition of those of the pure compounds i.e. CBZ and the host molecule.

In case of the β -CD complex, the major bands of CBZ are covered by the host molecule (Table). This is due to the inclusion of the drug in the β -CD cavity. Also, the carbonyl stretching at 1690 cm^{-1} for the drug is shifted to a lower wave number 1670 cm^{-1} in the inclusion complex. The formation of hydrogen bonds between CBZ and the host molecule may account for such shifts. In case of solid

dispersions, the drug is also covered with the host and there is a clear shift in all main bands of the drug in both of the comelt and coevaporate (Table). Also there is a lack of some of the characteristic peaks of CBZ. This refers to some sort of interaction between CBZ and PEG via hydrogen bonding.

2.4. Differential thermal analysis

The differential thermal analysis displays one endothermal CBZ peak at 222°C . PEG shows a single peak at 349°C . The two endothermic peaks at approximately 220°C and 350°C represent the two solid dispersions, i.e. comelt and coevaporate, since its height corresponds to about half that of PEG or CBZ peak for an amount of 200 mg of each sample. These results suggest that the CBZ peak is decreased to its half height in presence of PEG solid dispersion.

The thermograms of CBZ and β -CD show that β -CD has two endothermic peaks at 65°C and 276°C . The thermogram of the inclusion complex shows the complete disappearance of the endothermic peak of CBZ at 222°C . The appearance of two peaks at 60°C and 292°C are due to the presence of β -CD. This result confirms that an inclusion complex has been formed [6].

2.5. Dissolution

The dissolution profiles presented in Fig. 3 confirm that incorporation of CBZ in a water-soluble carrier significantly enhances the dissolution rate of the drug compared to the free drug. Thus, it can be seen that the dissolution rate of the CBZ/ β -CD complex is higher than that of the comelt or coevaporate of the drug with PEG 6000. This is very evident by comparing the amount of drug dissolved from the complex with that from the comelt or coevaporate during the initial 5 min of the dissolution run. The former is about twice that of the latter. On the other hand, considering the values of the dissolution efficiency of the drug, complex, comelt and coevaporate (31, 71, 61 and 41%, respectively), it can be seen that the dissolution rate of the drug from its comelt with PEG 6000 is higher than that of the corresponding coevaporate. The dissolution rate of the drug from its inclusion complex with β -CD is higher than from its solid dispersions with PEG 6000. In conclusion, inclusion complexation of CBZ in β -CD results in a very pronounced enhancement in the dissolution properties of the drug compared to the approach of solid dispersing the drug with water-soluble polymers. This result which runs parallel with more or less similar findings reported for tolbutamide [7], suggests the use of β -CD to improve the biological performance of CBZ.

3. Experimental

3.1. Materials

Carbamazepine (CBZ) (Aldrich, Milwaukee WI 53201 USA). Polyethylene glycol 6000. β -cyclodextrin (Merck, Darmstadt, Germany). All other

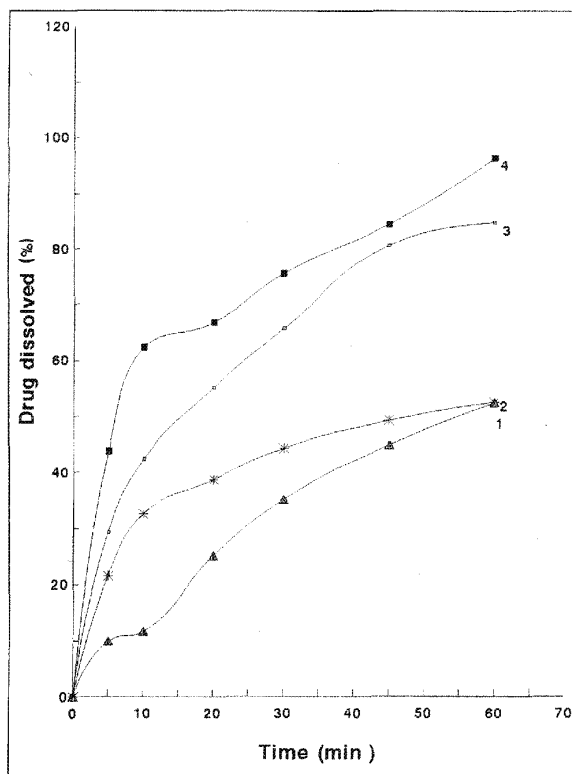


Fig. 3: Dissolution profiles of carbamazepine (1), carbamazepine - PEG 6000 coevaporate (2), carbamazepine - PEG 6000 comelt (3), and carbamazepine - β -cyclodextrin complex (4) in 0.1 N HCl at

3.2. Methods

3.2.1. Differential spectrum

Differential UV absorption spectrum of 0.02 mol/l of CBZ solution in presence of different concentrations of β -CD (5, 15, 20 mmol/l) was determined using a LKB spectrophotometer at the wave length range from 240 to 320 nm.

3.2.2. Continuous variation method

The continuous variation method described by Job [8] was used to determine the stoichiometric ratio of CBZ/ β -CD complex by spectrophotometric measurements at 285 nm.

3.2.3. Phase solubility studies

Phase solubility studies were performed according to the method reported by Higuchi et al. [5]. CBZ 20 mg was weighed out into 25 ml stoppered flasks. A constant volume of 5 ml distilled water was added to each container, then successively increasing portions of β -CD (0.002–0.0025 M) were added to these vessels which were closed and brought to a solubility equilibrium. The contents of the flasks were filtered through a Millipore membrane (HA 0.45 μ m). The CBZ concentration in the filtered solution was determined spectrophotometrically at 285 nm.

3.2.4. Sample preparation

3.2.4.1. Preparation of the CBZ comelt

CBZ and PEG 6000 (1:1) were melted together by first heating the PEG 6000 in an aluminum dish over an oil bath at 80 °C. The drug was then dissolved in the molten carrier and stirred to obtain a homogenous dispersion. Flash cooling of the dispersion by immersion in a bath of dry ice and acetone was employed. Indeed, it has been shown that rapid cooling give rise to faster dispersion rates. The dispersion was then dried under vacuum at room temperature for 24 h.

3.2.4.2. Preparation of the CBZ coevaporate

A mixture of CBZ and PEG 6000 (1:1) was dissolved in a sufficient volume of absolute ethanol and evaporation was carried out in vacuo at 25 °C. The hardened mass was removed from the container and dried under vacuum at room temperature for 24 h.

3.2.4.3. Preparation of the solid complex

The CBZ/ β -CD complex was prepared according to the kneading method. In this method, least amount of water was used, CD was kneaded like a paste with a small amount of water to which CBZ has been added without a solvent. The paste made of CD and CBZ was ground in a mortar, then dried under vacuum in presence of phosphorous pentoxide as drying agent at room temperature.

Each sample of comelt, coevaporate and solid complex, was – after drying – passed through a 250 μ m mesh. These samples were retained for the dissolution study as well as IR spectrophotometry and differential scanning calorimetry investigation.

3.2.5.4. IR spectrophotometry

The IR were measured as KBr disc using a Shimadzu 435 μ – 04 IR spectrophotometer.

3.2.6. Thermal measurements

The thermal behavior of the investigated samples were traced by differential thermal analysis (DTA). The DTA scans were carried out using a computerized Perkin Elmer DTA/TGA series under a dynamic N₂ purging gas atmosphere (at a constant rate of 50 cm³/min) and a heating rate of 5 °C/min.

3.2.7. Dissolution studies

Drug dissolution tests were performed according to the USP XXI method with the apparatus 2. For each sample, 900 ml of 0.1 N hydrochloric acid were stirred at 50 r.p.m. and maintained at 37 $\pm$ 0.5 °C. An amount of each sample equivalent to 25 mg CBZ was added to the medium after the equilibrium temperature was reached. Samples (5 ml) were withdrawn at various time intervals and filtered through a 0.22 μ m filter. The volume in the vessel was replaced with pure 0.1 N HCl after each sampling. The concentration of CBZ dissolved in the medium was determined spectrophotometrically at 285 nm.

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Stability and compatibility studies of cefazoline, ceftriaxone, cefotaxime and latamoxef with PVC infusion bags

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A rapid isocratic technique for the analysis of four cephalosporins, cefazoline, cefotaxime, ceftriaxone and latamoxef, in parenteral solutions by HPLC with UV detection and a C₁₈ column was developed. The stability and compatibility of drugs from solutions infused via plastic infusion bags through plastic administration sets have been examined. No significant drugs loss was observed during the simulated infusion (n = 4) for 1 h. No significant difference was found between infusion solutions (5% glucose or 0.9% sodium chloride). The stability of drugs was also studied in solution in PVC bags after storage at room temperature without protection from light and at +4 °C with protection from light. The results show the stability of drugs after 24 h at room temperature and 48 h storage at +4 °C to be satisfactory, irrespective of the infusion solution (5% glucose or 0.9% sodium chloride), except for the ceftriaxone solution that should not be

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1610 Preparations

Furo-Puren (Künge-Nattermann, Ger.).
Frusemide.

Oedema; hypertension.

Furorese (Hexal, Ger.).
Injection: Frusemide sodium.
Oedema; hypertension.

Furorese (Hexal, Ger.).
Tablets: Frusemide.
Oedema; hypertension.

Furosemide Injection (U.S.P. XXII).
Frusemide.
Prepared with the aid of sodium hydroxide.

Furosemide Tablets (U.S.P. XXII).
Frusemide.

Furospir (Mepha, Switz.).
Spironolactone, frusemide.
Oedema.

Furotricina (Biomedica, Ital.).
Tyrothricin; nitrofurazone.
Gynaecological infections.

Furoxone (Norwich Eaton, Austral.).
Furazolidone.
Infective diarrhoea.

Furoxone (Formenti, Ital.).
Furazolidone.
Intestinal infections.

Furoxone (SmithKline Beecham, S.Afr.).
Furazolidone.
Gastro-intestinal infections.

Furoxone (Procter & Gamble, USA).
Furazolidone.

Furinkulosin (Diabetyl, Ger.).
Faex medicinalis.
Skin disorders.

Fusaloyos (Servier, Spain).
Fusafungine.
Upper-respiratory-tract inflammation.

Fusid (Winthrop, Ger.).
Frusemide.
Oedema; hypertension.

Fusid (ICN, Neth.).
Frusemide.
Oedema; hypertension.

Fusidic Acid Oral Suspension (B.P. 1988).
Fusidic Acid Mixture.

Futraful (Taiho, Jpn).
Tegafur.
Malignant neoplasms.

Futura (Farmacologico Milanese, Ital.).
Aspartame.
Sugar substitute.

Fybogel (Reckitt & Colman, Austral.).
Ispaghula husk.
Dietary fibre supplement.

Fybogel (Reckitt, Eire).
Ispaghula husk.
Diverticular disease; spastic and irritable colon; constipation.

Fybogel (Reckitt & Colman, S.Afr.).
Ispaghula husk.
Bowel disorders.

Fybogel (Reckitt & Colman Pharmaceuticals, UK).
Ispaghula husk.
Constipation.

Fybranta (Norgine, UK).
Bran.
Constipation.

Fynnon Calcium Aspirin (SmithKline Beecham, UK).
Aspirin; calcium carbonate.
Pain; fever.

Fysioquens (Nourypharma, Neth.).
7 Tablets, ethinyloestradiol; 15 tablets, ethinyloestradiol; lynoestronol.
Biphasic oral contraceptive; dysmenorrhoea.

G-1 (Hauck, USA).
Paracetamol, butalbital; caffeine.

G Tril (Vinas, Spain).
Febaramate.
Agitation; tremor; insomnia; alcohol withdrawal.

Gabacet (Carion, Fr.).
Piracetam.
Cerebral vascular disorders.

Gabakalm (Camassium Co., UK).
Gamma aminobutyric acid; vitamins; minerals.

Gabbroral (Carlo Erba, Ital.).
Paromomycin sulphate.
Bacterial infections.

Gabomade† (Knoll, Spain).
Aminohydroxybutyric acid.
Emotional disorders; behaviour disorders; convulsions.

Gaboril Complex (Sigma-Tau, Spain).
Phenytoin; phenobarbitone; aminohydroxybutyric acid.
Epilepsy.

Gaboril Sedativo† (Sigma-Tau, Spain).
Crataegus; aminohydroxybutyric acid; passion flower; matricaria; valerian.
Anxiety; sleep disorders.

Gabrene (Synthelabo, Fr.).
Progabide.
Epilepsy.

Gabroral (Farmitalia, Spain).
Paromomycin sulphate.
Gastro-intestinal bacterial infections; gastro-intestinal amoebiasis; tapeworm infections.

Gadional (Cinfa, Spain).
Phosphoric acid; cod-liver oil; minerals; calcium pantothenate; gentian; fenugreek.
Tonic.

Gafir (Biotejama, Ital.).
Niperotidine hydrochloride.
Gastro-intestinal disorders.

Gaiarsol (Chameaud, Fr.).
Methylarsinic acid; guaiaacoli; aconite root; codeine; tolu balsam.
Coughs.

Galactogil (Elgi, Fr.).
Galega; tricalcium diphosphate; malt extract.
Insufficient milk production in lactating mothers.

Galactomin (Cow & Gate, UK).
Food for special diets.
Lactose, glucose, or galactose intolerance.

Galactomin-17 (Medifood-Trufood, Ital.).
Food for special diets.
Lactose intolerance.

Galactosquin (Mundipharma, Ger.).
Quinidine polygalacturonate.
Arrhythmias.

Galake (Galen, UK).
Dihydrocodeine tartrate; paracetamol.

Galantase (Tokyo Tanabe, Jpn).
Tilactase.
Lactose intolerance.

Galantase (Norlstan, S.Afr.).
Tilactase.
Lactose intolerance.

Galcodine (Galen, UK).
Codeine phosphate.
Dry coughs.

Galenamet (Galen, UK).
Cimetidine.

Galenamox (Galen, UK).
Amoxycillin trihydrate.
Bacterial infections.

Galenavoven-N† (Vogel & Weber, Ger.).
Tablets: Cort. syzygii jamb.; fel tauri; fol. boldo; fruct. ammi visn.; fruct. cardui mariae; herb. cynarae; herb. hyperici; rhiz. curcuma.
Gastro-intestinal disorders.

Galenavoven-N (Weber & Weber, Ger.).
Oral drops: Ammi visnaga; boldo; curcuma

Galénic (Galenic, Fr.).
Ruscus aculeatus; dextran sulphate; meflilot.
Peripheral vascular disorders.

Galenphol (Galen, UK).
Pholcodine.
Coughs.
Formerly known as Galphol.

Galfer (Galen, UK).
Ferrous fumarate.
Iron-deficiency anaemia.

Galfer F.A. (Galen, UK).
Ferrous fumarate; folic acid.
Iron and folic acid deficiency in pregnancy.

Galfer-Vit (Galen, UK).
Ferrous fumarate; vitamin B and C substances.
Iron deficiency.

Galfloxin (Galen, UK).
Flucloxacillin.

Galirène (Merck-Clevent, Fr.).
Calcium bromide; calcium lactate pentahydrate.
Insomnia; nervous disorders.

Gallium Complex (Blackmores, Austral.).
Gallium aparine; echinacea angustifolia; calendula officinalis; baptisia tinctoria; ascorbic acid; calcium pantothenate; pyridoxine hydrochloride; zinc amino acid chelate.
Tonic.

Gallamine Injection (B.P. 1988).
Gallamine triethiodide.

Gallamine Triethiodide Injection (U.S.P. XXII).

Gallucan (Röwo-29) (Pharmakon, Ger.).
Cholesterinum; terebinthina chios; berberis; anagallis arvensis; carduus marianus; china; aesculus; leptandra; podophyllum; chelidonium; nux vomica; belladonna.
Homeopathic preparation.

Galleb (Hoyer, Ger.).
Tinct. herb. chelidonii; tinct. rhiz. curcuma xanthi; tinct. rad. rubiae tinct.; tinct. sem. cardui mariae; tinct. fol. menthae pip.; tinct. rad. taraxaci c. herb.; tinct. rad. echinaceae purpur.; tinct. cort. frangulae.
Biliary disorders; post-hepatitis syndrome.

Galleb forte† (Hoyer, Ger.).
Herb. chelidonii; rad. rubiae tinct.; rhiz. curcuma xanthi; herb. virgaureae; fruct. ammeos visnaga; rad. taraxaci c. herb.; rad. echinaceae purpur.; fol. menthae pip.; fruct. cardui mariae; cort. frangulae; aescin.
Biliary disorders.

Gallamol N (Redel, Ger.).
Herb. chelidoni; herb. absinthi; fol. boldo; rad. taraxaci c. herb.; rhiz. rhei; flor. chamomillae; fel tauri.
Biliary disorders; gall stones; liver disorders.

Gallen-Leber-Tee Stada (Stada, Ger.).
Flor. calendulae; flor. calcatrippae; rad. gentiana; fruct. foeniculi; fruct. carvi; flor. chamomillae; rad. ononidis; cort. frangulae; herb. chelidonii; fol. menthae pip.; rad. taraxac. c. herb.; ol. carvi.
Herbal tea.

Gallensteinkapseln (Evers, Ger.).
Herb. hederac terrest.
Gall stones.

Gallaxier (Salushaus, Ger.).
Tablets: Rhiz. curcuma xanthi; fol. cynarae scolym.; fruct. cardui mariae; rad. taraxaci c. herb.; flor. chamomillae; fol. menthae pip.
Biliary disorders.

Gallaxier (Salushaus, Ger.).
Tea: Fol. cynarae scolym.; herb. taraxaci; rhiz. curcuma xanthi; fruct. cardui mariae; herb. cardui benedicti; fol. trifolii fibrini; herb. millefolii; rad. gentiana; herb. absinthii; rhiz. calami; flor. chamomillae; fruct. foeniculi; fructose.
Herbal tea.

Galliagene T.C.M. (Gallia, Fr.).
† For use with food for special diets

Gallialite (Gallia, Fr.).
Glucose; potassium citrate; sodium bicarbonate; sodium chloride; potassium chloride; magnesium sulphate; calcium chloride.
Diarrhoea; oral rehydration.

Gallieva (Gallia, Fr.).
Infant feed; food for special diets.
Milk-protein intolerance.

Gallitophen (Reinecke, Ger.).
Herb. burs. past.; cort. frangul.; follic. senae angust.; fol. betul.; herb. chelidon.; herb. euqiset.; herb. card. bened.; fruct. card. mar.; flor. chamomill.; herb. nasturt.; rad. et herb. taraxac.; herb. eschscholtziae calif.; fel tauri; berberis; card. mar.; ol. menth. pip.
Biliary disorders; liver disorders.

Gallium Citrate Ga 67 Injection (U.S.P. XXII).

Gallium-67 in the form of gallium citrate.

Gallium⁶⁷(Ga) Citrate Injection (B.P. 1988).

Gallium-67 in the form of gallium citrate.
gallo sanol N (Sanol, Ger.).
Fel tauri; cort. frangulae; aloes.

Biliary disorders; post-hepatitis convalescence.

Gallolingual (Pohl, Ger.).
Ethaverine hydrochloride; glyceryl trinitrate.
Smooth muscle spasms.

Gallo-Merz N (Merz, Ger.).
Dimethicone; rhiz. curcuma.
Gastro-intestinal disorders.

Gallo-Merz Spasmolyticum† (Merz, Ger.).
Ethaverine hydrochloride; dehydrocholic acid; pancreatin; cellulase; dimethicone; rhiz. curcuma.

Biliary disorders; gastro-intestinal spasm.

Gallapas (Pascoe, Ger.).
Chelidonium majus.
Gastro-intestinal and biliary-tract disorders.

Galloselect (Dreluso, Ger.).
Chamomilla; carduus marianus; lycopodium; menth. pip.; chelidonium; belladonna; natrium sulficum; taraxacum.
Homeopathic preparation.

Galloselect N (Dreluso, Ger.).
Herb. chelidonii; herba et rad. taraxaci; fruct. cardui mariae; rhei; fol. cynarae; flor. chamomillae; ol. menthae pip.; ol. carvi.
Biliary disorders; adjunct in chronic liver inflammation.

Galloway's Cough Syrup (LRC Products, UK).
Ipecacuanha liquid extract; squill vinegar; acetic acid; chloroform; ether.
Coughs.

Galpseud (Galen, UK).
Pseudoephedrine hydrochloride.
Nasal congestion.

Galpseud Plus (Galen, UK).
Pseudoephedrine hydrochloride; chlorpheniramine maleate.
Allergic rhinitis.

Galusan (Almirall, Spain).
Pipemidic acid.
Urinary-tract infections.

Gamadiabet† (Salvat, Spain).
Acetohexamide.
Diabetes mellitus.

Gamate B6 (Novag, Spain).
Aminobutyric acid; aminohydroxybutyric acid; magnesium glutamate hydrobromide pyridoxine.
Mental function impairment; senility.

Gamanil (E. Merck, UK).
Lofepamine hydrochloride.
Depression.

Gamastan (Cutter, Canada).
A normal immunoglobulin.
Passive immunisation.

Gambex (Continental Ethicals, S.Afr.).

Lindane.
Pediculosis.

Gambrollys (Gambro, Swed.).

Sodium chloride; potassium chloride; anhydrous magnesium chloride; anhydrous calcium chloride.
Haemodialysis solution.

Gambrosol (Gambro, Swed.).

Anhydrous glucose; sodium chloride; magnesium chloride hexahydrate; calcium chloride dihydrate.
Peritoneal dialysis solution.

Gameval (Alter, Spain).

Coccarboxylase; coenzyme A; flavine adenine dinucleotide; nadide; nadide phosphate; thioctic acid; guanosine diphosphate.
Tonic.

Gamibetal (SIT, Ital.).

Aminohydroxybutyric acid.
Epilepsy.

Gamibetal Complex (SIT, Ital.).

Aminohydroxybutyric acid; phenobarbitone; phenytoin sodium.
Epilepsy.

Gamibetal Plus (SIT, Ital.).

Aminohydroxybutyric acid; diazepam.
Epilepsy.

Gamimune N (Cutter, Canad.).

A normal immunoglobulin.
Passive immunisation; idiopathic thrombocytopenic purpura.

Gamimune N (Cutter, UK).

A normal immunoglobulin.
Agammaglobulinaemia; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura.

Gamimune N (Cutter, USA).

A normal immunoglobulin.
Primary humoral immunodeficiency; idiopathic thrombocytopenic purpura.

Gamma 16 (Merieux, Fr.).

A normal immunoglobulin.
Passive immunisation.

Gamma 16 (Rhône-Poulenc, Neth.; Merieux, Neth.).

A normal immunoglobulin.
Passive immunisation.

Gamma Citormina† (Ern, Spain).

Bioestimulins; a normal immunoglobulin; lignocaine hydrochloride.
Passive immunisation; hypogammaglobulinaemia.

Gamma Coq (Association Nationale, Fr.).

A pertussis immunoglobulin.
Passive immunisation.

Gamma EPA (Quest, UK).

Concentrated fish oil; vitamin E.

Gamma Glob Antiper Hubb (Hubber, Spain).

A pertussis immunoglobulin.

Passive immunisation.

Gamma Glob Antirub Hubb (Hubber, Spain).

A rubella immunoglobulin.

Passive immunisation.

Gamma Glob Antisamp Hubb† (Hubber, Spain).

A measles immunoglobulin.

Passive immunisation.

Gamma Marine (Quest, UK).

Evening primrose oil; borage oil; fish oil.

Gamma Oil (Quest, UK).

Evening primrose oil.

Gamma Oil Premium (Quest, Canad.).

Evening primrose oil.

Nutritional supplement.

Gamma Tétanos (Association Nationale, Fr.).

A tetanus immunoglobulin.

Passive immunisation.

Gammabion (Saboter, Spain).

A normal immunoglobulin.

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Gammabulin (Immuno, Ger.).

A normal immunoglobulin.
Passive immunisation.

Gammabulin (Immuno, Ital.).

A normal immunoglobulin.
Hypogammaglobulinaemia; passive immunisation.

Gammabulin (Immuno, Swed.).

A normal immunoglobulin.
Passive immunisation; hypogammaglobulinaemia.

Gammabulin (Immuno, UK).

A normal immunoglobulin.
Agammaglobulinaemia; hypogammaglobulinaemia; passive immunisation.

Gammabulin A (Immuno, Ger.).

A hepatitis A immunoglobulin.
Passive immunisation.

Gammabuline (Immuno, Switz.).

A normal immunoglobulin.
Hypogammaglobulinaemia; passive immunisation.

Gammadin (OFF, Ital.).

Povidone-iodine.
Skin and mucous membrane disinfection.

Gammagard (Baxter, Ger.).

A normal immunoglobulin.
Passive immunisation; hypogammaglobulinaemia.

Gammagard (Baxter, Swed.).

A normal immunoglobulin.
Hypogammaglobulinaemia.

Gammagard (Hyland, USA).

A normal immunoglobulin.
Immunodeficiencies; idiopathic thrombocytopenic purpura.

Gamma-Globuline (SRK, Switz.).

A normal immunoglobulin.
Passive immunisation.

Gammalonga Varicela-Zona (Alonga, Spain).

A varicella-zoster immunoglobulin.

Passive immunisation.

Gamma-M† (Behringwerke, Ger.).

Immunoglobulins (IgM and IgG).

Hypogammaglobulinaemia.

Gamma-Men (ISM, Ital.).

An anti-D immunoglobulin.

Prevention of rhesus sensitisation.

Gammamida Complex (Laproquifer, Spain).

Cyanocobalamin; glutamic acid; pyridoxine; thiamine.

Vitamin B deficiency; nausea and vomiting in pregnancy; muscular dystrophies; alcoholism.

Gamma-OH (Cernep, Fr.).

Sodium oxybate.

General anaesthesia.

GammaOil Premium (Quest, UK).

Evening primrose oil; vitamin E.

Gammaphénicol (Faure, Fr.).

Immunoglobulin; chloramphenicol.

Eye infections.

Gammaprotect (Biotest, Ger.).

A hepatitis B immunoglobulin.

Passive immunisation.

Gammaprotect Varizellen (Biotest, Ger.).

A varicella-zoster immunoglobulin.

Passive immunisation.

Gammar (Armour, USA).

A normal immunoglobulin.

Gamma-Tet (Behring, Ital.).

A tetanus immunoglobulin.

Passive immunisation.

Gamma-Veinine (Hoechst, S.Afr.).

A normal immunoglobulin.

Passive immunisation.

Gamma-Venin (Behringwerke, Ger.).

A normal immunoglobulin.

Passive immunisation.

Gamma-Venin (Behring, Ital.).

Gamma-Venin (Behring, Spain).

A normal immunoglobulin.
Passive immunisation; hypogammaglobulinaemia.

Gammistin (IBP, Ital.).

Brompheniramine maleate.

Hypersensitivity reactions.

Gammonativ (Kabi, Swed.).

A normal immunoglobulin.

Hypogammaglobulinaemia; idiopathic thrombocytopenic purpura.

Gamonil (E. Merck, Ger.).

Lofepamine hydrochloride.

Depression.

Gamonil (E. Merck, Switz.).

Lofepamine hydrochloride.

Depression.

Gamophen (Surgikos, UK).

Triclosan.

Skin cleanser.

Gamulin Rh (Armour, USA).

An anti-D immunoglobulin.

Ganda (Smith & Nephew, Ire).

Guanethidine monosulphate; adrenaline.

Glaucoma.

Ganda (International Vision Care, S.Afr.).

Guanethidine; adrenaline.

Open-angle glaucoma.

Ganda (Smith & Nephew Pharmaceuticals, UK).

Guanethidine monosulphate; adrenaline.

Primary open angle or secondary glaucoma.

Ganite (Fujisawa, USA).

Gallium nitrate.

Cancer-related hypercalcaemia.

Ganor (Thomae, Ger.).

Famotidine.

Gastro-intestinal disorders.

Gantanol (Roche, Canad.).

Sulphamethoxazole.

Bacterial infections.

Gantanol (Roche, USA).

Sulphamethoxazole.

Bacterial infections; adjunct in falciparum malaria.

Gantaprim (Lenza, Ital.).

Co-trimoxazole.

Bacterial infections.

Gantrim (Geymonat, Ital.).

Co-trimoxazole.

Bacterial infections.

Gantrimex (Geymonat, Ital.).

Syrup: Oxolamine citrate.

Respiratory-tract disorders.

Gantrimex (Geymonat, Ital.).

Tablets: Oxolamine phosphate.

Respiratory disorders.

Gantrisin (Roche, Austral.).

Sulphafurazole.

Ophthalmic infections.

Gantrisin (Roche, USA).

Eye drops: Sulphafurazole diethanolamine.

Bacterial eye infections.

Gantrisin† (Roche, USA).

Eye ointment: Sulphafurazole diethanolamine.

Bacterial eye infections.

Gantrisin (Roche, USA).

Oral suspension; syrup: Acetyl sulphafurazole.

Bacterial infections; adjunct in falciparum malaria.

Gantrisin (Roche, USA).

Tablets: Sulphafurazole.

Bacterial infections; adjunct in falciparum malaria.

Gaosueryl (Pharminter, Fr.).

Saccharin sodium.

Sugar substitute.

Garamycin (Essex, Austral.).

Garamycin (Schering, Canad.).

Gentamicin sulphate.

Bacterial infections.

Garamycin (Essex, Neth.).

Gentamicin sulphate.

Bacterial infections.

Garamycin (Schering, S.Afr.).

Cream: Gentamicin.

Skin and wound infections.

Garamycin (Schering, S.Afr.).

Eye drops; injection: Gentamicin sulphate.

Bacterial infections.

Garamycin (Schering-Plough, Swed.).

Gentamicin sulphate.

Bacterial infections.

Garamycin (Essex, Switz.).

Gentamicin sulphate.

Bacterial infections.

Garamycin (Schering-Plough, UK).

Gentamicin sulphate.

Bacterial infections of the ear and eye.

Garamycin (Schering, USA).

Gentamicin sulphate.

Bacterial infections.

Garasone (Schering, Canad.).

Gentamicin sulphate; betamethasone sodium phosphate.

Inflamed eye infections; otorrhea.

Garasone (Schering, S.Afr.).

Gentamicin sulphate; betamethasone phosphate.

Inflammatory eye infections.

Garaspirine (IPRAD, Fr.).

Infant suppositories: Aspirin; phenobarbitone.

Fever.

Garaspirine (IPRAD, Fr.).

Paediatric suppositories; adult suppositories; tablets: Aspirin; phenobarbitone; piperazine hydrochloride.

Fever; pain.

Gardan P† (Hoechst, Ger.).

Paracetamol.

Pain; fever.

Gardénal (Specia, Fr.).

Injection: Phenobarbitone sodium.

Epilepsy; anxiety.

Gardénal (Specia, Fr.).

Tablets: Phenobarbitone.

Epilepsy; anxiety.

Gardenal (May & Baker, S.Afr.).

Phenobarbitone.

Sedative; epilepsy; hypnotic.

Gardenal (Rhône, Spain).

Phenobarbitone.

Epilepsy; anxiety; febrile convulsions.

Gardenal Sodium (May & Baker, UK).

Phenobarbitone sodium.

Epilepsy.

Gardenale (Farmitalia Carlo Erba, Ital.).

Phenobarbitone sodium.

Insomnia; epilepsy.

Gardrine (Syntex, Fr.).

Enprostil.

Peptic ulcer.

Garfield (Ayerst, Canad.).

Multivitamin preparation.

Gargaril (Puerto Galiano, Spain).

Formaldehyde; menthol.

Mouth and throat inflammation.

Gargaril Sulfamida (Puerto Galiano, Spain).

Formaldehyde; sulphamylamide; menthol.

Mouth and throat inflammation.

Gargilon (Vemedica, Neth.).

Dequalinium chloride.

Throat pain.

Garia† (Alfarma, Spain).

Fluocinonide.

Skin disorders.

Garlic Breathless Capsules (Vitaplex, Austral.).

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TETRAHEDRON
LETTERS

Layered Structures Formed by Dinitrobenzoic Acids

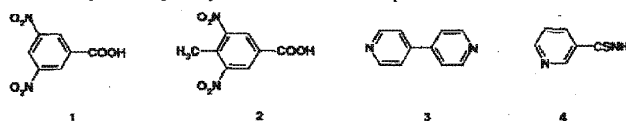
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Chemistry & Physics of Materials Unit,
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Jakkur P.O., Bangalore 560 064, India.

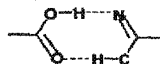
Received 27 August 1998; accepted 19 October 1998

Abstract: 3,5-dinitrobenzoic acid, **1** and 3,5-dinitro-4-methylbenzoic acid, **2**, form co-crystals with 4,4'-bipyridyl but only the latter forms a layered structure, which can incorporate anthracene molecules. Furthermore, **2** forms a pillared type structure with thioisocyanamide. © 1998 Elsevier Science Ltd. All rights reserved.

A variety of nanoporous inorganic structures are known.¹ Recently, there has been some effort to explore whether organic porous structures can be designed and synthesized by making use of supramolecular organization.² Thus, Yaghi et al.³ have reported a microporous metal-organic framework based on a trimetric acid-pyridine-cobalt complex. Recently, novel layered and channel structures formed by trihiocyanuric acid (TTCA) were reported from this laboratory.⁴ Crystallization of TTCA from acetone gave a layered structure, comparable to clays, pillared by acetone molecules while co-crystallization of TTCA from benzene solution gave a novel channel structure which could accommodate benzene. Encouraged by these findings, we wanted to examine other possible organic porous structures obtained by noncovalent synthesis.⁵ In this context, it appeared to us that 3,5-dinitrobenzoic acid, **1** and 3,5-dinitro-4-methylbenzoic acid, **2** were well suited to form such structures. This is because, **1** is known to form a structure with cavities when crystallized from benzene solution, the cavities accommodating molecules such as anthracene.⁶ In the absence of benzene, **1** does not form a layered structure. Crystallization of **2**, from most solvents, yields structures with cavities in a two-dimensional arrangement, which can accommodate anthracene.^{6a} We have investigated whether the cavities formed by **1** and **2** could be modified by incorporating an azaromatic donor molecule such as 4,4'-bipyridyl, **3**. In addition, we have examined the possibility of formation of layered structures by **1** and **2** by co-crystallization with other compounds.



Crystallization of **1** and **2** in the presence of **3** gave complexes **1a** and **2a** respectively with 2:1 stoichiometry.⁷ In both **1a** and **2a**, bipyridyl molecules break up the hydrogen bonds between the carboxyl groups as shown in Figure 1. Interestingly, interaction between the carboxylic acid and the bipyridyl molecule in these complexes occurs through the formation of a single O-H...N hydrogen bond⁸ (see Figure 1) unlike the pair-wise hydrogen bond coupling, consisting of O-H...N and C-H...O bonds as shown below, observed in other related systems.⁹ The H...N distances in **1a** and **2a** are 1.61 and 1.58-1.65 Å respectively. Furthermore, molecules of **2a** are arranged in two dimensions to yield planar sheets (Figure 2) which in turn are stacked in the three-dimensional packing while molecules of **1a** adopts a herringbone packing pattern.



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Although both 1a and 2a do not possess cavities, the two-dimensional arrangement in 2a, (Figure 1), which is similar to that of the structure of pure acid, 2⁴⁶ encouraged us to investigate the co-crystallization of 1a and 2a in the presence of anthracene. 1a did not yield any co-crystals with anthracene, but 2a gave crystals of a quality suitable for single crystal X-ray diffraction studies.

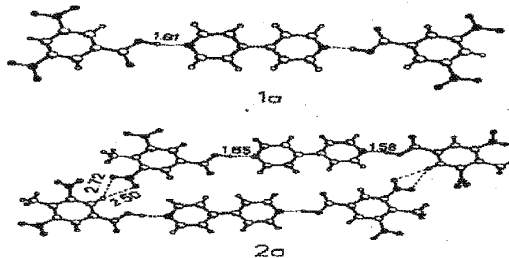


Figure 1: 1a) Recognition pattern between acid, 1 and 4,4'-bipyridyl in the molecular complex, 1a. The dashed lines represent hydrogen bonds and unique H...O distance is quoted. 2a) Two-dimensional arrangement of supermolecules of acid, 2 and 4,4'-bipyridyl in 2a. Notice the formation of a six membered ring formed through hydrogen bonds.

The complex of 2a with anthracene (designated as 2b⁷) is stabilized by the formation of O-H...N and C-H...O hydrogen bonds coupling⁹ (Figure 2), not found either in 2a or 1a. The H...N and H...O distances between 2 and 3 in the anthracene adduct, 2b, are 1.68 and 2.57 Å respectively. Figure 2 shows that the supermolecules are arranged in two dimensions in a hexagonal mode through the formation of C-H...O hydrogen bonds between anthracene and the neighbouring molecules of carboxylic acid, 2 such that a cavity of dimension 10 x 12 Å results. The anthracene molecules are accommodated in these cavities through the formation of C-H...O hydrogen bonds. The H...O distances are in the range of 2.76 – 2.93 Å. A comparison of the structure of 2b (Figure 2) with the anthracene adduct formed by the parent carboxylic acid, 2⁴⁶ alone indicates that the recognition pattern between anthracene and the acid 2 is not perturbed with the presence of bipyridyl molecule in 2b.

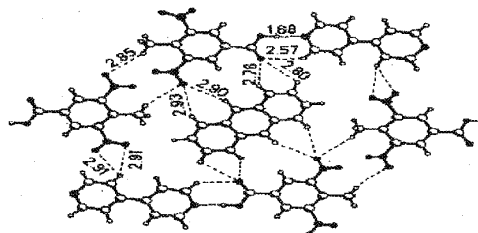


Figure 2: Two-dimensional arrangement of a cavity, formed by acid 2 and 4,4'-bipyridyl, which is filled by molecules of anthracene in the complex 2b.

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We have investigated the formation of pillared structures of **2** which forms layer structures even in the absence of guest molecules such as benzene. Crystallization of **2** from acetone gave a layered structure with no pillaring. We, therefore, crystallized **2** with compounds containing different types of hydrogen-bond donating and accepting sites. Crystallization of **2** with pyridine carboxylic acid or nicotinamide did not yield a molecular complex. We then examined the co-crystals of **2** with thionicotinamide, **4**, since the presence of sulfur could change the recognition pattern. It is known that sulfur-mediated hydrogen bonds such as N-H...S are indeed different from O-H...O, N-H...O and such hydrogen bonds.^{4,10} Thus, **2** and **4** yield a complex **2c** upon co-crystallization from methanol.

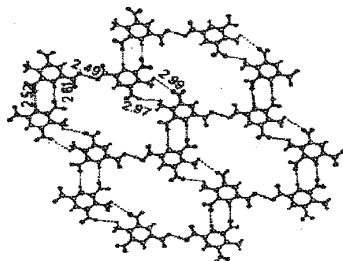


Figure 3: Two-dimensional arrangement of a layer of acid, **2** in the complex with thionicotinamide. The H...O bonds are shown in dashed lines and unique H...O distances are quoted for C-H...O hydrogen bond and O...O distance is quoted for O-H...O hydrogen bond.

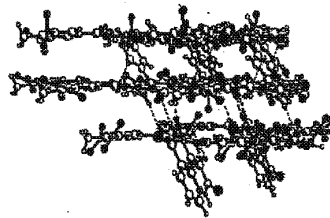
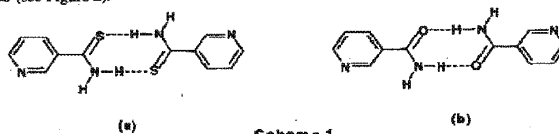


Figure 4: Stacking of layers in a three-dimensional arrangement in the complex, **2c**. Notice the pillaring of thionicotinamide molecules between the layers.

Crystal structure determination of the 2:1 adduct, **2c'**, formed by **2** with thionicotinamide reveals that the asymmetric unit contains two symmetry independent molecules. Packing analysis shows that the co-crystals of **2** and **4** adopt a pillared type structure.¹¹ Each of the symmetry dependent molecules of **2** interacts with neighbouring molecules to form two-dimensional planar sheets (Figure 3) which in turn stack alternately in a three-dimensional arrangement through π - π interaction. It is clear from Figure 3 that in each sheet, molecules are held together through formation of O-H...O and C-H...O hydrogen bonds. The H...O distances are in the 2.55 - 3.00 Å range. The -COOH groups of adjacent molecules form only a single O-H...O hydrogen bond rather than the well known cyclic hydrogen bonded system, as one of the acids is deprotonated. The mutual association of the molecules in each sheet, however, results in the formation of cavities of 7×12 Å. The molecules of **4** are intercalated in between the sheets, to yield a pillared type structure, as shown in Figure 4. It is evident from Figure 4 that the molecules of **4** are inclined to the layers of acid, **2** unlike anthracene molecules which are coplanar with the sheets observed in the crystal structure of complex, **2b** (see Figure 2).



Scheme 1

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It is rather surprising that thionicotinamide and nicotinamide show such different behaviour with respect to interaction with **2**. It appears that hydrogen bonding pattern shown in Scheme 1 plays a significant role. It is known that molecules with amide or thioamide groups exist as dimers rather than monomers. However, it is evident from Figure 4 that in the complex **2c**, the molecules of **4** intercalated in between the acid sheets are single. It is easier to obtain such single molecular units from **4** rather than nicotinamide as the dimers in the former are formed through weak N-H...S hydrogen bonds (Scheme 1a) whereas the dimers in nicotinamide result from the strong N-H...O hydrogen bonds (Scheme 1b).

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Crystal Engineering Using Anilic Acids and Dipyriddy Compounds through a New Supramolecular Synthon

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The anilic acids, 2,5-dihydroxy-1,4-benzoquinone (1a), 2,5-dibromo-3,6-dihydroxy-1,4-benzoquinone (bromanilic acid; 1b), 2,5-dichloro-3,6-dihydroxy-1,4-benzoquinone (chloranilic acid; 1c), and 2,5-dicyano-3,6-dihydroxy-1,4-benzoquinone (cyananilic acid; 1d), were cocrystallized with rigid organic ligands containing two pyridine rings, 2,4-bipyridine (2a), 4,4'-bipyridine (2b), 1,2-bis(2-pyridyl)ethylene (3a), 1,2-bis(4-pyridyl)ethylene (3b), 2,2'-dipyridylacetylene (4a), 3,3'-dipyridylacetylene (4b), and 4,4'-dipyridylacetylene (4c). Fourteen complexes 5-18 were obtained as single crystals, and their crystal structures were successfully determined by X-ray analysis. All complexes except those with 2a are 1:1 and are composed of an infinite linear or zigzag tape structure, the formation of which is ascribed to intermolecular O-H...N, N⁺-H...O, or N⁺-H...O⁻ hydrogen bonds or a combination of these between the anilic acids and the dipyriddy compounds. In the complexes 5 and 6, no infinite tape structure is observed although the molecular units connected by a similar hydrogen-bonding pattern are formed. For the 1:1 complexes, we have found two types of stacking arrangements, segregated stacks (7, 9, 12-15, 18) and alternated ones (8, 10, 11, 16, 17). In the complexes of 1c with the series of dipyriddyacetylenes 4 (14, 15, 17), the neutral, dication, and monocation states are formed depending on the nitrogen positions, which can be attributed to the different basicity of the pyridyl groups.

Introduction

Organic solid materials based on hydrogen-bonded donor and acceptor molecules have been the objects of recent intensive studies¹ aimed at building a new class of compounds which are interesting from viewpoints of basic science as well as of applications such as biological sensors and catalysis.²⁻⁶ Hydrogen bonding is expected to regulate electronic properties of solids and work as switching units for molecular devices. Rational design

based on crystal engineering⁷⁻⁹ including supramolecular chemistry⁶ is particularly important for the progress of this field. This is considered to be accomplished by fundamental studies on weak intermolecular interactions which govern orientation, recognition, and assembly of components in the solid state. Specific noncovalent interactions between different functionalities seem to control single and multicomponent crystallization.

Our work has focused on the development of new organic donor-acceptor (DA) interactions as supramo-

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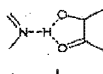
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lecular synthons for the preparation of ordered solid phases.⁶ Our strategy is to investigate geometrically and stoichiometrically matched donor and acceptor molecules which can be used to propagate oriented patterns in the crystal engineering. We are concerned with the use of organic component molecules which can form a variety of structures and mediate electron-proton transfer. Employing organic molecules to form crystalline architectures seems an attractive idea for a crystal engineering approach. Simple association of two complementary compounds through noncovalent interactions can be used to create organic materials with new remarkable physical properties and potential applications in optical and electronic devices, which are not possessed by either of the components alone.^{2c-e,13}

Our attempt is to develop a new tool for crystal engineering that is associated with a great variety of hydrogen-bonded DA-type compounds in which donor and acceptor molecules can be combined within robust hydrogen-bonded architectures. Development of new supramolecular synthons with specific bonding features is important to design materials with interesting features. We have chosen benzoquinone-type molecules with dihydroxy groups, anilic acids, which have excellent proton-donating properties and can undergo multistage deprotonation and protonation processes. These acids can be associated with a variety of proton acceptors as counterpart to give predictable supramolecular architectures. In the course of this work, we have prepared cyananilic acid (1d)⁷ as a poor electron acceptor molecule and studied it as a hydrogen-bonded counterion in conducting charge-transfer complexes with a variety of organic sulfur-containing donors.^{8,9} The monocation and dianion of 1d were assembled into supramolecular structures through the one- and two-dimensional hydrogen-bonded network.¹⁰ In our preliminary communication, we have used dipyrriyl-type bases as proton acceptors and constructed a new supramolecular synthon (1) motif.¹² We have also



prepared three rigid organic ligands containing pyridine

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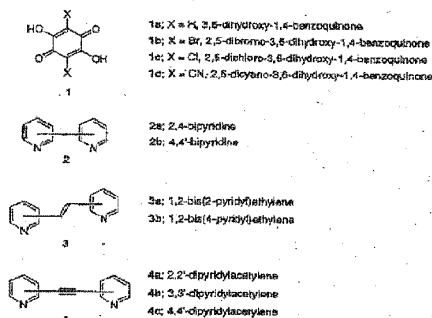
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Scheme 1



Crystalline Complexes

- | | |
|-------------------------------|-------------------------------|
| 5: complex between 1b and 2a | 12: complex between 1a and 4c |
| 6: complex between 1c and 2a | 13: complex between 1b and 4a |
| 7: complex between 1a and 2b | 14: complex between 1c and 4a |
| 8: complex between 1c and 2b | 15: complex between 1c and 4b |
| 9: complex between 1c and 3a | 16: complex between 1b and 4c |
| 10: complex between 1b and 3b | 17: complex between 1c and 4b |
| 11: complex between 1c and 3b | 18: complex between 1d and 4a |

rings separated by an acetylene spacer (4a-c) that formed crystalline complexes with a common organic acid (1c).¹² These complexes have infinite one-dimensional tape-like structures that lead to supramolecular polymeric systems. As a continuation of these works, we have attempted to combine a variety of proton donor and acceptor molecules to obtain novel supramolecular structures. In this paper, we will present the preparation of supramolecular complexes by complementary combination of proton donors (D) (anilic acids, 1) and proton acceptors (A) (bidentate nitrogen ligands, 2-4) via hydrogen-bonded interactions (Scheme 1).

Results

Preparation of Cocrystals. Generally, the formation of cocrystals of proton donors (D) and acceptors (A) requires the following conditions: (i) D and A molecules matched geometrically and stoichiometrically, (ii) facile acid-base reactions between D and A molecules, (iii) good solubility of the D and A molecules in solvents, and (iv) precipitation of the formed complexes from the solution. Considering the above conditions, we have successfully obtained single crystals of complexes 5-18 composed of anilic acids and dipyrriyl compounds. The following three simple procedures were used to obtain the above single crystals suitable for X-ray analysis: (i) slow diffusion using an H-shaped tube, (ii) mixing of two components in hot solutions, and (iii) slow evaporation technique. Methanol, ethanol, acetone, acetonitrile, and their mixture in various ratios were used as solvents for the preparation of these cocrystals. Details of the synthesis are explained in the Experimental Section.

Structural Analyses. The cocrystals of anilic acids with dipyrriyl compounds obtained here take various

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structures which were clarified by X-ray analysis. To rationally control the structures, we have examined the effects of the spacers and nitrogen positions in the dipyridyl compounds and substituents (H, Br, Cl, CN) of the anilic acid that influence the solubility, hydrogen-bonding ability, ionicity, geometry, and stacking arrangements of the molecules. The structures of the 14 complexes are discussed below. The geometry of the intermolecular hydrogen bonds for the complexes for which X-ray structures are first determined in this paper is summarized in Table 1.

Complexes 5 and 6. The complexes are isomorphous and crystallize in the monoclinic $P2_1/n$ space group, and the molecules 1b in 5 and 1c in 6 are located on the inversion center. The complexes have a 1:2 (D/A) stoichiometric ratio with the transfer of the two acidic protons of the donors to the nitrogen atoms of the acceptors to give a monoprotonated cation. The hydrogen atom positions in these cocrystals were identified on different Fourier maps and further confirmed by careful observation of C—O bond lengths and concerned hydrogen-bonding distances. The nitrogen atoms at the 4-position of the pyridine rings form a bifurcated interionic $N^+-H\cdots O^-$ (1.71 Å for 5 and 1.74 Å for 6) and $N^+-H\cdots O$ (2.29 Å for 5 and 6) hydrogen-bonded network (see Table 1). Thus, the robust synthon I generated at the 4-position forms molecular $A\cdots D\cdots A$ -type pairs. The views of such crystalline architecture and their synthon I are shown in Figure 1. There is no hydrogen-bonding interaction in the nitrogen atom at the 2-position of the pyridine ring, and as a consequence, no infinite (D $\cdots$ A)_n linkage was observed, in contrast to the structures of 1:1 complexes described below. Moreover, the pyridine rings are twisted at the central C—C bond with a dihedral angle of 18.4° for 5 and 15.4° for 6 between the ring planes. Therefore, the nitrogen atom at the 2-position of the pyridine ring is diverted much closer to the adjacent hydrogen-bonded $A\cdots D\cdots A$ pairs, where the distances between the planes of 1b,c and 2a within the DA pair are 3.42 Å for 5 and 3.40 Å for 6. The distances between the planes of the 2-pyridine rings (3.43 Å for 5 and 3.40 Å for 6) suggest close AA interactions in the adjacent hydrogen-bonded $A\cdots D\cdots A$ pairs. Thus, a pair of $A\cdots D\cdots A$ aggregation is close-packed in alternated stacking arrangements with other pairs from the DA- or AA-type connectivity (Figure 2).

Complex 7. The complex crystallizes in the monoclinic $C2/c$ space group, and both 1a and 2b are located on the inversion center. The geometry and the C=O, C—OH, and C—O bond distances are consistent with those of the typical neutral anilic acids.¹⁴ In this complex, no proton is transferred from the acid to the base molecule. However, intermolecular hydrogen-bonded H—O $\cdots$ N and —O $\cdots$ N distances of 2.63 and 3.08 Å are observed (Figure 3), which create the robust supramolecular synthon I. The 1a and 2b units are linked by O—H $\cdots$ N hydrogen bonds (1.55 Å) into a one-dimensional infinite molecular tape along the [1 0 2] direction. The angle between the two pyridine rings in 2b is 29.2°, and two molecules of

Table 1. Geometry of the Intermolecular Hydrogen Bonds between the Anilic Acids and the Dipyridyl Compounds in the Complexes 5–7, 10–13, 16, and 18

complex	D—H $\cdots$ A	distance ^a (Å)				angle ^b (deg)
		D—H	H $\cdots$ A	D $\cdots$ A	D—H $\cdots$ A	
5 ^c	N2—H2A $\cdots$ O2 ⁱⁱ	0.99(4)	1.71(4)	2.635(3)	155(3)	
	N2—H2A $\cdots$ O1 ⁱⁱ	0.99(4)	2.29(4)	2.951(3)	129(3)	
6 ^c	N2—H2 $\cdots$ O2 ⁱⁱ	0.96(3)	1.74(3)	2.621(2)	161(3)	
	N2—H2 $\cdots$ O2 ⁱⁱⁱ	0.96(3)	2.29(3)	2.969(3)	127(2)	
7	O1—H1 $\cdots$ N1	1.15(6)	1.55(6)	2.641(6)	157(6)	
10 ^c	N1—H1 $\cdots$ O1 ⁱⁱ	0.95(8)	1.71(8)	2.644(4)	167(8)	
	N1—H1 $\cdots$ O2 ^{iv}	0.95(8)	2.53(8)	3.077(4)	117(6)	
11	N1—H1 $\cdots$ O1	1.01(6)	1.68(6)	2.641(4)	164(5)	
	N1—H1 $\cdots$ O2	1.01(6)	2.49(6)	3.044(5)	114(4)	
12	O1—H1 $\cdots$ N1	1.07(5)	1.70(4)	2.654(5)	148(4)	
13 ^c	O2—H2A $\cdots$ N1 ⁱⁱ	1.18(10)	1.59(10)	2.642(8)	145(8)	
16 ^c	N1—H1 $\cdots$ O4 ⁱⁱ	1.04(6)	1.58(6)	2.577(4)	158(5)	
	N1—H1 $\cdots$ O3 ⁱⁱⁱ	1.04(6)	2.34(5)	2.571(5)	118(4)	
18 ^c	O2—H2A $\cdots$ N2 ⁱⁱ	1.21(9)	1.49(9)	2.617(4)	154(7)	
	N1—H1 $\cdots$ O1 ⁱⁱⁱ	0.86(2)	2.01(5)	2.738(8)	142(6)	
	N1—H1 $\cdots$ O2	0.86(2)	2.22(5)	2.927(9)	140(6)	

^a A hydrogen bond for which the H $\cdots$ A distance is below the sum of the covalent radius of A and 2.0 Å is listed. ^b A hydrogen bond for which D—H $\cdots$ A angle is above 110° is listed. ^c Symmetry code: i: $x + \frac{1}{2}, y + \frac{1}{2}, z - \frac{1}{2}$; ii: $-x + \frac{1}{2}, y - \frac{1}{2}, z + \frac{1}{2}$; iii: $x + \frac{1}{2}, -y + \frac{1}{2}, z - \frac{1}{2}$; iv: $-x + 2, y + \frac{1}{2}, -z + \frac{1}{2}$; v: $x, y + 1, z - 1$; vi: $-x - \frac{1}{2}, -y + \frac{1}{2}, z - \frac{1}{2}$; vii: $x + \frac{1}{2}, -y + \frac{1}{2}, z - \frac{1}{2}$; viii: $-x + 1, -y + 1, -z$.

1a in the tapes tilt toward the pyridine rings with the angles of 19.6° and 48.6°. Each molecule in the tapes forms a segregated stacking along the [0 1 1] direction (Figure 4).

Complex 8. The complex crystallizes in the monoclinic $P2_1/n$ space group, and both 1c and 2b are located on the inversion center. In this complex, both of the hydroxyl protons are transferred from 1c to the nitrogen atoms of the pyridine rings of 2b, and attractive one-dimensional infinite molecular tape structures are formed through the robust supramolecular synthon I. Details of the crystalline architecture are described in our preliminary communication.¹¹ The C—O bond distances are shorter than those found in other dianion structures. The ring C—C bond distances are also consistent with those of the dianion with an aromatic ring.¹⁴

Complex 9. The complex crystallizes in the triclinic $P\bar{1}$ space group, and both 1c and 3a are located on the inversion center. In the complex 9, the dianion of 1c is observed and the dianion has similar C—O and C—C bond distances to those in the complex 8.^{11,14} The central C=C bond length [1.313(5) Å] of 3a is a typical value of a double bond, and the configuration around the double bond is trans. The crystal architecture, stacking arrangement, and hydrogen-bonded linkage through the supramolecular synthon I are previously described and will not be discussed again.¹¹

Complexes 10 and 11. The complexes are isomorphous and crystallize in the monoclinic $P2_1/c$ space group, and 1b,c and 3b are located on the inversion center. Both of the acids 1b¹⁵ and 1c^{14,16} are fully deprotonated to produce the dianions. These structures also involve bifurcated $N^+-H\cdots O$ hydrogen bonds (2.64 and 3.08 Å for 10, 2.64 and 3.04 Å for 11) between the nitrogen atoms of 3b and the two oxygen atoms of 1b,c, thus

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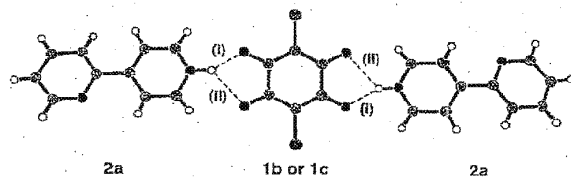


Figure 1. Hydrogen-bonded A...D...A pair of 5 and 6. Dotted lines show the intermolecular N-H...O hydrogen bonds: (i) 1.71 Å for 5 and 1.74 Å for 6; (ii) 2.29 Å for 5 and 6.

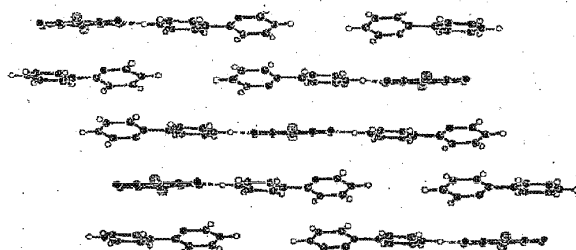


Figure 2. Alternated stacking arrangements of 6, which contain pyridine rings-bromanilate rings and pyridine rings-pyridine rings overlaps. Dotted lines show the intermolecular N-H...O hydrogen bonds.

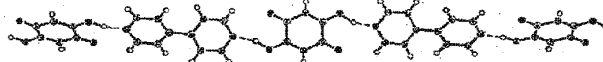


Figure 3. One-dimensional molecular tape of 7. Dotted lines show the intermolecular O-H...N hydrogen bonds (1.55 Å).

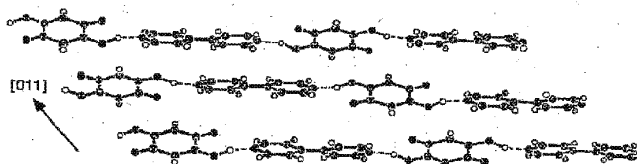


Figure 4. Segregated stacking arrangements along the [0 1 1] direction of 7. Dotted lines show the intermolecular O-H...N hydrogen bonds.

creating the robust supramolecular synthon I. In both 10 and 11, one-dimensional molecular tape structures are observed toward the two cross diagonal lines within the *ab* plane. The crossed tape structures are shown in Figure 5. Within the tape structures, the dihedral angles between the planes of 1b,c and the pyridine rings are 24.2° and 23.5° for 10 and 11, respectively. The molecular tapes in 10 and 11 run in a mild zigzag fashion because of the trans configuration of 3b. Moreover, the molecules 1b,c and 3b in 10 and 11 compose alternated stacks along the [1 1 0] and [-1 1 0] directions (Figure 6). The DA pair in the alternated stacking involves close contacts between the adjacent tapes, where the distances between the planes of 1b,c and 3b are 3.55 and 3.53 Å for 10 and 11, respectively.

Complex 12. The complex crystallizes in the monoclinic $P2_1/n$ space group, and both 1a and 4c are located on the inversion center. The bond distances and the angles of 1a in 12 are similar to those in the complex 7. Two molecules, 1a and 4c, connect with an intermolecular O-H...N hydrogen bonding (2.65 Å), and the dihedral angle between the planes of the pyridine ring of 4c and 1a is 4.5°. No proton transfer from 1a to 4c is observed. An infinite one-dimensional tape structure with an intertape distance of 3.4 Å is formed along the [2 0 1] direction. In addition, each component molecule forms a segregated stacking along the *a* axis (Figure 7).

Complexes 13 and 14. The complexes are isomorphous and crystallize in the triclinic $P1$ space group, and both 4a and 1b,c are located on the inversion center. The

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Crystal Engineering through Supramolecular Synthon

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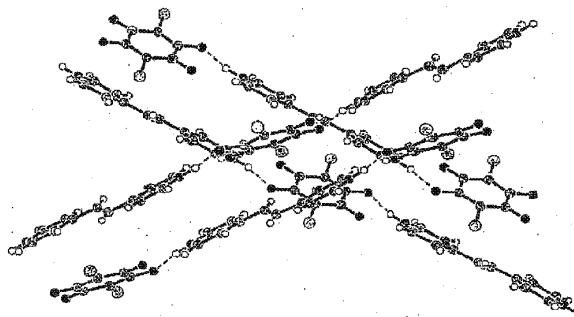


Figure 5. Two crossed one-dimensional molecular tapes of 10. Dotted lines show the intermolecular N-H...O hydrogen bonds.

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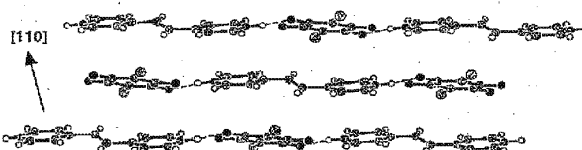


Figure 6. Alternated stacking arrangements along the [1 1 0] direction of 10. Dotted lines show the intermolecular N-H...O hydrogen bonds.

molecular structure and stacking arrangements of the complex 13 are similar to those of the complex 14, which was previously reported.¹² No proton transfer from 1b,c to 4a is observed. These complexes contain a zigzag one-dimensional tape structure with an infinite linkage of 1b,c and 4a through the supramolecular synthon I and have segregated stackings with DD- and AA-type pairs.

Complex 15. The complex crystallizes in the triclinic $P\bar{1}$ space group, and both 1c and 4b are located on the inversion center. The complex 15 contains 3.3 molecules of water. Both of the protons transfer from the hydroxyl groups of 1c to the nitrogen atoms of 4b. Thus, the two molecules, 1c and 4b, connect with interionic $N^+-H\cdots O^-$ (2.65 Å) and $N^+-H\cdots O^-$ (2.87 Å) hydrogen bonds and form the supramolecular synthon I. The molecular architecture displays a zigzag tape structure, which is viewed as a square grid-type network along the *c* axis (Figure 8). Within the network, cavities are formed, which are occupied by the water molecules. Each component molecule forms a segregated stacking along the *c* axis. Details of this interesting structure are described in our preliminary communication.¹³

Complexes 16 and 17. The complexes are isomorphous and crystallize in the monoclinic $P2_1/n$ space group, and both 1b,c and 4c are located on a general position. The molecular structure and stacking arrangements of the complex 16 are similar to those of the complex 17, which was previously reported.¹² In the crystal structure of 16, one pyridine ring of 4c is protonated and combines with 1b via bifurcated $N^+-H\cdots O^-$ (2.58 Å) and $N^+-H\cdots O^-$ (2.97 Å) hydrogen bonds, while the other pyridine ring is not protonated and forms $H-O\cdots N$ (2.62 Å) and $=O\cdots N$ (2.98 Å) hydrogen-bonding interactions (see Table

1). Thus, an infinite one-dimensional molecular tape structure is observed along the *c* axis (Figure 9). Two pyridine rings of 4c in 16 are twisted with dihedral angles of 78.0°. In this work, 16 and 17 are the only examples of complexes containing a dipyriddy compound with two perpendicular pyridine rings. The dihedral angles between the planes of 1b and the pyridine rings of 4c are 73.5° and 4.5° for the nonprotonated and protonated side, respectively. The component molecule 1b is partially overlapped with the protonated pyridine ring of 4c and forms an alternated DA-type stacking along the *b* axis with 4c.

Complex 18. The complex crystallizes in the triclinic $P\bar{1}$ space group, and both 1d and 4c are located on the inversion center. The geometry of 1d has similar C-O and C-C bond distances to those of our previously described complexes of 1d.^{9,16} The component molecules 1d and 4c connect via the bifurcated $N^+-H\cdots O^-$ and $N^+-H\cdots O^-$ hydrogen bonds ($N\cdots O$ distances, 2.74 and 2.93 Å) and form the robust supramolecular synthon I. This is the first example of the supramolecular synthon I with 1d. Thus, an infinite one-dimensional tape structure along the [1 1 0] direction is observed. The intertape distances, which are 3.22 and 3.42 Å for the distances between 1d-1d and 4c-4c planes, respectively, are very close. The dihedral angle between the plane of 1d and the pyridine ring of 4c is 59.6°. The most remarkable feature of the molecular tape in 18 is its bent structure with the angle of 121° at the hydrogen-bonding coupling part of the tape. This value is unusual compared to the

(16) Andersen, E. K.; Andersen, I. G. K. *Acta Crystallogr., Sect. B* 1975, 31, 375.

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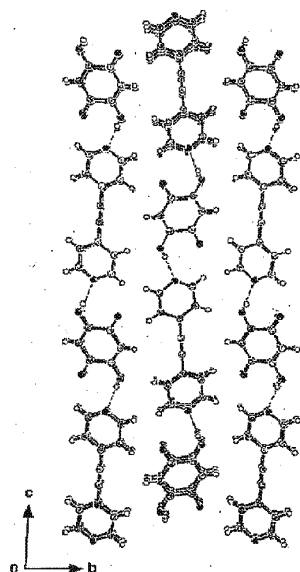


Figure 7. Packing diagram of 12 viewed along the *c* axis. One-dimensional molecular tape is formed along the [2 0 1] direction. Dotted lines show the intermolecular O-H...N hydrogen bonds (2.65 Å), and the C=O...N interaction is 3.04 Å.

other molecular tape structures described in this work (the corresponding angles for the tape structures of the complexes 7, 10–14, and 16 are 155°–178° with an average of 170°). Such features of the tape structure in 18 are illustrated in Figure 10. Each component molecule forms a segregated DD- and AA-type stacking along the *c* axis (Figure 11).

Discussion

We discuss here the factors determining the crystal structures described above. The structures of these complexes are related to the following factors: (i) the positions of the nitrogen atoms of the dipyrrolyl compounds, (ii) the proton-donating abilities of the acilic acids which are determined by the substituents, and (iii) the geometry of the one-dimensional molecular tape structures.

The donor–acceptor ratios of the complexes 5 and 6 are 1:2, while the other complexes 7–18 have 1:1 composition. The 1:2 complexes are obtained from only 2,4-bipyridine, while the 1:1 complexes are derived from the symmetrical dipyrrolyl compounds. In the 1:2 complexes, the hydrogen bond is formed at the 4-pyridyl ring and the nitrogen of the 2-pyridyl ring is not involved in the hydrogen bonding. This fact can be explained by the difference in the basicity of the pyridine rings depending

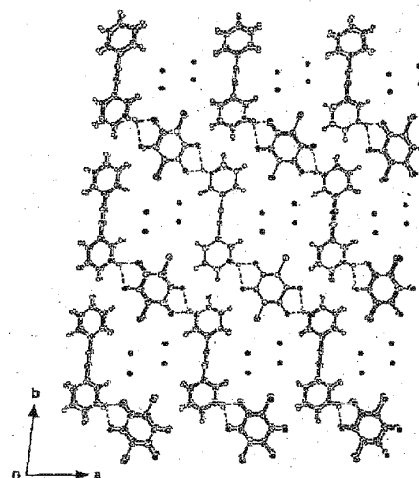


Figure 8. Square grid-type network of 15 viewed along the *c* axis. The cavities are occupied by the water molecules. Dotted lines show the intermolecular N-H...O hydrogen bonds.

on the nitrogen positions. The PM3 calculations¹⁷ show that the net atomic charges of the nitrogen atoms of 4- and 2-pyridyl rings in 2,4-bipyridine are −0.0719 and −0.0668, respectively, suggesting that the basicity is higher at the 4-position than it is at the 2-position.

In the 1:1 complexes, linear and zigzag molecular tape structures are observed. The linear tape structures are obtained only from the 4,4'-dipyrrolyl derivatives. On the other hand, the 2,2'- and 3,3'-isomers bring the zigzag tape structures. The 3,3'-isomer particularly gives a unique grid-like structure with a void. In the case of the complex 18, the zigzag tape structure is produced despite the 4,4'-isomer 4c in 18. Compared with other zigzag tape structures, the zigzag tape in 18 bends at the coupling part via intermolecular hydrogen bonds or at the supramolecular synthon I. Such a conformation of the tape causes close packing of the tapes and stabilizes the crystal structure. It is noteworthy that the linear tape structures appear in the monoclinic crystal system and the triclinic crystal system affords zigzag tapes.

The positions of nitrogen atoms of the pyridyl groups also affect the ionicity of the complexes. In the complexes of 1c with dipyrrolylacetylene 4 (complexes 14, 15, and 17), the neutral (from the 2,2'-derivative 4a), dication (from the 3,3'-derivative 4b), and monocation (from the 4,4'-derivative 4c) states are observed. Although molecular packing and morphology in the solid state may affect the proton transfer to the nitrogen atoms of the pyridyl groups, the major reasons for these phenomena can be attributed to the differences in the basicity of the pyridyl groups depending on the nitrogen positions.¹² This is

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Crystal Engineering through Supramolecular Synthesis

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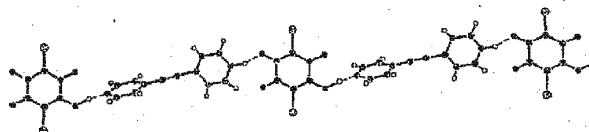


Figure 9. One-dimensional molecular tape of 16. Dotted lines show two types of the intermolecular hydrogen bonds, $N^+ \cdots H \cdots O$ (1.58 Å) and $O \cdots H \cdots N$ (1.43 Å).

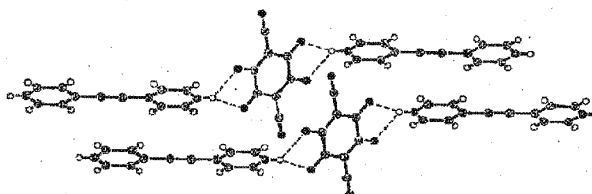


Figure 10. Two one-dimensional molecular tapes of 18. Dotted lines show the intermolecular $N^+ \cdots H \cdots O$ hydrogen bonds (2.01 and 2.22 Å).

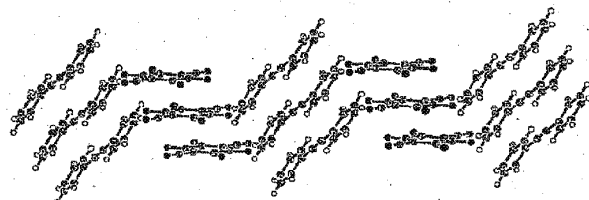


Figure 11. Segregated stacking arrangements along the *c* axis of 18. The interstack distances are 3.22 and 3.42 Å for the stacks of 1d and 4c, respectively.

supported by the PM3 calculations of the net atomic charge of the nitrogen atoms of 4 (4a, -0.0607; 4b, -0.0771; 4c, -0.0742).

Among the four anilic acids used in this work, 1a has the lowest proton-donating property, and the crystalline complexes 7 and 12 obtained from 1a are neutral. Acids 1b and 1c with moderate proton-donating ability afford monoprotonated or deprotonated complexes with dipyrindyl compounds containing nitrogen atoms at the 4- or 3-position of the pyridine rings. These acids form neutral complexes 18 and 14 with the weakest proton-accepting base 4a containing nitrogen atoms at the 2-position of the pyridine rings. Only the crystalline complex 18 obtained from the strongest proton donor 1d with 4c is fully deprotonated and involves relatively short contacts between the neighboring donor and acceptor molecules. The acid 1d rapidly produces colored powders with other dipyrindyl compounds 2–4, even if polar solvents are used for the preparation of complexes. The rapid complexation of 1d is attributed to its strong proton-donating ability.

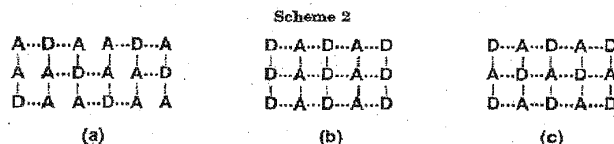
For the rational design of supramolecular architectures, strategies with structural predictability can be used in the construction of one-, two-, or three-dimensional patterns. A primary one-dimensional tape motif can be designed and obtained by using strong intermo-

lecular interactions such as hydrogen bonding. The addition of functional groups or weaker intermolecular interactions to the tapes can expand the one-dimensional networks into two-dimensional layers or sheets. A three-dimensional supramolecular architecture can be achieved by the same process to connect the two-dimensional layers. In this study, we have found three types of stacking arrangements, the patterns of which are illustrated in Scheme 2. In the complexes 5 and 6, the $A \cdots D \cdots A$ units overlap two-dimensionally to form a cross-linked layer network (Scheme 2a). For the 1:1 complexes, the segregated stacks (Scheme 2b) are obtained in 7, 9, 12–15, and 18 and the alternated ones (Scheme 2c) are realized in 8, 10, 11, 16, and 17. The molecular tapes in the complexes which gave the segregated stacks are roughly planar, and the dihedral angles between the rings are small. Thus, the favorable overlapping of the tapes causes the segregated stacks. In contrast, the molecular tapes in 8, 10, 11, 16, and 17 have larger dihedral angles between the rings such as a chain. This steric effect and the favorable charge-transfer interactions between the anilic acids and the dipyrindyl compounds might bring the alternated stacks.

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Conclusions

In this study, we have shown that the simple combination of anilic acids and dipyriddy compounds can create a variety of supramolecular architectures by self-assembly. The crystalline architectures described here are composed of an infinite one-dimensional molecular tape structure via the supramolecular synthon I with three types of intermolecular hydrogen bonds ($N^+ \cdots H \cdots O^-$, $N^+ \cdots H \cdots O$, and $O-H \cdots N$). Strong resemblances between the crystal structures of the segregated stacking type (7, 9, 12–15, and 18) or the alternated stacking type (8, 10, 11, 16, and 17) suggest the robustness and reproducing ability of the supramolecular synthon I. Charge-assistance effect¹⁸ enhances the robustness of the synthon I in this system. The positions of the nitrogen atoms of the dipyriddy compounds strongly affect the crystalline architecture and ionicity of the component molecules which can be determined by proton transfer.

Although the anilic acids are well-known to form coordination bonds with a variety of metals,^{14,15,18,19} they have not been well exploited for the rational design of organic solids.²⁰ This is the first example in which the anilic acids were used to create the supramolecular synthon I for crystal engineering purposes. The combination of two-component systems reported here may be a fundamental example for the design of low-dimensional structures. As an extension of our results, combination of other bidentate nitrogen ligands with proton donors would lead to an interesting crystalline architecture through a supramolecular synthon like I. Unusual physical properties such as conductivities may arise from charge-transfer interactions between component molecules.

Experimental Section

Starting Materials. Compounds 1d,^{7b} 4a,²¹ 4b,²² and 4c²³ were prepared according to the literature methods. Other compounds, 1a–c, 2, and 3, were commercially available and purified by usual methods. All the solvents were distilled before the use for the reactions.

General Procedures for the Preparation of Single Crystals. Method I. An equivalent molar amount (0.03–0.10 mmol) of the anilic acid and the dipyriddy compound was placed

at the bottom of the H-shaped tube, and the tube was filled with solvents (10–25 mL). After 8–30 days, crystals grew at room temperature.

Method II. A solution of the anilic acid (0.05–0.10 mmol) in a freshly distilled hot solvent (5–15 mL) was mixed with a solution of the dipyriddy compound (0.05–0.10 mmol) in a distilled hot solvent (5–10 mL). Within a week, the crystals suitable for single-crystal X-ray diffraction appeared in the flask.

Method III. A solution of the anilic acid (0.05–0.10 mmol) in 10–20 mL of a dry solvent was added to a solution of the dipyriddy compound (0.05–0.10 mmol) in 10–15 mL of a dry solvent. Slow evaporation at room temperature for 1–3 days afforded the colored solution. The single crystals suitable for single-crystal X-ray diffraction were grown from this solution by complete or partial evaporation of the solvent from the reaction mixture. The crystals were characterized by IR, elemental analysis, and X-ray crystallographic analysis.

Complex 5. Red prismatic crystals were prepared from the mixture of acetone–methanol by method I in 98% yield; mp 201–202 °C; IR (KBr): 2350–2800, 2176 (broad), 1630 (sharp), 1517, 1470 cm^{-1} . Anal. Calcd for $C_{26}H_{18}N_4O_4Br_2$ (1:2): C, 51.17; H, 2.97; N, 9.18. Found: C, 51.09; H, 3.02; N, 8.98.

Complex 6. Red prismatic crystals were prepared from methanol and acetone by method I in 98% yield; mp 214–215 °C; IR (KBr): 2350–2800, 2176 (broad), 1630 (sharp), 1519, 1476 cm^{-1} . Anal. Calcd for $C_{26}H_{18}N_4O_4Cl_2$ (1:2): C, 59.90; H, 3.48; N, 10.75. Found: C, 59.86; H, 3.43; N, 10.70.

Complex 7. Orange plate crystals were prepared from acetone by method II in 90% yield; mp 164–165 °C; IR (KBr): 2360 (broad), 1637, 1601 cm^{-1} . Anal. Calcd for $C_{26}H_{18}N_4O_4$ (1:1): C, 64.86; H, 4.08; N, 9.46. Found: C, 64.67; H, 4.17; N, 9.28.

Complex 8. Brown needle crystals were prepared from acetone by method I in 98% yield; mp 228 °C dec; IR (KBr): 2400–2800, 2170 (broad), 1632 (sharp), 1504, 1438 cm^{-1} . Elemental analysis was previously described.¹¹

Complex 9. Brown plate crystals were prepared from acetone–methanol by method I in 95% yield; mp 215–218 °C dec; IR (KBr): 2400–2800, 2124 (broad), 1640 (sharp), 1548, 1523 cm^{-1} . Elemental analysis was previously described.¹¹

Complex 10. Brown rod crystals were prepared from acetone–methanol (2:1) by method I, yield 92%; mp 252–263 °C dec; IR (KBr): 2250–2700, 2132 (broad), 1626 (sharp), 1508 cm^{-1} . Anal. Calcd for $C_{26}H_{18}N_4O_4Br_2$ (1:1): C, 45.03; H, 2.52; N, 5.53. Found: C, 44.99; H, 2.54; N, 5.58.

Complex 11. Reddish brown prismatic crystals were prepared from acetone–methanol (1:1) by method II in 80% yield; mp 230–232 °C dec; IR (KBr): 2250–2700, 2152 (broad), 1624 (sharp), 1494 cm^{-1} . Anal. Calcd for $C_{26}H_{18}N_4O_4Cl_2$ (1:1): C, 55.26; H, 3.09; N, 7.18. Found: C, 55.18; H, 3.08; N, 7.05.

Complex 12. Orange rod crystals were prepared from acetonitrile–ethanol by method III in 84% yield; mp 195–196 °C; IR (KBr): 2354 (broad), 1848, 1618, 1607 cm^{-1} . Anal. Calcd for $C_{26}H_{18}N_4O_4$ (1:1): C, 67.60; H, 3.78; N, 9.75. Found: C, 67.04; H, 3.84; N, 8.68.

Complex 13. Brown needle crystals were prepared from acetone by method I in 92% yield; mp 190–192 °C; IR (KBr): 2473 (broad), 1660, 1601 cm^{-1} . Anal. Calcd for $C_{26}H_{18}N_4O_4Br_2$ (1:1): C, 42.22; H, 2.11; N, 5.86. Found: C, 44.86; H, 1.92; N, 5.77.

Complex 14. Brown needle crystals were prepared from methanol–acetone (1:1) by method I in 83% yield; mp 194–

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195 °C; IR (KBr) 2484 (broad), 1660, 1607 cm^{-1} . Elemental analysis was previously described.¹²

Complex 15. Brown plate crystals were prepared from acetone by method I in 93% yield; mp 176–178 °C; IR (KBr) 2484 (broad), 1660, 1607 cm^{-1} . Elemental analysis was previously described.¹²

Complex 16. Brown plate crystals were prepared from acetonitrile–acetone (1:4) by method I in 99% yield; mp 218–220 °C; IR (KBr) 2280–2850, 2164, 2081, 1630, 1601, 1520 cm^{-1} . Anal. Calcd for $\text{C}_{18}\text{H}_{10}\text{N}_2\text{O}_4\text{Br}_2$ (1:1): C, 45.22; H, 2.11; N, 5.88. Found: C, 45.11; H, 2.11; N, 5.42.

Complex 17. Brown needle crystals were prepared from acetonitrile–acetone (1:1) by method I in 90% yield; mp 230–231 °C; IR (KBr) 2280–2650, 2156, 2062, 1625, 1500 cm^{-1} . Elemental analysis was previously described.¹²

Complex 18. Yellow needle crystals were prepared from acetonitrile by method II in 82% yield; mp >330 °C; IR (KBr) 2280–2880, 2203 (strong), 1632, 1543 cm^{-1} . Anal. Calcd for $\text{C}_{20}\text{H}_{10}\text{N}_2\text{O}_4$ (1:1): C, 63.69; H, 2.82; N, 15.64. Found: C, 64.01; H, 2.89; N, 15.42.

X-ray Crystallography. Reflection data were collected on a Rigaku AFC-7R diffractometer using Mo K α radiation ($\lambda = 0.71069 \text{ \AA}$) and Enraf-Nonius CAD4 diffractometer using Cu K α radiation ($\lambda = 1.54178 \text{ \AA}$) at 295 K. No absorption correction was applied for all crystals except the complexes 13 and 16. Absorption correction was applied to 13 and 16 using empirical procedures based on azimuthal ψ scans of seven reflections having an Eulerian angle, χ , near 90°. All structures were solved by direct methods and refined by full-matrix least-squares on F^2 with SHELX-97.²⁴ All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were localized in the Fourier maps and refined isotropically.

Crystal data for 5: $\text{C}_{10}\text{H}_{12}\text{Br}_2\text{N}_2\text{O}_4$, fw = 510.26, monoclinic, space group $P2_1/n$, $a = 8.827(1) \text{ \AA}$, $b = 11.838(1) \text{ \AA}$, $c = 11.191(1) \text{ \AA}$, $\beta = 92.62(3)^\circ$, $V = 1163.1(2) \text{ \AA}^3$, $Z = 2$, $D_c = 1.735 \text{ g cm}^{-3}$, $F(000) = 608$, $\mu(\text{Cu K}\alpha) = 4.770 \text{ mm}^{-1}$, crystal dimensions = $0.20 \times 0.20 \times 0.20 \text{ mm}^3$, 2645 reflections collected, 2391 independent ($R_{\text{int}} = 0.0356$), $R_1 = 0.0349$, $wR_2 = 0.0956$ for $I > 2\sigma(I)$, $R_1 = 0.0389$, $wR_2 = 0.0990$, $S = 1.069$ for all data.

Crystal data for 6: $\text{C}_{26}\text{H}_{12}\text{Cl}_2\text{N}_2\text{O}_4$, fw = 521.34, monoclinic, space group $P2_1/n$, $a = 8.6978(5) \text{ \AA}$, $b = 11.5877(6) \text{ \AA}$, $c = 11.2992(6) \text{ \AA}$, $\beta = 91.274(4)^\circ$, $V = 1183.6(1) \text{ \AA}^3$, $Z = 2$, $D_c = 1.527 \text{ g cm}^{-3}$, $F(000) = 536$, $\mu(\text{Cu K}\alpha) = 2.853 \text{ mm}^{-1}$, crystal dimensions = $0.25 \times 0.10 \times 0.10 \text{ mm}^3$, 2456 reflections collected, 2302 independent ($R_{\text{int}} = 0.0222$), $R_1 = 0.0353$, $wR_2 = 0.0869$ for $I > 2\sigma(I)$, $R_1 = 0.0701$, $wR_2 = 0.1004$, $S = 0.938$ for all data.

Crystal data for 7: $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_4$, fw = 296.28, monoclinic, space group $C2/c$, $a = 20.773(3) \text{ \AA}$, $b = 7.1901(7) \text{ \AA}$, $c = 9.157(1) \text{ \AA}$, $\beta = 93.855(7)^\circ$, $V = 1348.3(3) \text{ \AA}^3$, $Z = 4$, $D_c = 1.460 \text{ g cm}^{-3}$, $F(000) = 616$, $\mu(\text{Cu K}\alpha) = 0.892 \text{ mm}^{-1}$, crystal dimensions = $0.25 \times 0.10 \times 0.02 \text{ mm}^3$, 1184 reflections collected, 1150 independent ($R_{\text{int}} = 0.1124$), $R_1 = 0.0612$, $wR_2 = 0.1267$ for $I > 2\sigma(I)$, $R_1 = 0.2182$, $wR_2 = 0.1859$, $S = 0.963$ for all data.

Crystal data for 10: $\text{C}_{15}\text{H}_{12}\text{Br}_2\text{N}_2\text{O}_4$, fw = 480.12, monoclinic, space group $P2_1/c$, $a = 8.3546(5) \text{ \AA}$, $b = 8.0001(6) \text{ \AA}$, $c =$

13.261(1) $\text{ \AA}$, $\beta = 104.495(6)^\circ$, $V = 856.1(1) \text{ \AA}^3$, $Z = 2$, $D_c = 1.858 \text{ g cm}^{-3}$, $F(000) = 472$, $\mu(\text{Cu K}\alpha) = 1.858 \text{ mm}^{-1}$, crystal dimensions = $0.10 \times 0.10 \times 0.10 \text{ mm}^3$, 1868 reflections collected, 1750 independent ($R_{\text{int}} = 0.0202$), $R_1 = 0.0341$, $wR_2 = 0.0903$ for $I > 2\sigma(I)$, $R_1 = 0.0523$, $wR_2 = 0.1034$, $S = 0.870$ for all data.

Crystal data for 11: $\text{C}_{12}\text{H}_{12}\text{Cl}_2\text{N}_2\text{O}_4$, fw = 391.20, monoclinic, space group $P2_1/c$, $a = 8.3843(5) \text{ \AA}$, $b = 7.8904(5) \text{ \AA}$, $c = 12.923(3) \text{ \AA}$, $\beta = 105.033(7)^\circ$, $V = 825.8(2) \text{ \AA}^3$, $Z = 2$, $D_c = 1.573 \text{ g cm}^{-3}$, $F(000) = 400$, $\mu(\text{Cu K}\alpha) = 3.794 \text{ mm}^{-1}$, crystal dimensions = $0.10 \times 0.10 \times 0.02 \text{ mm}^3$, 1762 reflections collected, 1693 independent ($R_{\text{int}} = 0.0492$), $R_1 = 0.0468$, $wR_2 = 0.1236$ for $I > 2\sigma(I)$, $R_1 = 0.1204$, $wR_2 = 0.1589$, $S = 0.818$ for all data.

Crystal data for 12: $\text{C}_{18}\text{H}_{12}\text{N}_2\text{O}_4$, fw = 320.30, monoclinic, space group $P2_1/n$, $a = 3.815(2) \text{ \AA}$, $b = 10.594(2) \text{ \AA}$, $c = 18.393(1) \text{ \AA}$, $\beta = 95.49(2)^\circ$, $V = 740.0(4) \text{ \AA}^3$, $Z = 2$, $D_c = 1.438 \text{ g cm}^{-3}$, $F(000) = 332$, $\mu(\text{Mo K}\alpha) = 0.104 \text{ mm}^{-1}$, crystal dimensions = $0.20 \times 0.10 \times 0.03 \text{ mm}^3$, 1529 reflections collected, 1352 independent ($R_{\text{int}} = 0.0255$), $R_1 = 0.0472$, $wR_2 = 0.1088$ for $I > 2\sigma(I)$, $R_1 = 0.1238$, $wR_2 = 0.1280$, $S = 0.924$ for all data.

Crystal data for 13: $\text{C}_{18}\text{H}_{12}\text{Br}_2\text{N}_2\text{O}_4$, fw = 478.10, triclinic, space group $P1$, $a = 8.9452(2) \text{ \AA}$, $b = 11.0548(4) \text{ \AA}$, $c = 11.0525(3) \text{ \AA}$, $\alpha = 60.946(2)^\circ$, $\beta = 95.49(2)^\circ$, $\gamma = 84.022(8)^\circ$, $V = 418.04(3) \text{ \AA}^3$, $Z = 1$, $D_c = 1.895 \text{ g cm}^{-3}$, $F(000) = 294$, $\mu(\text{Cu K}\alpha) = 1.895 \text{ mm}^{-1}$, crystal dimensions = $0.35 \times 0.10 \times 0.02 \text{ mm}^3$, 1781 reflections collected, 1691 independent ($R_{\text{int}} = 0.0141$), $R_1 = 0.0320$, $wR_2 = 0.0869$ for $I > 2\sigma(I)$, $R_1 = 0.0850$, $wR_2 = 0.0892$, $S = 1.015$ for all data.

Crystal data for 16: $\text{C}_{18}\text{H}_{12}\text{Br}_2\text{N}_2\text{O}_4$, fw = 478.10, monoclinic, space group $P2_1/n$, $a = 13.211(1) \text{ \AA}$, $b = 6.9099(8) \text{ \AA}$, $c = 18.895(2) \text{ \AA}$, $\beta = 95.49(2)^\circ$, $V = 1696.5(3) \text{ \AA}^3$, $Z = 4$, $D_c = 1.872 \text{ g cm}^{-3}$, $F(000) = 938$, $\mu(\text{Cu K}\alpha) = 6.316 \text{ mm}^{-1}$, crystal dimensions = $0.20 \times 0.15 \times 0.05 \text{ mm}^3$, 3505 reflections collected, 3459 independent ($R_{\text{int}} = 0.0183$), $R_1 = 0.0368$, $wR_2 = 0.0986$ for $I > 2\sigma(I)$, $R_1 = 0.0587$, $wR_2 = 0.1118$, $S = 0.931$ for all data.

Crystal data for 18: $\text{C}_{20}\text{H}_{10}\text{N}_2\text{O}_4$, fw = 370.22, triclinic, space group $P1$, $a = 8.910(7) \text{ \AA}$, $b = 9.827(14) \text{ \AA}$, $c = 5.328(6) \text{ \AA}$, $\alpha = 102.71(14)^\circ$, $\beta = 104.98(9)^\circ$, $\gamma = 104.66(12)^\circ$, $V = 418.0(8) \text{ \AA}^3$, $Z = 1$, $D_c = 1.482 \text{ g cm}^{-3}$, $F(000) = 190$, $\mu(\text{Mo K}\alpha) = 0.107 \text{ mm}^{-1}$, crystal dimensions = $0.30 \times 0.20 \times 0.02 \text{ mm}^3$, 1620 reflections collected, 1516 independent ($R_{\text{int}} = 0.1185$), $R_1 = 0.0584$, $wR_2 = 0.1150$ for $I > 2\sigma(I)$, $R_1 = 0.3899$, $wR_2 = 0.1880$, $S = 0.890$ for all data.

Acknowledgment. We thank Professor K. Nakasugi, Dr. J. Toyoda, and Dr. Y. Morita of Osaka University for their continuous encouragement and advice for this work. M.B.Z. thanks the Institute for Molecular Science for postdoctoral fellowships. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: The X-ray crystallographic data (ORTEP drawings and tables of the crystal data, bond lengths and angles, atomic coordinates, and anisotropic thermal parameters) for 5–7, 10–13, 16, and 18. This material is available via the Internet at <http://pubs.acs.org>. JO001746I

(24) Sheldrick, G. M., *SHELX-97. Program for the Solution and the Refinement of Crystal Structures*; University of Göttingen: Göttingen, Germany, 1997.

**Notice of Reasons for Rejection
(Translation)**

Drafting Date: September 29, 2009
Dispatch Date: October 8, 2009
Sections Applied: 29 (1), 29(2), 36, and 37

This application is rejected for the reasons stated below. If the Applicant has any arguments against the reasons, such arguments should be submitted within three months from the dispatch date of this *Notice of Reasons for Rejection*.

Rejections

1. This application fails to comply with the requirements under Japanese Patent Law Section 37, for the reasons mentioned below.

2. The inventions claimed in the following claims are not patentable under Japanese Patent Law Section 29(1)(iii), because they have already been described in the documents listed below, which were distributed in or outside of Japan, or made publicly available through electric telecommunication lines, prior to the filing of the present application.

3. The inventions described in the claims indicated below are not patentable under Japanese Patent Law Section 29(2), because they could have easily been made by a person with ordinary skill in the art to which the invention pertains, prior to the filing of this application, on the basis of the inventions described in the documents listed below, which were distributed in or outside of Japan, prior to the filing of this application.

4. The claims of this application fail to comply with the requirements under Japanese Patent Law Section 36(6)(i), for the reasons mentioned below.

5. The claims of this application fail to comply with the requirements under Japanese Patent Law Section 36(6)(ii), for the reasons mentioned below.

Reasons (Regarding the cited documents, see List of Cited Documents)

[A]

Claims: 1-36

Rejection 1

Remarks: Based on the relationship between independent and dependent Claims and categories of the inventions, the Claims can be divided as follows:

- Product inventions relating to Claims 1-19 (Invention 1)
- A product invention relating to Claim 20 (Invention 2)
- A product invention relating to Claim 21 (Invention 3)
- A product invention relating to Claim 22 (Invention 4)
- A product invention relating to Claim 23 (Invention 5)
- A product invention relating to Claim 24 (Invention 6)
- Method inventions relating to Claims 25-28 (Invention 7)
- Method inventions relating to Claims 29-32 (Invention 8)
- Method inventions relating to Claims 33-36 (Invention 9)

Even when any one of Inventions 1-6 is the specified invention, Inventions 7-9 are neither a method of producing the product of the specified invention, a method of using the product of the specified invention, nor a method of dealing with the product of the specified invention. Therefore, it is not recognized that those inventions fulfill the relationship defined in Japanese Patent Law Section 37 (iii).

Since the present application fails to comply with Japanese Patent Law Section 37, the claims other than claims 1-24 have not been further examined for other requirements, except for the requirements under Section 37.

[B]

Claims: 1-24

Rejection 4

Remarks: Claim 1 specifies “a multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between two or more independent molecular entities, wherein at least one of said two or more independent molecular entities is a pharmaceutical molecule”.

However, having reviewed the descriptions of the specification, what is substantially produced in the Examples is only co-crystals of two kinds of compounds or co-crystals of two kinds of compounds and water.

Therefore, the products encompassed by the above multiple-component phase

composition other than co-crystals are not supported sufficiently by the specification.

Please note that as mentioned above, since the products encompassed by the above multiple-component phase composition other than co-crystals are not supported sufficiently by the specification, in this Notice, the examination regarding novelty and inventive-steps has been conducted assuming that the multiple-component phase composition is co-crystal.

[C]

Claims: 1-19, 21, 23, and 24

Rejections 2 and 3

Cited Documents: 1-9

Remarks: Cited Document 1 describes a 1:1 carbamazepine/formamide co-crystal (See page 508, right column, Schema 2 and the same column, the fourth-third lines from the bottom), which is identical to the co-crystal described in Example 17.

Cited Document 2 describes an inclusion complex of Carbamazepine with β -cyclodextrin (1:1) (See page 960, lines 1-3). In a broader sense, an inclusion complex is a kind of co-crystal.

Cited Document 3 describes "Caboril Complex" which is recognized as a complex of phenyloin, phenobarbitone, and aminohydroxybutiric acid.(See page 1610, column 2).

A complex can be recognized as a kind of co-crystal in a broader sense (Regarding "complex", the same applies to the following Cited Documents.).

Cited Document 4 describes a phenazone/paracetamol (acetaminophene) complex compound in a form of a molecular complex compound having a hydrogen bonding including phenazone and paracetamol in an almost equivalent molar ratio (Page 1, left column, lines 2-9).

Cited Document 5 describes a 1:1 molecular complex of mebendazole with propionic acid. Cited Document 5 also describes that the complex forms intermolecular hydrogen bonding (See page 11, abstract, and page 13, Fig.2 and such).

Cited Document 6 describes a 1:1 complex between 5-chlorosalicylic acid and theophylline. Cited Document 6 also describes that the complex forms intermolecular hydrogen bonding (See page 710, abstract and such).

Cited Document 7 describes a 1:1 molecular complex of theophylline and p-nitroaniline. Cited Document 7 also describes that the complex forms intermolecular hydrogen bonding in the crystal structure (See page 2390, abstract and page 2391, Figure 2

and such).

Cited Document 8 describes a 1:1 complex of theophylline and p-nitrophenol. Cited Document 8 also describes that the complex forms intermolecular hydrogen bonding (See page 2333, abstracts and such).

Cited Document 9 describes a 2:1 molecular complex of theophylline and 5-fluorouracil as the monohydrate. Cited Document 9 also describes that the complex forms intermolecular hydrogen bonding (See page 1857, abstract and right column, lines 9-12 and such).

Therefore, the inventions of Claims 1-19, 21, 23, and 24 are the inventions described in any one of Cited Documents 1-9 or at least, would have been easily achieved by one skilled in the art on the basis of the descriptions of any one of Cited Documents 1-9.

[D]

Claims: 1-24

Rejection 3

Cited Documents: 1-11

Remarks: As described in Cited Documents 1-9, producing co-crystals regarding various kinds of compounds was frequently conducted from before the priority date of this application.

Furthermore, as described in Cited Documents 10 and 11, it was well known before the priority date of this application that when producing co-crystals with compounds having π -electron systems or having groups which can form hydrogen bonds, intermolecular interactions such as hydrogen bonding or π - π interactions occurred (See Cited Document 10, Figure 1-4, and page 9833, the second-fifth lines counting from the Figure and Cited Document 11, page 5987 abstracts, page 5989 Table 1, and Figure 1-11 and such.).

Therefore, producing co-crystals consisting of two kinds of compounds and confirming the occurred intermolecular interactions in the obtained co-crystals do not present any difficulties for one skilled in the art.

[E]

Claim: 11

Rejection 5

Remarks: (1) The descriptions using parentheses in Claim 11 make the scope of the invention unclear.

(2) "Profen" recited in Claims 9 and 22 is not a usual name of the chemical compound. Therefore, it is unclear what compound this term indicates. (Is this an error of either of "ibuprofen" or "flurbiprofen"?)

(*)When amending, please note that no new matter must be introduced. At the same time, it is desirable that the Applicant clearly indicates in a *Written Argument* support from the original specification and such.

List of Cited Documents

1. H. Wounderlich et al., Pharmazie, 1991, Vol. 46, No. 7, P. 507-509
2. S. A. EL=NAHHAS, Pharmazie, 1996, Vol. 51, No. 12, P. 960-963
3. JAMES E. F. REYNOLDS, Martindale. The extra pharmacopeia, The PHARMACEUTICAL PRESS, 1993, P. 1610
4. Japanese Patent Application Kokoku Publication No. (JP-B) 46-33588 (examined, published Japanese patent application)
5. Mino R. Caira et al., Journal of Chemical Crystallography, 1998, Vol. 28, No. 1, P. 11-15
6. Eli Shefter, Journal of Pharmaceutical Sciences, 1969, Vol. 58, No. 6, P. 710-714
7. Shuich Zaitu et al., Acta Crystallographica Section C, 1995, Vol. 51, P. 2390-2392
8. Katsuyuki Aoki et al., Acta Crystallographica Section B, 1978, Vol. 34, P. 2333-2336
9. Shuich Zaitu et al., Acta Crystallographica Section C, 1995, Vol. 51, P. 1857-1859
10. V. R. Pedireddi et al., Tetrahedron Letters, 1998, Vol. 39, P. 9831-9834
11. Md. Badrus Zaman et al., Journal of Organic Chemistry, 2001, Vol. 66, P. 5987-5995

Record of Prior Art Search Results

This record is not a component of the reasons for rejection.

- Prior art references: None

整理番号: 発送番号: 667854 発送日: 平成21年10月 8日 1

拒絶理由通知書

特許出願の番号	特願2003-572946
起案日	平成21年 9月29日
特許庁審査官	三輪 繁 4148 4C00
特許出願人代理人	清水 初志 (外 1名) 様
適用条文	第29条第1項、第29条第2項、第36条、第37条

この出願は、次の理由によって拒絶をすべきものです。これについて意見がありましたら、この通知書の発送の日から3か月以内に意見書を提出してください。

理 由

1. この出願は、下記の点で特許法第37条に規定する要件を満たしていない。
2. この出願の下記の請求項に係る発明は、その出願前に日本国内又は外国において、頒布された下記の刊行物に記載された発明又は電気通信回線を通じて公衆に利用可能となった発明であるから、特許法第29条第1項第3号に該当し、特許を受けることができない。
3. この出願の下記の請求項に係る発明は、その出願前に日本国内又は外国において頒布された下記の刊行物に記載された発明又は電気通信回線を通じて公衆に利用可能となった発明に基いて、その出願前にその発明の属する技術の分野における通常の知識を有する者が容易に発明をすることができたものであるから、特許法第29条第2項の規定により特許を受けることができない。
4. この出願は、特許請求の範囲の記載が下記の点で、特許法第36条第6項第1号に規定する要件を満たしていない。
5. この出願は、特許請求の範囲の記載が下記の点で、特許法第36条第6項第2号に規定する要件を満たしていない。

記 (引用文献等については引用文献等一覧参照)

[A]

- ・請求項 1－36
- ・理由 1

特許請求の範囲の請求項は、独立請求項－従属請求項の関係及び発明の категорияにより、以下のように区分し得る。

- ・請求項1－19に係る物の発明（発明1）
- ・請求項20に係る物の発明（発明2）
- ・請求項21に係る物の発明（発明3）
- ・請求項22に係る物の発明（発明4）
- ・請求項23に係る物の発明（発明5）
- ・請求項24に係る物の発明（発明6）
- ・請求項25－28に係る方法の発明（発明7）
- ・請求項29－32に係る方法の発明（発明8）
- ・請求項33－36に係る方法の発明（発明9）

そして、物の発明である発明1－6のいずれを特定発明としても、該特定発明に対して、方法の発明である発明7－9は、その物を生産する方法の発明、その物を使用する方法の発明、その物を取り扱う方法の発明の関係となっていないから、特許法第37条第3号の関係を満たしているとはいえない。

よって、この出願は特許法第37条の規定に違反しているので、請求項1－24以外の請求項に係る発明については特許法第37条以外の要件についての審査を行っていない。

[B]

- ・請求項 1－24
- ・理由 4

請求項1では、「2種以上の独立した分子実体間の分子間相互作用により維持される固相を含む多構成要素相組成物であって、該2種以上の独立した分子実体のうち少なくとも1種が薬剤分子である、多構成要素相組成物」が特定されている。

しかしながら、本願明細書の発明の詳細な説明を検討すると、実施例において実質的に製造されているのは、2種の化合物又は2種の化合物及び水を組み合わせて結晶化した共結晶が記載されているのみである。

したがって、請求項1－24規定の多構成要素相組成物に包含される物のうち、共結晶以外については、発明の詳細な説明中に十分なサポートが存在するとは

なお、上述のように、共結晶以外の多構成要素相組成物については、発明の詳細な説明中に十分なサポートが存在するとはいえないので、本拒絶理由通知書においては、請求項1－24規定の「多構成要素相組成物」が「共結晶」であるものとして、新規性・進歩性等の審査を行った。

[C]

- ・請求項 1－19, 21, 23, 24
- ・理由 2, 3
- ・引用文献等 1－9
- ・備考

引用文献1には、カルバマゼピンとホルムアミド（1：1）の共結晶が記載されている（第508頁右欄Schema 2及び同欄下から第4行一下から第3行）。

ここで、カルバマゼピンとホルムアミド（1：1）の共結晶は、本願実施例17に記載されたものと同一である。

引用文献2には、カルバマゼピンと β -シクロデキストリン（1：1）の包接錯体が記載されている（第960頁第1－3行等）。

そして、包接錯体は、広義には、共結晶の一種とみなせる。

引用文献3には、フェニトイン、フェノバルビタール、アミノヒドロキシ酪酸の錯体と認められる「C a b o r i l C o m p l e x」が記載されている（第1610頁第2欄）。

そして、Complex（錯体）は、広義には、共結晶の一種とみなせる。（「錯体」については、以下に引用する文献においても同様である。）。

引用文献4には、結晶性粉末であって、水素結合を有する分子錯化合物の形でほぼ等モル比のフェナゾンとパラセタモールを含んでいる、フェナゾン・パラセタモール（アセトアミノフェン）錯化合物が記載されている（第1頁左欄第2－9行）。

引用文献5には、メベンダゾールとプロピオン酸（1：1）の分子錯体が記載されており、分子間で水素結合が生じることも記載されている（第11頁要約部、第13頁Fig. 2等）。

引用文献6には、5-クロロサリチル酸とテオフィリン（1：1）の錯体が記載されており、分子間で水素結合が生じることも記載されている（第710頁Abstract等）。

引用文献7には、テオフィリンとp-ニトロアニリン（1：1）の分子錯体が記載されており、結晶構造中で水素結合が生じることも記載されている（第2390頁からのAbstract、第2391頁Fig. 2等）。

引用文献8には、テオフィリンとp-ニトロフェノール(1:1)の錯体が記載されており、分子間で水素結合が生じることも記載されている(第2333頁からのAbstract等)。

引用文献9には、一水和物としてのテオフィリンと5-フルオロウラシル(2:1)の分子錯体が記載されており、分子間で水素結合が生じることも記載されている(第1857頁Abstract、同頁右欄第9-12行等)。

よって、本願請求項1-19, 21, 23, 24に係る発明は、引用文献1-9のいずれかに記載された発明であるか、少なくとも引用文献1-9のいずれかから当業者が容易になし得たものである。

[D]

- ・請求項 1-24
- ・理由 3
- ・引用文献等 1-11
- ・備考

引用文献1-9に記載のように、様々な化合物について、共結晶を製造することは、本願優先日前から行われていたことである。

そして、引用文献10, 11に記載のように、 π 電子系を有する化合物や水素結合を形成する基を有する化合物を共結晶とした場合、水素結合や π - π 相互作用等の分子間相互作用が生じることも本願優先日前から知られていたことである(引用文献10: Figure 1-4、第9833頁Figureの下第2-5行; 引用文献11: 第5987頁要約部、第5989頁Table 1、Figure 1-11等)。

してみれば、2種以上の化合物から構成される共結晶を製造し、得られた共結晶について、生じる分子間相互作用を確認することは、当業者にとり格別困難なことではない。

[E]

- ・請求項 11
- ・理由 5

(1) 請求項11の括弧書きを使用した記載は、発明の範囲を不明確にするものである。

(2) 請求項9, 22の「プロフェン」は、一般的に使用されている化学物質名ではなく、いかなる化学物質を示すのか明確でない。

(「イブプロフェン」又は「フルルビプロフェン」のことか?)

(*) 補正をするときは、新規事項の追加とならないよう留意されたい。

またその際、補正の根拠となる明細書又は図面中の該当記載箇所について、意見書中で明示されることが望ましい。

引用文献等一覧

1. H. Wunderlich et al., Pharmazie, 1991年, Vol. 46, No. 7, p. 507-509
2. S.A. EL-NAHHAS, Pharmazie, 1996年, Vol. 51, No. 12, p. 960-963
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5. Mino R. Caira et al., Journal of Chemical Crystallography, 1998年, Vol. 28, No. 1, p. 11-15
6. Eli Shefter, Journal of Pharmaceutical Sciences, 1969年, Vol. 58, No. 6, p. 710-714
7. Shyuichi Zaitu et al., Acta Crystallographica Section C, 1995年, Vol. 51, p. 2390-2392
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11. Md. Badruz Zaman et al., Journal of Organic Chemistry, 2001年, Vol. 66, p. 5987-5995

(注) 法律又は契約等の制限により、提示した非特許文献の一部又は全てが送付されない場合があります。

先行技術文献調査結果の記録

・調査した分野 IPC A61K 9/00
 47/00
 31/00
DB名 CAplus(STN)

整理番号: 発送番号:667854 発送日:平成21年10月 8日 6/E

この先行技術文献調査結果の記録は拒絶理由を構成するものではありません。

(*) この拒絶理由通知の内容に関するお問い合わせ、または面接のご希望がございましたら下記までご連絡下さい。

特許審査第三部 医療 三輪 繁

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FAX. 03 (3581) 1342

Electronic Acknowledgement Receipt	
EFS ID:	6493359
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/Jenny Bedner
Filer Authorized By:	Frank Christopher Eisenschenk
Attorney Docket Number:	USF.106XC1
Receipt Date:	20-NOV-2009
Filing Date:	03-MAR-2003
Time Stamp:	10:54:41
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		IDS-supp6.pdf	455442	yes	4
			d48f5ebcb21d1e2005a26437011abda720e f1ded		

	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Transmittal Letter		1	2	
	Information Disclosure Statement (IDS) Filed (SB/08)		3	4	
Warnings:					
Information:					
2	Foreign Reference	JP-46-33588.pdf	329178	no	3
			976c23a726f5a1fe7950757fd347ceb7a811795a		
Warnings:					
Information:					
3	NPL Documents	Wunderlich.pdf	481775	no	3
			d8b50945bea2f36832273e4992d56e1ab6cbbe51		
Warnings:					
Information:					
4	NPL Documents	ElNahhas.pdf	664747	no	4
			5315de2bc37e0424d1cff997fd67719d22e33e39		
Warnings:					
Information:					
5	NPL Documents	Martindale.pdf	512261	no	3
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Warnings:					
Information:					
6	NPL Documents	Pedireddi.pdf	360900	no	4
			0e8e9d9b6d0b937f35dd8af35be5492b85360e1d		
Warnings:					
Information:					
7	NPL Documents	Zaman.pdf	1408428	no	9
			13abc64a3721523ab3658f87dbecce24d08761d2		
Warnings:					
Information:					
8	NPL Documents	JP-OfficeAction.PDF	885502	no	11
			a3f83728c348f4a218196c2a469b2bc2b277273c		
Warnings:					
Information:					
Total Files Size (in bytes):			5098233		

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.

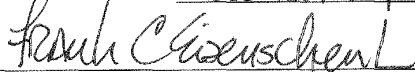
National Stage of an International Application under 35 U.S.C. 371

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.

I hereby certify that this correspondence is being electronically transmitted to the United States Patent and Trademark Office on November 20, 2009.



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

SUPPLEMENTAL INFORMATION
DISCLOSURE STATEMENT
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

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

Sir:

In accordance with 37 C.F.R. § 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.

Applicants recently received a Notice of Reasons for Rejection that is under examination in Japan in a corresponding application. In that Notice, two of the cited references (listed as R1 and F1 on the attached Form PTO/SB/08) are in a foreign language. The Notice in the related application has been translated by a foreign agent and a copy of the original Japanese language Notice of Reasons for Rejection and the translation are provided in this Supplemental Information Disclosure Statement along with the references cited in the Notice. It is believed that the English language translation of the Japanese Notice of Reasons for Rejection provides a discussion of the foreign language documents and the relevant teachings for which the references were cited. Applicants note

J:\USF\106XC1\PTOIDS.supp6.doc\DNB/jb

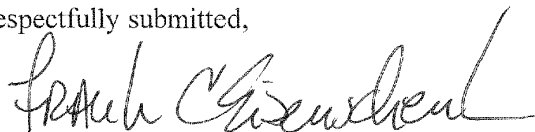
that a partial translation is provided for Japanese Patent Application No. JP-B 46-33588, listed as F1 on the attached form.

The undersigned hereby certifies that each item of information contained in this Supplemental Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Supplemental Information Disclosure Statement.

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 C.F.R. §§ 1.97 and 1.98 are met by the foregoing statement.

Respectfully submitted,



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FCE/sl

Attachment: Form PTO/SB/08

I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on March 5, 2010

Glenn P. Ladwig
Glenn P. Ladwig, Patent Attorney, Reg. No. 46,853

AMENDMENT UNDER 37 CFR §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 : Sahar Javanmard
Art Unit : 1617
Applicants : Michael J. Zaworotko, Brian Moulton, Nair Rodriguez-Hornedo
Serial No. : 10/378,956
Filed : March 3, 2003
Confirm. No. : 4742
For : Multiple-Component Solid Phases Containing at Least One Active Pharmaceutical Ingredient

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

AMENDMENT UNDER 37 CFR §1.111

Applicants request that the period for response in the above-identified patent application be extended two months through and including March 5, 2010, the fee for which has been paid at the time this Amendment was filed.

In response to the Office Action dated October 5, 2009, please amend the above-identified application as follows:

JAUSF106XC1\Amend-Resp\Amd3.doc/DNB/jnw

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 identified 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), wherein the identified co-crystal formers are solids at room temperature and under atmospheric pressure; 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 compound, a food additive, a low toxicity organic, and a metal-organic complex.

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 (currently amended). 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 identified 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, wherein the selected co-crystal formers are solids at room temperature and under atmospheric pressure; 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~~ selected co-crystal formers.

39 (New). The method of claim 25, wherein the at least one co-crystal former is a GRAS compound.

40 (New). The method of claim 25, wherein the at least one co-crystal former is a food additive.

41 (New). The method of claim 25, wherein the at least one co-crystal former is a low toxicity organic.

42 (New). The method of claim 25, wherein the at least one co-crystal former is a metal organic complex.

43 (New). The method of claim 25, wherein the at least one co-crystal former comprises at least two heterocyclic groups.

44 (New). The method of claim 25, wherein the at least one co-crystal former is bipyridine.

45 (New). The method of claim 25, wherein the at least one co-crystal former is bis(pyridyl)ethene.

46 (New). The method of claim 25, wherein said evaluating of (a) comprises determining the crystal structure of said active pharmaceutical ingredient.

47 (New). The method of claim 25, wherein said evaluating of (a) comprises experimentally determining the structure of at least one pure solid phase of said active pharmaceutical ingredient.

48 (New). The method of claim 25, wherein the at least one functionality identified in step (c) is an unsaturated N-heterocycle, saturated N-heterocycle, aldehyde, amide, carboxylic acid, nitro, ketone, or sulfoxide.

49 (New). The method of claim 25, wherein the at least one functionality identified in step (c) is a carboxylic acid.

Remarks

Claims 25, 27, 28, 37, and 38 were pending in the subject application. By this Amendment, claims 25, 27, and 38 have been amended and new claims 39-49 have been added. The undersigned avers that no new matter is introduced by this Amendment. Support for the new claims and 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, and 37-49 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

By this Amendment, claims 39-49 have been added. Written support for claims 39-42 can be found, for example, in claim 27 as originally filed and page 11, paragraph [0042] of the specification. Written support for claims 43-47 can be found at pages 4-6, paragraphs [0009] – [0013] of the specification. Written support for claims 48 and 49 can be found, for example, at page 4, paragraph [0009], the figures, and within the descriptions thereof.

Claims 25, 27, 28, and 38 are rejected under 35 USC §103(a) as obvious over Homeyer *et al.* (U.S. Patent No. 2,665,277). The Office Action indicates that Homeyer *et al.* teach a method of making morphine phosphate hemihydrate, and that it would have been obvious for one of skill in the art at the time the invention was made to carry out the claimed methods. Applicants respectfully assert that the claimed invention is not obvious over the cited reference and traverse the rejection of record.

As an initial matter, by this Amendment, Applicants have amended independent claim 25 to recite that the identified co-crystal former is a solid at room temperature and under atmospheric pressure, and amended independent claim 38 to recite that the selected co-crystal former is a solid at room temperature and under atmospheric pressure. Support for these amendments can be found, for example, at pages 16-33, in Examples 1-19, which describe the production of multiple-component solid phase compositions with co-crystal formers that are solid at room temperature and atmospheric pressure, and multiple-component solid phase compositions with co-crystal formers that are liquid at room temperature and under atmospheric pressure. For example, co-crystal formers that are liquid at room temperature and under atmospheric pressure include acetic acid (Example 12), butyric acid

(Example 15), dimethyl sulfoxide (Example 16), and formic acid (Example 18). Co-crystal formers that are solid at room temperature and atmospheric pressure include bipyridine (Example 1), 4,4'-bipyridine (Examples 3-5), *p*-phthalaldehyde (Example 7), nicotinamide (Example 8), saccharin (Example 9), 2,6-pyridinedicarboxylic acid (Example 10), 5-nitroisophthalic acid (Example 11), and adamantanetetracarboxylic acid (Example 13). Applicants have also amended claims 25 and 38 for antecedent basis.

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)). Homeyer *et al.* fail to teach many of the limitations recited in the claims pending and as currently amended. Homeyer *et al.* describe the production of a multiple-component solid phase composition based upon morphine phosphate and water, i.e., a hydrate. In contrast, the claims of the subject application as currently amended recite the production of 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, and in which the co-crystal former used in the multiple-component solid phase composition is a solid at room temperature and under atmospheric pressure.

Furthermore, as acknowledged by the Examiner at page 3 of the Office Action, the Homeyer *et al.* patent “does not specifically teach the concept of identifying and evaluating the structures for their chemical functionalities.” Although it is unclear to which specific steps the Examiner is referring, Applicants presume that the Examiner is referring to at least steps (b) – (d) in claims 25 and 38.

The key to supporting any rejection under 35 U.S.C. §103(a) is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007) noted that the analysis supporting a rejection under 35 U.S.C. §103(a) should be made explicit. There must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. MPEP §2142.

The Office Action indicates that Homeyer *et al.* teach a method of making morphine phosphate hemihydrate, and that “it would have been obvious for one of skill in the art at the time the invention was made that one would identify and evaluate the structures in order to assess whether or not the components have the capability of forming supramolecular synthons.” Applicants respectfully submit that the foregoing is a conclusory statement, tantamount to a mere statement that the claimed invention is within the capabilities of one of ordinary skill in the art, which is not sufficient to establish *prima facie* obviousness (MPEP §2143.01). There must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. For example, the Office Action does not articulate why, based on the teaching of the Homeyer *et al.* patent, it would be obvious carry out each of the following steps:

- (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).

There is no discussion of co-crystal formers within the Homeyer *et al.* patent, and the reference fails to teach 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. The Office Action extends the teaching of a process for preparing monobasic morphine phosphate hemihydrate to the deliberate, rational design of multiple component crystal compositions based on the identification of appropriate co-crystal formers. The Office Action does not establish why, in view of the teaching of the monobasic morphine phosphate hemihydrate of the Homeyer *et al.* patent, it would be obvious to prepare multiple-component crystal compositions in the manner claimed with

a reasonable expectation of success. Obviousness does not require absolute predictability; however, at least some degree of predictability is required. MPEP §2143.02.

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.

Claims 25, 27, 37, and 38 are rejected under 35 USC §103(a) as obvious over Ammar *et al.* (*Egypt J. Pharmacol. Sci.*, 35(1-6):209-223 (1994)) in view of Desiraju (*Angew. Chem. Int. Ed. Engl.*, 34:2311-2327 (1995)). Applicants respectfully submit that the claimed invention is not obvious over the cited references.

The Office Action indicates that Ammar *et al.* teach the water solubility of carbamazepine in the presence of nicotinamide and that “there are spectral changes occurring between the interaction which may give an indication of a molecular interaction between carbamazepine and the compounds tested, including nicotinamide, which forms a complex-formation between carbamazepine and the compounds” (emphasis added). Furthermore, the Office Action indicates that it would have been obvious to have employed the teachings of Ammar *et al.* “wherein the active pharmaceutical ingredient (carbamazepine) is evaluated and determined to have the capability of forming supramolecular synthons with itself, and that the chemical functionalities (*i.e.*, H-bonding) are present in order to non-covalently bond to a second supramolecular synthon (nicotinamide).” The Examiner concludes that one of skill in the art would expect that it would be possible to form co-crystals of the instant pharmaceutical agents because they possess all of the prerequisites (*i.e.* hydrogen bonding), according to the teachings of Ammar *et al.* and Desiraju.

As indicated in Applicants’ remarks in response to the rejection based on Homeyer *et al.*, 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. Ammar *et al.* fail to teach many of the limitations recited in the claims pending and as currently amended. As acknowledged by the Examiner at page 4 of the Office Action, the Ammar *et al.* publication “does not specifically recite Applicants’ steps as set forth in claim 25,” which, as amended, include:

- (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 identified 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), wherein the identified co-crystal formers are solids at room temperature and under atmospheric pressure; 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.

The Ammar *et al.* publication does not disclose 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, and in which the co-crystal former used in the multiple-component solid phase composition is a solid at room temperature and under atmospheric pressure. Rather, Ammar *et al.* disclose the possible existence of “complexes” in solution. Such “complexes” may include solvent, be solvent-dependent, or have multiple ratios.

Applicants respectfully submit that the presence of inherent matter must be grounded on more than speculation, it must be a certainty. *Ethyl Molded Product Co. v. Betts Package Inc.*, 9 USPQ 2d 1001, 1032-1033 (I.D.KY 1988). The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981); MPEP §2112. Furthermore, when the reference is silent as to the asserted inherent characteristic, while such a gap in the reference may be filled with recourse to extrinsic evidence, the extrinsic evidence

must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary

skill in the art. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *In re Robertson*, 49 USPQ 2d 1949, 1950-1951 (Fed. Cir. 1999).

Furthermore, the existence of a complex in solution does not convey to one of ordinary skill in the art that the complex can be isolated as a crystalline solid (crystallization is often controlled by kinetics), or how it can be isolated. The existence of a complex in solution does not inform one of ordinary skill in the art what forces may be holding the complex together (*i.e.*, supramolecular synthons, or other forces). The existence of a complex in solution for an individual pair of molecules does not impart to persons of ordinary skill in the art a reasonable expectation that they can extrapolate that pair into a genus of related compounds, as the subject specification demonstrates. Thus, even if a 1:2 complex of carbamazepine and nicotinamide does exist in the Ammar *et al.* publication, it has little bearing on the existence of groups of multiple-component crystalline compositions, nor does it convey a reasonable expectation of success in deliberately and rationally producing such multiple-component crystalline compositions in accordance with the methods of the invention.

The Desiraju publication does not cure the deficiencies of the Ammar *et al.* publication. The Desiraju publication does not teach supramolecular heterosynthons (supramolecular synthons between complementary but different functional groups) that are persistent and therefore amenable to use for designing multiple-component crystalline compositions, *i.e.*, they will occur even in the presence of other functional groups. The Office Action does not establish that carbamazepine was evaluated and determined to have the capability of forming supramolecular synthons with itself, and that the chemical functionalities are present in order to non-covalently bond to nicotinamide, such that one of ordinary skill in the art would then be motivated to look to Desiraju to carry out each step of the claimed methods with a reasonable expectation of success.

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. MPEP §2143.01. Obviousness does not require absolute predictability, however, at least some degree of predictability is required. MPEP §2143.02. Evidence showing there was no reasonable

expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). The cited references do not impart persons of ordinary skill in the art with a reasonable expectation of success in carrying out the claimed methods for the reasons cited above. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §103(a) is respectfully requested.

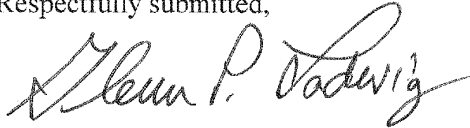
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position.

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 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,



Glenn P. Ladwig
Patent Attorney
Registration No. 46,853
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

GPL/jnw

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:		Glenn Ladwig/J'Nese Williams		
Attorney Docket Number:		USF.106XC1		
Filed as Small Entity				
Utility under 35 USC 111(a) Filing Fees				
Description		Fee Code	Quantity	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 2 months with \$0 paid		2252	1	245

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
Total in USD (\$)				245

Electronic Acknowledgement Receipt	
EFS ID:	7154464
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:	Glenn Ladwig/J'Nese Williams
Filer Authorized By:	Glenn Ladwig
Attorney Docket Number:	USF.106XC1
Receipt Date:	05-MAR-2010
Filing Date:	03-MAR-2003
Time Stamp:	17:56:16
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	\$245
RAM confirmation Number	4716
Deposit Account	190065
Authorized User	EISENSCHENK,FRANK C.
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 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)					
Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)					
Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)					
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Amd3.pdf	1128565 e8d06d45874bb9d5a859756dc512bb656a c525dc	yes	14
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	5	
	Applicant Arguments/Remarks Made in an Amendment		6	14	
Warnings:					
Information:					
2	Fee Worksheet (PTO-875)	fee-info.pdf	30382 d4e23a19771514c5556c36a33cdd9011ed3 8b4c3	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			1158947		
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. <u>New Applications Under 35 U.S.C. 111</u> 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. <u>National Stage of an International Application under 35 U.S.C. 371</u> 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. <u>New International Application Filed with the USPTO as a Receiving Office</u> 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.					

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875					Application or Docket Number 10/378,956		Filing Date 03/03/2003		☐ To be Mailed	
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APPLICATION AS FILED – PART I					OTHER THAN SMALL ENTITY					
(Column 1)		(Column 2)		SMALL ENTITY ☒		OR		SMALL ENTITY		
FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)	RATE (\$)	FEE (\$)	RATE (\$)	FEE (\$)	RATE (\$)	
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	375	N/A		N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A		N/A		N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A		N/A		N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X \$ =		OR	X \$ =		X \$ =		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X \$ =		OR	X \$ =		X \$ =		
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))			If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$250 (\$125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).							
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))										
					TOTAL	375	TOTAL			

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

APPLICATION AS AMENDED – PART II					OTHER THAN SMALL ENTITY						
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OR		SMALL ENTITY	
AMENDMENT	03/05/2010	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	RATE (\$)	ADDITIONAL FEE (\$)	RATE (\$)	ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	* 16	Minus	** 36	=	0	OR	X \$ =	X \$ =	0	
	Independent (37 CFR 1.16(h))	* 2	Minus	***9	=	0	OR	X \$ =	X \$ =	0	
☐ Application Size Fee (37 CFR 1.16(s))											
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))											
					TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE			

(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OR		SMALL ENTITY		
AMENDMENT	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	RATE (\$)	ADDITIONAL FEE (\$)	RATE (\$)	ADDITIONAL FEE (\$)	RATE (\$)	ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =		OR	X \$ =	X \$ =		
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =		OR	X \$ =	X \$ =		
☐ Application Size Fee (37 CFR 1.16(s))												
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))												
					TOTAL ADD'L FEE		OR	TOTAL ADD'L 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.

This collection of information is required by 37 CFR 1.16. 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: 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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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 06/24/2010 SALIWANCHIK LLOYD & SALIWANCHIK A PROFESSIONAL ASSOCIATION PO Box 142950 GAINESVILLE, FL 32614			EXAMINER JAVANMARD, SAHAR	
			ART UNIT 1627	PAPER NUMBER
			NOTIFICATION DATE 06/24/2010	DELIVERY MODE ELECTRONIC

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.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

DETAILED ACTION

Status of the Application

This Office Action is in response to Applicant's arguments filed on March 5, 2010. Claim(s) 25, 27, and 38 have been amended. Claim(s) 39-49 have been newly added. Claim(s) 25, 27-28, 37-49 are pending and examined herein.

Response to Arguments

In view of Applicant's amendments, the 103(a) rejection of claims 25, 27, 28, and 38 as being unpatentable over Homeyer et al. (US 2,665,277) is hereby withdrawn.

In view of Applicant's amendments, the 103(a) rejection of claims 25, 27, 37, and 38 as being unpatentable over Ammar (*Egypt J. Pharmacol. Sci.*, 1994) in view of Desiraju (*Angew. Int. Ed. Engl.*, 1995) of record is hereby withdrawn.

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, 27-28, 38, and 46-49 are rejected under 35 U.S.C. 102(b) as being anticipated by Zaworotko (US Patent No. 5,994,365).

Zaworotko teaches 1,8-DAA-3,6-(Me)₂ (100 mg, 0.48 mmol) and fumaric acid (56 mg, 0.48 nmol) were ground together with mortar and pestle and dissolved in 50 mL acetone. This solution was allowed to reflux for 1 hour and cool for 24 hours with slow evaporation. Crystalline material was collected by suction filtration and confirmed to be the fumaric acid/1,8-DAA-3,6-(Me)₂ hemiacetone 1:2 cocrystal as confirmed by single X-ray crystallography (P-1; a=8.0995(28) b=8.6333(25) c=12.236(2) α =88.498(3) β =85.152(4) γ =64.360(2) (column 16, example 9), meeting the limitations of the instant claims.

Claims 39-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Zaworotko (US Patent No. 5,994,365) as applied to claims 25, 27-28, 38, and 46-49 above as evidenced by Felthouse (2001).

Zaworotko is discussed above.

As is well known by the skilled artisan fumaric acid is a food Generally Recognized As Safe (GRAS) (see FDA website) and further evidenced by Felthouse, fumaric acid is a food additive with low toxicity (page 2), and is capable of forming metal organic complexes (page 3), thus the meeting the limitations of the instant claims.

Claims 39-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Sanzu (JP-B-46-33588, employing translation submitted by Applicant 11/20/09) of record.

Sanzu teaches a novel method for producing phenazone (antipyrine) paracetamol (acetoaminophen) complex compounds. The phenazone paracetamol complex compound is obtained is a fine, white crystalline powder and is a molecular complex compound with hydrogen bonds that comprises an almost equimolar amount of phenazone and paracetamol. The melting point of this complex compound is approximately 108-110°C and the compound indicates a discontinuous IR spectrum. Thin layer chromatography proves that this complex compound comprises phenazone and paracetamol.

Sanzu teaches the phenazone paracetamol complex compound is produced by directly heating and melting an equimolar amount of the two compounds. It is also possible to produce the complex compound by dissolving or dispersing the said two compounds in water or other solvents and obtain by filtration the complex compound that precipitates out of the solvent. The complex compound thus obtained is then dried. Furthermore, when organic solvents such as acetone or alcohol are used, evaporation of the solvent after precipitation of the complex compound is also possible. To produce the complex compound by either direct heating and melting of the starting material mixture, or by precipitation from solvent, equimolar amounts of phenazone and paracetamol are usually used. Also when water is used as solvent, using equimolar amounts is preferred, but excess amounts of either phenazone or paracetamol is also acceptable. The two starting material components are added to warm water and the complex compound is allowed to crystallize. In this case, when phenazone is in excess, this remains in solution whereas when paracetamol is in excess, as this is insoluble in

water, it remains in the aqueous solvent as a suspension.

The complex compound produced by such methods comprises phenazone and paracetamol in a molar ratio of approximately 1:1 or a weight percentage of phenazone approximately 59-53%, paracetamol approximately 41-47% (see translation), meeting the limitations of the instant claims.

Conclusion

Claims 25, 27-28, 37-42, and 46-49 are not allowed.

Claims 43-45 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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 1627

/SREENI PADMANABHAN/

Application/Control Number: 10/378,956

Page 7

Art Unit: 1627

Supervisory Patent Examiner, Art Unit 1627

Notice of References Cited	Application/Control No. 10/378,956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.	
	Examiner SAHAR JAVANMARD	Art Unit 1627	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-5,994,365	11-1999	Zaworotko et al.	514/292
	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	Felthouse, "MALEIC ANHYDRIDE, MALEIC ACID, AND FUMARIC ACID", 2001, http://www.huntsman.com/performance_products/media/komaleic.pdf
	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.

<i>Index of Claims</i> 	Application/Control No. 10378956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.
	Examiner SAHAR JAVANMARD	Art Unit 1627

✓	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	09/28/2009	06/18/2010					
	1	-	-	-					
	2	-	-	-					
	3	-	-	-					
	4	-	-	-					
	5	-	-	-					
	6	-	-	-					
	7	-	-	-					
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	23	-	-	-					
	24	-	-	-					
	25	✓	✓	✓					
	26	-	-	-					
	27	✓	✓	✓					
	28	✓	✓	✓					
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	32	-	-	-					
	33	-	-	-					
	34	-	-	-					
	35	-	-	-					
	36	-	-	-					

<i>Index of Claims</i> 	Application/Control No. 10378956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.
	Examiner SAHAR JAVANMARD	Art Unit 1627

✓	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	09/28/2009	06/18/2010					
	37	✓	✓	✓					
	38	✓	✓	✓					
	39			✓					
	40			✓					
	41			✓					
	42			✓					
	43			O					
	44			O					
	45			O					
	46			✓					
	47			✓					
	48			✓					
	49			✓					

Search Notes 	Application/Control No. 10378956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.
	Examiner SAHAR JAVANMARD	Art Unit 1627

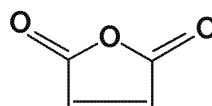
SEARCHED			
Class	Subclass	Date	Examiner
424	400 (update 6/17/10)	9/30/2008	

SEARCH NOTES		
Search Notes	Date	Examiner
EAST (searched each inventor name)(update 6/17/10)	8/31/2009	SJ
EAST (keyword search)(update 6/17/10)	8/31/2009	SJ
Pubmed	8/31/2009	SJ
Google(update 6/17/10)	8/31/2009	SJ

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

/S. J./ Examiner.Art Unit 1627	
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MALEIC ANHYDRIDE, MALEIC ACID, AND FUMARIC ACID



By

**Timothy R. Felthouse, Joseph C. Burnett, Ben Horrell,
Michael J. Mummey, and Yeong-Jen Kuo**

**Huntsman Petrochemical Corporation
Austin Laboratories
7114 North Lamar Boulevard
Austin, Texas 78752-2310**

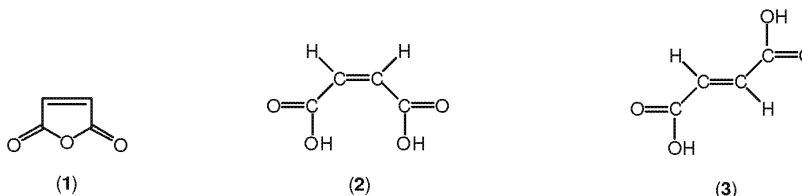
**Submitted for *Kirk Online*
April 26, 2001**

Adobe pdf file created on July 24, 2001

Note: Due to "turning off" highlights for tracking changes, the printed copy of this manuscript shows some formatting problems at the bottom of page 3 as well as Editor notes within the text for insertion of drawings, tables, and figures. The Kirk Online publication will not have these formatting problems: http://jws-edck.interscience.wiley.com:8095/kirk_articles_fs.html

MALEIC ANHYDRIDE, MALEIC ACID, AND FUMARIC ACID

Maleic anhydride [108-31-6] (1), maleic acid [110-16-7] (2), and fumaric acid [110-17-8] (3) are multifunctional chemical intermediates that find applications in nearly every field of industrial chemistry. Each molecule contains two acid carbonyl groups and a double bond in the α , β position.



Maleic anhydride and maleic acid are important raw materials used in the manufacture of phthalic-type alkyd and unsaturated polyester resins, surface coatings, lubricant additives, plasticizers (qv), copolymers (qv), and agricultural chemicals (see ALKYD RESINS; POLYESTERS UNSATURATED; LUBRICATION AND LUBRICANTS). Both chemicals derive their common names from naturally occurring malic acid [6915-15-7]. Other names for maleic anhydride are 2,5-furandione, dihydro-2,5-dioxofuran, toxilic anhydride, or *cis*-butenedioic anhydride. Maleic acid is also called (*Z*)-2-butenedioic acid, toxilic acid, malenic acid, maleinic acid, or *cis*-1,2-ethylenedicarboxylic acid.

Fumaric acid occurs naturally in many plants and is named after *Fumaria officinalis*, a climbing annual plant, from which it was first isolated. It is also known as (*E*)-2-butenedioic acid, allomaleic acid, boletic acid, lichenic acid, tumaric acid, or *trans*-1,2-ethylenedicarboxylic acid. It is used as a food acidulant and as a raw material in the manufacture of unsaturated polyester resins, quick-setting inks, furniture lacquers, paper sizing chemicals, and aspartic acid [56-84-8].

Maleic anhydride and the two diacid isomers were first prepared in the 1830s (1) but commercial manufacture did not begin until a century later. In 1933 the National Aniline and Chemical Co., Inc., installed a process for maleic anhydride based on benzene oxidation using a vanadium oxide catalyst (2). Maleic acid was available commercially in 1928 and fumaric acid production began in 1932 by acid-catalyzed isomerization of maleic acid.

Physical Properties

Physical constants (3–25) for maleic anhydride, maleic acid, and fumaric acid including solid and solution properties are given in Tables 1–3. From single crystal x-ray diffraction data (10), maleic anhydride is a nearly planar molecule with the ring oxygen atom lying 0.003 nm out of the molecular plane. A twofold rotation axis bisects the double bond and passes through the ring oxygen atom. Figure 1 summarizes the

bond distance for maleic anhydride (10). Similar bond distances and angles for maleic anhydride were obtained using electron diffraction (11) and double resonance modulation microwave spectroscopic (12) techniques. Values of the Raman polarizability were reported for single crystals of maleic anhydride (13). Density functional theory has been applied to maleic anhydride to give optimized geometry, harmonic vibrational frequencies, and electron affinity (14).

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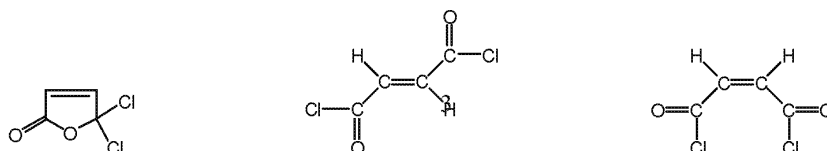
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Maleic and fumaric acids have physical properties that differ due to the cis and trans configurations about the double bond. Aqueous dissociation constants and solubilities of the two acids show variations attributable to geometric isomer effects. X-ray diffraction results for maleic acid (15) reveal an intramolecular hydrogen bond that accounts for both the ease of removal of the first carboxyl proton and the smaller dissociation constant for maleic acid compared to fumaric acid. Crystals of maleic acid usually form as twins due to the presence of lattice pseudosymmetries (16). Two crystal forms are known for fumaric acid with the monoclinic form (often also twinned) obtained by evaporation from solution (17). The triclinic form, β -fumaric acid, is formed through sublimation at 130°C under reduced pressure (18). Both maleic and fumaric acids are planar molecules with packing within the lattice into extended chains in which carboxyl groups interlink by O-H $\cdots$ O bonds into cyclic pairs (19). Maleic acid isomerizes to fumaric acid with a derived heat of isomerization of -22.7kJ/mol (-5.43kcal/mol) (21). The activation energy for the conversion of maleic to fumaric acid is 66.1kJ/mol (15.8kcal/mol) (22).

Chemical Properties

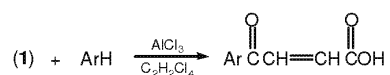
The *General References* and two other reviews (20, 26) provide extensive descriptions of the chemistry of maleic anhydride and its derivatives. The broad industrial applications for this chemistry derive from the reactivity of the double bond in conjugation with the two carbonyl oxygens.

Acid Chloride Formation. Monoacid chlorides of maleic and fumaric acid are not known. Treatment of maleic anhydride or maleic acid with various reagents such as phosgene [75-44-5] (qv), phthaloyl chloride



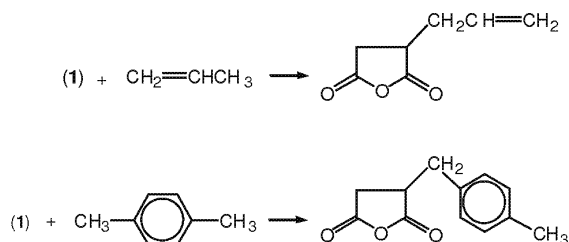
[88-95-9], phosphorus pentachloride [10026-13-8], or thionyl chloride [7719-09-7] gives 5,5-dichloro-2(5*H*)furanone [133565-92-1] (4) (27). Similar conditions convert fumaric acid to fumaryl chloride [627-63-4] (5) (27,28). Nonecyclic maleyl chloride [22542-53-6] (6) forms in 11% yield at 220°C in the reaction of one mole of maleic anhydride with six moles of carbon tetrachloride [56-23-5] over an activated carbon [7440-44-4] catalyst (29).

Acylation. In chlorinated solvents, maleic anhydride reacts with aromatic hydrocarbons (ArH) in the presence of aluminum chloride [7446-70-0], AlCl₃, to form β-aroyleacrylic acids (30).



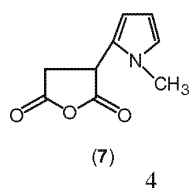
Under Friedel-Crafts conditions, *trans*-1,2-dibenzoyl ethylene [959-28-4] is synthesized by the reaction of one mole of fumaryl chloride with two moles of benzene (31) (see FRIEDEL-CRAFTS REACTIONS).

Alkylation. Maleic anhydride reacts with alkene and aromatic substrates having a C–H bond activated by α,β-unsaturation or an adjacent aromatic resonance (32,33) to produce the following succinic anhydride derivatives.



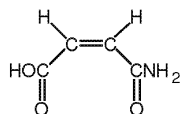
Typical reaction conditions are 150 to 300°C and up to 2 MPa pressure. Polyalkenyl succinic anhydrides are prepared under these conditions by the reaction of polyalkenes in a nonaqueous dispersion of maleic anhydride, mineral oil, and surfactant (34).

N-Alkylpyrroles react with maleic anhydride to give the electrophilic substitution product (7) and not the Diels-Alder addition product found for furan and thiophene compounds (35). However, the course of this reaction can be altered by coordination of the pyrrole compound to a metal center.

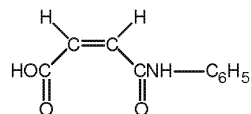


4

Amidation. Reaction of maleic anhydride or its isomeric acids with ammonia [7664-41-7] (qv), primary amines (qv), and secondary amines produces mono- or diamides. The monoamide derivative from the reaction of ammonia and maleic anhydride is called maleamic acid [557-24-4] (**8**). Another monoamide derivative formed from the reaction of aniline [62-53-3] and maleic anhydride is maleanilic acid [555-59-9] (**9**).



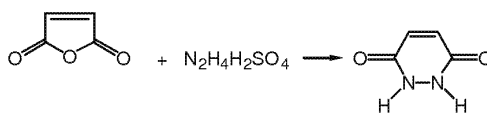
(8)



(9)

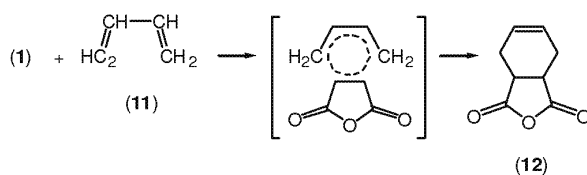
The reactions of primary amines and maleic anhydride yield amic acids that can be dehydrated to imides, polyimides (qv), or isoimides depending on the reaction conditions (36–38). However, these products require multistep processes. Pathways with favorable economics are difficult to achieve. Amines and pyridines decompose maleic anhydride, often in a violent reaction. Carbon dioxide [124-38-9] is a typical end product for this exothermic reaction (39).

Maleic hydrazide [123-33-1] (**10**) is one of a number of commercial agricultural chemicals derived from maleic anhydride. Maleic hydrazide was first prepared in 1895 (40) but about 60 years elapsed before the intermediate products were elucidated (41).

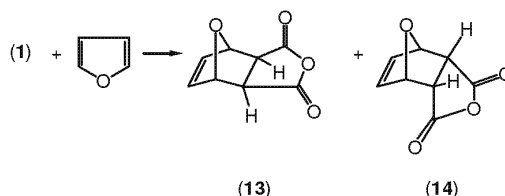


(10)

Concerted Nonpolar Reactions. Maleic anhydride exemplifies the model dienophile for cycloaddition with dienes such as 1,3-butadiene [106-99-0] (**11**) (42). Tetrahydrophthalic anhydride [85-43-8] (**12**) or its derivatives are produced in this Diels-Alder reaction.



The success of the cycloaddition reaction of maleic anhydride varies greatly depending on which heterocyclic diene is used. The cycloaddition of maleic anhydride to furan [110-00-9] occurs in a few seconds under ambient conditions (43,44). Although the endo adduct (**14**) is favored kinetically, the exo adduct (**13**) is isolated.



Endo adducts are usually favored by interactions between the double bonds of the diene and the carbonyl groups of the dienophile. As was mentioned in the section on alkylation, the reaction of pyrrole compounds and maleic anhydride results in a substitution at the 2-position of the pyrrole ring (35,45). Thiophene [110-02-1] forms a cycloaddition adduct with maleic anhydride but only under severe pressures and around 100°C (46). Addition of electron-withdrawing substituents about the double bond of maleic anhydride increases rates of cycloaddition. Both α -(carbomethoxy) maleic anhydride [69327-00-0] and α -(phenylsulfonyl) maleic anhydride [120789-76-6] react with 1,3-dienes, styrenes, and vinyl ethers much faster than tetracyanoethylene [670-54-2] (47).

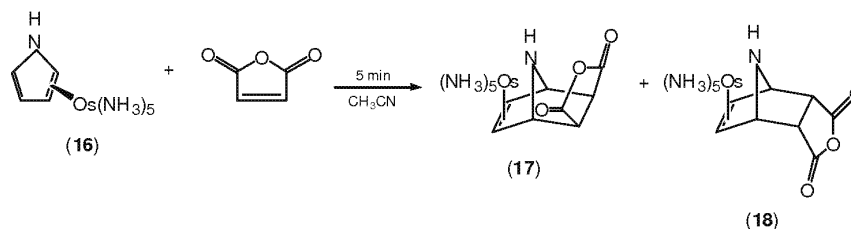
Other Diels-Alder Reactions. Since maleic anhydride, its two isomeric acids, and the alkyl- or aryl substituted acid derivations readily form Diels-Alder adducts, vegetable oil lipids such as soybean oil react in Diels-Alder fashion with these maleic or fumaric compounds to form an important class of emollients used in human skin and hair preparations (48). The preferred adduct in this class is maleated soybean oil. It is used for both cleansing and lathering properties as well as mildness and skin conditioning. (49-52). Generally, dienophiles such as maleic and fumaric compounds react readily in Diels-Alder type reactions, but use of solid Lewis acid catalysts was disclosed recently (53) for reaction of maleic acid and fumaric dienophiles with dienes such as cyclopentadiene, acrolein, furan, 4-methoxyisoxazole, and related compounds. Perfumes having a “woody odor” form from the Diels-Alder reaction of maleic anhydride with pure isomers of trimethylvinyl cyclopentenes (54). Two further reactions of the Diels-Alder adduct involving adduct reduction to the diol followed by dehydrating cyclization of the diol form the 11-oxa-tricyclo[7.3.0.0^{2,6}]dodecene derivative (**15**). Compound (**15**) and four double bond isomers represent a class of woody fragrance compounds in which the tetrahydrofuran ring adopts a trans configuration. Studies on regio- and stereochemical structural assignments of Diels-Alder adducts with maleic anhydride continue to be reported (55).

For the past 20 years, the reaction between coal and maleic anhydride has been known (56) but identification of the reactive functional groups in coal has remained a mystery. Recently, convincing evidence has been presented that suggests diene groups in coal react by way of Diels-Alder reactions to form maleic anhydride adducts. Solid-state ¹³C NMR data on the maleic anhydride-coal adduct support the Diels-Alder reaction although elemental analysis shows higher maleic anhydride content in the adduct than

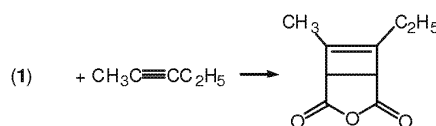
can be accounted for by solely diene groups in the coal. Nevertheless, all other possible reactions of maleic anhydride with coal were excluded including the ene reaction, polymerizations, ester formation from maleic anhydride, radical addition, Michael addition, electron transfer interaction (charge-transfer complex), and physical entrapment. While this study (57) appears to solve the mystery behind the maleic anhydride-coal reaction, it challenges current coal structures and invites further work.

Metal-Induced Cycloadditions. The effect of coordination on the metal-induced cycloadditions of maleic anhydride and the isostructural heterocycles furan, pyrrole, and thiophene has been investigated (58). Each heterocycle is bound to an Os(II) center in the complex $[(\text{NH}_3)_5\text{Os}(2,3\text{-}\eta^2\text{-L})]^{2+}$, where L= furan, pyrrole, and thiophene. Although neither the furan nor thiophene complexes react with maleic anhydride over a period of 10 days, the pyrrole complex (16) reacts rapidly at room temperature and 101.3 kPa to form a mixture of endo (18) and exo (17) complexes. An azomethine ylide intermediate was postulated as the key intermediate through which maleic anhydride added to the 2- and 5-positions of the coordinated pyrrole ring.

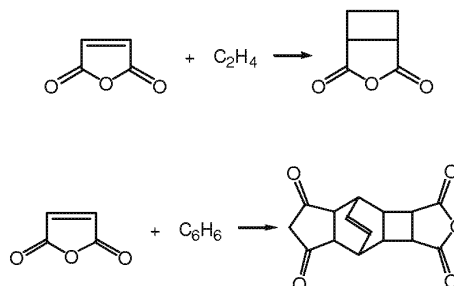
2+2 Cycloadditions. Cyclobutene adducts are formed from the reaction of acetylenic derivatives and maleic



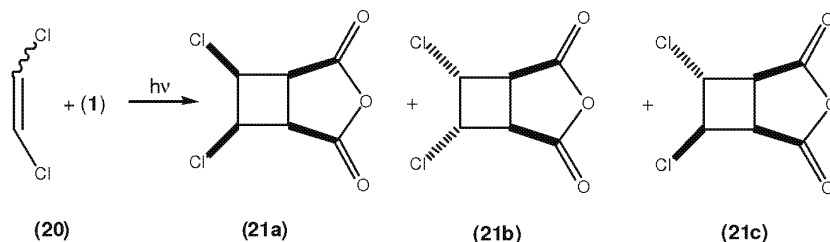
anhydride through a 2+2 cycloaddition (59). The reaction is photochemically catalyzed (see PHOTOCHEMICAL TECHNOLOGY).



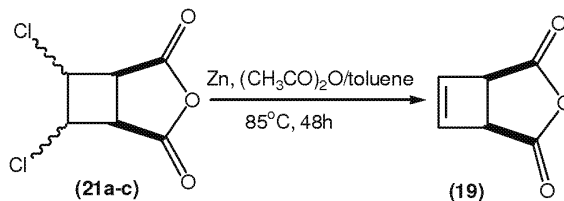
Cyclobutane derivatives are formed after exposing a mixture of alkenes and maleic anhydride to light. Photoadducts are formed by reaction of maleic anhydride with ethylene [74-85-1] (60) and benzene (61).



A new two-step route to *cis*-cyclobut-3-ene-1,2-dicarboxylic anhydride (**19**) has been described that uses [2+2] photochemical cycloaddition between (E)-1,2-dichloroethene (**20**) and maleic anhydride (**62**).



Compound (**21**) is a mixture of these dichloro isomers (**21a** = 1R*, 2S*, 3R*, 4S*; **21b** = 1R*, 2S*, 3S*, 4R*; **21c** = 1R*, 2S*, 3R*, 4R*) that in ethylacetate solvent are produced in 85% yield in the amounts of 18% (**21a**), 44% (**21b**), and 38% (**21c**). Reductive chlorine elimination of **21** with activated zinc in acetic anhydride/toluene solution gives (**19**) in 80% yield.



Ene Reaction. Maleic anhydride and maleate and fumarate esters participate in thermal ene reactions (63) with alkenes having an allylic hydrogen. An ene reaction is the thermal reaction of an alkene having an allylic hydrogen (an ene) with a compound containing a double or triple bond to form a new bond with migration of the ene double bond and 1,5-hydrogen shift. Alkenylsuccinic anhydrides are produced. ¹³C-nmr spectroscopy has been used to determine regioselectivity, selectivity for endo and exo, and selectivity for *cis* and *trans* in the reaction (200°C, 16 h) of maleic anhydride with the nine linear decene isomers (64). The results show a slight preference for maleic anhydride addition to the least hindered end of the decene isomer. Similar reaction conditions were used to form ene adducts with mono- and disubstituted oligoisobutylenes (65,66).

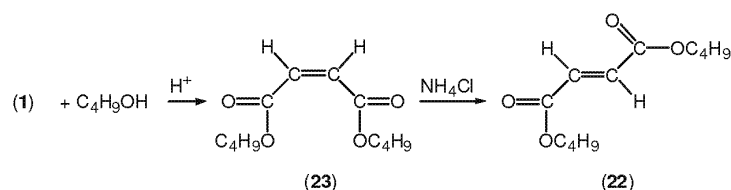
Decomposition and Decarboxylation. Maleic anhydride undergoes anaerobic thermal decomposition in the gas phase in a homogeneous unimolecular reaction to give carbon monoxide, carbon dioxide, and acetylene [74-86-2] in equimolar amounts. The endothermic ($\Delta H = +142 \text{ kJ/mol}$ (33.9 kcal/mol)) decomposition was studied in a quartz tube with and without quartz packing in the temperature range of about 370 to 490°C (67). The same linear Arrhenius plot was obtained for packed and unpacked reaction vessels. The same decomposition products were found during photolysis between 220 and 350 nm (67). Catalysts alter the

decomposition profile for maleic anhydride. The decomposition of maleic acid in an aqueous solution over a bed of Y zeolite, which contains copper and sodium at around 200°C, occurs with 95% conversion. The selectivity of the zeolite catalyst to acrylic acid [79-10-7] is 91%.

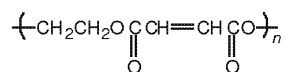
Maleic anhydride is decomposed in the liquid phase by various nitrogen bases. Treatment of maleic anhydride in refluxing acetic acid with 2-aminopyridine [504-29-0] gives, after work-up in 4 N H₂SO₄ at 100°C, the decarboxylative dimerization product, 2,3-dimethylmaleic anhydride [766-39-2] (75% yield), and CO₂ (68). Homopolymers of maleic anhydride form in the liquid phase upon addition of pyridine [110-86-1] (69,70). At a maleic anhydride/pyridine ratio of 1.64 in acetone solution at 25°C, reproducible oligomers having molecular weights of 400 to 700 are formed (70). Exothermic decomposition of maleic anhydride can occur with amines and alkali (39,69). Explosions can result from this reaction (39).

Electrophilic Addition. Electrophilic reagents attack the electron-deficient bond of maleic anhydride (26). Typical addition reagents include halogens, hydrohalic acids, and water.

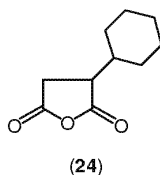
Esterification. Both mono - and dialkyl maleates and fumarates are obtained on treatment of maleic anhydride or its isomeric acids with alcohols or alkoxides (26). An extensive review is available (71). Alkyl fumarates (22) often are made from isomerization of the corresponding maleate (23) (72).



Glycols and epoxides react with maleic anhydride to give linear unsaturated polyesters (73,74). Ethylene glycol and maleic anhydride combine to form the following repeating unit. This reaction is the first step in industrially important polyester resin production (see POLYESTERS, UNSATURATED).



Free-Radical Reactions. Free-radical reactions of maleic anhydride are important in polymerizations and monomer synthesis. Nucleophilic radicals such as the one from cyclohexane [110-82-7] serve as hydrogen donors that add to maleic anhydride at the double bond to form cyclohexylsuccinic anhydride [5962-96-9] (24) (75).



Free-radical reaction rates of maleic anhydride and its derivatives depend on polar and steric factors. Substituents added to maleic anhydride that decrease planarity of the transition state decrease the reaction rate. The reactivity decreases in the order maleic anhydride > fumarate ester > maleate ester.

Grignard-Type Reactions. Grignard reagents provide nucleophilic addition to the maleyl carbonyl groups but yields are often poor (26). Phenyl addition to dimethyl maleate has been demonstrated with a palladium-based catalyst system (75). A solution of dimethyl maleate, iodobenzene [591-50-4], triethylamine [121-44-8], and palladium diacetate [19807-27-3] (1 mol %) in acetonitrile [75-05-8] after reflux for 5 h gives 39% (*Z*)-dimethyl phenylmaleate [29576-99-6] and 54% (*E*)-dimethyl phenylmaleate [29394-47-6] without loss of unsaturation.

Halogenation. Halogens add directly to the double bond of maleic anhydride to give dihalosuccinic acids. However, different procedures are used for dihalomaleic anhydride derivatives. Fluorinated C₄ substrates offer access to difluoromaleic anhydride [669-78-3] (76,77). Hexafluoro-2,5-dihydrofuran [24849-02-3] is distilled into sulfur trioxide [7446-11-9] at 25°C. Addition of trimethyl borate [121-43-7] initiates a reaction which upon heating and distillation leads to a 53% yield of difluoromaleic anhydride. The molecular structure of difluoromaleic anhydride has been determined by both gas-phase electron diffraction and microwave spectroscopy (78). Structural and theoretical data within the dihalomaleic anhydride series (X=X,F,Cl, or Br) indicate an interplay between steric and electronic effects such that neither effect accounts for the observed bond distances and angles (78). Dichloromaleic anhydride [1122-17-4] can be prepared with 92% selectivity by oxidation of hexachloro-1,3-butadiene [87-68-3] with SO₃ in the presence of iodine-containing molecules (79). Passing vaporized hexachlorobutadiene over a vanadium–phosphorus oxide catalyst also gives dichloromaleic anhydride (80). A benzene solution of tetrabromofuran [32460-09-6] can be photooxidized to dibromomaleic anhydride [1122-12-9] in 85% yield with uv light (81). Radical chain mechanisms are suggested.

Hydration and Dehydration. Maleic anhydride is hydrolyzed to maleic acid with water at room temperature (82). A process has been reported for continuous hydration of maleic anhydride at a constant temperature near 65°C in a continuous stirred tank reactor (83). By limiting the aqueous maleic anhydride acid

concentration to 40% and the temperature to below 85°C, fumaric acid will not form in higher than 0.1% by weight of the reaction mixture. Catalysts enhance formation of fumaric acid from maleic anhydride hydrolysis through maleic acid isomerization.

Hydration of fumaric acid proceeds at high temperatures and pressures to give DL-malic acid [6915-15-7], $\text{HOOCCH}_2\text{CHOHCOOH}$ (26).

Maleic acid can be thermally dehydrated to maleic anhydride (84), dehydrated from aqueous solution (85-87), or dehydrated through azeotropic distillation. Solvents such as xylenes (88) or dibutyl phthalate [84-74-2] (89) are preferred but conditions must be carefully adjusted to avoid isomerization to fumaric acid.

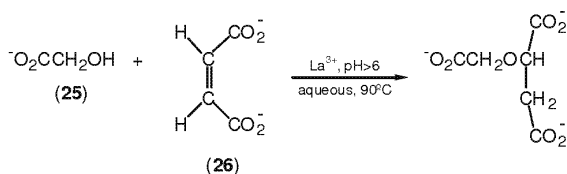
Hydroformylation. Esters of maleate and fumarate are treated with carbon monoxide and hydrogen in the presence of appropriate catalysts to give formyl derivatives. Dimethyl fumarate [624-49-7] is hydroformylated in 1:1 CO/H₂ at 100°C and 11.6 MPa pressure with a cobalt [7440-48-4] catalyst to give an 83% yield of dimethyl formylsuccinate [58026-12-3] product (90).

Isomerization. Production of maleic anhydride readily gives maleic acid by controlled hydrolysis. To avoid isomerization of maleic acid to fumaric acid, maleic acid processing must avoid conditions favorable for fumaric acid formation. Maleic acid is isomerized to fumaric acid by both thermal treatment and a variety of catalytic species. A historical account of geometric isomerism of maleic and fumaric acids is given by Ihde (91). Isomerization of maleic acid occurs above the 130 to 140°C melting point range but below a temperature of about 230°C, at which point fumaric acid is dehydrated to maleic anhydride. Derivatives of maleic acid such as acid esters can also be isomerized. Kinetic data are available for the isomerization of the cis to trans diacids in the absence of a catalyst (92,93), in the presence of thiourea catalyst (94, 95), and in the presence of both thiourea catalyst and ultrasound (95). The data suggest that neither carbonium ion nor succinate intermediates are involved in the isomerization. Rather, conjugate addition to the double bond imparts sufficient single bond character to afford rotation about the central C-C bond of the diacid (96). Highly polar solvents such as dimethylformamide (DMF) or dimethylsulfoxide (DMSO) facilitate cis to trans isomerization in the presence of 4,4'-bipyridine (97). No isomerization of maleic acid occurs in DMF or DMSO in the absence of 4,4'-bipyridine.

Ligation to Metal Atoms. Maleic anhydride and its diacid isomers coordinate to metal atoms through either the double bond or the carboxylate oxygen atoms when the diacid is deprotonated. Generally, low valent (soft) metals prefer coordination to the double bond, while high valent (hard) metals coordinate through the

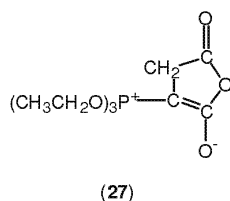
carboxylate oxygen atoms of the deprotonated diacids (98). Examples of double-bond coordination in maleic anhydride, maleic acid, and fumaric acid include molybdenum bis(maleic anhydride) carbonyl complex, $\text{Mo}(\text{CO})_2(2,3\text{-}\eta^2\text{-C}_4\text{H}_2\text{O}_3)_2(\text{CH}_3\text{CN})_2$ (99), the *endo*- and *exo*- (R,R) palladium(L)(2,3- $\eta^2\text{-C}_4\text{H}_2\text{O}_3$) complexes of maleic anhydride where L is 1-diphenylphosphino-2,1'-(1-dimethylaminopropanediyl)ferrocene (100); the singly deprotonated maleic acid complex of Cu(I), $\text{Cu}(2,3\text{-}\eta^2\text{-C}_4\text{H}_4\text{O}_4)\cdot\text{H}_2\text{O}$ (101); *cis*-tetracarbonyl (2-3- η^2 -maleic acid) iron complex, $\text{Fe}(2,3\text{-}\eta^2\text{-C}_4\text{H}_4\text{O}_4)(\text{CO})_4$ (102), and *trans*-tetracarbonyl (2-3- η^2 -fumaric acid) iron complex, $\text{Fe}(2,3\text{-}\eta^2\text{-C}_4\text{H}_4\text{O}_4)(\text{CO})_4$ (102). These structures were determined by single-crystal x-ray diffraction data. In the case of the Mo(0) complex, the trans coordinated maleic anhydride molecules are almost mutually orthogonal (85.2°) to one another. 2,3- η^2 -Maleic anhydride coordinated to Mo(0) has a central C–C bond length of 0.1420 nm (99) compared to a C–C double bond length of 0.1303 nm for maleic anhydride (10-12). This increase in the central C–C bond length suggests significant π -backbonding interaction (98). The 2,3- η^2 -maleic acid in the Cu (I) hydrogen maleate complex (101) shows the same trend with a central C-C bond length of 0.1405 (10) nm. Singly deprotonated maleic acid coordinates through symmetrical carboxylate oxygens to Zn(II) in the structure zinc maleic acid complex, $\text{Zn}(\text{O}_2\text{CCH=CHCO}_2\text{H})_2\cdot 4\text{H}_2\text{O}$ (103); through both symmetrical carboxylate oxygen atoms and the C = C bond to Cu (I) in $\text{Cu}(\eta^2\text{-C}_4\text{H}_4\text{O}_4)\cdot\text{H}_2\text{O}$ (101); through bridging carboxylate oxygen atoms (O–C–O) in the Ag (I) complex, $\text{Ag}(\text{O}_2\text{CCH=CO}_2\text{H})$ (104); and through only one carboxylate oxygen atom in the Sb (V) complex $(\text{H}_5\text{C}_6)_4\text{Sb}-(\text{O C (O)CH=CHCO}_2\text{H})$ (105). Hydrogen bonding in crystals of maleic and fumaric acid is remarkably similar in the organometallic complexes of $(2,3\text{-}\eta^2\text{-C}_4\text{H}_4\text{O}_4)\text{Fe}(\text{CO})_4$ (106), where $\text{C}_4\text{H}_4\text{O}_4$ is either maleic or fumaric acid (102). The maleate dianion coordinates to a single metal center in the Be(II) complex, $\text{K}_2[\text{Be}(\text{C}_4\text{H}_4\text{O}_4)_2]\cdot\text{H}_2\text{O}$ (107). In contrast, the coordinatively saturated $\text{Sb}(\text{C}_6\text{H}_5)_4^+$ species affords maleate bonding through only a single carboxylate oxygen atom resulting in a bridging maleate dianion between two Sb(V) centers in the compound bis(tetraphenylantimony) maleate (105).

Nucleophilic Addition. Nucleophilic reagents attack the β -carbon position in the conjugated maleic and fumaric frameworks. Basic reaction conditions favor these condensations for the addition of glycolate (25) to maleate [142-44-9] (26):



This Michael-type addition is catalyzed by lanthanum (3+) [16096-89-2] (108). Ethylene glycol [107-21-1] reacts with maleate under similar conditions (109). A wide range of nucleophilic reagents add to the maleate and fumarate frameworks including alcohols, ammonia, amines, sulfinic acids, thioureas, Grignard reagents, Michael reagents, and alkali cyanides (26).

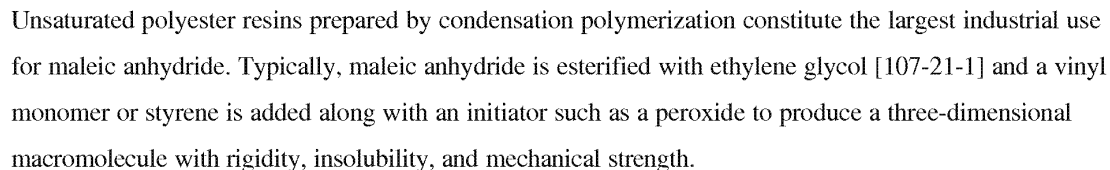
Thiols and phosphines add to maleic anhydride to give α -thiosuccinic anhydrides (110) and phosphoranylidene-maleic anhydride adducts (111). Triethyl phosphite [122-52-1] reacts with maleic anhydride to give the ylide structure (27) (112). Hydrolysis of this adduct (27) leads to succinic acid [110-15-6], maleic acid, triethyl phosphate [78-40-0], and diethyl phosphite [762-04-9].



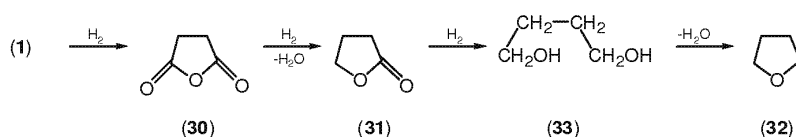
Oxidation. Maleic and fumaric acids are oxidized in aqueous solution by ozone [10028-15-6] (qv) (113). Products of the reaction include glyoxylic acid [298-12-4], oxalic acid [144-62-7], and formic acid [64-18-6]. Catalytic oxidation of aqueous maleic acid occurs with hydrogen peroxide [7722-84-1] in the presence of sodium tungstate(VI) [13472-45-2] (114) and sodium molybdate(VI) [7631-95-0] (115). Both catalyst systems avoid formation of tartaric acid [133-37-9] and produce *cis*-epoxysuccinic acid [16533-72-5] at pH values above 5. The reaction of maleic anhydride and hydrogen peroxide in an inert solvent (methylene chloride [75-09-2]) gives permaleic acid [4565-24-6], $\text{HOOC}-\text{CH}=\text{CH}-\text{CO}_3\text{H}$ (116) which is useful in Baeyer-Villiger reactions. Both maleate and fumarate [142-42-7] are hydroxylated to tartaric acid using an osmium tetroxide [20816-12-0] /iodate [15454-31-6] catalyst system (117).

Polymerization. Maleic anhydride which contains a double bond and an anhydride group is used in both addition and condensation polymerization schemes. Research since the early 1960s has shown that homopolymerization occurs using γ and uv radiation, free-radical initiators, pyridine bases, and electrochemical initiation. Although the polymerization mechanism is unknown, poly(maleic acid) has been shown recently using ^{13}C nmr spectroscopy (118) to arise from poly(maleic anhydride) in which racemic (maleic anhydride groups oriented in a *cis*-configuration across the backbone carbon chains) propagation is preferred by about a factor of two over mesomeric propagation. Melt functionalization of polypropylene has shown homopolymerization of maleic anhydride occurs up to 190°C, about 30°C higher than thought possible (119).

Aqueous ring-opening metathesis polymerization (ROMP) was first described in 1989 (153) and it has been applied to maleic anhydride (154). Furan [110-00-9] reacts in a Diels-Alder reaction with maleic anhydride to give exo-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate anhydride [6118-51-0] (**28**). The condensed product is treated with a soluble ruthenium(III) [7440-18-8] catalyst in water to give upon acidification the polymer (**29**). Several applications for this new copolymer have been suggested (154).

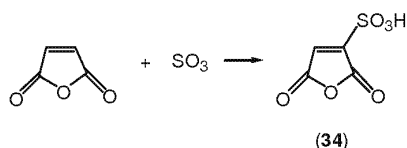


Reduction. Heterogeneous catalytic reduction processes provide effective routes for the production of maleic anhydride derivatives such as succinic anhydride [108-30-5] (**30**), succinates, γ -butyrolactone [96-48-0] (**31**), tetrahydrofuran [109-99-9] (**32**), and 1,4-butanediol [110-63-4] (**33**). The technology for production of 1,4-butanediol from maleic anhydride has been reviewed (155-159).



Several companies have developed hydrogenation technology for conversion of maleic anhydride, maleic acid, or dialkyl maleates to 1,4-butanediol or its hydrogenatable precursors γ -butyrolactone and tetrahydrofuran (160-169). These processes use maleic anhydride (166) or dialkyl maleate (160-162) in the vapor phase over heterogeneous copper catalysts in fixed-bed reactors, aqueous maleic acid over multimetallic (Pd, Ag, Re) extrudates in trickle bed reactors (163-165), or aqueous maleic acid with slurries of bimetallic (Ru, Re) carbon catalysts in slurry reactors (169). Routes to partially reduced products from maleic anhydride have been reported for succinic anhydride using a samarium (II) iodide complex with hexamethylphosphoric triamide (170) or homogeneous rhodium-phosphine catalyst (171) and succinic acid using an electrochemical route (172). γ -Butyrolactone is obtained directly over heterogeneous copper-containing catalysts (173) by hydrogenation of maleic anhydride in the gas phase.

Sulfonation. Maleic anhydride is sulfonated to α -sulfomaleic anhydride [40336-85-4] (**34**) with sulfur trioxide [7446-11-9] (174,175). Uses for this monomer have not been published.



Manufacture

Process Technology Evolution. Maleic anhydride was first commercially produced in the early 1930s by the vapor-phase oxidation of benzene [71-43-2]. The use of benzene as a feedstock for the production of maleic anhydride was dominant in the world market well into the 1980s. Several processes have been used for the production of maleic anhydride from benzene with the most common one from Scientific Design. Small amounts of maleic acid are produced as a by-product in production of phthalic anhydride [85-44-9]. This can be converted to either maleic anhydride or fumaric acid. Benzene, although easily oxidized to

maleic anhydride with high selectivity, is an inherently inefficient feedstock since two excess carbon atoms are present in the raw material. Various C₄ compounds have been evaluated as raw material substitutes for benzene in the production of maleic anhydride. Fixed- and fluid-bed processes for production of maleic anhydride from the butenes present in mixed C₄ streams have been practiced commercially. None of these processes is currently in operation.

Rapid increases in the price of benzene and the recognition of benzene as a hazardous material intensified the search for alternative process technology in the United States. These factors led to the first commercial production of maleic anhydride from butane [106-97-8] at Monsanto's J. F. Queeny plant in 1974. By the early 1980s, the conversion of the U.S. maleic anhydride manufacturing capacity from benzene to butane feedstock was well under way using catalysts developed by Monsanto, Denka, and Halcon. One factor that inhibited the conversion of the installed benzene-based capacity was that early butane-based catalysts were not active and selective enough to allow the conversion of benzene-based plant without significant loss of nameplate capacity. In 1983, Monsanto started up the world's first butane-to-maleic anhydride plant, incorporating an energy efficient solvent-based product collection and refining system. This plant was the world's largest maleic anhydride production facility in 1983 at 59,000t/yr capacity, and through rapid advances in catalyst technology has been debottlenecked to a current capacity of 105,000t/yr (1999). Advances in catalyst technology, increased regulatory pressures, and continuing cost advantages of butane over benzene have led to a rapid conversion of benzene- to butane-based plants. By the mid-1980s in the United States 100% of maleic anhydride production used butane as the feedstock.

Coincident with the rapid development of the butane-based fixed-bed process, several companies have developed fluidized-bed processes. Two companies, Badger and Denka, collaborated on the development of an early fluid-bed reaction system which was developed through the pilot-plant stage but was never commercialized. Three fluid-bed, butane-based technologies were commercialized during the latter half of the 1980s by Mitsubishi Kasei, Sohio (British Petroleum), and Alusuisse. A second fluidized-bed technology for the oxidation of butane to maleic anhydride, known as transport bed, has been developed by Du Pont. A world-scale plant in Spain for the production of THF by the hydrogenation of maleic acid using this technology began production in 1996 (177).

Europe has largely converted from benzene-based to butane-based maleic anhydride technology with the construction of several new butane based facilities by CONDEA-Huntsman, Pantochim and Lonza. Growth in the worldwide maleic anhydride industry is predominantly in the butane-to-maleic anhydride route, often at the expense of benzene-based production. Table 4 shows 1993 and 2000 worldwide maleic production

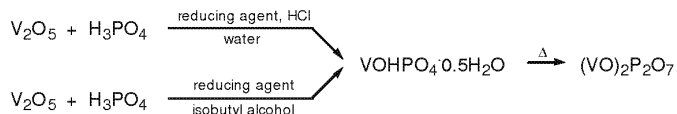
capacity broken down in categories of fixed-bed benzene, fixed-bed butane, fluidized-bed butane, and phthalic anhydride coproduct. As can be seen from this table, both fixed- and fluidized-bed butane routes have grown dramatically with the fixed-bed route adding 336,000t/yr capacity compared to 90,000t/yr for the fluid-bed process. Only a few newer benzene-based fixed-bed processes have been built since the early 1980s and these were built where the availability of butane was limited. The fluidized-bed butane-based process is experiencing some growth, but based on growth rates from Table 4 (178,179), it does not appear destined to challenge fixed-bed technology. The announcement from Huntsman Specialty Chemicals Corp., formerly Monsanto, and DWE (180), that they intend to cooperate in the development of catalyst and reactor technology to permit operation at 50% higher productivity than the standard nonflammable fixed-bed butane process indicates that the largest companies in fixed-bed technology are confident that further advances are possible. Three fixed-bed processes, from Huntsman (181), Pantochim (182), and Scientific Design (183) and two fluidized-bed processes, from Alusiusse-Lummus (ALMA) (184) and BP Chemicals (185), are currently offered for license.

Placeholder for Float Table 4.

Butane-Based Catalyst Technology. The increased importance of the butane-to-maleic anhydride conversion route has resulted in efforts being made to understand and improve this process. Since 1980, over 225 U.S. patents have been issued relating to maleic anhydride technology. The predominant area of research concerns the catalyst because it is at the heart of this process. The reasons for this statement are twofold. First, there is the complexity of this reaction: for maleic anhydride to be produced from butane, eight hydrogen atoms must be abstracted, three oxygen atoms inserted, and a ring closure performed. This is a 14-electron oxidation that occurs exclusively on the surface of the catalyst. The second reason for the emphasis placed on the catalyst is that all of the commercial processes use the same catalyst. This catalyst is the only commercially viable system that selectively produces maleic anhydride from butane.

The catalyst used in the production of maleic anhydride from butane is vanadium–phosphorus–oxide (VPO). Several routes may be used to prepare the catalyst (186-188), but the route favored by industry involves the reaction of vanadium (V) oxide [1314-62-1] and phosphoric acid [7664-38-2] to form vanadyl hydrogen phosphate, $\text{VOHPO}_4 \cdot 0.5\text{H}_2\text{O}$. This material is then heated to eliminate water from the structure and irreversibly form vanadyl pyrophosphate, $(\text{VO})_2\text{P}_2\text{O}_7$ (186,189). Vanadyl pyrophosphate is believed to be the catalytically active phase required for the conversion of butane to maleic anhydride (190,191).

The reaction of V_2O_5 with H_3PO_4 to form $VOHPO_4 \cdot 0.5H_2O$ can be carried out in either an aqueous or organic medium such as isobutyl alcohol [78-83-1] (88,186). Two possible routes are as follows.



The use of an organic medium yields an increase in the surface area of the $VOHPO_4 \cdot 0.5H_2O$ (88,191). This increase in surface area is carried over to the resulting vanadyl pyrophosphate phase (186) and is desirable because a concurrent increase in activity toward butane oxidation is observed (88, 192). Alternatively, some patented technologies purport precursors as intercalation compounds with the formula $VOHPO_4 \cdot 0.5H_2O \cdot (C_nH_{2n+1})_zX$, where $1.5 < z < 1.9$, $0 < n < 20$, and X = oxygen, nitrogen, or sulfur containing functional group that forms hydrogen bonds with the $VOHPO_4$ layers (193,194). The use of vanadyl phosphite as a precursor is also claimed (195,196). Other routes to effective precursors have focused on co-solvents, cluster compounds or heteropolyacids as starting materials (193, 197-201).

An additional effect of the use of an organic medium in the catalyst preparation is creation of more defects in the crystalline lattice when compared to a catalyst made by the aqueous route (186). These defects persist in the active phase and are thought to result in creation of strong Lewis acid sites on the surface of the catalysts (186,202). These sites are viewed as being responsible for the activation of butane on the catalyst surface by means of abstraction of a hydrogen atom, as supported by a recent detailed FTIR spectroscopic investigation (203).

There are two types of patented technologies for the transformation of $VOHPO_4 \cdot 0.5H_2O$ into $(VO)_2P_2O_7$ (88). In the first procedure, the vanadyl hydrogen phosphate is transformed through heating to 415°C in a controlled environment with combinations of nitrogen, air, and steam (204). The second procedure is an *in situ* process that transforms the vanadyl hydrogen phosphate into the active phase while the catalyst is placed in the maleic reactor (205). This procedure entails slow heating of the catalyst in air with gradual introduction of butane to the gas stream. The use of the *in situ* activation method requires little capital investment. However, the possibility of inhomogenities in the activated catalyst exists due to nonuniformities in reactor flow distribution. On the other hand, the controlled environment procedure reduces plant downtime and increases the homogeneity of the catalyst in the reactor.

Promoters are sometimes added to the vanadium phosphorus oxide (VPO) catalyst during synthesis (205-211) to increase its overall activity and/or selectivity. Promoters may be added during formation of the catalyst precursor ($\text{VOHPO}_4 \cdot 0.5\text{H}_2\text{O}$), or impregnated onto the surface of the precursor before transformation into its activated phase. They are thought to play a twofold structural role in the catalyst (206). First, promoters facilitate transformation of the catalyst precursor into the desired vanadium phosphorus oxide active phase, while decreasing the amount of nonselective VPO phases in the catalyst. For example, a molybdenum containing VPO catalyst tends to decrease the amount of certain undesirable by-products including acrylic acid (212,213). The second role of promoters is to participate in formation of a solid solution, which controls the activity of the catalyst.

The bulk structure of the catalytically active phase is not completely known and is under debate in the literature (190,214-216). The central point of controversy is whether $(\text{VO})_2\text{P}_2\text{O}_7$ alone or in combination with other phases is the most catalytically active for the conversion of butane to maleic anhydride. The heart of this issue concerns the role of structural disorder in the bulk and how it arises in the catalyst (190,217,218). Most researchers agree that the catalysts with the highest activity and selectivity are composed mainly of $(\text{VO})_2\text{P}_2\text{O}_7$ that exhibits a clustered or distorted platelet morphology (190). It is also generally acknowledged that during operation of the catalyst, the bulk oxidation state of the vanadium in the catalyst remains very close to the +4 valence state (190).

Only the surface layers of the catalyst solid are generally thought to participate in the reaction (190,216). This implies that while the bulk of the catalyst may have an oxidation state of 4+ under reactor conditions, the oxidation state of the surface vanadium may be very different. It has been postulated that both V^{4+} and V^{5+} oxidation states exist on the surface of the catalyst, the latter arising from oxygen chemisorption (216). Phosphorus enrichment is also observed at the surface of the catalyst (190,191). The exact role of this excess surface phosphorus is not well understood, but it may play a role in active site isolation and consequently, the oxidation state of the surface vanadium.

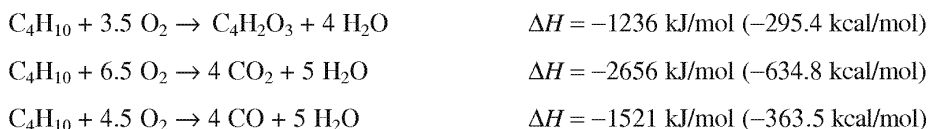
Vanadium phosphorus oxide-based catalysts are unstable in that they tend to lose phosphorus over time at reaction temperatures. Hot spots in fixed-bed reactors tend to accelerate this loss of phosphorus. This loss of phosphorus also produces a decrease in selectivity (88,219). Many steps have been taken, however, to alleviate these problems and create an environment where the catalyst can operate at lower temperatures. For example, volatile organophosphorus compounds are fed to the reactor to mitigate the problem of phosphorus loss by the catalyst (220). The phosphorus feed also has the effect of controlling catalyst activity and thus improving catalyst selectivity in the reactor. The catalyst pack in the reactor may be

stratified with an inert material (221-223). Stratification has the effect of reducing the extent of reaction per unit volume and thus reducing the observed hot spots in catalyst temperature (223). Aluminizing the reactor wall that is in contact with the catalyst also minimizes undesirable side reactions (224). These measures have minimized concerns of heat removal in the reactor and improved catalyst performance.

Fluidized-bed reactor systems put other unique stresses on the VPO catalyst system. The mixing action inside the reactor creates an environment that is too harsh for the mechanical strength of a vanadium phosphorus oxide catalyst, and thus requires that the catalyst be attrition resistant (184,225-229). To achieve this goal, vanadium phosphorus oxide is usually spray dried with colloidal silica [7631-86-9] or polysilicic acid [1343-98-2]. Vanadium phosphorus oxide catalysts made with colloidal silica are reported to have a loss of selectivity, while no loss in selectivity is reported for catalysts spray dried with polysilicic acid (225). Even with the increased mechanical properties, the continuous operation of a fluidized-bed or recirculating solids reactor subjects the catalyst to harsh enough conditions such that even the strongest catalyst is eventually reduced to extremely fine material which is lost from the reactor. The catalyst inventory therefore diminishes and needs to be replenished. To maintain maleic anhydride production levels, fresh catalyst needs to be constantly added to the system (230) or some means to regenerate the catalyst must be employed (231-233). While a supported VPO catalyst is not yet operated commercially, there are efforts to develop such a catalyst (234-236).

Benzene-Based Catalyst Technology. The catalyst used for the conversion of benzene to maleic anhydride consists of supported vanadium oxide [11099-11-9]. The support is an inert oxide such as kieselguhr, alumina [1344-28-1], or silica, and is of low surface area (237). Supports with higher surface area adversely affect conversion of benzene to maleic anhydride. The conversion of benzene to maleic anhydride is a less complex oxidation than the conversion of butane, so higher catalyst selectivities are obtained. The vanadium oxide on the surface of the support is often modified with molybdenum oxides. There is approximately 70% vanadium oxide and 30% molybdenum oxide [11098-99-0] in the active phase for these fixed-bed catalysts (238). The molybdenum oxide is thought to form either a solid solution or compound oxide with the vanadium oxide and result in a more active catalyst (237).

Butane-Based Fixed-Bed Process Technology. Maleic anhydride is produced by reaction of butane with oxygen using the vanadium phosphorus oxide heterogeneous catalyst discussed earlier. The butane oxidation reaction to produce maleic anhydride is very exothermic. The main reaction by-products are carbon monoxide and carbon dioxide. Stoichiometries and heats of reaction for the three principal reactions are as follows:



Air is compressed to modest pressures, typically 100 to 200 kPa (~15–30 psig) with either a centrifugal or axial compressor, and mixed with superheated vaporized butane. Static mixers are normally employed to ensure good mixing. Butane concentrations are often limited to less than 1.7 mol % to stay below the lower flammable limit of butane (239). Operation of the reactor at butane concentrations below the flammable limit does not eliminate the requirement for combustion venting, and consequently most processes use rupture disks on both the inlet and exit reactor heads. A flow diagram of the Huntsman fixed-bed maleic anhydride process is shown in Figure 2.

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Fig. 2: Schematic flow diagram of the Huntsman fixed-bed maleic anhydride process. MA=maleic anhydride.

The highly exothermic nature of the butane-to-maleic anhydride reaction and the principal by-product reactions require substantial heat removal from the reactor. Thus the reaction is carried out in what is effectively a large multitubular heat exchanger which circulates a mixture of 53% potassium nitrate [7757-79-1], KNO_3 ; 40% sodium nitrite [7632-00-0], NaNO_2 ; and 7% sodium nitrate [7631-99-4], NaNO_3 . Reaction tube diameters are kept at a minimum 25–30 mm in outside diameter to facilitate heat removal. Reactor tube lengths are between 3 and 6 meters. The exothermic heat of reaction is removed from the salt mixture by the production of steam in an external salt cooler. Reactor temperatures are in the range of 390 to 430°C. Despite the rapid circulation of salt on the shell side of the reactor, catalyst temperatures can be 40 to 60°C higher than the salt temperature. The butane to maleic anhydride reaction typically reaches its maximum efficiency (maximum yield) at about 85% butane conversion. Reported molar yields are typically 50 to 60%.

Efficient utilization of waste heat from a maleic anhydride plant is critical to the economic viability of the plant. Often site selection is dictated by the presence of an economic use for by-product steam. The steam can also be used to drive an air compressor, generate electricity, or both. Alternatively, an energy consuming process, such as a butanediol plant, can be closely coupled with the maleic anhydride plant. Several such

plants have been announced (240). Design and integration of the heat recovery systems for a maleic anhydride plant are very site specific. Heat is removed from the reaction gas through primary and sometimes secondary heat exchangers. In addition to the heat recovered from the reactor and process gas heat exchangers, additional heat can be recovered from the destruction of unreacted butane, the carbon monoxide by-product, and other by-products which cannot be vented directly to the atmosphere. This destruction is done typically in a specially designed thermal oxidizer or a modified boiler.

Reactor operation at 80 to 85% butane conversion to produce maximum yields provides an opportunity for recycle processes to recover the unreacted butane in the stream that is sent to the oxidation reactor. Patents have been issued on recycle processes (241) both with and without added oxygen. Pantochim has announced the commercialization of a partial recycle process (182). Mitsubishi Chemical Corporation has announced plans to add butane recovery from the offgas of their fluid bed process through the use of BOC Gases' proprietary selective hydrocarbon separation system (PETROX) (242). This technology is particularly well suited to use in fluid bed processes where the hydrocarbon to air ratio is relatively high and in world areas where butane has a high value relative to its energy content. Operation of the butane to maleic anhydride process in a total recycle configuration can produce molar yields that approach the reaction selectivity which is typically 65 to 75%, significantly higher than the 50 to 60% molar yields from a single pass, high conversion process. The Du Pont transport bed process achieves its high reported yields at least partially through implementation of recycle technology. Recovery of the fuel value of the butane in the off-gas from a single pass configuration plant reduces the economic attractiveness of recycle operation.

Butane-Based Fluidized-Bed Process Technology. Fluidized-bed processes offer the advantage of excellent control of hot spots by rapid catalyst mixing, simplification of safety issues when operating above the flammable limit, and a simplified reactor heat-transfer system. Some disadvantages include the effect of back mixing on the kinetics in the reactor, product destruction and by-product reactions in the space above the fluidized bed, and vulnerability to large-scale catalyst releases from explosion venting.

A schematic flow diagram for the ALMA fluidized-bed process is shown in Figure 3 (184). Compressed air and butane are typically introduced separately into the bottom of the fluidized-bed reactor. Heat from the exothermic reaction is removed from the fluidized bed through steam coils in direct contact with the bed of fluidized solids. Fluidized-bed reactors exploit the extremely high heat-transfer coefficient between the bed of fluidized solids and the steam coils. This high heat-transfer coefficient allows a relatively small heat-transfer area in the fluid-bed process for the removal of the heat of reaction compared to the fixed-bed process. Gas flow patterns in a commercial scale fluid-bed reactor are generally backmixed, which can lead

to maleic anhydride destruction. Patents have been issued for mechanical modifications to the reactor internals that claim to control backmixing (243). Other methods to reduce backmixing include introduction of catalyst fines (small particles of catalyst) to decrease bubble size and operation of the reactor in the turbulent, fast fluidization regime in an attempt to minimize bubbling (225). Fluidized-bed reactors require a significant amount of space above the catalyst level to allow the solids to separate from the gases. This exposure of the product to high temperatures at relatively long residence times can lead to side reactions and product destruction. Fluidized-bed processes are operated at high butane concentrations (184) but at longer gas residence times than fixed-bed processes.

Placeholder for Figure 3 (malefelt.a01/f003.eps).

Fig. 3: Schematic flow diagram of the ALMA fluidized-bed process (184). BFW=boiler feed water.

The product stream contains gases and solids. The solids are removed by using either cyclones, filters, or both in combination. Cyclones are devices used to separate solids from fluids using vortex flow. The product gas stream must be cooled before being sent to the collection and refining system. The ALMA process uses cyclones as a primary separation technique with filters employed as a final separation step after the off-gas has been cooled and before it is sent to the collection and refining system (243). As in the fixed-bed process, the reactor off-gas must be incinerated to destroy unreacted butane and by-products before being vented to the atmosphere.

Fluidized-bed reaction systems are not normally shut down for changing catalyst. Fresh catalyst is periodically added to manage catalyst activity and particle size distribution. The ALMA process includes facilities for adding back both catalyst fines and fresh catalyst to the reactor.

Butane-Based Transport-Bed Process Technology. Du Pont announced the commercialization of a moving-bed recycle-based technology for the oxidation of butane to maleic anhydride (176,244). Although maleic anhydride is produced in the reaction section of the process and could be recovered, it is not a direct product of the process. Maleic anhydride is recovered as aqueous maleic acid for hydrogenation to tetrahydrofuran [109-99-9] (THF).

The reaction technology known as transport bed is a circulating solids technology where the oxygen required in the oxidation of butane to maleic anhydride is provided by the VPO catalyst and the catalyst is reoxidized in a separate step. The exclusion of gas-phase oxygen from the reaction step is claimed to enhance selectivity (225,246). Separation of butane oxidation from catalyst reoxidation allows both steps to be

independently optimized. The circulating solids system is similar to catalytic cracking as can be seen from an examination of Figure 4.

Placeholder for Figure 4 (malefelt.a01/f004.eps).

Fig. 4: Du Pont transport-bed process for making THF from butane (176).

Fresh butane mixed with recycled gas encounters freshly oxidized catalyst at the bottom of the transport-bed reactor and is oxidized to maleic anhydride and CO_x during its passage up the reactor. Catalyst densities ($80\text{--}160\text{kg/m}^3$) in the transport-bed reactor are substantially lower than the catalyst density in a typical fluidized-bed reactor ($480\text{--}640\text{kg/m}^3$) (176). The gas flow pattern in the riser is nearly plug flow which avoids the negative effect of backmixing on reaction selectivity. Reduced catalyst is separated from the reaction products by cyclones and is further stripped of products and reactants in a separate stripping vessel. The reduced catalyst is reoxidized in a separate fluidized-bed oxidizer where the exothermic heat of reaction is removed by steam coils. The rate of reoxidation of the VPO catalyst is slower than the rate of oxidation of butane, and consequently residence times are longer in the oxidizer than in the transport-bed reactor.

Maleic anhydride in the product stream is removed and converted to a maleic acid solution in a water scrubbing system. The maleic acid is sent to the hydrogenation to produce THF while the reactor off-gas after scrubbing is sent to the recycle compressor. A small purge stream is sent to incineration.

Benzene-Based Fixed-Bed Process Technology. The benzene fixed-bed process is very similar to the butane fixed-bed process and, in fact, the Scientific Design butane process has evolved directly from its benzene process. Benzene-based processes are easily converted to butane-based processes. Typically, only a catalyst change, installation of butane handling equipment, and minor modifications to the recovery process are required. The benzene reaction is a vapor-phase partial oxidation reaction using a fixed-bed catalyst of mixed vanadium and molybdenum oxides. The reactors used are the same multitubular reactors cooled by circulating a molten mixture of $\text{KNO}_3\text{--NaNO}_2\text{--NaNO}_3$ salts described in the previous section on the butane process. The benzene concentrations used are about 1.5 mol % or just below the lower flammable limit of benzene in air. Unlike the butane reaction, the reactor normally operates at conversions greater than 95% and molar yields greater than 70%. The benzene oxidation reaction runs a little cooler than the butane oxidation reaction with typical reactor temperatures being in the 350 to 400°C range.

The reactor off-gas is cooled by one or more heat exchangers and sent to the collection and refining section of the plant. Unreacted benzene and by-products are incinerated.

Recovery and Purification. All processes for the recovery and refining of maleic anhydride must deal with the efficient separation of maleic anhydride from the large amount of water produced in the reaction process. Recovery systems can be separated into two general categories: aqueous- and nonaqueous-based absorption systems. Solvent-based systems have a higher recovery of maleic anhydride and are more energy efficient than water-based systems.

The Huntsman solvent-based collection and refining system will be used as a generic model for solvent-based recovery systems (see Fig. 2). The reactor exit gas is cooled in two heat exchangers for energy recovery. The cooled gas product stream is passed to a solvent absorber where a proprietary solvent is used to absorb, almost completely, the maleic anhydride contained in the product stream. The solvent stream, coming from the bottom of the absorber with a high concentration of maleic anhydride, known as rich oil, is sent to a stripper where the rich oil is heated and maleic anhydride is vacuum stripped from the solvent. The vacuum-stripped maleic anhydride is typically greater than 99.8% purity, and is sent to the purification section of the plant where it is batch distilled to produce extremely pure maleic anhydride. A small slip stream of the solvent which has had the maleic anhydride removed by stripping is sent to the solvent purification section of the plant where impurities are removed.

The Scientific Design water-based collection and refining system is in broad use throughout the world in butane-based and benzene-based plants (183,247). The reactor off-gas is cooled from reaction temperatures in a gas cooler with generation of steam. The off-gas is then sent to a tempered water-fed aftercooler where it is cooled below the dew point of maleic anhydride. The liquid droplets of maleic anhydride are separated from the off-gas by a separator. The condensed crude is pumped to a crude tank for storage. The maleic anhydride remaining in the gas stream after partial condensation is removed in a water scrubber by conversion to maleic acid which accumulates in the acid storage section at the bottom of the scrubber. The acid solution is converted to crude maleic anhydride in a dual purpose dehydrator/refiner. Xylene [1330-20-1] is used as an azeotropic agent for the conversion of maleic acid to maleic anhydride. Water from the dehydration step is recycled to the scrubber. When the conversion of the acid solution to crude maleic anhydride is complete, condensed crude maleic anhydride is added to the still pot and a batch distillation refining step is conducted.

The UCB collection and refining technology (owned by BP Chemicals (185,248-250)) also depends on partial condensation of maleic anhydride and scrubbing with water to recover the maleic anhydride present in the reaction off-gas. The UCB process departs significantly from the Scientific Design process when the

maleic acid is dehydrated to maleic anhydride. In the UCB process the water in the maleic acid solution is evaporated to concentrate the acid solution. The concentrated acid solution and condensed crude maleic anhydride is converted to maleic anhydride by a thermal process in a specially designed reactor. The resulting crude maleic anhydride is then purified by distillation.

Fumaric Acid. Fumaric acid for commerce is derived from maleic acid through catalytic isomerization. Purified maleic anhydride is the main source of maleic acid. In addition, crude maleic acid may be used as recovered in benzene oxidation or phthalic anhydride manufacture (23). Numerous catalysts exist for maleic acid isomerization (92-94) but three types are widely used: mineral acids (251), peroxycompounds with bromides (252) and bromates (253), and sulfur-containing compounds such as thiourea [62-56-6] (94) and its derivatives (254). Little change in process technology has occurred since the 1970s. Processing is simplest with purified maleic anhydride as the raw material. High purity fumaric acid is produced through crystallization of the aqueous mixture, washing, and drying (255). A process for recovery of fumaric acid from molten maleic anhydride refining has been described (256). Decolorizing and crystallization techniques are used to treat impure maleic solutions (257).

Shipment

Molten maleic anhydride is shipped in tank rail cars, tank trucks, and isotanks (for overseas shipments). Tank rail cars are typically constructed of lined carbon steel and are insulated and equipped with steam coils. Tank rail cars of up to 20k gallons are used. Tank trucks are typically constructed of stainless steel [12597-68-1], insulated, and equipped with steam coils. Tank trucks of up to 4.5k gallons are used. Isotanks are typically constructed of stainless steel and are insulated and equipped with steam coils. Isotanks of up to 4.5k gallons are used.

Solid form maleic anhydride is produced from molten maleic anhydride as briquettes or pastilles weighing 0.5 to 20 g. Flaked maleic anhydride is used in some areas of the world but is not generally accepted in the United States because of the high dust content. Briquettes or pastilles are packed in 50-lb or 25-kg bags and supersacks of up to 2500 lbs (1136 kg). Outside the United States, the standard bag weight is 25 kg. Typical bag construction is either polyethylene or multi-ply paper with at least one polyethylene layer. Solid form maleic anhydride can be stored in bags for several months in a cool, dry location.

Fumaric acid is shipped in solid form, the particle size varying based upon the specification. The standard shipping containers are 50-lb bags (25kg bags outside the United States), supersacks of up to 2500 lbs, and occasionally bulk hopper truck.

Economic Aspects

Data for the production and sales of maleic anhydride and fumaric acid in the United States between 1986 and 2000 are shown in Table 5 (258,259). Production of maleic anhydride during this time period grew ~3% on average per annum with production downturns reaching a minimum in 1991. Production of fumaric acid in the United States has declined during the same period as producers in the United States have rationalized and customers have switched to the less costly maleic anhydride in all applications where that is possible. Table 6 presents the producers of maleic anhydride in the United States as of 2000 (258). All production of maleic anhydride in the United States in 2000 was butane-based using fixed-bed reactor technology. Only one producer of fumaric acid remained in the United States in 2000 as shown in Table 6. Bartek in Canada does represent a significant factor in the supply of fumaric acid to the United States. The Bartek facility has a capacity of 17.3 kt/yr, out of which fumaric acid production is tolled for Huntsman.

Placeholder for Float Table 5 (KO Table 5.doc)

Placeholder for Float Table 6 (KO Table 6.doc)

Capacities of maleic anhydride facilities worldwide are presented in Table 7. The switch of feedstock from benzene to butane was completed in the United States in 1985, being driven by the lower unit cost and lower usage of butane in addition to the environmental pressures on the use of benzene. Worldwide, the switch from benzene to butane is continuing.

Placeholder for Float Table 7 (KO Table 7.doc)

Between 1992 and 2000, maleic anhydride capacity increases have been pronounced in Asia. This has resulted in a significant oversupply situation in that world area. Western Europe has also experienced a pronounced increase in capacity. North America has experienced a relatively modest increase in capacity which resulted from the construction of a new plant, debottlenecks of existing plants, and one rationalization.

Specifications

The general sales specification under which maleic anhydride is sold in the United States specifies a white fused mass or briquettes of 99.5% minimum assay and 52.5°C minimum crystallization point. The melt

color specification is 20 APHA maximum with a maximum APHA color of 40 after two hours of heating at 140°C. The solution of 4 grams of maleic anhydride in 10 milliliters of water are to be complete and that solution to be colorless. The acidity as maleic acid is a maximum of 0.2%.

Fumaric acid is sold as resin-grade and food-grade. The general sales specification under which resin-grade fumaric acid is sold in the United States specifies white, crystalline granules with a minimum assay of 99.6% and maximum ash content of 0.05%. The moisture specification is 0.3% maximum with <10ppm heavy metals. The color of a 5% solution in methanol is to be less than 10 APHA. Food-grade fumaric acid calls for somewhat lower impurity levels. Particle size and particle size distribution are important in many applications.

Analytical and Test Methods

The test methods used by industry to determine if a sample of maleic anhydride is within specifications (260) are ASTM methods D2930, D1493, and D3366. These methods describe procedures for the determination of maleic acid content, the crystallization point, and the color properties of the maleic anhydride sample, respectively. By quantitative determination of these properties, a calculation of the overall purity of the maleic anhydride sample can be made.

The free maleic acid content in maleic anhydride is determined by direct potentiometric titration (261). The procedure involves the use of a tertiary amine, *N*-ethylpiperidine [766-09-6], as a titrant. A tertiary amine is chosen as a titrant since it is nonreactive with anhydrides (261,262). The titration is conducted in an anhydrous solvent system. Only one of the carboxylic acid groups is titrated by this procedure. The second hydrogen's dissociation constant is too weak to titrate (261). This test method is not only used to determine the latent acid content in refined maleic anhydride, but also as a measure of the sample exposure to moisture during shipping.

The other two methods used by industry to examine the purity of maleic anhydride are the crystallization point (263) and color determination of the sample (264). These tests determine the temperature at the point of solidification of the molten sample and the initial color properties of the melt. Furthermore, the color test also determines the color of the sample after a two-hour heat treatment at 140°C. The purpose of these tests is to determine the deviation in properties of the sample from those of pure maleic anhydride. This deviation is taken as an indication of the amount of contaminants in the maleic anhydride sample. Six international test standards relating to maleic anhydride have been published (265) that include crystallization point determination, color of molten maleic anhydride, free acidity using potentiometric method, maleic

anhydride content using a titrimetric method, ash determination, and determination of iron content in maleic anhydride.

Other analytical techniques are also available for the determination of maleic anhydride sample purity. For example, maleic anhydride content can be determined by reacting it with a known excess of aniline [62-53-3] in an alcohol mixture (266). The solution is then titrated with an acid to determine the amount of unconsumed aniline. This number is then used to calculate the amount of maleic anhydride reacted and thus its concentration. Another method of a similar type has also been reported (267).

Finally, the techniques of nmr, infrared spectroscopy, and thin-layer chromatography also can be used to assay maleic anhydride (268). Maleic anhydride has been analyzed by gas chromatography (269,270) and a detailed review of this analysis has appeared (271) focusing on the products formed during n-butane oxidation. The isomeric acids can be determined by polarography (272), thermal analysis (273), paper and thin-layer chromatographies (274), and nonaqueous titrations with an alkali (275), ion-exclusion chromatography (276), isotachopheresis (277), and high-pressure liquid chromatography (278,279). Maleic and fumaric acids may be separated by both gel filtration (280) and ion-exchange techniques (281).

Health and Safety Factors (Toxicology)

Maleic Anhydride. The ACGIH threshold limit value in air for maleic anhydride is 0.25 ppm and the OSHA permissible exposure level (PEL) is also 0.25 ppm (282). Maleic anhydride is a corrosive irritant to eyes, skin, and mucous membranes. Pulmonary edema (collection of fluid in the lungs) can result from airborne exposure. Skin contact should be avoided by the use of rubber gloves. Dust respirators should be used when maleic anhydride dust is present. Maleic anhydride is combustible when exposed to heat or flame and can react vigorously on contact with oxidizers. The material reacts exothermically with water or steam. Violent decompositions of maleic anhydride can be catalyzed at high temperature by strong bases (sodium hydroxide, potassium hydroxide, calcium hydroxide, alkali metals, amines, etc.). Precaution should be taken during the manufacture and use of maleic anhydride to minimize the presence of basic materials in maleic anhydride.

Maleic Acid. Maleic acid is produced by the hydration of maleic anhydride. The hazards of its use are analogous to those of maleic anhydride. It is a skin and severe eye irritant. It is combustible when exposed to heat or flame. As discussed above, contamination with bases should be avoided where the material is to be handled at high temperature and high concentration because of the potential decomposition hazard.

Fumaric Acid. Fumaric acid is used as a beverage acidulant for human consumption as well as many industrial uses. Its acidic properties can cause skin and eye irritation. It will combust when exposed to heat or flame and can react vigorously with oxidizing agents.

Table 8 lists toxicological data (282).

Placeholder for Float Table 8 (KO Table 8.doc)

Uses

Maleic anhydride is truly a remarkable molecule in that it possesses two types of chemical functionality making it uniquely useful in chemical synthesis and applications. Maleic anhydride itself has few, if any, consumer uses but in derivatized form it is extremely versatile in the consumer uses in which it is found. The chemical structure of each maleic anhydride derivative of significant commercial interest can be found in a more detailed reference (237).

The distribution of end uses for maleic anhydride is presented in Table 9 for the year 2000 (258). The majority of the maleic anhydride produced is used in unsaturated polyester resin (see POLYESTERS, UNSATURATED). Unsaturated polyester resin is then used in both glass-reinforced applications and in unreinforced applications. The distribution of end uses for unsaturated polyester resin is shown in Table 10 for the year 2000 (284).

Placeholder for Float Table 10 (KO Table 10.doc)

There are many unsaturated polyester resin formulations. A typical unsaturated polyester resin formulation consists of an aromatic dibasic acid (or anhydride) such as phthalic anhydride, an unsaturated dibasic acid (or anhydride) such as maleic anhydride and a glycol such as propylene glycol. The polyester chains are then cross-linked through the double bond with vinyl cross linking agents such as styrene. Reinforcement in the form of glass fibers or other reinforcement fibers may be added to provide the strength requirements of the end product. The exact unsaturated polyester formulation, its cross linking agent, and reinforcement fiber, if any, are selected to optimize the performance of the end product.

Fumaric acid and malic acid [6915-15-7] are produced from maleic anhydride. The primary use for fumaric acid is in the manufacture of paper sizing products (see PAPERMAKING ADDITIVES). Fumaric acid is also used as a food acidulant, as is malic acid. Malic acid is a particularly desirable acidulant in certain beverage selections, specifically those sweetened with the artificial sweetener aspartame [22839-47-0].

Lube oil additives represent another important market segment for maleic anhydride derivatives, the molecular structure of importance being adducts of polyalkenyl succinic anhydrides (see LUBRICATION AND LUBRICANTS). These materials act as dispersants and corrosion inhibitors (see DISPERSANTS; CORROSION AND CORROSION CONTROL). One particularly important polyalkenyl succinic anhydride molecule in this market is polyisobutylene succinic anhydride (PIBSA) where the polyisobutylene group has a molecular weight of 900 to 1500. Other polyalkenes are also used. Polyalkenyl succinic anhydride is further derivatized with various amines to produce both dispersants and corrosion inhibitors. Another type of dispersant is a polyester produced from a polyalkenyl succinic anhydride and pentaerythritol [115-77-5].

Maleic anhydride is used in a multitude of applications in which a vinyl copolymer is produced by the copolymerization of maleic anhydride with other molecules having a vinyl functionality. Typical copolymers (and their end uses) are styrene-maleic (engineering thermoplastic, paper treatment chemical, floor polishes, emulsifiers, protective colloids, antisoil agents, dispersants, stabilizing agent, adhesives, detergents, cosmetics, and toiletries), diisobutylene-maleic (dispersing agent), acrylic acid-maleic (detergent ingredient), butadiene-maleic (sizing agent), and C₁₈ alpha olefin-maleic (emulsification agent and paper coating).

The use of maleic anhydride in the manufacture of agricultural chemicals has declined in the United States over the last decade. Malathion [121-75-2] (S-[1,2-dicarbethoxyethyl]O,O-dimethyldithiophosphate) and Difolatan [2425-06-1] (cis-N-[1,1,2,2-tetrachloroethylthio]-4-cyclohexene-1,2-dicarboximide) are no longer produced in the United States and Alar [1596-84-5] (N-dimethylaminosuccinamic acid) volumes have been significantly reduced by intense environmental scrutiny. Maleic hydrazide, Captan [133-06-2] (cis-N-[trichloromethylthio]-4-cyclohexene-1,2-dicarboximide), Endothall [145-73-3] (7-oxabicyclo[2,2,1]-heptane-2,3-dicarboxylic acid, disodium salt), and several other maleic derivatives continue use in a number of agricultural functions: plant growth regulation, fungicides, insecticides, and herbicides (see FUNGICIDES, AGRICULTURAL; INSECT CONTROL TECHNOLOGY; HERBICIDES).

There are numerous further applications for which maleic anhydride serves as a raw material. These applications prove the versatility of this molecule. The popular artificial sweetener aspartame [22839-47-0] is a dipeptide with one amino acid (L-aspartic acid [56-84-8]) which is produced from maleic anhydride as

the starting material. Processes have been reported for production of poly(aspartic acid) [26063-13-8] (286-288) with applications for this biodegradable polymer aimed at detergent builders, water treatment, and poly(acrylic acid) [9003-01-4] replacement (286,289,290) (see DETERGENCY). Alkenylsuccinic anhydrides made from several linear alpha olefins are used in paper sizing, detergents, and other uses. Sulfosuccinic acid esters serve as surface active agents. Alkyd resins (qv) are used as surface coatings. Chlorendric anhydride [115-27-5] is used as a flame resistant component (see FLAME RETARDANTS). Tetrahydrophthalic acid [88-98-2] and hexahydrophthalic anhydride [85-42-7] have specialty resin applications. Gas barrier films made by grafting maleic anhydride to polypropylene [25085-53-4] film are used in food packaging (qv). Poly(maleic anhydride) [24937-72-2] is used as a scale preventer and corrosion inhibitor (see CORROSION AND CORROSION CONTROL). Maleic anhydride forms copolymers with mono-O-methyl-oligoethylene glycol vinyl ethers that are partially esterified for biomedical and pharmaceutical uses (291) (see PHARMACEUTICALS).

An important developing use for maleic anhydride is the production of products in the 1,4-butanediol- γ -butyrolactone-tetrahydrofuran family. Kvaerner Process Technology licenses a process (155) for producing 1,4-butanediol from maleic anhydride. This technology can be used to produce the product mix of the three molecules as needed by the producer. Two plants were in operation in 1998 using the Kvaerner technology, having a combined capacity of 50 kt/yr 1,4-butanediol. Several other plants using the Kvaerner technology are under construction or have been announced. SISAS produces 1,4-butanediol from maleic anhydride in their facility in Feluy, Belgium. DuPont produces tetrahydrofuran in Spain from maleic anhydride. The DuPont technology oxidizes butane to maleic anhydride, which is recovered as maleic acid and then reduced to tetrahydrofuran. BP Amoco have announced a facility in Lima, OH to produce 1,4-butanediol from maleic anhydride using their own technology.

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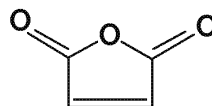
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MALEIC ANHYDRIDE, MALEIC ACID, AND FUMARIC ACID



Copies of Tables and Figures

Tables 1 to 10 (11 pages)

Figures 1 to 4 (4 pages)

Abstract and Key Words (1 page)

Table 1. Physical Properties of Maleic Anhydride, Maleic Acid, and Fumaric Acid

Property	Maleic Anhydride	Maleic Acid	Fumaric Acid	Ref.
formula	C ₄ H ₂ O ₃	C ₄ H ₄ O ₄	C ₄ H ₄ O ₄	
formula weight	98.06	116.07	116.07	
mp, °C	52.85	138-139 ^a 130-130.5 ^b 144 (air)	287	3,4
bp, °C	202	ca 138 (dec)	282 (air)	5
sp gr, at 20/20°C, solid	1.48 ^c	1.590	1.635	4
molar volume		81	79	7
heat of formation, kJ/mol ^d	-470.41	-790.57	-811.03	8
free energy of formation, kJ/mol ^d		-625.09	-655.63	
heat of combustion, kJ/mol ^d	-1389.5	-1355.2	-1334.7	8
heat of hydrogenation, kJ/mol ^d		-153.2	-130.3	8
heat capacity, kJ/(K mol) ^d				
solid	0.1199	0.1356	0.1418	8
liquid	0.164			
heat of sublimation, kJ/mol ^d	71.5	105.4	123.6	8
heat of vaporization, kJ/mol ^d	54.8			8
heat of fusion, kJ/mol ^d	13.55			8
heat of hydrolysis, kJ/mol ^d	-34.9			8
dipole moment, 10 ⁻³⁰ C•m ^e	13.2	10.6	8.17	9
crystalline form	orthorhombic	monoclinic	monoclinic prismatic, needles, or leaflets	10,15,17,18
space group	P2 ₁ 2 ₁ 2 ₁	P2 ₁ /c	P2 ₁ /c P $\overline{1}$	10,15,17,18
<i>a</i> , nm	0.5322	0.7473	0.7619 0.5264	
<i>b</i> , nm	0.7009	1.0098	1.5014 0.7618	
<i>c</i> , nm	1.0987	0.7627	0.6686 0.4487	
α, deg	90	90	90 106.85	
β, deg	90	123.59	112.0 86.33	
γ, deg	90	90	90 134.94	
dissociation constant, at 25°C				20
<i>K</i> ₁		1.14 x 10 ⁻²	9.57 x 10 ⁻⁴	
<i>K</i> ₂		5.95 x 10 ⁻⁷	4.13 x 10 ⁻⁵	
heat of neutralization, KJ/mol ^d	126.9			6

^a Crystallized from water.

^b Crystallized from alcohol; sublimes at 165°C at 0.23 kPa.

^c Specific gravity at 70/70°C, molten = 1.3 (6).

^d To convert kJ to kcal, divide by 4.184.

^e In dioxane at 25°C. To convert C•m to debye, divide by 3.336×10^{-30} .

Table 2. Solubility^a of Maleic Anhydride, Maleic Acid, and Fumaric Acid, g/100 g Solution

Solvent	Maleic Anhydride ^b	Maleic Acid ^c	Fumaric Acid
Water ^d			
at 25°C		44.1	0.70
40°C		52.9	1.05
60°C		58.9	2.34
97.5°C		79.7	
100°C			8.93
acetone			
at 20°C		38.6	
25°C	227		
29.7°C		26.3	1.69
benzene, at 25°C	50	0.024	0.003
toluene, at 25°C	23.4		
<i>o</i> -xylene, at 25°C	19.4		
kerosene (bp 190-210°C), at 25°C	0.25		
methanol, at 22.5°C		41.0	
ethanol			
at 0°C		30.2	
22.5°C		34.4	
95% ethanol, at 29.7°C		41.1	5.44
1-propanol			
at 0°C		20.0	
22.5°C		24.3	
chloroform, at 25°C	52.5	0.11	0.02
carbon tetrachloride, at 25°C	0.6	0.002	0.027
diethyl ether, at 25°C		7.57	0.71
2-butenenitrile, at 50°C		4.38	0.034
ethyl acetate, at 25°C	112		

^a refs. 9 and 20; g/100 g solution unless otherwise noted.

^b In g/100 g solvent.

^c Heat of solution = 18.6 kJ/mol (4.45 kcal/mol) (6).

^d At all temperatures given maleic anhydride hydrolyzes slowly.

Table 3. Other Properties of Maleic Anhydride

Property	Value	Property	Value
flash point, ^a °C		vapor pressure, ^c kPA ^f	
open cup	110	at 44.0°C	0.13
closed cup	102	63.4°C	0.67
flammable limits, ^{a,b} vol %		78.7°C	1.3
lower	1.4-3.4	95.0°C	2.7
upper	7.1	111.8°C	5.3
autoignition temperature, ^a °C	477	122.0°C	8.0
vapor density ^a (air = 1)	3.38	135.8°C	13.3
viscosity, ^c mPa s (= cP)		155.9°C	26.7
at 60°C	0.61	179.5°C	53.3
90°C	1.07	202.0°C	100
150°C	0.6		
pH of water solutions ^d			
1 x 10 ⁻² M	2.42		
5 x 10 ⁻³ M	2.62		
1 x 10 ⁻⁴ M	3.10		
polarographic half-wave potential, ^d V			

^a Ref 23

^b Ref 24

^c Ref 20

^d Ref 25

^e Ref 9

^f To convert kPa to mm Hg, multiply by 7.5

Table 4. World Maleic Anhydride Capacity by Reactor Type

Reactor (Feed)	<u>1993 Actual^a</u>		<u>2000 Actual^b</u>	
	Kt/yr	%	Kt/yr	%
Fixed Bed (butane)	369	43.0	704	51.8
Fixed Bed (benzene)	325	37.9	388	28.5
Fluid Bed (butane)	127	14.8	217	16.0
Fixed Bed (phthalic anhydride co-product)	37	4.3	50	3.7
Total	858	100.0	1359	100.0

^a Ref. 178

^b Industry Sources

Table 5. Production and Sales in the United States

Year	<u>Maleic Anhydride^a</u>	Sales kt	<u>Fumaric Acid^b</u>
	Production kt		Production kt
1986	163.0	137.1	14.5
1987	173.4	141.7	15.4
1988	194.4	162.3	15.9
1989	199.5	169.9	15.4
1990	192.3	160.2	15.4
1991	183.7	142.9	12.2
1992	197.7	159.7	13.2
1993	199.6	151.9	13.2
1994	219.4	175.9	6.4
1995	238.1	205	4.5
1996	247.2	212	4.5
1997	242.7	220	4.5
1998	256.3	223	4.5
1999	256 ^c	228 ^c	4.5 ^c
2000	250 ^c	223 ^c	4.5 ^c

^a Ref 258

^b Ref 259

^c Industry Sources

Table 6. Maleic Anhydride^a and Fumaric Acid^b Producers in the United States, 2000

<u>Producer</u>	<u>Location</u>	<u>Capacity kt/year</u>
Ashland ^a	Neal, WV	43.1 ^c
Ashland ^a	Neville Island, PA	20.4 ^c
Bayer ^a	Baytown, TX	54.4 ^c
BP-Amoco ^a	Joliet, IL	45.4 ^c
Huntsman ^a	Pensacola, FL	105.0 ^c
Tate & Lyle ^b	Duluth, MN	5.5 ^c
	TOTAL	273.8

^a Ref 258

^b Ref 259

^c Industry Sources

Table 7. World Maleic Anhydride Nameplate Capacities^a

	1992 Capacity <u>kt/year</u>	2000 Capacity <u>kt/year</u>
North America	235	311
South & Central America	44	41
Western Europe	168	456
Central & Eastern Europe	64	58
Asia	315	483
Africa	10	10
TOTAL	836	1359

^a Industry Sources

Table 8. Toxicological Data for Maleic Anhydride, Maleic Acid, and Fumaric Acid^a

	Maleic Anhydride	Maleic Acid	Fumaric Acid
Oral, rat, LD ₅₀ , mg/kg	400	708	10,700
Oral, mouse, LD ₅₀ , mg/kg	465	2400	
Skin, rabbit, LD ₅₀ , mg/kg	2620	1560	20,000
Intraperitoneal, rat, LD ₅₀ , mg/kg	97		
LD _{Lo} , mg/kg			587
Subcutaneous, rat, TD _{Lo} , mg/kg	1220		

^a Ref. 282

Table 9. Uses for Maleic Anhydride in the United States, 2000^{a,b}

<u>Product</u>	<u>% of Demand</u>
Unsaturated Polyester Resins	63
Fumaric and Malic Acid	5
Lube Oil Additives	11
Maleic Copolymers	8
Agricultural Chemicals	2
Others	11
TOTAL	100

^a Ref. 258

^b Industry Sources

Table 10. Uses for Unsaturated Polyester in the United States, 2000^{a, b}

<u>Product</u>	<u>Demand</u>
Marine	16.2
Construction	34.2
Corrosion	10.4
Transportation	15.0
Electrical	1.9
Other	22.3
TOTAL	100.0

^a Ref. 284

^b Industry Sources

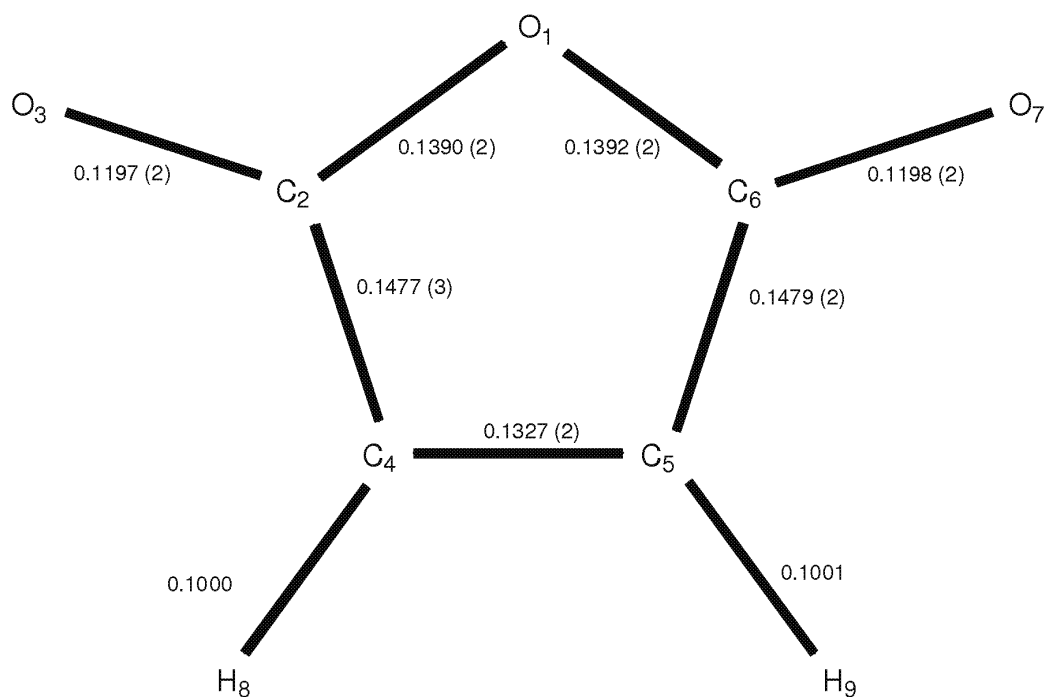


Figure 1. Bond distances in nm (estimated standard deviations in parentheses) for the structure of maleic anhydride determined by single crystal x-ray diffraction methods at 110K (10). The maleic anhydride molecule is nearly planar. The plane containing the O₁, C₄, and C₅ atoms has no other atomic nuclei in the molecule deviating from the plane by more than 0.0036 nm.

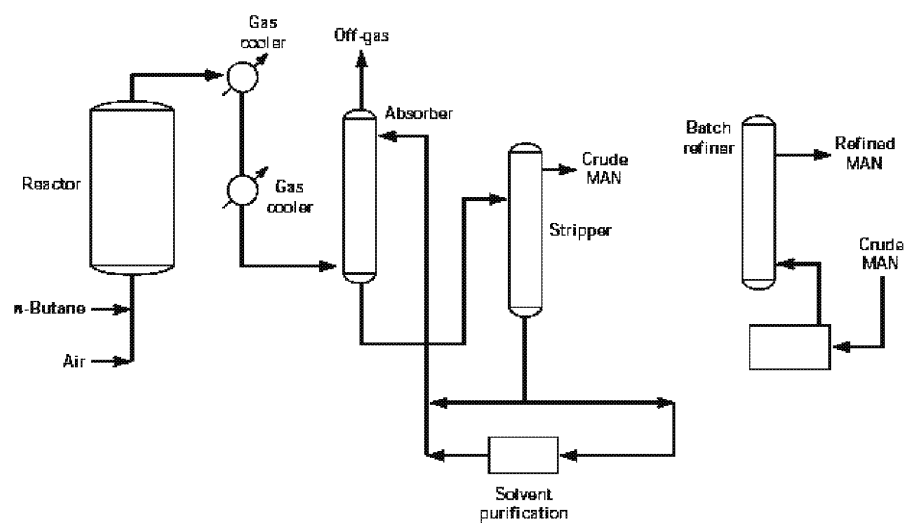


Figure 2

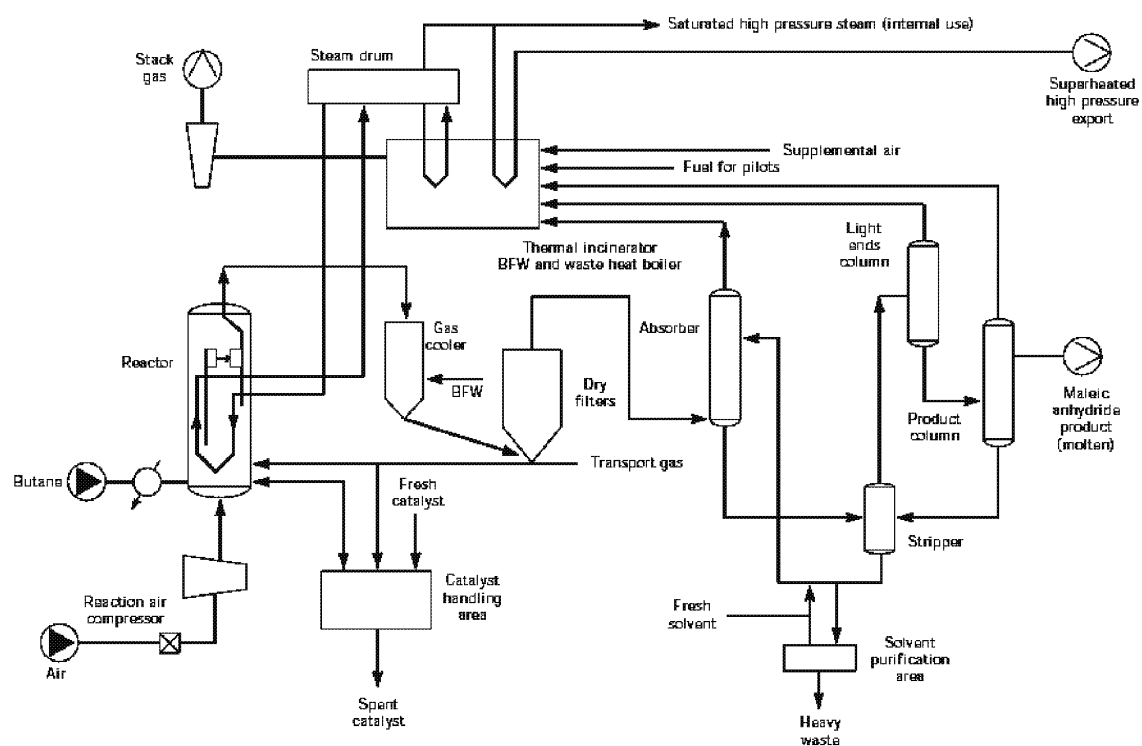


Figure 3

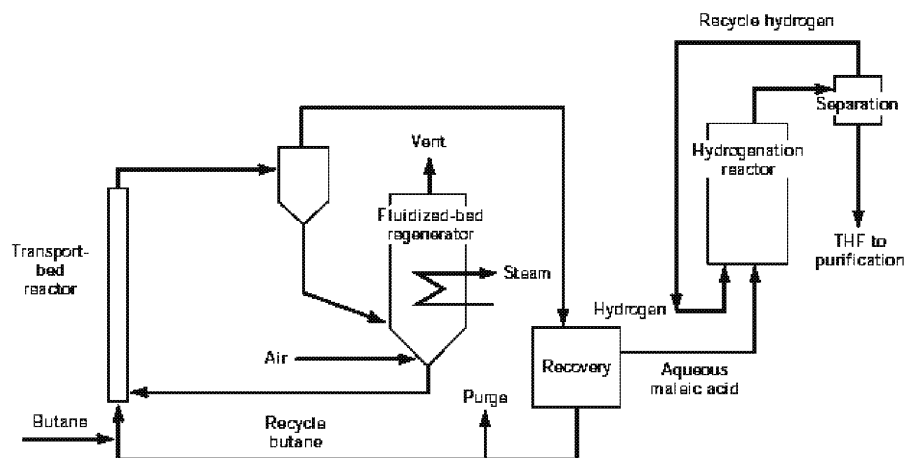


Figure 4

Abstract. Scientific and technological developments in the manufacture and use of maleic anhydride, maleic acid, and fumaric acid are reviewed over the past 20 years. Physical and chemical properties for these three chemicals are updated with literature citations when available. Key derivatives are summarized including acid chlorides and reaction products of these chemicals formed from acylation, alkylation, amidation, concerted nonpolar reactions of various kinds, decomposition and decarboxylation, electrophilic addition, esterification, free-radical reactions, Grignard-type reactions, halogenation, hydration and dehydration, hydroformylation, isomerization, ligation to metal atoms, nucleophilic addition, oxidation, polymerization, reduction, and sulfonation. Manufacturing processes for maleic anhydride are described including those using fixed-bed, fluidized-bed, and transport-bed technologies for selective oxidation of butane. A survey is given of catalyst developments through the end of 2000. Regardless of the reactor type used, all catalysts producing maleic anhydride from butane consist of a vanadyl pyrophosphate phase, $(VO)_2P_2O_7$. Details are presented on maleic anhydride and its two diacid isomers with respect to shipment, economic aspects, specifications, analytical and test methods, toxicology, and principal uses.

Key Words: butane, catalyst, fumaric, maleic, oxidation, vanadium

Substitute for form 1449A/PTO			Complete if Known		
INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(use as many sheets as necessary)</i>			Application Number	10/378,956	
			Filing Date	March 3, 2003	
			First Named Inventor	Sahar Javanmard	
			Art Unit	1617	
			Examiner Name	Michael J. Zaworotko	
Sheet	1	of	2	Attorney Docket Number	USF.106XC1

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		First Named Inventor	Sahar Javanmard
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	R1	WUNDERLICH, H. F. <i>et al.</i> "The Derivatives of carbamazepine with ammonium halogenides and formamide" <i>Pharmazie</i> , 1991, pp. 507-509, Vol. 46, No. 7.	
	R2	EL-NAHHAS, S. A. "Physico-chemical characteristics of carbamazepine- β -cyclodextrin inclusion compounds and carbamazepine-PEG solid dispersions" <i>Pharmazie</i> , 1996, pp. 960-963, Vol. 51, No. 12.	
	R3	REYNOLDS, J. E. F. (ed). Martindale, The Extra Pharmacopoeia, 1993, The Pharmaceutical Press, London, England, 13 th edition, p. 1610.	
	R4	PEDIREDDI, V. R. <i>et al.</i> "Layered Structures Formed by Dinitrobenzoic Acids" <i>Tetrahedron Letters</i> , 1998, pp. 9831-9834, Vol. 39.	
	R5	ZAMAN, M. B. <i>et al.</i> "Crystal Engineering Using Anilic Acids and Dipyriddy Compounds through a New Supramolecular Synthon" <i>J. Org. Chem.</i> , 2001, pp. 5987-5995, Vol. 66,.	
	R6	Japanese Notice of Reasons for Rejection dated October 8, 2009, Japanese Application No. 2003-572946.	x
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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
S11	1	wo "0151919"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/12 14:51

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
S16	5	S13 S14	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	WITH	OFF	2008/09/12 15:00
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
S20	47880	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetaminophen	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2008/09/30 08:31
S21	1329	co crystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/30 08:31
S22	126	S20 S21	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 08:31

S23	18	S20 S21	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	SAME	OFF	2008/09/30 08:31
S24	2	S22 and @pd<"20020301"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 08:45
S25	283	cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/30 08:48
S26	18	S20 S25	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 08:48
S27	57	co crystal.ti.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/30 09:39
S28	14	S27 drug	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 09:39
S29	458	Pharmaceutical co adj crystal compositions drugs	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 09:55
S30	543	Pharmaceutical co adj crystal composition drug	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 09:55
S31	543	Pharmaceutical (co adj crystal) composition drug	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 09:56
S32	29	Pharmaceutical (co adj crystal) composition drug	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	SAME	OFF	2008/09/30 09:56
S33	47	S31 and @pd<"20030303"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 09:56

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
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
S51	9	((("7452555") or ("7446107") or ("7205413") or ("7078526"))).PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2009/08/31 06:23
S52	4	("2003/0224006").URPN.	USPAT	OR	OFF	2009/08/31 06:38
S53	3	("2665277").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2009/08/31 07:13
S54	2904	active pharmaceutical ingredient	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/08/31 07:18
S55	53594	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetaminophen	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2009/08/31 07:18
S56	607	S54 S55	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 07:18
S57	335	cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2009/08/31 07:19

S58	13	S56 S57	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 07:19
S59	27058	hydrogen bond	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/08/31 07:20
S60	28	S56 S59	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 07:20
S61	58	co-crystal former	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/08/31 07:21
S62	14	S55 S61	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 07:22
S63	2904	active pharmaceutical ingredient	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/08/31 08:44
S64	791	S63 crystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 08:44
S65	20	S63 cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 08:44
S66	2904	active pharmaceutical ingredient	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/08/31 08:58
S67	53594	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetaminophen	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2009/08/31 08:58
S68	607	S67 S66	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 08:58

S69	210	S68 CRYSTAL	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 08:58
S70	4	((("7452555") or ("7446106") or ("7205413") or ("7078526"))).PN.	USPAT	OR	OFF	2009/09/28 10:26
S71	95	phosphate hemihydrate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/09/28 14:42
S72	54110	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetaminophen	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2009/09/28 14:42
S73	5	S72 S71	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/09/28 14:42
S74	2	((("3028420") or ("5521207"))).PN.	USPAT	OR	OFF	2009/09/28 14:52
S75	19	API cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/09/28 15:02
S76	0	ep "0548028"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/09/28 15:46
S77	6	supramolecular synthon	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/09/28 22:18
S78	20	US-2711411-\$.DID. OR US-4198507-\$. DID. OR US-4368197-\$.DID. OR US- 4994604-\$.DID. OR US-5177262-\$. DID. OR US-5332834-\$.DID. OR US- 5338644-\$.DID. OR US-5380867-\$. DID. OR US-5412094-\$.DID. OR US- 5523090-\$.DID. OR US-5614342-\$. DID. OR US-5998413-\$.DID. OR US- 6001996-\$.DID. OR US-6268385-\$. DID. OR US-6570036-\$.DID. OR US- 20030162226-\$.DID. OR US- 20030166581-\$.DID. OR US- 20030224006-\$.DID. OR US- 20040019211-\$.DID.	US-PGPUB; USPAT; USOCR; EPO; JPO	OR	OFF	2009/09/28 23:04

S79	20	US-20040106053-\$.DID. OR US-20040106055-\$.DID. OR US-20040171062-\$.DID. OR US-20040176335-\$.DID. OR US-20050070551-\$.DID. OR US-20050181041-\$.DID. OR US-20050169982-\$.DID. OR US-20050252649-\$.DID. OR US-20050256127-\$.DID. OR US-6559293-\$.DID. OR US-6699840-\$.DID. OR US-20040053853-\$.DID. OR US-3536809-\$.DID. OR US-3598123-\$.DID. OR US-3845770-\$.DID. OR US-3916899-\$.DID. OR US-4008719-\$.DID. OR US-4267179-\$.DID. OR US-4764604-\$.DID.	US-PGPUB; USPAT; USOCR; EPO; JPO	OR	OFF	2009/09/28 23:07
S80	15	US-4916134-\$.DID. OR US-5006513-\$.DID. OR US-5059595-\$.DID. OR US-5073543-\$.DID. OR US-5120548-\$.DID. OR US-5354556-\$.DID. OR US-5414997-\$.DID. OR US-5474997-\$.DID. OR US-5591767-\$.DID. OR US-5633015-\$.DID. OR US-5639476-\$.DID. OR US-5661151-\$.DID. OR US-5674533-\$.DID. OR US-5707975-\$.DID. OR US-5733566-\$.DID.	US-PGPUB; USPAT; USOCR; EPO; JPO	OR	OFF	2009/09/28 23:08
S81	35195	bipyridine phthalaldehyde nicotinamide saccharin pyridinecarboxylic adj acid nitroisophthalic adj acid adamantanetetracarboxylic adj acid	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2010/06/17 10:11
S82	59011	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetaminophen	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2010/06/17 10:12
S84	2951	S81 S82	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 10:12
S85	1424	co-crystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 10:12
S86	39	S84 S85	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 10:12
S87	147955	(active pharmaceutical ingredient) or API	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2010/06/17 10:29

S88	725	S87 S81	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 10:29
S89	35	S88 S85	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 10:29
S90	3689	(active pharmaceutical ingredient)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2010/06/17 10:31
S91	143	S81 S90	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 10:31
S92	23	S91 S85	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 10:31
S93	11	((MICHAEL) near2 (ZAWOROTKO)). INV.	US-PGPUB; USPAT	OR	OFF	2010/06/17 10:36
S94	6	((BRIAN) near2 (MOULTON)).INV.	US-PGPUB; USPAT	OR	OFF	2010/06/17 10:36
S95	5	((NAIR) near2 (RODRIGUEZ- HORNEDO)).INV.	US-PGPUB; USPAT	OR	OFF	2010/06/17 10:36
S96	14	S93 S94 S95	US-PGPUB; USPAT	OR	OFF	2010/06/17 10:36
S97	103	S85 S81	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 11:41

EAST Search History (Interference)

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6/18/2010 1:43:51 PM**C:\Documents and Settings\sjavaanmard\My Documents\EAST\Workspaces\10378956.wsp**

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Application	Document	Mailroom Date	Attorney Docket No.
10378956	CTFR	06/24/2010	USF.106XC1
	892	06/24/2010	USF.106XC1
	1449	06/24/2010	USF.106XC1

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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 10/25/2010 SALIWANCHIK LLOYD & SALIWANCHIK A PROFESSIONAL ASSOCIATION PO Box 142950 GAINESVILLE, FL 32614			EXAMINER JAVANMARD, SAHAR	
			ART UNIT	PAPER NUMBER
			1627	
			NOTIFICATION DATE	DELIVERY MODE
			10/25/2010	ELECTRONIC

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.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

Interview Summary	Application No.	Applicant(s)	
	10/378,956	ZAWOROTKO ET AL.	
	Examiner	Art Unit	
	SAHAR JAVANMARD	1627	

All participants (applicant, applicant's representative, PTO personnel):

(1) SAHAR JAVANMARD. (3) GLEN LADWIG.

(2) SREENI PADMANABHAN. (4) MARK BUESE; MICHAEL ZAWOROTKO.

Date of Interview: 13 October 2010.

Type: a) ☒ Telephonic b) ☐ Video Conference
c) ☐ Personal [copy given to: 1) ☐ applicant 2) ☐ applicant's representative]

Exhibit shown or demonstration conducted: d) ☒ Yes e) ☐ No.
If Yes, brief description: APPLICANT FAXED PROPOSED AMENDMENTS.

Claim(s) discussed: ALL.

Identification of prior art discussed: ZAWOROTKO (PATENT 5,994,365) AND SANZU (JP-B-46-33588).

Agreement with respect to the claims f) ☐ was reached. g) ☒ was not reached. h) ☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Rejections of record were discussed based on Applicant's proposed claims. Examiner will consider claims accordingly when Applicant responds to the outstanding Final Office action.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

/S. J./ Examiner, Art Unit 1627	/SREENI PADMANABHAN/ Supervisory Patent Examiner, Art Unit 1627
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Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record

A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.

All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

- 1) A brief description of the nature of any exhibit shown or any demonstration conducted,
- 2) an identification of the claims discussed,
- 3) an identification of the specific prior art discussed,
- 4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
- 5) a brief identification of the general thrust of the principal arguments presented to the examiner.
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
- 6) a general indication of any other pertinent matters discussed, and
- 7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

UM00014714

NOVARTIS EXHIBIT 1517

Novartis v. Regents, IPR2023-01347

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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	10/106XC1
Filing Date	March 3, 2010
First Named Inventor	Michael J. Zaworotko
Art Unit	1617
Examiner Name	Sahar Javanmard
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 _____

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, any underpayment of fees, or credit any overpayments, to

- a. ☐ Deposit Account No. _____
- i. ☒ RCE fee required under 37 CFR 1.17(e)
- ii. ☒ Extension of time fee (37 CFR 1.136 and 1.17)
- 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

Signature	<i>Mark A. Buese</i>	Date	October 22, 2010
Name (Print/Type)	MARK A. BUESE, PH.D.	Registration No.	52,669

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.

Signature		Date	
Name (Print/Type)		Date	

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 1.11 and 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.

UM00014715

NOVARTIS EXHIBIT 1517

Novartis v. Regents, IPR2023-01347

Page 3451 of 4460

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:		Mark A. Buese/Paula Shultz		
Attorney Docket Number:		USF.106XC1		
Filed as Small Entity				
Utility under 35 USC 111(a) 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	65	65

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
Request for continued examination	2801	1	405	405
Total in USD (\$)				470

Electronic Acknowledgement Receipt	
EFS ID:	8681482
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:	Mark A. Buese/Paula Shultz
Filer Authorized By:	Mark A. Buese
Attorney Docket Number:	USF.106XC1
Receipt Date:	22-OCT-2010
Filing Date:	03-MAR-2003
Time Stamp:	12:40:55
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	\$470
RAM confirmation Number	10190
Deposit Account	190065
Authorized User	EISENSCHENK,FRANK C.
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 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)					
Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)					
Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)					
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Amd4.pdf	936624 13c82e2982529916b7dd7284cc52c97b2280e4fa	yes	10
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Amendment Submitted/Entered with Filing of CPA/RCE		1	1	
	Claims		2	6	
	Applicant Arguments/Remarks Made in an Amendment		7	10	
Warnings:					
Information:					
2		SIDS3.pdf	236561 d366a9be3596c6a118f54128612c567b299315b9	yes	3
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Transmittal Letter		1	2	
	Information Disclosure Statement (IDS) Filed (SB/08)		3	3	
Warnings:					
Information:					
3	NPL Documents	Desiraju-2010.pdf	1490674 8c133021ebc10cdcf3908742f147b1a2d8de6aeb	no	9
Warnings:					
Information:					
4	Request for Continued Examination (RCE)	Exec-RCE4.pdf	188922 a2126523c0b49d8e5d241c81d244a70a791e1538	no	1
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					

5	Fee Worksheet (PTO-875)	fee-info.pdf	32258 4670f9e03a1bd53488e651fb59b1e9dd732441b8	no	2
Warnings:					
Information:					
Total Files Size (in bytes):				2885039	
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. <u>New Applications Under 35 U.S.C. 111</u> 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. <u>National Stage of an International Application under 35 U.S.C. 371</u> 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. <u>New International Application Filed with the USPTO as a Receiving Office</u> 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.					

I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on October 22, 2010

Mark A. Buese
Mark A. Buese, Ph.D., Patent Agent

AMENDMENT UNDER 37 CFR §1.114
Examining Group 1617
Patent Application
Docket No. USF.106XC1
Serial No. 10/378,956

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
Confirm. 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 22313-1450

AMENDMENT UNDER 37 CFR §1.114

Applicants request that the period for response in the above-identified patent application be extended one month through and including October 25, 2010, the fee for which has been paid at the time this Amendment was filed.

This response is accompanied by a Request for Continued Examination, a reference, and an Information Disclosure Statement.

This response includes a Summary of an Examiner Interview.

In response to the Office Action dated June 24, 2010, please amend the above-identified application as follows:

J:\USF\106XC1\Amend-Resp\Amd4.doc\DNB/mab

In the Claims

1-24 (canceled).

25 (currently amended). A method for the design and preparation of a co-crystal~~supramolecular synthon~~, said method comprising:

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

(b) ~~determining whether the active pharmaceutical ingredient contains~~ comprising at least one chemical functionality, is capable of wherein at least one of said chemical functionalities forms a first supramolecular synthon forming of a supramolecular homosynthon comprising a hydrogen bond 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 identified chemical functionality is capable of forming a noncovalent bond to the supramolecular synthon formed by the active pharmaceutical ingredient;~~

(d) ~~identifying selecting at least one co-crystal formers from among a plurality of candidate co-crystal formers, wherein said selected co-crystal former(s) forms having a second supramolecular synthon between at least one complementary chemical functionality of said co-crystal former(s) that is identified identified in step (c), wherein the identified to form a non-covalent bond with at least one of said chemical functionalities of said API, wherein at least one of said selected co-crystal formers in its pure form are is a solids at room temperature and under atmospheric pressure; and~~

(e) ~~preparing a multiple-component solid phase composition, wherein the multiple-component solid phase composition is a co-crystal that comprises comprising stoichiometric proportions of said the active pharmaceutical ingredient API and at least one of the identified said selected co-crystal former(s) upon formation of said second supramolecular synthon by said non-covalent bonding between said complementary chemical functionality of said co-crystal former(s) and said chemical functionality of said API.~~

26 (canceled).

27 (currently amended). The method of claim 25, wherein ~~the said~~ at least one co-crystal former is a second different active pharmaceutical ingredient API different from said API of (a).

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

29-36 (canceled).

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

38 (currently amended). ~~The~~ A method of claim 25, wherein said selecting of (b) for identifying complementary chemical functionalities in order to form a desired supramolecular synthon, said method comprising comprises:

(a) ~~selecting an active pharmaceutical ingredient and evaluating the~~ chemical functionalities of structure of said active pharmaceutical ingredient API;

(b) ~~considering~~ 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 candidate 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 with at least one of said chemical functionalities of the active pharmaceutical ingredient~~ API, and wherein the identified chemical functionality is

~~capable of forming a noncovalent bond to the supramolecular synthon formed by the active pharmaceutical ingredient;~~

~~(dc) identifying said plurality of candidate co-crystal formers s-as having at least onesa-id complementary chemical functionalitiesy identified-considered in step (eb) and selecting said said selectedidentified co-crystal former(s) from said plurality of candidate co-crystal formers for the preparation of said co-crystala multiple-component solid-phase composition, wherein the selected co-crystal formers are solids at room temperature and under atmospheric pressure; 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 selected co-crystal formers.~~

39 (previously presented). The method of claim 25, wherein the at least one co-crystal former is a GRAS compound.

40 (previously presented). The method of claim 25, wherein the at least one co-crystal former is a food additive.

41 (previously presented). The method of claim 25, wherein the at least one co-crystal former is a low toxicity organic.

42 (previously presented). The method of claim 25, wherein the at least one co-crystal former is a metal organic complex.

43 (previously presented). The method of claim 25, wherein the at least one co-crystal former comprises at least two heterocyclic groups.

44 (previously presented). The method of claim 25, wherein the at least one co-crystal former is bipyridine.

45 (previously presented). The method of claim 25, wherein the at least one co-crystal former is bis(pyridyl)ethene.

46 (currently amended). The method of claim 25, wherein said ~~evaluating of (a) first~~ supramolecular synthon is identified from ~~comprises determining~~ the crystal structure of said ~~active pharmaceutical ingredient~~ API.

47 (currently amended). The method of claim 25, wherein said ~~evaluating of (a)~~ comprises experimentally first supramolecular synthon is identified by determining the structure of at least one pure solid phase of said ~~active pharmaceutical ingredient~~ API.

48 (currently amended). The method of claim 25, wherein the at least one ~~functionality~~ identified complementary chemical functionality in step (e) is an unsaturated N-heterocycle, saturated N-heterocycle, aldehyde, amide, carboxylic acid, nitro, ketone, or sulfoxide.

49 (currently amended). The method of claim 25, wherein the at least one ~~functionality~~ identified complementary chemical functionality in step (e) is a carboxylic acid.

50 (new). The method of claim 25, wherein said identified complementary chemical functionality of said co-crystal former is complementary to said chemical functionality of said API that comprises said first supramolecular synthon and forms said second supramolecular synthon with the loss of said first supramolecular synthon to form said co-crystal.

51 (new). The method of claim 25, wherein said identified complementary chemical functionality of said co-crystal former is complementary to said chemical functionality of said API other than said chemical functionality that forms said first supramolecular synthon, wherein said first supramolecular synthon is retained in addition to said second supramolecular synthon of said co-crystal.

52 (new). The method of claim 25, wherein said chemical functionality that comprises said first supramolecular synthon is an acid, amide, alcohol, phenol, thiol, or other hydrogen bond former, comprising a hydrogen bond donor, wherein no covalent bonds are formed upon

said non-covalent bonding between said complementary chemical functionality that forms said second supramolecular synthon and said chemical functionality of said API.

53 (new). The method of claim 25, wherein said complementary chemical functionality that comprises said second supramolecular synthon is an amine, amide, unsaturated aromatic nitrogen bases, or other supramolecular heterosynthon hydrogen bond former that lacks a hydrogen bond donor, wherein no covalent bonds are formed upon said non-covalent bonding between said complementary chemical functionality and said chemical functionality of said API to form said second supramolecular synthon.

Summary of an Examiner Interview

Applicants and Applicants' representative wish to thank Examiner Javanmard and Supervisory Examiner Padmanabhan for the courtesy of the telephonic interview conducted with an inventor, Dr. Michael Zaworotko, and advocates for the applicants, Mr. Glenn P. Ladwig and the undersigned, on October 13, 2010, regarding the amendment to the claims and features of the method that is claimed. The remarks and amendments set forth herein are consistent with the substance of the interview and are believed to address the outstanding issues as discussed during the interview.

Remarks

Claims 25, 27, 28, and 37-49 were pending in the subject application. By this Amendment, claims 25, 27, 28, 37, 38, and 46-49 have been amended and new claims 50-53 have been added. The undersigned avers that no new matter is introduced by this Amendment. Support for the new claims and amendments can be found throughout the subject specification and in the claims as previously presented. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 25, 27, 28, and 37-53 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

By this Amendment, claims 25, 27, 28, 37, 38, and 46-49 have been amended and claims 50-53 have been added. Written support for the amendment to claim 25 can be found, for example, in paragraphs [0008]-[0012] and [0038]-[0042] of the specification. Written support for the amendment of claim 38 can be found, for example, in paragraphs [0041]-[0043] of the specification. Amendments to claims 27, 28, 37, 46, 47, 48, and 49 can be found in previously presented claims 27, 28, 37, 46, 47, 48, and 49; where amendment was made to have antecedent basis with amended claim 25. Written support for claim 50 can be found, for example, in: paragraph [0040] of the specification; Examples 2-6, 10, 11, 13, 18, and 19; and Figures 5, 6, 7, 8, 9, 14, 15, 17, 22, and 23. Written support for claim 51 can be found, for example, in: paragraph [0039] of the specification; Examples 7, 8, 9, 18, and 16; and Figures 5, 6, 7, 8, 9, 14, 15, 17, 22, and 23. Written support for claims 52-53 can be found in paragraph [0047] of the specification.

Claims 25, 27, 28, 38 and 46-49 are rejected under 35 U.S.C. §102(b) as being anticipated by Zaworotko (US Patent No. 5,994,365). Applicants respectfully traverse this ground for rejection. Applicants assert that Zaworotko does not teach each and every limitation of claims 25, 27, 28, 38 and 46-49. As is well known in the law, an Examiner must identify the elements of the claim as having a meaning based on the specification and prosecution history to determine if the alleged anticipating reference teaches this element, see in *Lindemann v. American Hoist and Derrick Co.*, 221 USPQ 481 (Fed. Cir. 1984), where the court stated:

Anticipation requires the presence in a single prior art reference, disclosure of each and every element of the claimed invention, arranged as in the claim. *Connell v. Sears Roebuck and Co.*, 722 F.2d 1542, 220 USPQ 193 (Fed. Cir. 1983); *SSIH Equip. S.A. v. USITC*, 718 F.2d 365, 216 USPQ 678 (Fed. Cir. 1983). In deciding the issue of anticipation, the [examiner] must identify the elements of the claims, determine their meaning in light of the specification and prosecution history, and identify corresponding elements disclosed in the allegedly anticipating reference. *SSIH, supra; Kalman [v. Kimberly-Clarke]*, 713 F.2d 760, 218 USPQ 781 (Fed. Cir. 1983)] (emphasis added). 221 USPQ at 485.

The office action states that Zaworotko, entitled “Substituted Diazaanthracene Compounds having Pharmaceutical Utility” teaches co-crystal formation between a diazaanthracene, the active pharmaceutical ingredient (API) 1,8-DAA-36-(Me)₂, and a co-crystal former, fumaric acid. This composition found in example 9 of Zaworotko does not teach an API that has a first supramolecular synthon comprising a hydrogen bond, as recited in amended claim 25, as the API has no hydrogen bond donor. Homosynthons are disclosed, for example in paragraph [0009], page 4 of the specification with examples thereof given in Examples 1-19 and Figures 4A, 5A, 6C, 7B, 8B, 10A, 14A, 15A, 16A, 17A, 18A, 19A, 20A, 21A, 22A, and 23A. These homosynthon functionalities are those that contain hydrogen bond donors and hydrogen bond acceptors, as would be appreciated upon inspection by those skilled in the art. The ability to form a homosynthon is lacking in 1,8-DAA-36-(Me)₂, which although possessing a pair of hydrogen acceptors, lacks any hydrogen bond donors.

Zaworotko does not teach a method for selecting at least one co-crystal former from among a plurality of candidate co-crystal formers. Rather, a co-crystal was formed with no disclosed evaluation of potential co-crystal formers, nor is there any disclosure that a co-crystal was even considered a possible outcome. Chance formation of a co-crystal is not the present invention. Presently, and certainly at the time of the invention, “the idea that a crystal can

contain more than one type of molecular entity is counter intuitive.” (see Desiraju page 673 2nd paragraph left column “Crystal Engineering: A Brief Overview” *J. Chem. Sci.* **2010**, 122(5), 667-75, attached herewith and with an accompanying IDS). The claimed invention is directed to co-crystals where candidate co-crystal formers are considered based on functionalities that are complementary to those of the API, and a selected co-crystal former is used that possesses the identified functionality that would indicate co-crystal formation is a probable outcome. As Zaworotko does not teach every element of the claim arranged as in the claim, Zaworotko can not anticipate the presently claimed invention. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested. Applicants respectfully request allowance of claims 25, 27, 28, 38 and 46-49.

Claims 39-42 are rejected under 35 U.S.C. §102(b) as being anticipated by Zaworotko (US Patent No. 5,994,365) as evidenced by Felthouse (2001). Applicants respectfully traverse this ground for rejection. Zaworotko does not teach each and every limitation of claims as addressed above. Felthouse teaches fumaric acid to be a food additive and, therefore as a GRAS, but does not address the deficiencies of Zaworotko. Therefore, Zaworotko as evidenced by Felthouse, does not teach every element of the claim arranged as in the claim and can not anticipate the presently claimed invention. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested. Applicants respectfully request allowance of claims 39-42.

Claims 39-42 are rejected under 35 U.S.C. §102(b) as being anticipated by Sanzu (JP-B-46-33588). Applicants respectfully traverse this ground for rejection. Sanzu does not teach each and every limitation of claims 39-42. Sanzu does not teach a co-crystal and therefore can not teach a method to prepare a co-crystal former. By definition, and as presently claimed, a co-crystal, being a single crystalline entity, has a fixed stoichiometry of component molecules. Sanzu teaches either a mixed crystal or a solid solution where “The complex compound produced by such methods comprises phenazone and paracetamol in a molar ratio of *approximately* 1:1 or a weight percentage of phenazole *approximately* 59-53%, paracetamol *approximately* 41-47%.” (see last paragraph of the translation of Sanzu emphasis added). The composition of a co-crystal will not vary in stoichiometry by $\pm 10\%$, and therefore, Sanzu does

not teach a co-crystal. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested. Applicants respectfully request allowance of claims 39-42.

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.

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.

Submitted herewith is a supplemental Information Disclosure Statement (IDS), accompanied by the form PTO/SB/08, and a copy of the reference listed herein. Applicants request that the reference in the IDS be made of record in the subject application.

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 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,



Mark A. Buese, Ph.D.
Patent Agent
Registration No. 52,669
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

MAB/ps

I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on October 22, 2010

Mark A. Buese
Mark A. Buese, Patent Agent

INFORMATION DISCLOSURE
STATEMENT
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
Confirm No. : 4742
Filed : March 3, 2003
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

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

Sir:

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

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

Applicants respectfully assert that the substantive provisions of 37 C.F.R. §§ 1.97 and 1.98 are met by the foregoing statement.

J:\USF\106XC1\IDS\SIDS3.doc\ps

If any additional fee is required, or to credit any overpayment, please use Deposit Account No. 19-0065.

Respectfully submitted,



Mark A. Buese, Ph.D.
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Fax No.: 352-372-5800
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Gainesville, FL 32614-2950

MAB/ps

Attachments: Form PTO/SB/08; copy of reference cited therein.

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.

Substitute for form 1449B/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(use as many sheets as necessary)</i>				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	Sahar Javanmard
Sheet	1	of	1	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	DESIRAJU, G.R., "Crystal engineering: A brief overview," <i>J. Chem. Sci.</i> , September 2010, pp. 667-675, Vol. 122, No. 5.	
	R2		
	R3		
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Crystal engineering: A brief overview

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Abstract. Crystal structures of organic and metal-organic compounds have been determined in enormous numbers over the past century, and at the time of writing this review, the Cambridge Structural Database has just crossed the half million mark. The possibility of designing a particular crystal packing is, however, of more recent origin and the subject of *crystal engineering* has addressed this possibility, more or less systematically, during the past 30 years. Crystal engineering demands a detailed and thorough knowledge of intermolecular interactions, which act as the supramolecular glue that binds molecules into crystals. It also requires systematic strategies for the design of a crystal, the architectural blueprint as it were. Finally, this enterprise needs to be geared towards a useful property in that the crystal that is being designed is a functional one. All these features of the subject are directly or indirectly connected with the fact that there is a very large database of known crystal structures that is available to the crystal engineer. This review attempts to briefly survey the current scenario in this expanding subject.

Keywords. Crystallography; crystal structure; hydrogen bond; polymorphism; pharmaceuticals.

1. Introduction

Crystal engineering is concerned with the construction of crystal structures of organic and metal organic species, using design principles that are derived from an understanding of the intermolecular interactions that prevail in molecular solids.¹ Ideally, the crystal to be designed has a specific function whether it is chemical reactivity of a desired kind, an optical, magnetic or electronic property, or still the ability to absorb within the crystal another small molecule.^{2–4} To summarise, crystal engineering is the rational design of functional molecular solids. This subject has been in active investigation for around 30 years.⁵ The conceptual origins of crystal engineering go much further back in time and indeed right back to the origins of X-ray crystallography when Bragg noted similarities between the crystal structures of naphthalene and anthracene.⁶ In the modern context, the concepts of crystal engineering are applicable to any kind of intermolecular assembly whether it is protein ligand recognition, the design of supramolecular polymers, systems for drug delivery or the study of organized media other than crystalline solids. Crystal engineering is accordingly of very wide scope and it has brought together investigators from many disciplines.⁷ These include organic chemistry, inorganic chemistry,

physical chemistry, X-ray crystallography, materials sciences and computational chemistry.

The first phase of this subject is exemplified by the work of Robertson who was perhaps the first to systematically relate molecular structure of organic compounds with their crystal structure.⁸ Robertson surveyed the crystal structures of a large number of polynuclear aromatic hydrocarbons in the 1940s and 1950s. The determination of a crystal structure was an extremely difficult task in those days and Robertson's crystallographic investigations are of an almost heroic nature. He divided these flat aromatic molecules into two categories: in the first, the molecular thickness is comparable to the length and breadth; in the second the thickness is small in comparison with the two other dimensions. Each of these categories was associated with a certain type of crystal structure – the former with what we would now term the herringbone packing displayed by naphthalene and the latter with the stacked structure as exemplified by coronene. Although this work was carried out 60 years ago, its consequences impinge on the subject of crystal engineering even today because the essential question in crystal engineering remains 'Given the molecular structure of an organic compound, what is its crystal structure?' In other words how do molecules recognize one another during the crystallization event? This question is easy

to phrase but it is extremely difficult to answer. At the present time there is no general answer to this question.

Indeed this question can be sub-divided into several smaller questions as shown in the following scheme:

One $\rightarrow$ Few $\rightarrow$ Many $\rightarrow$ Crystal.

The fact is that a crystal is built up from a large number of molecules and this building up (aufbau) need not be a smooth and continuous process in which the final structure of the crystal is established and is recognizable from the very initial stages of molecular assembly. A few molecules assemble to form a cluster; several clusters may assemble to form larger entities and these entities interact with each other through an event that we term as nucleation, which leads in turn to the first crystal. Local order and organization within the small and then the larger clusters must lead eventually to long range periodicity that one associates with the crystalline state.⁹ However, one does not know when and how this happens. A small cluster need not necessarily be a good model for a larger cluster and a large cluster in turn may not necessarily be a good model for the even larger clusters. In other words, there may be discontinuities in the process of building up of clusters that leads to nucleation and growth of a crystal. Therefore, the observation and understanding of the molecule-to-crystal progression is a difficult task and there are no easy answers. X-Ray crystallography provides information on the final crystal structure of a molecule. At the present time, the structural chemist is restricted to the knowledge of the structures of just the starting molecule and the final crystal. One does not know the structures of the species during the intermediate stages of aggregation in any great detail although certain lines of research are beginning to cast some light on these interesting transitory stages of the supramolecular reaction that we call crystallization.¹⁰⁻¹³

Systematic crystal engineering was launched with the contributions of Schmidt in the Weizmann Institute. The contributions from this group in the 1950s and 1960s, on the solid state photochemical reactivity of *trans*-cinnamic acids and other alkenes, laid the foundation of the subject.¹⁴ Schmidt is usually credited with having introduced the term *crystal engineering* into the chemical literature although there is an earlier report by Pepinsky wherein the term is actually mentioned for the very first time.¹⁵

The work in the Weizmann Institute was followed, after the death of Schmidt in 1972, by other contributions from Israel most notably from the groups of Cohen,¹⁶ Herbststein,¹⁷ Lahav and Leiserowitz.¹⁸ These developments were paralleled by work of Curtin and Paul from the University of Illinois on phase transitions, gas-solid reactions, crystal polarity and polymorphism.¹⁹ Also notable in the early years is work from the group of Wegner and Enkelmann on diacetylene polymerization²⁰ and from the University of Cambridge on topotaxy and defect controlled topochemistry²¹ (Thomas and Jones). All these early studies are of outstanding importance and allowed the subject of crystal engineering to gain some sort of identity thereby attracting the interest of crystallographers, chemists and materials scientists to its ranks.

The next phase of crystal engineering may be said to have begun in the late 1980s. Typical contributions of this period include a paper by Ermer on the crystal structure of adamantane-1,3,5,7-tetracarboxylic acid.²² The novel analysis of the complex packing of this molecule in the crystal, in terms of interpenetrated networks, is the forerunner of the topological approach to the description of crystal structures of molecular solids. Continuing on this theme, a paper in 1990 by Robson, on interpenetration as a theme in the crystal structures of some coordination compounds, is of fundamental importance and was the starting point of investigations on coordination polymers²³ which in turn has led to identification of some of these compounds as metal organic framework structures (MOF).²⁴ The study of coordination polymers is a vast enterprise today and numerically speaking, there are probably more workers in this branch of crystal engineering than in any other. Restrictions of length prevent one from presenting a more detailed discussion on this vital aspect of the subject.

A paper by Desiraju and Gavazzotti in 1989 entitled 'From molecular to crystal structure; 'polynuclear aromatic hydrocarbons' echoes Robertson's work in a more quantitative manner and identified the molecule $\rightarrow$ crystal transformation as the key issue in crystal engineering.²⁵ The appearance of a book by Desiraju in 1989 entitled 'Crystal engineering: The design of organic solids' showed that the subject of crystal engineering goes far beyond organic solid state reactivity.¹ This book is still the only single author book on the subject. Desiraju defined crystal engineering as 'the understanding of

intermolecular interactions in the context of crystal packing and in the utilisation of such understanding in the design and new solids with desired physical and chemical properties'. This definition seems to have stood the test of time and the subject today includes three distinct activities which form a continuous consequence (i) the study of intermolecular interactions; (ii) the study of packing modes in the context of these interactions with the aim of designing a strategy for crystal construction and; (iii) the study of crystal properties. These three stages represent the what, the how and the why of crystal engineering.²⁶ The final development in the kick off-stage of crystal engineering was the identification of an organic crystal as a *supramolecular par excellence* by Dunitz in 1991.²⁷ Dunitz based his argument on the paradigm of supramolecular chemistry which was recognized just few years earlier, in 1987, through the award of a Nobel Prize to Pedersen, Cram and Lehn.

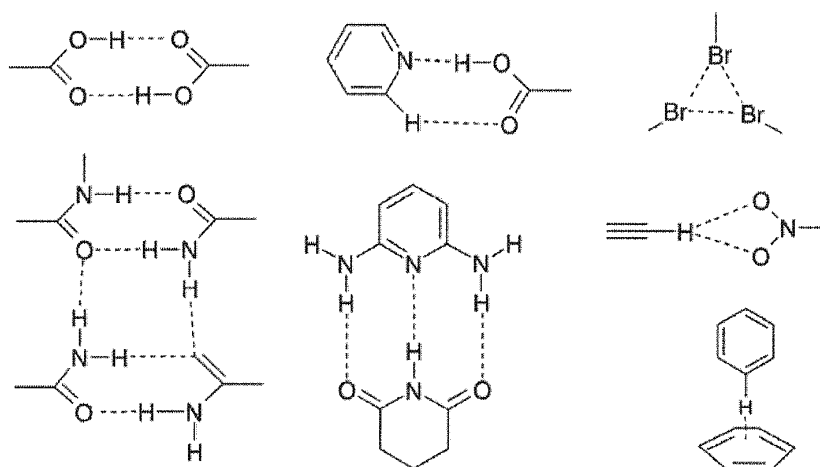
2. Supramolecular retrosynthesis

The central dogma of supramolecular chemistry was enunciated by Lehn who stated that just as a molecule is built with atoms by connecting them with covalent bonds, a supramolecule is built up with molecules using intermolecular interactions as connectors.²⁸ The idea of molecular recognition therefore became closely integrated with supramolecular chemistry. Taking up from Dunitz's concept of a crystal as a supramolecular entity, Desiraju suggested that crystal engineering, the design and construction of a molecular crystal, is a form of solid state supramolecular synthesis.²⁹ Continuing these analogies further, a polymorph of an organic solid is the supramolecular equivalent of what a structural isomer is in molecular chemistry,³⁰ crystallization becomes a supramolecular reaction and the crystal nucleus may be likened to a transition state.¹² It was in the middle 1990s that the concept of crystal engineering entered the mainstream of organic chemistry. Three definitive reviews appeared in this and related contexts: Whitesides described non-covalent synthesis as a way of using physical organic chemistry to make molecular aggregates,³¹ Desiraju defined supramolecular synthons as structural units within crystals that can be formed by known or conceivable synthetic operations (scheme 1),²⁹ Stoddart defined two types of supramolecular synthesis,³² the first is more akin to

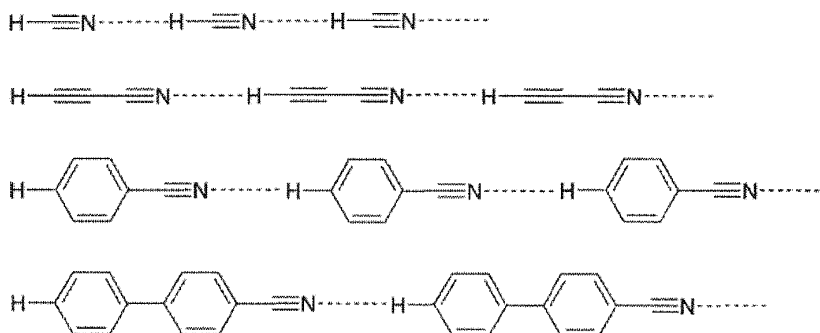
Desiraju's definition of crystal engineering and involves a building up of supramolecular entities with intermolecular interactions; the second utilizes supramolecular synthesis as an aid to the building up of exotic molecular entities, like rotaxanes, catenanes and more recently exotic topological shapes like Borromean rings.³³

Supramolecular synthons are kinetically defined structural units that express the core features of a crystal structure and which encapsulate the essence of crystals in terms of molecular recognition. Synthons consist of molecular fragments and the supramolecular associations between them such as hydrogen bonds and other directional interactions. We have already referred to the crucial problem in crystal engineering, namely that a smaller cluster need not be the best model for a larger cluster – indeed an important assumption in synthon theory is that the supramolecular synthon is a reasonable approximation to the entire crystal despite the simplifications that are inherent, and indeed necessary, in its definition.

The main aim of crystal engineering is to make particular crystal structures from particular molecules. Unfortunately, crystal structures do not correspond in a straightforward manner to molecular functionality. This lack of modularity is a serious issue. In the language of complex systems, one states that a crystal structure is an emergent property of molecules. Because the synthetic step in crystal engineering is not always straightforward, one of the practical aims of the subject is to identify similar molecules that lead to similar crystal constructs (identify at least those systems, where an element of modularity is present when going from molecule → crystal). If a certain molecular similarity also leads to packing similarity in the form of similar supramolecular synthons, then the use of other similar molecules is also expected to lead to predictable crystal structures. Considering compounds **1** through **4**, one notes that **1**, hydrogen cyanide, is the prototype for a linear chain based on C–H...N hydrogen bonds (scheme 2).³⁴ The crystal structure was determined more than 50 years ago and is from the classical era.³⁵ Introduction of extra hydrocarbon groups between the cyano and ethynyl groups in compound **1** furnishes compounds **2** through **4**. Introduction of a C≡C group between cyano and ethynyl groups gives **2**, cyanoacetylene. However, this extra acetylene functionality has little effect on the linear chain of molecules that is formed. Once



Scheme 1. Representative supramolecular synthons.



Scheme 2. Supramolecular retrosynthesis.

again the $\text{C-H}\cdots\text{N}\equiv\text{C}$ hydrogen bond is seen. In **3**, 4-ethynylbenzonitrile, the group that intervenes between the cyano and ethynyl groups is a 1,4-disubstituted phenyl ring. Once again there is no change in the type of linear chain pattern that is formed with $\text{C-H}\cdots\text{N}\equiv\text{C}$ bonds. Finally, in **4**, 4-ethynyl-4'-cyanobiphenyl, the phenyl ring in **3** is replaced by a 4,4'-disubstituted biphenyl fragment. We note that the linear chain with $\text{C-H}\cdots\text{N}\equiv\text{C}$ hydrogen bonds is conserved in all four crystal structures. The nature of the hydrocarbon fragment that comes between the cyano and ethynyl groups has little effect on the formation of the supramolecular linear chain. In other words it may be reasonably expected that other molecules that contain ethynyl and cyano functionalities, preferably at 180° to each other, will also form the same kind of linear chain. Alternatively, one might say that the hydrocarbon

functionalities in these molecules are structurally *well insulated* from the cyano and ethynyl groups. Such molecules (**1** through **4**) are well-suited for crystal engineering applications because the crystal structures lend themselves easily to retrosynthetic analysis with supramolecular synthons. This text book example provides a good illustration as to how synthon theory is being applied to real systems in crystal engineering.

3. The synthon as a simplifier of crystal structures

Modular behaviour as described above for ethynyl cyanobenzenes is not the norm for organic molecules. Crystal structures are of course related to molecular structures, but this relationship is generally not a simple one. The behaviour of a functional

group in a molecule during crystallization depends upon the nature and positioning of all the other functional groups in the molecule. Crystal structures are emergent properties. To complicate matters further, hydrocarbon residues, which are generally not regarded as functional groups in the molecular chemistry, certainly count as functionalities in supramolecular chemistry and crystal engineering. Therefore our understanding of the molecule $\rightarrow$ crystal paradigm in crystal engineering is not at all straightforward. A simplification is required and is furnished through the supramolecular synthon. The general idea is that a good or robust synthon is one which appears in a large number of cases wherein a particular set of molecular functionalities is present. If the same set of molecular functionalities is present in another molecule then it is expected that the same supramolecular synthon will appear. Ideally, even if other functional groups are present they will not *interfere* with the appearance of the supramolecular synthon under discussion. To paraphrase, certain functionalities are more critical to the appearance of certain structural features in the final structures. The synthon is the device through which information content passes from molecular structure to crystal structure. It is a means of simplifying a crystal structure. The synthon is a model for the entire crystal structure and it is one which is hopefully representative of the complete crystal. The entire arena is an energy and structural space of great complexity with local energy minima connected by several intersecting and non-intersecting paths. Good synthons help one to traverse this landscape with maximum efficiency. Other methods of structure simplification have also been proposed. Gavezzotti has used space group information to generate small clusters of molecules.³⁶ Etter considered only strong hydrogen bonds to reduce crystal structures down to the topology of these interactions.³⁷ The synthon model is in contrast of the two modes of simplification mentioned above. It is a probabilistic model and is concerned with the frequency of occurrence of sub-structural units which are representative not only of the final crystal but also of patterns that evolve during crystallization. If a pattern is noticed often enough it is assumed to be kinetically favoured and is likely to recur in other crystals of related molecules. Crystallization is inherently a kinetic process and the supramolecular synthon is a manifestation of these kinetic factors.

4. Intermolecular interactions

A very large number and variety of intermolecular interactions have been used in crystal engineering. Most notable among such interactions are hydrogen bonds that arise from the polar region of molecules and a herringbone and stacking reactions that arise from the non-polar regions of aromatic molecules and hydrophobic interaction that arise from aliphatic regions. The hydrogen bond is especially important because it is both strong and directional.³⁸ Therefore it is a very effective design element in crystal engineering. A very large variety of hydrogen bonds are known. In addition to the stronger variety such as $\text{O}-\text{H}\cdots\text{O}$ and $\text{N}-\text{H}\cdots\text{O}$ there are weaker varieties like $\text{C}-\text{H}\cdots\text{O}$, $\text{C}-\text{H}\cdots\pi$ and other varieties that incorporate metal atoms, multiple atom acceptors and other donor and acceptor groups of very feeble effectiveness.³⁹ These hydrogen bonds have a greater or lesser effect on the outcome of the final crystal structure. Their study is a vast undertaking and the ways in which different kinds of hydrogen bonds interact with one another in crystals is in itself a topic of immense proportions. Suffice it to say that the majority of papers that one reads currently in structural crystal engineering exemplify the role of hydrogen bonds of one kind or another. Other interactions that have become popular in recent times include halogen bonds in which an electrophilic halogen atom plays the same role as the hydrogen atom does in a hydrogen bond.⁴⁰ Interactions between halogen atoms such as $\text{Cl}\cdots\text{Cl}$, $\text{Br}\cdots\text{Br}$ and $\text{I}\cdots\text{I}$ are special cases of halogen bonding.⁴¹ Interactions between heavy atoms such as gold, for example the *aurophilic* $\text{Au}\cdots\text{Au}$ interaction have also been used in crystal engineering.⁴² The general idea has been described for the ethynyl cyanobenzenes in section 2. A molecule is chosen so that there are appropriate hydrogen bond donor and acceptor groups in suitable locations of the molecule. The location and positioning of these groups is so selected such that an extended array of molecules connected with hydrogen bonds is obtained. The chicken-wire structure of the 1 : 1 molecular complex of cyanuric acid and melamine is a classic example of the use of hydrogen bonds in designing a layered crystal structure.⁴³

Interaction interference is a notable stumbling application to modular construction of a crystal structure. Accordingly interference needs to be firstly identified, then understood and finally tackled and

even incorporated, if necessary, in the design strategy. As mentioned earlier not all crystal structures can be understood in a modular manner based on molecular functionalities. In fact the converse is almost the more common occurrence. Different types of interactions interfere with each other and the more dominant interaction (stronger and more directional) will dominate the packing and the weaker interactions are necessarily subsumed and are compromised. A number of recent papers have addressed the problem of interference.⁴⁴ In optimal cases, interference may even be used in the design strategy and if a sufficiently large number of crystal structures are known, it is possible to predict more crystal structures within the structural family; this has been demonstrated in a series of geminal alkynols.⁴⁵

5. Polymorphism

Polymorphism refers to the phenomenon wherein a given molecule exists in more than one crystal form.⁴⁶ It was originally conjectured that polymorphism is the enemy of crystal engineering – it was referred to as the Nemesis of crystal engineering.¹ More recent work has shown that this phenomenon is of fundamental significance in understanding crystal packing, crystal structure prediction and even in the unravelling of the mechanisms of crystallization. An additional, but by no means inconsequential reason for the importance of polymorphism is that different polymorphs of a drug molecule have been deemed in some cases to warrant separate legal protection in the form of patents. Accordingly there is a tremendous interest, in the pharmaceutical industry, to understand this phenomenon.

Polymorphism is of fundamental interest. Why should any molecule crystallize in more than one form especially when it appears that molecular recognition is such a subtle and specific event that demands an exact matching in geometrical and chemical terms of the various interacting molecules? Many reasons for polymorphism have been adduced and one of the most appealing ones is that several metastable and kinetic crystal forms may be obtained during crystallization before the most stable crystal structure, namely the thermodynamic form, appears.⁴⁷ Some of these kinetic forms may be indefinitely stable. For example, although graphite is the most stable polymorph of elemental carbon, diamond which is a metastable polymorph, is indefinitely stable under ambient conditions. The outcome of crystalli-

zation may lead to either or both kinetic and thermodynamic products thereby leading to polymorphism.

The study of polymorphism is a major activity in the practice of crystal engineering today. The subject may be studied through the crystallization of various crystal forms and the measurement of their properties by techniques such as single crystal X-ray crystallography, powder X-ray diffraction, differential scanning calorimetry, infrared and Raman spectroscopy and more recent more exotic techniques such as terahertz spectroscopy. From the applied viewpoint of the pharmaceutical industry it is important to be able to detect very small amounts of one polymorph in the presence of a large excess of another. Typically, the polymorph which is suspected to be present in a small amount enjoys legal protection whereas the polymorph in excess is free of patent coverage. Accordingly, an innovator company would like to show that a solid form being marketed by a generic competitor contains an infringing polymorph. Conversely, the generic company would like to show that the form which it is marketing is free of the polymorph that enjoys patent protection. All this means that there is a tremendous impetus towards making of instrumentation that can detect crystal forms at ever increasing levels of sensitivity.

Polymorphism may also be studied through computational methods. Any crystal structure is associated with energy stabilization with respect to its isolated molecules. This is the energy that must be put into a crystal in order to dissociate it into its constituent molecules, in other words the heat of sublimation. Current methods of crystal structure prediction generate a very large number of putative crystal structures associated with certain energies.⁴⁸ Computed forms with the lowest energy are assumed to be ones that are obtained experimentally. These computations involve the optimization of atom-atom potentials which are empirical parameters that are related through force fields that are undergoing constant refinement and improvement. Unfortunately methods of crystal structure prediction that depend on energies of crystal structures are not quite so useful if the thermodynamic form is different from the kinetic form, and the latter is the one obtained during crystallization.⁴⁹ These and other difficulties continue to engage the attention of computational chemists who are involved in the exercise of crystal structure prediction (CSP). The Cambridge Crystallographic Data Centre organizes blind

tests in CSP every few years in which the experimental crystal structures of a few molecules are held confidentially while contestants make computational predictions about their crystal structures.⁵⁰ After several months, the results of the computational groups are compared with the experimental structures. Methods of CSP have improved vastly over the past decade; one particular group obtained the correct answers for all four molecules that had been supplied for the most recent test.⁵¹ At the time of writing this review, another blind test was in progress with co-crystals, salts and polymorphs among the molecules given for the exercise.

6. Multi-component molecular crystals

From antiquity, crystallization has been known to be a technique of purification. Its inherent nature is that of exclusion. From a solution containing numerous compounds or a melt of several compounds, crystallization generally yields a single compound in a high state of purity. Molecular recognition is a very specific phenomenon and when a solution or melt is in a condition of supersaturation or supercooling, a kinetically controlled process that we call nucleation occurs and results in the appearance of a single component solid phase that is called a crystal. Accordingly, the idea that a crystal can contain more than one type of molecular entity is counter intuitive. Unless there are specific chemical reasons, multi-component molecular crystals are normally not expected. Within this category of substance, one may include crystals that contain two compounds both of which are normally isolated as pure crystalline solids. One may also include crystals that contain molecules of one type along with solvent molecules that are an integral part of the crystal structure, in other words they are arranged with long term periodicity and are structured regularly. It is mostly a technical nicety to distinguish between these two types of multi-component molecular crystals.⁵²

The first type of binary crystal has been referred to in the past as solid solution, molecular compound, addition compound, molecular complex and co-crystal.⁵³ The term *co-crystal* is usually employed to refer to a crystal in which two distinct molecular components are linked with hydrogen bonds. In these co-crystals, hydrogen bonds of the type A...B between components A and B are stronger are more specific than hydrogen bonds say

of the type A...A or B...B. This is the driving force for co-crystal formation. Sometimes the acidity of the hydrogen bond donor and the basicity of the hydrogen bond acceptor are so high that proton transfer takes place across the hydrogen bond (any hydrogen bond is a case of incipient proton transfer) so that a salt is formed.⁵⁴ This salt is between an organic cation and organic anion. Beyond a point, it is artificial to differentiate between a co-crystal which consists of neutral molecules and a salt which consists of ions. Other types of multi-component molecular crystals are mediated with interactions other than hydrogen bonding, say $\pi\cdots\pi$ stacking interactions and hydrophobic interactions between hydrocarbon residues. However, the term *co-crystal* is, rightly or wrongly, used when the two components are held together with hydrogen bonds.

Co-crystals have become particularly important because of their relevance in the pharmaceutical industry.⁵⁵ In the same way that patent protection can be extended for a drug by the discovery of new polymers, such protection may also be obtained by the isolation of co-crystals between the drug and a small neutral organic molecule called a co-former.⁵⁶ Co-crystallization of a drug is desirable if the co-crystals have better physical properties when compared to the parent drug. These could be better solubility, better stability or longer shelf life. Co-crystals of a drug generally have a good chance to enjoy patent protection over and above the parent drug because: (i) they are clearly new chemical entities; (ii) their design and preparation involve several elements of non-obviousness and; (iii) they generally have novel and useful properties. Generics are engaged in research aimed at generating large numbers of co-crystals for their drugs. The typical drug molecule contains a number of hydrogen bond donor and acceptor groups. Therefore these molecules are particularly amenable to the formation of (hydrogen bond based) co-crystals. The structure of the co-former for any particular drug molecule is readily obtained by the application of synthon theory. Synthons between the drug and the co-former molecules are necessarily of an unsymmetrical nature and have been termed as *heterosynthons* in contrast to the *homosynthons*, like the carboxylic acid dimer, that are obtained in the crystal structures of single component crystals. The design and properties of co-crystals is of active concern today in the practice of crystal engineering.⁵⁷

7. Conclusions

Crystal engineering has completed the stages of early growth and has now entered a period of maturity and consolidated development. A considerable body of structural data has been obtained and analysed and generalizations for crystal packing are being developed with this data. New uses and applications are being suggested for crystals that are being designed systematically. For co-ordination polymers, applications such as absorption of gases and liquids is of major importance but optimization of magnetic and electric properties is also well-studied. Design of molecular crystals for optical, electronic and chemical properties continues to be a major undertaking. Function will be of major importance in the future. The prediction of crystal structures is a major challenge and represents the cutting edge of computational crystal engineering. Unravelling the mechanism of crystallization is one of the Holy Grails of crystal engineering and several researchers are using both crystallography and non-crystallographic methods to make inroads into this complex and challenging question.

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875					Application or Docket Number 10/378,956		Filing Date 03/03/2003		☐ To be Mailed		
APPLICATION AS FILED – PART I											
(Column 1)			(Column 2)			SMALL ENTITY ☒ OR		OTHER THAN SMALL ENTITY			
FOR		NUMBER FILED	NUMBER EXTRA		RATE (\$)	FEE (\$)	OR		RATE (\$)	FEE (\$)	
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))		N/A	N/A		N/A		OR		N/A		
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))		N/A	N/A		N/A		OR		N/A		
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))		N/A	N/A		N/A		OR		N/A		
TOTAL CLAIMS (37 CFR 1.16(i))		minus 20 =	*		X \$ =		OR		X \$ =		
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 =	*		X \$ =		OR		X \$ =		
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))		If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$250 (\$125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).									
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))											
* If the difference in column 1 is less than zero, enter "0" in column 2.											
APPLICATION AS AMENDED – PART II											
(Column 1)			(Column 2)			(Column 3)		SMALL ENTITY OR		OTHER THAN SMALL ENTITY	
AMENDMENT	10/22/2010	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	OR		RATE (\$)	ADDITIONAL FEE (\$)
	Total (37 CFR 1.16(i))	* 20	Minus	** 36	= 0	X \$26 =	0	OR		X \$ =	
	Independent (37 CFR 1.16(h))	* 1	Minus	***9	= 0	X \$110 =	0	OR		X \$ =	
	☐ Application Size Fee (37 CFR 1.16(s))										
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))										
	TOTAL ADD'L FEE										
(Column 1)			(Column 2)			(Column 3)		SMALL ENTITY OR		OTHER THAN SMALL ENTITY	
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	OR		RATE (\$)	ADDITIONAL FEE (\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =		OR		X \$ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =		OR		X \$ =	
	☐ Application Size Fee (37 CFR 1.16(s))										
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))										
	TOTAL ADD'L 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.											

Legal Instrument Examiner:
 /FLORENCE R. PATTERSON/

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Substitute for form 1449A/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(use as many sheets as necessary)</i>				Complete if Known	
				Application Number	10/378,956
				Filing Date	March 3, 2003
				First Named Inventor	Michael J. Zaworotko
				Art Unit	1627
				Examiner Name	Sahar Javanmard
Sheet	1	of	11	Attorney Docket Number	USF.106XC1

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number - Kind Code* (if known)			
	U1	US-2002/0006951	01-17-2002	Hageman <i>et al.</i>	All
	U2	US-2002/0013357	01-31-2002	Nadkarni, Sreekant <i>et al.</i>	All
	U3	US-2002/0015735	02-07-2002	Hedden <i>et al.</i>	All
	U4	US-2002/0034542	03-21-2002	Thombre <i>et al.</i>	All
	U5	US-2002/0037925	03-28-2002	Dewey <i>et al.</i>	All
	U6	US-2002/0042446	04-11-2002	Dewey <i>et al.</i>	All
	U7	US-2002/0071857	06-13-2002	Tugrul T. Kararli <i>et al.</i>	All
	U8	US-2002/0107250	08-08-2002	Hariharan <i>et al.</i>	All
	U9	US-2002/0119193	08-29-2002	Trang T. Le <i>et al.</i>	All

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	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
		Country Code ³ - Number ⁴ - Kind Code ⁵ (if known)				
	F1	FR 2849029 A1	06-25-2004	Laboratoire L. Lafon <i>et al.</i>	All	
	F2	JP 46-33588	10-01-1971	Sanzu Inc.	All	
	F3	JP 54-095589	07-28-1979	Sumitomo Chemical Co.	All	
	F4	EP 1167355	10-01-2003	Fako Ilacilari A.S.	All	
	F5	GB 1297261 A	11-22-1972	E.R. Squibb & Sons, Inc.	All	
	F6	GB 2169601 A	07-16-1986	Tate & Lyle Public Limited Company	All	
	F7	WO 1995/23596 A1	09-08-1995	The Boots Company PLC	All	

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				Art Unit	1627
				Examiner Name	Sahar Javanmard
Sheet	2	of	11	Attorney Docket Number	USF.106XC1

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		Number - Kind Code* (if known)			
	U10	US-2003/0069190	04-10-2003	Abdel-Magid <i>et al.</i>	All
	U11	US-2004/0019211	01-29-2004	Remenar <i>et al.</i>	All
	U12	US-2004/0106055	06-03-2004	Molaire <i>et al.</i>	All
	U13	US-2004/0171062	09-02-2004	Hirth <i>et al.</i>	All
	U14	US-2005/0256127	11-17-2005	Ku <i>et al.</i>	All
	U15	US-2006/0223794	10-05-2006	Bourghol Hickey <i>et al.</i>	All
	U16	US-2007/0015841	01-18-2007	Tawa <i>et al.</i>	All
	U17	US-2007/0021510	01-25-2007	Hickey <i>et al.</i>	All
	U18	US-2007/0059356	03-15-2007	Almarsson <i>et al.</i>	All

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		Country Code ³ - Number ⁴ - Kind Code ⁵ (if known)				
	F8	WO 1996/33193 A1	10-24-1996	Janssen Pharmaceutica N.V.	All	
	F9	WO 2000/07583 A3	02-17-2000	Brookhaven Science Associates	All	
	F10	WO 2000/32189 A1	06-08-2000	G.D. Searle & Co.	All	
	F11	WO 2000/50020 A2	08-21-2000	University of Cincinnati	All	
	F12	WO 2000/72841 A1	12-07-2000	Berlant, Jeffrey	All	
	F13	WO 2001/41536 A2	06-14-2001	Pharmacia Corporation	All	
	F14	WO 2001/41760 A3	06-14-2001	Pharmacia Corporation	All	

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				Application Number	10/378,956
				Filing Date	March 3, 2003
				First Named Inventor	Michael J. Zaworotko
				Art Unit	1627
				Examiner Name	Sahar Javanmard
Sheet	3	of	11	Attorney Docket Number	USF.106XC1

U.S. PATENT DOCUMENTS					
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	U19	US-2007/0293674	12-20-2007	Scoppettuolo <i>et al.</i>	All
	U20	US-3,970,651	07-20-1976	Kaplan <i>et al.</i>	All
	U21	US-4,008,321	02-15-1977	Kamishita <i>et al.</i>	All
	U22	US-4,513,006	04-23-1995	Maryanoff <i>et al.</i>	All
	U23	US-4,853,379	08-01-1989	Shroot <i>et al.</i>	All
	U24	US-4,925,674	05-15-1990	Giannini <i>et al.</i>	All
	U25	US-4,927,855	05-22-1990	Lafon	All
	U26	US-4,994,604	02-19-1991	Tung <i>et al.</i>	All
	U27	US-5,242,942	09-07-1993	Costanzo <i>et al.</i>	All

FOREIGN PATENT DOCUMENTS						
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	F15	WO 2001/42222 A2	06-14-2001	Pharmacia Corporation	All	
	F16	WO 2001/45706 A1	06-28-2001	Pharmacia Corporation	All	
	F17	WO 2001/51919 A2	07-19-2001	Transform Pharmaceuticals, Inc.	All	
	F18	WO 2001/78724 A1	10-25-2001	Pharmacia Corporation	All	
	F19	WO 2001/91750 A1	12-06-2001	Pharmacia Corporation	All	
	F20	WO 2002/000627 A1	01-03-2002	Fako Ilaclari A.S.	All	
	F21	WO 2002/056878 A2	07-25-2002	Pharmacia Corporation	All	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(use as many sheets as necessary)</i>			Application Number	10/378,956	
			Filing Date	March 3, 2003	
			First Named Inventor	Michael J. Zaworotko	
			Art Unit	1627	
			Examiner Name	Sahar Javanmard	
Sheet	4	of	11	Attorney Docket Number	USF.106XC1

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	U28	US-5,273,760	12-28-1993	Oshlack <i>et al.</i>	All
	U29	US-5,286,493	02-15-1994	Oshlack <i>et al.</i>	All
	U30	US-5,324,351	06-28-1994	Oshlack <i>et al.</i>	All
	U31	US-5,356,467	10-18-1994	Oshlack <i>et al.</i>	All
	U32	US-5,366,738	11-22-1994	Rork <i>et al.</i>	All
	U33	US-5,384,327	01-24-1995	Costanzo <i>et al.</i>	All
	U34	US-5,466,823	11-14-1995	Talley <i>et al.</i>	All
	U35	US-5,472,712	12-05-1995	Oshlack <i>et al.</i>	All
	U36	US-5,510,496	04-23-1996	Talley <i>et al.</i>	All

FOREIGN PATENT DOCUMENTS						
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		Country Code ³ - Number ⁴ - Kind Code ⁵ (if known)				
	F22	WO 2002/056915 A2	07-25-2002	Cephalon, Inc.	All	
	F23	WO 2002/10125 A1	02-07-2002	Teva Pharmaceutical Industries Ltd.	All	
	F24	WO 2002/102376 A1	12-27-2002	Pharmacia Corporation	All	
	F25	WO 2003/033462 A2	04-24-2003	The Regents of the University of Michigan	All	
	F26	WO 2005/053612 A2	06-16-2005	Shire Laboratories, Inc.	All	

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Substitute for form 1449A/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(use as many sheets as necessary)</i>				Complete if Known	
				Application Number	10/378,956
				Filing Date	March 3, 2003
				First Named Inventor	Michael J. Zaworotko
				Art Unit	1627
				Examiner Name	Sahar Javanmard
Sheet	5	of	11	Attorney Docket Number	USF.106XC1

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number - Kind Code* (if known)			
	U37	US-5,521,207	05-28-1996	Graneto	All
	U38	US-5,563,165	10-08-1996	Talley <i>et al.</i>	All
	U39	US-5,631,250	05-20-1997	Bunnell <i>et al.</i>	All
	U40	US-5,633,272	05-27-1997	Talley <i>et al.</i>	All
	U41	US-5,641,512	06-24-1997	Cimiluca	All
	U42	US-5,703,232	12-30-1997	Bunnell <i>et al.</i>	All
	U43	US-5,736,541	04-07-1998	Bunnell <i>et al.</i>	All
	U44	US-5,753,688	05-19-1998	Talley <i>et al.</i>	All
	U45	US-5,753,693	05-19-1998	Shank	All
	U46	US-5,760,007	06-02-1999	Shank <i>et al.</i>	All
	U47	US-5,760,068	06-02-1998	Talley <i>et al.</i>	All
	U48	US-5,932,598	08-03-1999	Talley <i>et al.</i>	All
	U49	US-5,935,933	08-10-1999	Shank <i>et al.</i>	All
	U50	US-5,952,187	09-14-1999	Stenglein <i>et al.</i>	All
	U51	US-5,972,986	10-26-1999	Seibert <i>et al.</i>	All
	U52	US-5,985,902	11-16-1999	Talley <i>et al.</i>	All
	U53	US-5,998,380	12-07-1999	Ehrenberg <i>et al.</i>	All
	U54	US-6,054,136	04-25-2000	Farah <i>et al.</i>	All
	U55	US-6,071,537	06-06-2000	Shank	All
	U56	US-6,132,420	10-17-2000	Dionne <i>et al.</i>	All
	U57	US-6,156,781	12-05-2000	Talley <i>et al.</i>	All
	U58	US-6,191,117	02-20-2001	Kozachuk	All

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				Application Number	10/378,956
				Filing Date	March 3, 2003
				First Named Inventor	Michael J. Zaworotko
				Art Unit	1627
				Examiner Name	Sahar Javanmard
Sheet	6	of	11	Attorney Docket Number	USF.106XC1

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		Number - Kind Code* (if known)			
	U59	US-6,201,010	03-13-2001	Cottrell	All
	U60	US-6,245,357	06-12-2001	Edgren <i>et al.</i>	All
	U61	US-6,270,787	08-07-2001	Ayer	All
	U62	US-6,283,953	09-04-2001	Ayer <i>et al.</i>	All
	U63	US-6,287,295	09-11-2001	Chen <i>et al.</i>	All
	U64	US-6,294,192	09-25-2001	Patel <i>et al.</i>	All
	U65	US-6,319,903	11-20-2001	Carrazana <i>et al.</i>	All
	U66	US-6,323,266	11-27-2001	Phillips	All
	U67	US-6,333,050	12-25-2001	Wong <i>et al.</i>	All
	U68	US-6,342,249	01-29-2002	Wong <i>et al.</i>	All
	U69	US-6,348,458	02-19-2002	Hamied <i>et al.</i>	All
	U70	US-6,365,185	04-02-2002	Ritschel <i>et al.</i>	All
	U71	US-6,368,626	04-09-2002	Bhatt <i>et al.</i>	All
	U72	US-6,375,978	04-23-2002	Kleiner <i>et al.</i>	All
	U73	US-6,384,034	05-07-2002	Simitchieva <i>et al.</i>	All
	U74	US-6,403,640	06-11-2002	Stoner <i>et al.</i>	All
	U75	US-6,413,965	07-02-2002	Banavara L. Mylari	All
	U76	US-6,420,394	07-16-2002	Supersaxo	All
	U77	US-6,488,962	12-03-2002	Berner <i>et al.</i>	All
	U78	US-6,503,884	01-07-2003	Ehrenberg <i>et al.</i>	All
	U79	US-6,579,895	06-17-2003	Karim <i>et al.</i>	All
	U80	US-6,613,790	09-02-2003	Jeffrey Carter	All

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				Application Number	10/378,956
				Filing Date	March 3, 2003
				First Named Inventor	Michael J. Zaworotko
				Art Unit	1627
Examiner Name	Sahar Javanmard				
Sheet	7	of	11	Attorney Docket Number	USF.106XC1

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	U81	US-7,132,579	11-07-2006	Neckebrook <i>et al.</i>	All
	U82	US-7,452,555	11-18-2008	Childs	All
	U83	US-7,459,449	12-02-2008	Rolf Keltjens	All
	U84	US-2007/0026078	02-01-2007	Almarsson <i>et al.</i>	All
	U85	US-2009/0088443	04-02-2009	Remenar <i>et al.</i>	All
	U86	US-2006/0134198	06-22-2006	Tawa <i>et al.</i>	All

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document		Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Country Code ³	Number ⁴ - Kind Code ⁵ (if known)			
	F27		WO 2005/077894 A1	08-25-2005	Transform Pharmaceuticals, Inc.	All
	F28		WO 2005/118577 A1	12-15-2005	Transform Pharmaceuticals, Inc.	All
	F29		WO 2004/060347 A2	07-22-2004	Transform Pharmaceuticals, Inc.	All

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			Application Number	10/378,956	
			Filing Date	March 3, 2003	
			First Named Inventor	Michael J. Zaworotko	
			Group Art Unit	1627	
			Examiner Name	Sahar Javanmard	
			Attorney Docket Number	USF.106XC1	
Sheet	8	of	11		

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	R1	AAKERÖY, C.B. <i>et al.</i> "Do Polymorphic Compounds Make Good Cocrystalizing Agents? A Structural Case Study that Demonstrates the Importance of Synthon Flexibility" <i>Crystal Growth & Design</i> , 2003, 3(2):159-165.		
	R2	BASTIN, R.J. <i>et al.</i> "Salt Selection and Optimisation Procedures for Pharmaceutical New Chemical Entities" <i>Organic Process Research & Development</i> , 2000, 4:427-435.		
	R3	BRADER, M.L. <i>et al.</i> "Hybrid insulin cocrystals for controlled release delivery" <i>Nature Biotechnology</i> , August 2002, 20:800-804.		
	R4	BRITTAIN, H.G. <i>et al.</i> "Polymorphism in Pharmaceutical Solids" 1999, New York: Marcel Dekker, pp. 183, 202-208, 219.		
	R5	COWAN, J.A. <i>et al.</i> "Neutron diffractions studies of the 1:1 and 2:1 cocrystals of benzene-1,2,4,5-tetracarboxylic acid and 4,4'-bipyridine" <i>Acta Crystallographica Section C: Crystal Structure Communications</i> , 2006, C62:o157-o161.		
	R6	DATABASE WPI, Section Ch, Week 197936, Derwent Publishing Ltd., London, Great Britain, Class B02, AN 1979-65538B, XP002282989 and JP 54 095589A (Sumitomo) 1979 Abstract.		
	R7	DAVIDOVICH, M. <i>et al.</i> "Detection of Polymorphism by Powder X-Ray Diffraction Interference by Preferred Orientation" <i>American Pharmaceutical Review</i> , 2004, pp. 10, 12, 14, 16, 100, Vol. 7, No. 1.		
	R8	DAVIES, N.M. <i>et al.</i> "Clinical Pharmacokinetics and Pharmacodynamics of Celecoxib: A Selective Cyclo-Oxygenase-2 Inhibitor" <i>Clin Pharmacokinet</i> , March 2000, 38(3):225-242.		
	R9	DE JONG, E.M.G.J. <i>et al.</i> "Dystrophic Psoriatic Fingernails Treated with 1% 5-Fluorouracil in a Nail Penetration-Enhancing Vehicle: A Double-Blind Study" <i>Dermatology</i> , 1999, 199:313-318.		
	R10	DEAN, J.A. "Analytical Chemistry Handbook" 1995, New York: McGraw-Hill, Inc., pp. 10.24-10.26.		
	R11	Definition of solvate, The Free Dictionary, http://www.thefreedictionary.com/solvate , accessed online on 21 July 2009, pp. 1-3.		
	R12	DOELKER, E. "Crystalline Modifications and Polymorphism changes during drug manufacturing" <i>Annales Pharmaceutiques Francaises</i> , 2002, 60(3):161-176.		

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		Filing Date	March 3, 2003
		First Named Inventor	Michael J. Zaworotko
		Group Art Unit	1627
		Examiner Name	Sahar Javanmard
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Sheet	9	of	11

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	R13	DOELKER, E. "Physicochemical behavior of active substances. Consequences for the feasibility and stability of pharmaceutical forms" <i>S.T.P. Pharma Practiques</i> , 1999, 9(5):399-409.	
	R14	DUNITZ, J.D. "Are crystal structures predictable" <i>Chem Commun.</i> , 2003, pp. 545-548.	
	R15	DVORKIN et al. "Crystal and Molecular Structure of a Complex 18-crown-6 with 6-chloro-7-sulfamido-3,4-dihydro-1,2,4-benzothiadiazine-1, 1-dioxide (hypothiazide) of 1:1 Composition" <i>Kristallagafiya</i> , 1990, 35(3):682-686.	
	R16	EL-NAHHAS, S.A. " Physico-Chemical characteristics of Carbamazepine-beta-cyclodextrin inclusion compounds and carbamazepine-peg solid dispersions" <i>Pharmazie</i> , 1996, 51(12):960-963.	
	R17	FAUGHT, E. <i>et al.</i> "Topiramate Dose-Ranging Trial in Refractory Partial Epilepsy" <i>Amer. Epilepsy Soc. Proc.</i> , 1995, pg. 33, Vol. 36, Supp. 4.	
	R18	FITZGERALD, G.A. <i>et al.</i> "The Coxibs, Selective Inhibitors of Cyclooxygenase-2", <i>New England Journal of Medicine</i> , August 9, 2001, 345(6):433-442.	
	R19	FLEISCHMAN, S.G. <i>et al.</i> "Crystal Engineering of the Composition of Pharmaceutical Phases: Multiple-Component Crystalline Solids Involving Carbamazepine" <i>Crystal Growth & Design</i> , 2003, 3(6):909-919.	
	R20	FUNG, H.L. <i>et al.</i> "Solvent Effects on Comparative Dissolution of Pharmaceutical Solvates" <i>Chemical and Pharmaceutical Bulletin</i> , 1974, 22(2):454-458.	
	R21	JAIN, N.K. <i>et al.</i> "Polymorphism in Pharmacy" <i>Indian Drugs</i> , 1986, 23(6):315-329.	
	R22	Japanese Notice of Reasons for Rejection dated October 8, 2009, Japanese Application No. 2003-572946, 11 pages.	
	R23	KIRCHNER, M.T. <i>et al.</i> "Co-crystals with Acetylene: Small Is not Simple" <i>Chem. Eur J.</i> , 2010, 16:2131-2146.	
	R24	KLEIN, C.L. <i>et al.</i> "Molecular Structure of Two Conformationally Restrained Fentanyl Analogues: cis- and trans-Isomers of N-[3-Methyl-1-[2-(1,2,3,4-tetrahydro)naphthyl]-4-piperidinyl]-N-phenylpropanamide" <i>Journal of Pharmaceutical Sciences</i> , November 1985, 74(11):1147-1151.	

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			Filing Date	March 3, 2003
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			Examiner Name	Sahar Javanmard
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	R25	MUZAFFAR, N.A. <i>et al.</i> "Polymorphism and Drug Availability" <i>Journal of Pharmacy (Lahore)</i> , 1997, 1(1):59-66.	
	R26	OSORIO-LOZADA, A. <i>et al.</i> "Synthesis and determination of the absolute stereochemistry of the enantiomers of adrafinil and modafinil" <i>Tetrahedron: Asymmetry</i> , 2004, 15:3811-3815.	
	R27	OSWALD, I.D.H. <i>et al.</i> "The formation of paracetamol (acetaminophen) adducts with hydrogen-bond acceptors" <i>Acta Crystallographica Section B</i> , 2002, B58:1057-1066.	
	R28	OTSUKA, M. <i>et al.</i> "Effect of Polymorphic Forms of Bulk Powders on Pharmaceutical Properties of Carbamazepine Granules" <i>Chem Pharm Bull</i> , 1999, 47(6):852-856.	
	R29	PEDIREDDI, V.R. <i>et al.</i> "Layered Structures Formed by Dinitrobenzoic Acids" <i>Tetrahedron Letters</i> , 1998, 39:9831-9834.	
	R30	Physician's Desk Reference, 56th Edition, 2002, pp. 2590-2595.	
	R31	Press Release. "Clinical Development of Topiramate for Obesity Extended to Simplify Dosing, Improve Tolerability". http://www.orthomcneil.com/news/article020402.html (February 4, 2002), New Jersey, 2 pages.	
	R32	PRIVITERA, M. <i>et al.</i> "Dose-Ranging Trial with Higher Doses of Topiramate in Patients with Resistant Partial Seizures", <i>Amer. Epilepsy Soc. Proc.</i> , 1995, pg. 33, Vol. 36, Supp. 4.	
	R33	REYNOLDS, J.E.F. (ed). "Martindale, The Extra Pharmacopoeia" 1993, London, England: The Pharmaceutical Press, 13 th Edition, pp. 1431 (e.g., Acetaminophen, Aspirin, and Caffeine Tablets), 1465 (e.g., Aspirin plus C), 1521 (Codafen Continus), 1610 (Gaboril Complex).	
	R34	ROSENFELD, W.E. "Topiramate: A Review of Preclinical, Pharmacokinetic, and Clinical Data" <i>Clinical Therapeutics</i> , 1997, 19(6):1294-1308.	
	R35	RUBINO, J.T. <i>et al.</i> "Influence of solvent composition on the solubilities and solid-state properties of the sodium salts of some drugs" <i>International Journal of Pharmaceutics</i> , 1990, 65:141-145.	
	R36	SACHDEO, S.K. <i>et al.</i> "Topiramate: Double-Blind Trial as Monotherapy", <i>Amer. Epilepsy Soc. Proc.</i> , 1995, pg. 33, Vol. 36, Supp. 4.	

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		Application Number	10/378,956		
		Filing Date	March 3, 2003		
		First Named Inventor	Michael J. Zaworotko		
		Group Art Unit	1627		
		Examiner Name	Sahar Javanmard		
Sheet	11	of	11	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
	R37	SALEM, M.S. <i>et al.</i> "Preparation, characterisation and transformation of terfenadine polymorphic forms" <i>International Journal of Pharmaceutics</i> , 1996, 141:257-259.	
	R38	THAYER, A.M. <i>et al.</i> "Form and Function" <i>Chemical & Engineering News</i> , June 18, 2007, 85(25):17-30 (8 pages).	
	R39	U.S. Pharmacopia #23, 1995, p. 1843.	
	R40	WALSH, R.D.B. <i>et al.</i> " Crystal Engineering of the composition of pharmaceutical phases". <i>Chem. Commun.</i> , 2003, pp. 186-187.	
	R41	WEISSBUCH, I. <i>et al.</i> "Understanding and Control of Nucleation, Growth, Habit, Dissolution and Structure of Two- and Three-Dimensional Crystals Using 'Tailor-Made' Auxiliaries" <i>Acta Cryst.</i> , 1995, B51:115-148.	
	R42	WUNDERLICH, H.F. <i>et al.</i> " The Derivatives of carbamazepine with ammonium halogenides and formamide" <i>Pharmazie</i> , 1991,46(7):507-509.	
	R43	ZAMAN, M.B. <i>et al.</i> "Crystal Engineering Using Anilic Acids and Dipyrldyl Compounds through a New Supramolecular Synthon" <i>J. Org. Chem.</i> , 2001, 66:5987-5995.	
	R44	ZERKOWSKI, J.A. <i>et al.</i> "Steric Control of Secondary, Solid-State Architecture in 1:1 Complexes of Melamines and Barbiturates That Crystallize as Crinkled Tapes" <i>J Am Chem Soc</i> , 1004, 116:4298-4304.	
	R45	DESIRAJU, G.R. "The C--H...O Hydrogen Bond in Crystals: What Is It?" <i>Acc. Chem. Res.</i> , 1991, pp. 24:290-296.	
	R46		
	R47		
	R48		

Examiner Signature		Date Considered	
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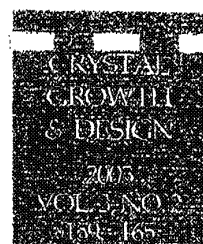
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Do Polymorphic Compounds Make Good Cocrystallizing Agents? A Structural Case Study that Demonstrates the Importance of Synthons Flexibility

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Ⓢ This paper contains enhanced objects available on the Internet at <http://pubs.acs.org/crystal>.

ABSTRACT: The ability of four polymorphic compounds, isonicotinamide (1), 2-amino-5-nitropyridine (2), 4-chlorobenzamide (3), and maleic hydrazide (4), to form molecular cocrystals has been examined in a systematic structural study. Compounds 1–3 participate in a wide variety of binary and ternary (in the case of 1) cocrystals with aromatic or aliphatic compounds substituted with a multitude of functional groups. However, despite considerable efforts, it has not been possible to form any cocrystals with 4. The reason for this may be due to the fact that even though there are three known polymorphs of 4, they all contain the same hydrogen-bonding synthons. In contrast, the polymorphs of 1–3 display considerable synthon flexibility, e.g., different hydrogen bond interactions are present in polymorphs of the same compound. Because 1–3 can form robust synthons in a variety of ways, whereas 4 always engages in the same primary hydrogen bond interactions, it may explain why the former compounds are readily able to accommodate other molecules within the same lattice whereas there are no known cocrystals of 4.

Introduction

The ability to change key physical properties, e.g., solubility, crystal morphology, mechanical stability, etc., of a specialty chemical while retaining its essential biophysical or molecular activity is of enormous commercial and fundamental interest. Classic examples of how this can be achieved are regularly demonstrated through the conversion of a pharmacologically active molecule into its chloride or nitrate salt.¹ Alternatively, many drugs are manufactured and processed as solvates, normally as a hydrate. Despite the fact that these two avenues can lead to materials that eventually become commercially viable, potentially useful drugs may never reach this point because they fail to meet one or more of the stringent standards required from the point of view of processing, storage, or bioavailability. Recent developments in solid state organic chemistry and crystal engineering² may furnish an alternative approach that can offer better control (and tunability) of fundamental physical properties of specialty chemicals.

If a crystalline material that contains both a pharmaceutically relevant molecule and a structure-directing (but biologically/environmentally passive) component can be rationally assembled through intermolecular synthesis, then the inherent activity of the drug molecule remains intact while the physical properties of the bulk material are modified. The efficient preparation of such cocrystals hinges on an *a priori* ability to identify reliable and versatile cocrystallizing agents (CAAs) without having to resort to endless crystallization experiments.³

A good CAA should be able to form intermolecular interactions with the target molecule that are more favorable than the homomeric interactions that exist between target...target or between CAA...CAA.⁴ The CAA must also have the ability to "tolerate" the presence of a different molecular building block within the same crystalline lattice, which makes it seem reasonable to search for CAAs among polymorphic compounds.⁵ Polymorphism means that a compound is found in more than one crystalline manifestation, which,⁶ in turn, indicates that such compounds display a degree of structural flexibility. In other words, the multidimensional potential energy surface that describes the thermodynamics governing the molecular recognition processes that eventually leads to crystal growth is likely to be rather shallow with many accessible local energy minima.

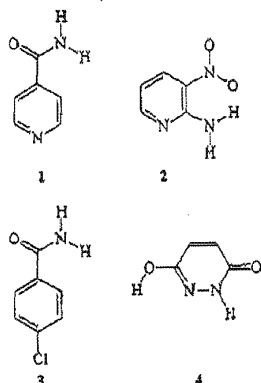
The hypothesis that polymorphic compounds are more likely to form cocrystals than are compounds that never display polymorphism is, at this stage, little more than a notion based upon empirical observations. However, from a practical perspective, it would be extremely useful to have access to reliable guidelines for how we might focus and target a search for reliable CAAs for a specific family of compounds. Furthermore, if we encounter cases that do not follow our initial hypothesis, it would be equally important to be able to rationalize the results in the context of intermolecular forces and molecular recognition. To address some of these challenges, we herein report our results from a structural study on three polymorphic compounds, isonicotinamide (1), 2-amino-5-nitropyrimidine (2), 4-chlorobenzamide (3), and maleic hydrazide (4) and several cocrystals thereof. The reason for selecting these four compounds (apart from the fact that they are all polymorphic) is that they are all potentially capable of engaging in

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Scheme 1. Four Polymorphic Molecules Capable of Forming a Variety of Hydrogen-Bonded Synthons*



* isoNicotinamide, 1; 2-amino-3-nitropyridine, 2; 4-chloroben-zamide, 3; and maleic hydrazide, 4.

several well-defined and robust intermolecular hydrogen bond motifs (Scheme 1).^{7,8}

Experimental Section

Crystal Growth and Polymorphism of 1. Upon recrystallization of 1 from nitrobenzene or nitromethane, colorless, rodlike crystals, 1a, were formed. When 1 was recrystallized from a wide variety of other solvents, e.g., ethanol, water, tetrahydrofuran (THF), dioxane, etc., colorless platelike crystals, 1b, were obtained. No other crystalline forms have been obtained either by slow evaporation or by liquid/vapor diffusion methods. Sublimation under reduced pressure yields crystals with a structure corresponding to that of 1a.

Crystal Growth and Polymorphism of 2. Compound 2 is known to exist in three different polymorphic forms. Form I 2a appears as yellow needles.⁹ Form II 2b can be obtained by recrystallization from ethanol at ambient temperature (yellow, diamond-like crystals).¹⁰ Form III 2c was obtained when 2 was recrystallized from ethanol at ambient conditions in the presence of fumaric acid (yellow, thick plates).¹⁰ No other polymorphs have been reported to date.

Crystal Growth and Polymorphism of 4. Compound 4 is known to exist in three different crystalline forms: 4a (form I) is triclinic,¹¹ 4b (form II) is monoclinic,¹² and 4c (form III), another monoclinic structure, can be obtained by slowly cooling a solution of 4 in acetic acid.¹³

Cocrystals of 1.¹⁴ (a) **2-Hexenoic Acid/1** (1:1), 11. Compound 1 (0.050 g; 0.41 mmol) dissolved in ethanol (3 mL) was mixed with 2-hexenoic acid (0.047 g; 0.41 mmol) dissolved in ethanol (3 mL) in a small test tube. After 48 h of slow evaporation at room temperature, colorless, needlelike crystals formed on the side of the test tube (mp 110–112 °C).

(b) **4-Nitrobenzoic Acid/1** (1:1), 12. Compound 1 (0.050 g; 0.41 mmol) dissolved in ethanol (5 mL) was mixed with 4-nitrobenzoic acid (0.068 g; 0.41 mmol) dissolved in ethanol (5 mL) in a small test tube. After 48 h of slow evaporation at room temperature, rectangular, colorless crystals formed on the side of the test tube (mp 181–183 °C).

(c) **3,5-Dinitrobenzoic Acid/4-Methylbenzoic Acid** (1:1), 13. Equimolar quantities of 1 (0.050 g; 0.41 mmol), 3,5-dinitrobenzoic acid (0.086 g; 0.41 mmol), and 4-methylbenzoic acid (0.056 g; 0.41 mmol) were dissolved separately in ethanol (3 mL) and mixed together in a small test tube. After 48 h of slow evaporation at room temperature, pale yellow, irregular prisms were formed on the side of the test tube (mp 141–143 °C).

Cocrystal of 2. (a) **2-Amino-3-nitropyridine/2** (1:1), 21. 2-Amino-3-nitropyridine (0.250 g; 1.68 mmol) and 2 (0.254 g; 1.81 mmol) were dissolved together in hot ethanol (50 mL). Slow evaporation at ambient conditions yielded yellow, needlelike crystals that consistently grew in clumps from one point (mp 178–181 °C).

Cocrystals of 3. (a) **3,5-Dinitrobenzoic Acid/3** (1:1), 31. Compound 3 (0.064 g; 0.41 mmol) and 3,5-dinitrobenzoic acid (0.086 g; 0.41 mmol) were dissolved together in hot methanol (8 mL). Slow evaporation at ambient conditions yielded colorless, platelike crystals (mp 154–156 °C).

(b) **3-Dimethylaminobenzoic Acid/3** (1:1), 32. Compound 3 (0.064 g; 0.41 mmol) and 3-dimethylaminobenzoic acid (0.068 g; 0.41 mmol) were dissolved together in hot ethanol (8 mL). Slow evaporation at ambient conditions yielded pale yellow, irregular prism crystals (mp 118–121 °C).

(c) **Fumaric Acid/3** (1:1), 33. Compound 3 (0.065 g; 0.42 mmol) and fumaric acid (0.024 g, 0.21 mmol) were dissolved together in hot ethanol (8 mL). Slow evaporation at ambient conditions yielded colorless, block crystals (mp 174–178 °C). Crystals of individual components could also be found and were confirmed by single-crystal X-ray diffraction.

Cocrystals of 4. Despite numerous attempts (about 25 different compounds) at forming cocrystals with 4 and a variety of aromatic (including heterocyclic) or aliphatic compounds with different functional groups, e.g., carboxylic acids, amides, oximes, etc., we were only ever able to isolate unreacted starting materials. Crystal growth experiments involved slow evaporation and liquid/vapor diffusion using a range of solvents, e.g., MeOH, EtOH, MeCN, etc. Essentially, 4 was put through the same cycle of experiments as were 1–3.

Single-Crystal X-ray Diffraction. Single crystals were placed in paratone, mounted on a glass pin, and transferred into the cold stream of the diffractometer. Crystal data for 11–13 were collected and integrated using a Bruker SMART 1000 system with graphite monochromated Mo K α ($\lambda = 0.71073$ Å) radiation at 173 K. Crystal data for 21 were collected at 301 K and for 31–33 at 203 K. Crystal data for 1a,b were collected using a Siemens P4 four circle diffractometer with graphite monochromated Mo K α radiation at ca. 150 K in a dinitrogen stream. Crystal stability was monitored by measuring standard reflections every 100 reflections, and there were no significant variations ($< \pm 1\%$). ψ -Scans were employed for data collection, and Lorentz and polarization corrections were applied. Each of the structures was solved by direct methods, using SHELXS-97 and refined using SHELXL-97. Nonhydrogen atoms were found by successive least-squares refinement on F^2 and refined with anisotropic parameters. All hydrogen atoms, except for those on the methyl group in 13, were located on the difference map. A riding model with fixed thermal parameters ($u_H = 1.2U_{eq}$) for the atom that the hydrogen atoms are riding was applied, except for 32, where the methyl hydrogen atoms were calculated. Crystallographic data for 1a,b, 11–13, 21, and 31–33 can be found in Table 1.

Results

Crystal Structure of 1 (Form I). Form I of 1 is monoclinic with one molecule in the asymmetric unit. The molecular geometry does not display any unexpected behavior, and the amide moiety is slightly twisted out of the plane of the aromatic ring (80.5°) (Figure 1).

The amide moieties in 1a generate a slight variation on the extended ribbonlike motif, which occurs frequently in primary amides. There is a self-complementary N–H $\cdots$ O head-to-head synthon between adjacent molecules, and neighboring dimers are connected into an infinite assembly through symmetry-related N–H $\cdots$ O hydrogen bonds aligned perpendicular to the long axis of the dimers (Figure 2).

Table 1. Crystallographic Data for 1a,b, 11–13, 21, and 31–33

compd	1a	1b	11	12	13
formula	C ₆ H ₅ N ₃ O	C ₆ H ₅ N ₃ O	C ₁₂ H ₁₂ N ₂ O ₂	C ₁₂ H ₁₂ N ₂ O ₂	C ₂₁ H ₁₂ N ₄ O ₃
FW	122.13	122.13	236.27	289.25	470.39
temp (K)	173(2)	173(2)	173(2)	173(2)	173(2)
cryst syst	monoclinic	monoclinic	monoclinic	monoclinic	triclinic
space group, Z	P2 ₁ /c, 4	P2 ₁ /c, 4	P2 ₁ /c, 8	P2 ₁ /c, 8	P1, 2
a (Å)	10.176(1)	15.735(3)	20.445(4)	20.512(4)	7.763(1)
b (Å)	5.7319(6)	7.998(2)	5.2309(9)	5.1675(8)	8.722(1)
c (Å)	23.008(4)	9.885	23.008(4)	23.694(5)	15.743(2)
α (deg)					93.483(2)
β (deg)	98.042(3)	105.59(2)	98.981(3)	90.66(3)	98.981(3)
γ (deg)					93.913(7)
V (Å ³)	579.5(1)	1198.2(6)	2442.3(7)	2511.3(0)	1047.8(2)
density (g/cm ³)	1.400	1.354	1.285	1.630	1.491
M _{calc} (mm ⁻¹)	0.100	0.096	0.098	0.120	0.119
θ range	2.92–27.49	1.34–22.48	1.72–28.04	2.51–26.19	2.61–28.9
range h	–13 to 13	–16 to 16	–28 to 26	–26 to 26	–9 to 10
range k	0 to 7	–8 to 8	–8 to 6	–6 to 5	–11 to 11
range l	–13 to 0	0 to 10	–30 to 30	–30 to 31	–19 to 20
refl collected	1418	1880	8158	8293	7248
ind refl (R _{int})	1334 (0.0164)	1565 (0.0151)	2808 (0.1235)	2759 (0.0544)	2622 (0.0640)
data/restraints/params	1334/0/82	1565/0/163	2808/0/154	2759/0/190	4682/0/307
R/R _w ^a (obs data)	0.0385/0.0985	0.0487/0.1185	0.0736/0.1794	0.0432/0.1097	0.0432/0.1052
R/R _w ^a (all data)	0.0494/0.1050	0.0528/0.1258	0.1128/0.1969	0.0678/0.1200	0.0839/0.1208
Δρ _{max/min} (e Å ⁻³)	0.229/–0.218	0.179/–0.280	0.229/–0.388	0.315/–0.232	0.314/–0.199
compd	21	31	32	33	
formula	C ₉ H ₈ N ₂ O ₄	C ₁₄ H ₁₀ ClN ₃ O ₇	C ₁₈ H ₁₇ ClN ₂ O ₃	C ₁₈ H ₁₆ Cl ₂ N ₂ O ₃	
FW	279.23	367.70	320.77	427.23	
temp (K)	301(2)	203(2)	203(2)	203(2)	
cryst syst	monoclinic	triclinic	triclinic	triclinic	
space group, Z	P2 ₁ (1)/n, 4	P1, 2	P1, 2	P1, 2	
a (Å)	11.788(3)	7.246(1)	7.173(1)	9.2874(8)	
b (Å)	5.161(1)	8.626(1)	8.369(2)	10.1386(9)	
c (Å)	19.975(5)	13.281(2)	12.397(3)	10.481(1)	
α (deg)		92.566(3)	88.638(4)	86.428(6)	
β (deg)	95.275(5)	101.875(3)	80.875(4)	72.174(6)	
γ (deg)		109.472(3)	77.483(4)	89.506(7)	
V (Å ³)	1210.0(5)	760.0(2)	752.0(3)	935.6(2)	
density (g/cm ³)	1.533	1.807	1.417	1.517	
M _{calc} (mm ⁻¹)	0.124	0.298	0.268	0.356	
θ range	1.93–28.26	2.52–28.14	1.59–28.28	2.05–26.25	
range h	–15 to 14	–9 to 9	–9 to 9	–12 to 12	
range k	–6 to 6	–11 to 11	–11 to 10	–13 to 13	
range l	–26 to 26	–16 to 17	–15 to 16	–13 to 13	
refl collected	10 429	5265	5256	6971	
ind refl (R _{int})	2757 (0.1056)	3375 (0.0358)	3371 (0.0309)	4128 (0.0291)	
data/restraints/params	2757/0/182	3375/0/227	3371/0/200	4128/0/254	
R/R _w ^a (obs data)	0.0555/0.1433	0.0452/0.1021	0.0545/0.1277	0.0389/0.1003	
R/R _w ^a (all data)	0.1112/0.1890	0.0724/0.1141	0.1014/0.1513	0.0546/0.1082	
Δρ _{max/min} (e Å ⁻³)	0.221/–0.304	0.301/–0.283	0.287/–0.820	0.361/–0.289	

Somewhat surprisingly, there are no prominent hydrogen bond interactions involving the pyridine nitrogen atom (Table 2). Although adjacent molecules are positioned tail-to-tail, the rings are not coplanar and the symmetry-related C...N distances are over 3.47 Å (Figure 3).

Crystal Structure of 1 (Form II). Form II of 1 is also monoclinic but with two molecules in the asymmetric unit. As in 1a, there are no remarkable intra-

molecular features in either molecule, and the amide moiety is twisted out of the plane in each molecule (by 25.4 and 24.0°, respectively) (Figure 4).

In 1b, the dimeric head-to-head motif has been abandoned in favor of an N–H(amide)···N(pyridine),

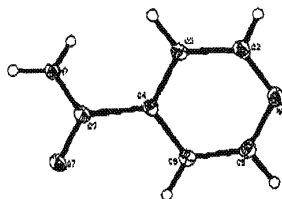


Figure 1. Thermal ellipsoids (50%) and numbering scheme in 1a.

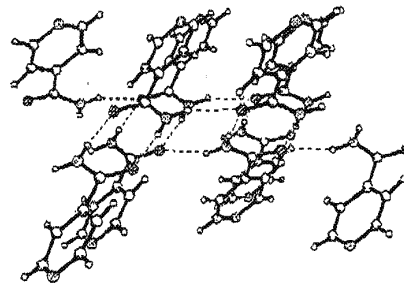


Figure 2. Dominating hydrogen bond interactions in 1a. @ A 3D rotatable image of 1a in PDB format is available.

Table 2. Hydrogen Bond Geometries^a

Hydrogen Bonds for 1a (Å and °)				
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(7)-H(72)...O(7)#1	0.89	2.08	2.9364(14)	157.9
N(7)-H(71)...O(7)#2	0.86	2.08	2.9368(16)	173.5
C(2)-H(2)...N(1)#3	0.88	2.63	3.4275(19)	151.1
C(8)-H(8)...N(1)#4	0.98	2.72	3.4790(19)	135.0

Hydrogen Bonds for 1b (Å and °)				
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(7)-H(71)...N(1)#1	0.97	2.02	2.982(3)	171.4
N(7)-H(72)...O(7)#2	0.93	2.01	2.934(2)	170.4
N(17)-H(171)...N(11)#1	0.96	2.02	2.974(3)	168.7
N(17)-H(172)...O(17)#3	0.96	1.99	2.947(3)	174.0

Hydrogen Bonds for 11 (Å and °)				
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(7)-H(72)...O(17)#1	2.09	2.952(2)	163.4	
N(7)-H(71)...O(7)#2	2.02	2.8720(19)	169.3	
O(18)-H(18)...N(1)	1.87	2.5768(19)	178.2	

Hydrogen Bonds for 12 (Å and °)				
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(7)-H(71)...O(7)#1	1.94	2.880(2)	168.0	
N(7)-H(72)...O(10)#2	2.02	2.919(3)	160.9	
O(11)-H(11)...N(1)	1.66	2.655(3)	169.2	

Hydrogen Bonds for 13 (Å and °)				
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(7)-H(71)...O(27)	1.93	2.886(2)	176.0	
N(7)-H(72)...O(17)#1	2.09	2.995(2)	167.9	
O(18)-H(18)...N(1)	1.69	2.5479(19)	159.8	
O(28)-H(28)...O(7)	1.87	2.6428(18)	168.4	

Hydrogen Bonds for 21 (Å and °)				
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2)-H(21)...N(11)	0.88	2.21	3.074(3)	169.8
N(2)-H(22)...O(2)#1	0.82	2.32	2.970(3)	136.3
N(12)-H(121)...N(1)	0.97	1.99	2.959(3)	178.9
N(12)-H(122)...N(13)#2	0.92	2.14	3.057(3)	173.3
N(2)-H(22)...O(2)	0.82	2.11	2.677(3)	126.7

Hydrogen Bonds for 31 (Å and °)				
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(7)-H(72)...O(14)#1	0.95	2.81	2.890(2)	118.8
N(7)-H(71)...O(18)	0.97	2.01	2.967(2)	167.0
O(17)-H(17)...O(7)	1.06	1.50	2.531(2)	169.8

Hydrogen Bonds for 32 (Å and °)				
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(7)-H(71)...O(18)	0.99	1.98	2.937(3)	164.6
N(7)-H(72)...O(18)#1	0.87	2.22	3.045(3)	156.4
O(17)-H(17)...O(7)	0.91	1.68	2.586(3)	172.9

Hydrogen Bonds for 33 (Å and °)				
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(7)-H(71)...O(32)	0.88	2.10	2.957(2)	164.3
N(7)-H(72)...O(22)	0.81	2.12	2.930(2)	172.9
N(17)-H(171)...O(22)	0.89	2.08	2.942(2)	164.4
N(17)-H(172)...O(32)#1	0.81	2.23	3.027(2)	168.2
O(21)-H(21)...O(17)	0.85	1.71	2.565(2)	172.7
O(31)-H(31)...O(7)	0.80	1.73	2.518(2)	168.5

^a Symmetry transformations used to generate equivalent atoms. 1a: #1, $x, -y + 1/2, z - 1/2$; #2, $-x, -y + 1, -z$; #3, $-x + 1, y + 1/2, z - 1/2$; #4, $-x + 1, -y - 1, -z$. 1b: #1, $x, y - 1, z$; #2, $x, -y + 1/2, z - 1/2$; #3, $x, -y - 1/2, z - 1/2$. 11: #1, $-x - 1/2, y + 1, -z + 1$; #2, $-x, -y + 1, -z + 1$. 12: #1, $-x, -y + 1, -z$; #2, $-x - 1/2, y - 1, -z$. 13: #1, $x, y - 1, z$. 21: #1, $-x + 1, -y, -z$; #2, $-x, -y + 2, -z$. 31: #1, $-x + 1, -y + 4, -z + 1$. 32: #1, $-x - 2, -y, -z + 1$. 33: #1, $x + 1, y, z$.

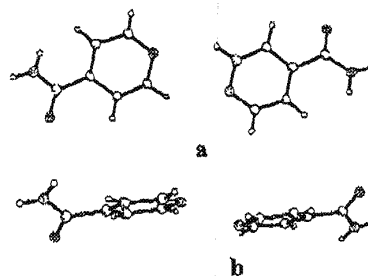


Figure 3. (a) Face-on view of the orientation of adjacent molecules in 1a. Although the relative positions of the molecules indicate the existence of complementary C-H...N hydrogen bonds, the edge-on view (b) makes this less likely as the rings are not coplanar.

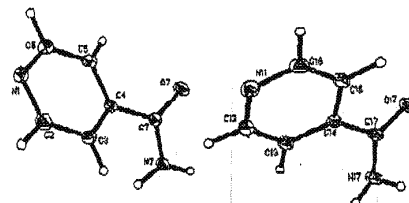


Figure 4. Thermal ellipsoids (30%) and numbering scheme in 1b.

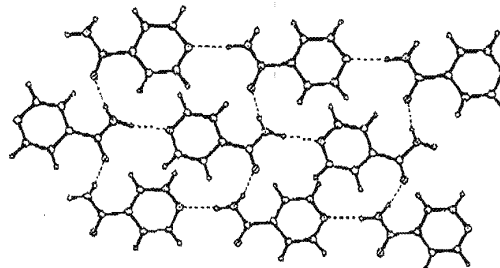


Figure 5. One of the two unique infinite 2D assemblies (ribbons) in 1b (both networks have identical connectivity).

@ A 3D rotatable image of 1b in PDB format is available.

head-to-tail, interaction and a catemeric N-H...O hydrogen bond; the direction of the catemer is almost perpendicular with respect to the chain generated by the amide...pyridine interaction (each asymmetric molecule gives rise to an independent assembly but with identical hydrogen bond connectivity) (Figure 5). We have not observed any phase changes between polymorphs even after an extended period of time (several years).

Crystal Structure of 2-Hexenoic Acid/1 (1:1), 11. The crystal structure of 11 contains one molecule of the carboxylic acid and one molecule of 1. These two building blocks are connected into a tetrameric supermolecule constructed from a dimeric, head-to-head amide...amide interaction plus two symmetry equivalent acid...pyridine interactions (Figure 6). The anti amide hydrogen atom forms a hydrogen bond with the

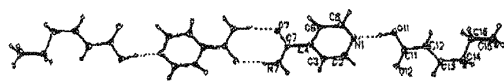


Figure 6. Thermal ellipsoids (30%) and numbering scheme in 11.

⊗ A 3D rotatable image in PDB format is available.

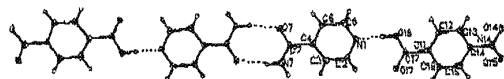


Figure 7. Thermal ellipsoids (30%) and numbering scheme in 12.

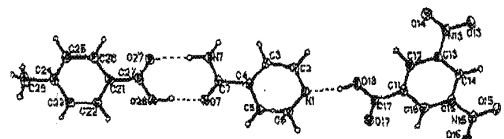


Figure 8. Thermal ellipsoids (30%), numbering scheme, and the complete ternary supermolecule in 13.

⊗ A 3D rotatable image in PDB format is available.

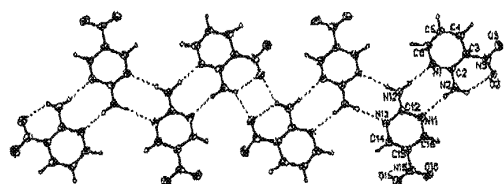


Figure 9. Extended hydrogen-bonded 1D network in 21.

⊗ A 3D rotatable image in PDB format is available.

carbonyl group of an adjacent carboxylic acid. There are no other notable hydrogen bonds in 11 (Table 2).

Crystal Structure of 4-Nitrobenzoic Acid/1 (1:1), 12. The crystal structure of 12 contains one molecule of the carboxylic acid and one molecule of 1. As is the case in 11, the two components are connected into a tetrameric supermolecule constructed from a dimeric, head-to-head amide...amide interaction plus a pair of symmetry equivalent acid...pyridine interactions (Figure 7). The anti amide hydrogen atom forms a hydrogen bond with the carbonyl group of an adjacent carboxylic acid. There are no other notable hydrogen bonds in 12.

Crystal Structure of 3,5-Dinitrobenzoic Acid/1/4-Methylbenzoic Acid (1:1:1), 13. The crystal structure of 13 is a 1:1:1 ternary cocrystal that contains a three component supermolecule with the expected connectivity. The stronger acid ($pK_a = 2.9$)¹⁶ interacts with the pyridine nitrogen atom, and the weaker acid ($pK_a = 4.4$)¹⁶ competes successfully for the amide moiety and forms a heteromeric hydrogen-bonded motif (Figure 8). This motif is consistent with that reported for several other ternary cocrystals of 1 and two carboxylic acids of different strength.¹⁶

Crystal Structure of 2/2-Amino-5-nitropyrimidine (1:1), 21. The asymmetric unit of 21 contains one molecule of each component. Near linear, symmetry-related, N...H...N hydrogen bond interactions connect

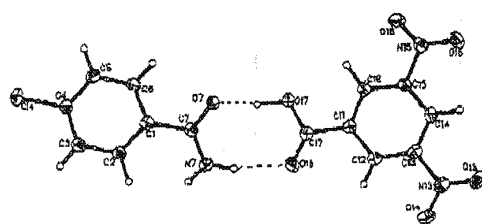


Figure 10. Thermal ellipsoids (30%) and numbering scheme in 31.

⊗ A 3D rotatable image in PDB format is available.

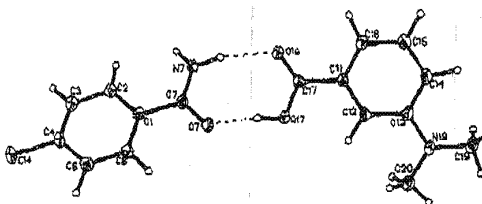


Figure 11. Thermal ellipsoids (30%) and numbering scheme in 32.

⊗ A 3D rotatable image in PDB format is available.

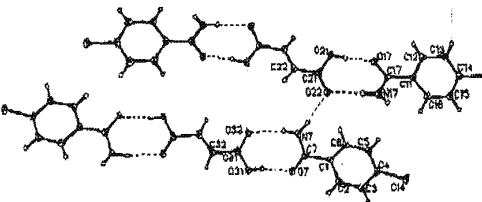


Figure 12. Thermal ellipsoids (30%) and numbering scheme in 33.

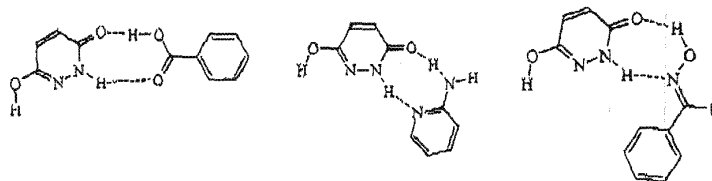
⊗ A 3D rotatable image in PDB format is available.

neighboring molecules into tetrameric (A...B...B...A) assemblies. Adjacent tetramers are linked into infinite chains via symmetry-related N-H...O hydrogen bonds (Figure 9).

Crystal Structure of 3,5-Dinitrobenzoic Acid/3 (1:1), 31. The asymmetric unit of 31 consists of one molecule of each component connected by an acid/amide heterodimer (Figure 10). The anti amide hydrogen atom forms a hydrogen bond with a nitro moiety from an adjacent acid molecule. The binary supermolecules form extended stacks with adjacent heterodimer oriented in an antiparallel fashion.

Crystal Structure of 3-Dimethylaminobenzoic Acid/3 (1:1), 32. The asymmetric unit of 32 consists of one molecule of each component connected by an acid/amide heterodimer (Figure 11). The anti amide hydrogen atom forms a hydrogen bond with the carbonyl of an adjacent acid molecule. The acid and amide molecules stack separately as AAAA and BBBB, such that each individual molecular dipole is canceled by the dipole of the molecule above or below it.

Crystal Structure of Fumaric Acid/3 (1:2), 33. The asymmetric unit of 33 consists of two molecules of the

Scheme 2. Three Examples of Known Synthons that Could Facilitate the Formation of Cocrystals Involving **4**

amide and two inequivalent halves of the acid forming two different acid/amide heterodimers (Figure 12). The anti amide hydrogen atoms form a hydrogen bond with a carbonyl of an adjacent acid molecule. The three component (A...B...A) heterodimer stacks in an alternating pattern of ABAABA.

Discussion

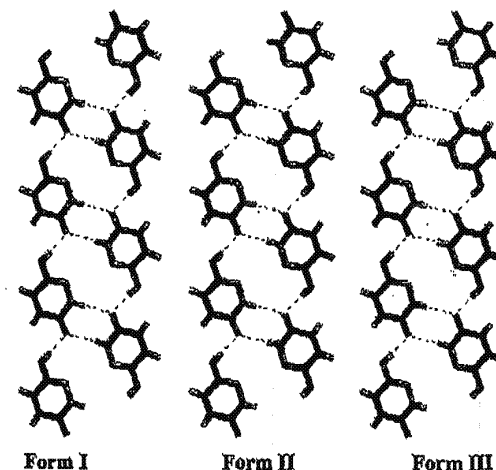
We have shown that cocrystals can readily be formed from both **2**, **1**, and **3** with a variety of aliphatic and aromatic carboxylic acids. This is in agreement with the suggestion that polymorphs make good CAs (provided that solubility differences are not too large). However, we have been completely unsuccessful in forming any kind of cocrystals with **4**, despite the fact that it exists by itself in three different crystalline forms. We have tried a range of crystallization techniques as well as an extensive series of molecular compounds that in principle, can form effective complementary hydrogen bond interactions with a 2-pyridone moiety (e.g., carboxylic acids, 2-aminopyrimidines, 2-aminopyrimidines, oximes, etc.) (Scheme 2).

The failure to produce any cocrystals with **4** obviously casts doubts on the notion that polymorphic compounds make good CAs unless there is a significant structural difference in the polymorphic behavior of **1–4**. We decided to take a closer look at all the polymorphs **1a,b**, **2a–c**, **3a–c**, and **4a–c** in an attempt to uncover possible reasons for the unwillingness of **4** to participate in molecular cocrystals. Previous work on polymorphs containing extensive hydrogen-bonded networks has demonstrated that even very complex intermolecular interactions and subtle structural differences are readily identified and categorized through a systematic use of graph-set notation.¹⁷ Consequently, a graph-set analysis was applied to the hydrogen bond patterns displayed by **1a,b**, **2a–c**, and **3a–c**. The two polymorphs of isonicotinamide, **1a** and **1b**, display very different intermolecular connectivities. In **1a**, there is a "classic" amide...amide head-to-head interaction as well as the commonly occurring N–H...O link between adjacent dimers resulting in a $C(4)R_2^2(8)$ notation for the primary hydrogen bonds in this polymorph. However, the primary intermolecular forces in **1b** are significantly different as there is a catemeric amide...amide hydrogen bond, $C(4)$, as well as an amide...pyridine interaction, $C(7)$. A similar classification of the three polymorphs of **2** reveals that the expected intramolecular amine...nitro hydrogen bond is present in all three forms. In addition, **2b** and **2c** have identical intermolecular connectivities and the primary hydrogen bond motifs are thus described with the same graph-set notation, $R_2^2(12)R_2^2(8)S(6)$. In **2a**, however, there are infi-

nite hydrogen-bonded ribbons that are described by the following notation, $R_2^2(10)R_2^2(8)S(6)$. The structures of **3a** and **3c** reveal the amide moieties forming the classic amide one-dimensional catemer, $C(4)R_2^2(8)R_2^2(8)$. The difference between the two structures lies in the arrangement of aromatic rings with respect to one another. While the graph-set notation for **3b** is similar to **3a** and **3c**, the larger hydrogen-bonded ring creates a two-dimensional network, $C(4)R_2^2(8)R_2^2(16)$. In contrast, all three polymorphs of **4** contain the same hydrogen-bonded ladders held together by identical synthons; $S(7)R_2^2(14)R_2^2(8)$ (Figure 13).

The fact that these three different polymorphs all contain the same extended networks was also noted in the original paper, "Three Forms of MH(4) Provide a Unique Example of Polymorphic Structures Built of Similar Hydrogen-Bonded Aggregates. The Same Hydrogen-Bonded Supramolecular Aggregates Organize into Different Lattices of Different Symmetries..."¹²

A detailed structural examination of **1–4** has enabled the identification of significant differences, in terms of molecular recognition patterns, between the different polymorphs that in turn, may provide practical guidelines for distinguishing between (or ranking) candidates that are potentially suitable as CAs. Cocrystals are not necessarily easy to prepare since such heteromeric systems are only likely to appear if the noncovalent forces between different molecules are more favorable than those that exist between molecules in the corre-

**Figure 13.** Primary hydrogen bond motifs in the three known polymorphs of **4** display the same connectivity.

sponding homomeric crystals. An important consideration when attempting to prepare cocrystals is to choose a CA that is already known to be polymorphic. Clearly, if a molecular compound exists in several polymorphs, it has demonstrated a structural flexibility and it is not as energetically locked into a single type of crystalline lattice or packing mode. However, as the current study shows, structural flexibility alone is not always enough. It may be equally important to select molecules that can adopt alternative packing patterns as well as display synthon flexibility, an ability to participate in several different robust and well-defined intermolecular interactions that can satisfy the demands of multiple hydrogen bond donors/acceptors on a variety of molecules.

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Note Added After ASAP Posting

An earlier version of this paper posted ASAP on January 28, 2003 contained an incorrect name (2-amino-3-nitropyridine/2) in two paragraphs describing compound 21 in Experimental Section and Results. The corrected name (2-amino-5-nitropyrimidine/2) appears in this version posted February 7, 2003. Links to web-enhanced object files were added March 5, 2003.

Supporting Information Available: X-ray crystallographic files (CIF). This material is available and free of charge via the Internet at <http://pubs.acs.org>.

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Salt Selection and Optimisation Procedures for Pharmaceutical New Chemical Entities

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Abstract:

Selection of an appropriate salt form for a new chemical entity provides the pharmaceutical chemist and formulation scientist with the opportunity to modify the characteristics of the potential drug substance and to permit the development of dosage forms with good bioavailability, stability, manufacturability, and patient compliance. Salts are most commonly employed for modifying aqueous solubility, however the salt form selected will influence a range of other properties such as melting point, hygroscopicity, chemical stability, dissolution rate, solution pH, crystal form, and mechanical properties. Where possible, a range of salts should be prepared for each new substance and their properties compared during a suitable preformulation program. Since it is normally possible to fully develop only one salt form, its properties should be appropriate to the primary route of administration and dosage form. An understanding of the influence of drug and salt properties on the finished product is essential to ensure selection of the best salt. The drug properties required for one dosage form may be quite different from those required for another. A well designed salt selection and optimisation study provides a sound base on which to build a rapid and economic product development programme.

Introduction

Modern drug discovery processes involve the screening of vast numbers of compounds that may have been made by the Company's research laboratories over many years. Added to these may be the many thousands of compounds that have been manufactured as libraries of structurally related series by "combinatorial chemistry" techniques. All of these compounds are generally dissolved in dimethylsulphoxide (DMSO) solution and screened in an enzyme- or receptor-based assay system. If the number of "hits" produced is large, the numbers are usually refined by further screening and selection until a manageable number of "leads" is available. Many of these leads will show only weak or moderate activity and further refinement and optimisation is invariably necessary. These optimisation procedures usually involve numerous structural modifications, aided by computational techniques, until a small number (usually 1–5) of highly active "candidates" remain.

These candidates are usually free bases, free acids, or neutral molecules, rather than their salts. Also, because of the generally higher molecular weights of modern drug substances and the increased use of DMSO solutions in the screening processes, it is becoming apparent that there is a tendency towards ever more lipophilic candidates being presented. Frequently, when first proposed as potential development candidates, they are often amorphous or partially crystalline as little effort has been made to investigate formal crystallisation procedures. The need for water-soluble candidates has been recognised^{1–4} for many years before the advent of 'combinatorial chemistry'.

Investigations into the Possibilities of Salt Formation

When first presented for initial preformulation investigations, normally the amount of drug substance available from Discovery Chemistry rarely exceeds 1 g. To maximize the amount of data gained from such small quantities, semi-micro techniques have been developed and are used regularly within our groups. Invariably, the first information generated for each candidate is the calculated pK_a value of each ionisable group in the molecule.^{5–8} This is quickly checked against the value determined experimentally on 1–2 mg of sample by potentiometric titration (e.g., Sirius Model GLpKa apparatus, Sirius Analytical Instruments Ltd.). Knowledge of the pK_a value enables potential salt forming agents (counterions) to be selected, for each candidate, based on lists that are available in the literature.^{9–11} For the formation of a stable salt, it is widely accepted that there should be a minimum difference of about 3 units between the pK_a value

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Table 1. Classification of common pharmaceutical salts

salt class	examples
	Anions
inorganic acids	hydrochloride, hydrobromide, sulfate, nitrate, phosphate
sulfonic acids	mesylate, ^b esylate, ^c isethionate, ^d tosylate, ^e napsylate, ^f besylate ^g
carboxylic acids	acetate, propionate, maleate, benzoate, salicylate, fumarate
anionic amino acids	glutamate, aspartate
hydroxyacids	Citrate, lactate, succinate, tartrate, glycolate
fatty acids	hexanoate, octanoate, decanoate, oleate, stearate
insoluble salts	pamoate (embonate), polystyrene sulfonate (resinate)
	Cations
organic amines	triethylamine, ethanolamine, triethanolamine, meglumine, ethylenediamine, choline
insoluble salts	procaine, benzathine
metallic	sodium, potassium, calcium, magnesium, zinc
cationic amino acids	arginine, lysine, histidine

^a Based on data from various sources.⁹⁻¹¹ ^b Methane sulfonate. ^c Ethane sulfonate. ^d 2-Hydroxyethane sulfonate. ^e Toluene sulfonate. ^f Naphthalene sulfonate. ^g Benzene sulfonate.

of the group and that of its counterion, especially when the drug substance is a particularly weak acid or base. Occasionally, exceptions may be found where a salt has an acceptable stability, despite there being a smaller difference in the pK_a values.

A microplate technique has been developed for the screening of salts; this involves dissolving approximately 50 mg of sample in a suitable, volatile solvent and adding a fixed volume of this solution, containing about 0.5 mg of sample, into each microplate well. Concentrated solutions of each potential counterion in equimolar proportion, or other appropriate stoichiometric ratio, are prepared and a few microlitres of each is added sequentially to each well. Thus, all of the wells in line 1 (x -direction) will contain the same combination of sample and counterion 1; all of the wells in line 2 contain the same combination of sample and counterion 2, etc. Different, potential crystallising solvents can be investigated methodically in the y -direction. The wells are inspected using an inverted microscope (Leica, Model DMIRB) at regular intervals for the appearance of crystals. Occasionally, crystallisation can be promoted by evaporation of any excess solvent in some wells using a slow stream of dry nitrogen gas.

Once the combinations of counterion and solvent(s) are identified, studies at a slightly larger scale (usually 10–50 mg, occasionally up to 500 mg) can be initiated to confirm the suitability and viability of the crystals. These studies can help identify problems with low melting points, determined by hot-stage microscopy, and hygroscopicity, if processed on a suitable apparatus (e.g., Dynamic Vapour Sorption Analyser, model DVS-1, Surface Measurement Systems Ltd.). Frequently these studies can also give preliminary information on the existence of solvates and hydrates, especially if differential scanning calorimetry (DSC, Mettler Toledo DSC, model 820), thermal gravimetric analysis (TGA, Mettler Toledo TGA, model 850) and hot-stage microscopy are also used in the evaluation process.

In parallel with these studies, a preliminary high performance liquid chromatographic (HPLC) method is quickly developed to give an estimate of the purity of the sample, whilst infrared and other spectroscopic techniques may be

used to define the salt and the stoichiometry. Knowledge of the approximate purity is important at this stage as the presence of high levels of some impurities can often hinder crystallisation or alter the polymorphic form obtained.

Therefore, from these preliminary, small-scale studies, a range of potential salt formers and recrystallisation solvents can be quickly identified. Following further scale-up to gram quantities, more comprehensive data can be obtained to evaluate their suitability for use in formulations.

Choice of the Salt Former

Although the choice of salt is governed largely by the acidity or basicity of the ionisable group, safety of the counterion, drug indications, route of administration and the intended dosage form must also be considered. Toxicological and pharmacological implications of the selected salt former must be considered as well as the effects of the parent drug. Salt formers can be subdivided into a number of categories, depending upon their functionality and purpose. Some of the most frequently used examples are listed in Table 1.

The vast majority of salts are developed to enhance the aqueous solubility of drug substances. For weakly basic drug substances, salts of an inorganic acid (e.g., hydrochloride, sulphate, or phosphate), a sulphonc acid (mesylate or isethionate), a carboxylic acid (acetate, maleate or fumarate), a hydroxyacid (citrate or tartrate), or possibly an amino acid (arginine or lysine) could be considered. Hydrochloride salts have often been the first choice for weakly basic drugs, since as a consequence of the low counterion pK_a , salts can nearly always be formed, and recrystallisation from organic solvents is normally straightforward. However, the potential disadvantages of hydrochloride salts may include unacceptably high acidity in formulations (e.g., parenteral products), the risk of corrosion, less than optimal solubility due to the risk of salting out and the potential for poor stability if the drug is acid labile and hygroscopic.²

Occasionally, salts may be also prepared to decrease drug substance solubility for use in suspension formulations where very low solubility is necessary to prevent "Ostwald ripening", for taste-masking, or to prepare an extended release product. Embonate salts have been used in suspension

Table 2. ^a Preformulation studies that are normally considered for comparison of salt forms and parent compound for oral dosage forms

test	suitable techniques	comments
dissociation constant and basic physico-chemical properties	potentiometry, solubility, UV spectroscopy	determine pK_a for parent drug
melting point	capillary m.pt., hot stage microscopy, differential scanning calorimetry	perform on each salt and compare to parent
aqueous solubility	overnight equilibration at 25 °C; analysis by UV spectroscopy or HPLC	Perform on each salt and compare to parent
pH of solution		Examine pH of saturated solution if quantities permit.
cosolvent solubility	overnight equilibration at 25 °C. analysis by UV spectroscopy or HPLC	Determine solubilities in ethanol, poly(ethylene glycol), propylene glycol and glycerol and compare to parent.
common ion effect on solubility	overnight equilibration at 25 °C in suitable media and analysis by UV spectroscopy or HPLC	compare solubility in demineralized water with 1.2% NaCl for salts and parent
hygroscopicity	use DVS apparatus or expose to various RH values and measure weight gain after 1 week	perform at 53, 93, and 97% RH, and other values of interest; assign hygroscopicity classification to each salt ¹³
intrinsic dissolution rate	use Wood's apparatus ¹⁴	compare dissolution rates at various pHs (can provide data on wettability)
crystal shape and appearance	SEM or optical microscopy	Compare crystal habits and levels of agglomeration
particle size	SEM and laser diffraction	Examine particle size distributions.
polymorphism/pseudopolymorphism	recrystallizations, HSM, DSC, TGA	preliminary exploration
powder properties	bulk density measurement	determine Carr's compressibility index
stability	various	perform on parent drug and undertake preliminary tests on appropriate salts

formulations to increase the duration of action (e.g., chlorpromazine embonate). On some occasions, the selection of a salt with only modest aqueous solubility may be more suitable for use in tablet products prepared by wet granulation since the use of highly soluble salts can be detrimental to the granulation process. Depending on the dose required, aqueous solubilities in the range 0.1–1.0 mg/mL will normally be sufficient to satisfy the dissolution requirements for standard, solid, oral dosage forms of drugs with good to moderate potency. However, for parenteral solution products, higher solubilities, perhaps 10 mg/mL or greater, depending on the required dose and dose volume, may be required. For parenteral formulations, the pH of solution (normally within an acceptable range of 3–10 for intravenous solution) should be monitored to help ensure that the formulation will be well tolerated.

Salts are also frequently prepared for the reasons other than solubility modification; it is frequently necessary to prepare a specific salt to either achieve adequate physical stability or for taste masking (e.g., dextropropoxyphene napsylate suspension). Manipulation of drug substance solubility by selection of salts may also be employed to modify the pharmacokinetic profile of the drug (e.g., benzathine penicillin and insulin zinc complexes used in parenteral formulations). Salt formation may be also advantageous where the melting point of the active moiety is low, and it is necessary to mill or micronise the active ingredient to achieve adequate homogeneity. A suitably stable salt may have a melting point that is 50–100 °C higher than the free acid or free base. Also, being more ionic, the crystals are

likely to be less plastic and more easily deformed by brittle fracture.

Scale-up of the Formation of Salts

The information from the preliminary crystallisation studies is communicated to the Process Chemistry group, who by this time will have started their investigations into possible manufacturing routes for each of the candidates remaining. At this stage in the development process, Process Chemistry usually aim to quickly manufacture 50–200 g of the one or two candidates that may remain to progress them towards initial clinical evaluation. The manufacturing route may be the same as used by the Discovery Chemistry group but usually is significantly different. The aims of both the Process Chemistry and Preformulation groups for the following 12–18 months is to collaborate extensively to ensure that, for the chosen candidate, there will be a viable synthetic route to the chosen form of the drug substance.

A significant portion of this batch is destined for the preparation of 3–4 g of each of the salts that were thought to be viable from the smaller-scale studies. A similar sized portion of the free base/acid is also taken for comparison purposes. The combination of individual studies undertaken on each of these 3–4 g portions varies depending on the type(s) of dosage form ultimately required for marketing. Occasionally, it may be necessary to undertake a pharmacokinetic evaluation of each salt in comparison with the free acid/base. The dosage forms most commonly used for the drug substances encountered during preliminary clinical investigations are tablets/capsules, inhalation dosage forms and injections.

Table 3. Tests to be considered for the evaluation of candidate salts

test to be considered	amount required, mg
Structural Analysis	
mass spectroscopy ^a	1
¹ H NMR ^a	5
¹³ C NMR ^a	25
Ir spectrum	1
UV spectrum	1
fluorescence spectrum ^a	1
elemental analysis	10
Physicochemical Properties	
melting range	2
pK _a ^a	5
C log P/log P ^a	5
preliminary polymorphism study	200–500
X-ray diffraction	20
aqueous solubility ^b	100
pH – solubility profile	500
cosolvent solubilities ^c	300
propellant solubility ^d	500
Physical Properties	
hygroscopicity	20
microscopy (SEM/optical)	10
particle size (Malvern)	100
size reduction (sonication)	300
Impurities (hplc)	
related substances ^a	10
degradation products ^a	10
chiral purity ^a	10
Stability Studies	
stability to hydrolysis (pH 2, 7, 10) ^a	15
stability to oxidation (peroxide/peracid) ^a	15
stability to photolysis ^a	15

^a Determined on free acid/base only. ^b Would include solubility in saline, 5% dextrose and some buffers. ^c Also solubilities in complexing agents/surfactant systems where appropriate. ^d Propellants and propellant/cosolvent systems for inhalation dosage forms.

Tables 2 and 3 show the types of tests normally chosen, the information that they can produce and the amount of sample normally required for these common dosage forms.

What to Develop: Salt or Free Acid/Base?

The results obtained from each of these tests are tabulated for the free acid/base, together with each of the salts, and discussed in detail between the Formulation Scientists, Preformulation Analysts, Physical Chemists, Process Chemists, and occasionally Pharmacokineticists. The Preformulation Scientists assess the relative merits of each form for use in the proposed clinical formulations and whether the properties such as solubility are adequate to give the high concentrations required in the various pre-clinical formulations. Process Chemistry need to assess the likely yield of each salt, as salt formation creates an additional step in the manufacturing process. Usually, the decision-making process results in the proposal of a single salt for further study, although occasionally it is seen that none of the salts have optimum properties, and two different salts can be proposed for in-depth study. Also, it is occasionally found that the overall properties of the free acid/base are much better than any of the salts. This occurs more frequently where the

candidate has a low pK_a value and the resulting salts are less stable than required or when the salts are particularly hygroscopic or when they exhibit complex polymorphism/pseudopolymorphism (hydration or solvation).

These relatively simple investigations give much useful information very quickly; it should be noted, however, that the preliminary polymorphism study is far from the in-depth study that is always undertaken later. This preliminary study uses a range of protic and aprotic solvents of widely differing polarity and will normally show the presence of a stable hydrate or solvate.

Once a decision is agreed upon within the group, a document that gives a précis of the discussions and the basis for the proposal is normally drafted for agreement by senior management. Examples of these salt selection studies are given below:

Example No. 1 (RPR 111423)

RPR 111423 is a candidate drug substance that has been evaluated for the treatment of symptoms related to infection by AIDS. It is a crystalline, very weak base with a pK_a at 4.25. A comprehensive screening of possible salts demonstrated only a monohydrochloride (RPR 111423A) and a mesylate (RPR 111423B) could be isolated as crystalline solids.

It was decided that the free base should be taken through the simple evaluation process in comparison with these two salts. It was expected that the drug substance could be required in the form of tablets or capsules, with an injection form needed for some pre-clinical studies and for the determination of absolute bioavailability in man. Because of its high activity in screening studies, there was a possibility that very low dose oral formulations might be needed. This may require micronised drug substance to enable content uniformity requirements to be met; this micronised material would also be expected to enhance dissolution.

The results from the relatively simple studies undertaken are given in Table 4. The two salts clearly demonstrated the predictable problems associated with a relatively low pK_a value; the salts were quite weak and dissociated to liberate the free base in media with pH values below the pK_a. The very low solubility of the free base resulted in immediate precipitation following dissociation. There was clear evidence for multiple polymorphism for each of the salts, and establishing the existence of a stable polymorph, or a suitable pseudopolymorph, may have been necessary before a decision could be made on which of the two salts could be developed further.

The corresponding results for the free base indicated that it appeared to be the better candidate; it showed no evidence of polymorphism, and it was not hygroscopic. The two major areas that required further investigation were whether it had sufficient solubility in gastrointestinal media and whether it could be micronised. Studies performed on samples of drug substance and on simple capsule formulations demonstrated that the dissolution rates of micronised free base were equivalent or superior to those of the salts under the same conditions.

Table 4. Comparison of some simple properties of RPR111423 and its two salts

test	result for RPR 111423 (base)		result for RPR 111423A (hydrochloride)		result for RPR 111423B (mesylate)	
appearance	off-white to cream, crystalline powder		pale yellow, highly agglomerated powder		cream to pale yellow, highly agglomerated powder	
particle size by microscopy, μm	10–100 (large rhombic crystals)		2×1 (microcrystalline laths)		7×1 (microcrystalline laths)	
melting range, $^{\circ}\text{C}$	241–244		242		210	
preliminary polymorphism study	no other form detected		at least four polymorphs detected; metastable forms revert to original on standing		at least six polymorphs detected; phase changes detected on grinding or micronisation; reverts to original form on heating	
other thermal behavior	nothing detected		loss of HCl detected at 110–120 $^{\circ}\text{C}$		nothing detected	
aqueous solubility, mg/mL	at 25 $^{\circ}\text{C}$	at 37 $^{\circ}\text{C}$	at 25 $^{\circ}\text{C}$	at 37 $^{\circ}\text{C}$	at 25 $^{\circ}\text{C}$	at 37 $^{\circ}\text{C}$
- at pH 1	11.6	14.7	25.7	28.2	131.4	204.1
- at pH 2	0.71	0.89	2.51	4.58	6.11	8.91
- at pH 4	0.03	0.05	0.05	0.13	0.01	0.02
- at pH 6	0.01	0.02	0.01	0.02	0.03	0.34
- at pH 6.8	0.01	0.02	0.01	0.02	0.01	0.02
- in demineralized water	0.01	0.02	0.36	0.99	0.33	0.50
pH of saturated solution, at 20 $^{\circ}\text{C}$, in water	6.50		2.43		2.74	
addition of water to concentrate						
- at pH 2	no changes detected		some precipitation of free base		some precipitation of free base	
- at pH 4	no changes detected		extensive precipitation of free base		extensive precipitation of free base	
hygroscopicity (hygrostat for 14 days)	non-hygroscopic <0.2%w/w water uptake at any RH		slightly hygroscopic 2.3% w/w uptake at 53% RH 22% w/w uptake at 97% RH		moderately hygroscopic 3.7% w/w uptake at 53% RH 32% w/w uptake at 97% RH	

Example No. 2 (RPR 127963)

RPR 127963 is a candidate drug substance that has been evaluated for the treatment of cardiovascular diseases; it is a crystalline, very weak base with a pK_a at 4.10. In common with most similar drug substances intended for the treatment of cardiovascular disease, it was considered that a high-dose (up to 250 mg) solid, oral dosage form and a correspondingly high-dose (up to 50 mg/mL) injection would be ultimately required. In line with our standard protocol, a comprehensive evaluation of possible salts was undertaken, and this demonstrated that five crystalline salts (a hydrochloride, a mesylate, a citrate, a tartrate, and a sulphate) could be readily produced. It was decided to quickly profile each of these salts in comparison with the free base. The results of these studies are given in Table 5.

When the anhydrous free base was evaluated, the existence of an additional mono-, di-, and trihydrate was found quite rapidly. It was shown that all four of these forms could be interconverted under conditions that might be expected to be found in granulation processing. The other potential problem with the anhydrate was the low melting point. In considering the results obtained for the various salts, the solubilities of the citrate and the tartrate were much lower than required for an injectable form and lower than ideal for high dosage formulations. An additional problem for the tartrate salt was the high hygroscopicity. Both of these salts were rejected before completion of the full evaluation. The hydrochloride salt was also shown to have several problems such as lower than ideal solubility, probable multiple polymorphism, and the formation of hydrates.

Thus, the mesylate and the sulphate were the two salts that remained; both had high melting points, excellent aqueous solubility, and were non-hygroscopic. The free base still remained a possible candidate, if a stable hydrate could be found. It was therefore decided to undertake some additional evaluations on these three forms; the results from these are presented in Table 6.

These additional results demonstrate a slight advantage in favour of the sulphate salt because of its greater solubility in cosolvents. This would give the formulator a better chance of achieving a higher dose in an injectable formulation. It was considered that the sulphate salt (RPR 127963E) could be studied further in the more detailed evaluations that would follow over the next few months. The mesylate or the free base (if a suitably stable hydrate could be found) would provide a possible back-up, should unforeseen problems arise.

Example No. 3 (RPR 200765)

RPR200765 is a candidate drug substance proposed for the treatment of rheumatoid arthritis. It is another crystalline, weak base with a pK_a of 5.3 which formed salts with a wide selection of counterions. It was expected that doses of 100–125 mg of RPR200765 in capsules would be required for clinical studies.

Early studies suggested that RPR200765 free base was unacceptable for use in solid, oral dosage forms due to a very poor aqueous solubility of approximately 10 $\mu\text{g/mL}$ and poor bioavailability in animal models. However, RPR200765 would form stable salts with hydrochloride, hydrobromide,

Table 5. Comparison of some simple properties of RPR127963 and its five salts

test	result for free base (RPR 127963)	result for HCl salt (RPR 127963A)	result for mesylate salt (RPR 127963B)	result for citrate salt (RPR 127963C)	result for tartrate salt (RPR 127963D)	result for sulfate salt (RPR 127963E)
appearance	yellow, crystalline powder	yellow, crystalline powder	yellow, crystalline powder	yellow, crystalline powder	yellow, crystalline powder	yellow, crystalline powder
particle size (microscopy), μm	1–3 μm (agglomerates of microcrystals)	1–3 μm (agglomerates of microcrystals)	tightly packed spherulites of agglomerated microcrystals 18 μm diameter.	microcrystals (2–3 μm) with some aggregates (70 μm)	rounded agglomerates of microcrystals in domains (70 μm)	aggregates of microcrystals (10–15 μm)
melting range, $^{\circ}\text{C}$	119–123	166–191 (re-grows at about 166, recrystallizes at 191, then melts at about 275)	280.9–282.2	130.2–134.3	198.5–201.6	305.7–308.9
preliminary polymorphism study	several hydrates detected	two monohydrates and one anhydrate	no evidence of polymorphs	stable hemihydrate detected	unstable anhydrate	no evidence of polymorphs
aqueous solubility (25 $^{\circ}\text{C}$), mg/mL						
- in demineralized water	n.d. ^a	3.92	108	0.83	0.89	~50
- in 0.1 M HCl	n.d.	5.2	50.4	n.d.	n.d.	5.9
- in 0.1 M NaOH	0.020	0.019	0.022	n.d.	n.d.	0.018
- in dextrose 5%w/v	n.d.	2.84	90	n.d.	n.d.	~40
pH of saturated solution	n.d.	2.33	1.76	2.49	2.56	1.32
hygroscopicity	n.d.	non-hygroscopic	non-hygroscopic	non-hygroscopic	very hygroscopic	non-hygroscopic

^a n.d. = Not determined.

Table 6. Comparison of additional properties of RPR127963 (anhydrate), its mesylate (RPR 127963B) and sulfate (RPR 12963E) salts

test	result for free base anhydrate (RPR 127963)	result for mesylate salt (RPR 127963)	result for sulfate salt (RPR 127963)
solubility in cosolvents at 25 $^{\circ}\text{C}$, mg/mL			
ethanol	190	0.6	0.2
propylene glycol	35.4	0.7	1.7
poly(ethylene glycol) 400	188	0.2	0.2
dimethylsulphoxide	> 500	14	110
N-methylpyrrolidone	> 400	4.4	8.5
glycerol	42	n.d. ^a	2.7
peanut oil	0.18	none detected	none detected
intrinsic dissolution rate, $\text{mg}\cdot\text{min}^{-1}\cdot\text{cm}^{-2}$			
- in water	0.01	n.d.	n.d.
- in 0.01 M HCl	0.35	7.3	7.7
powder flow properties	n.d.	Good, but becomes much worse with increasing humidity	Sticks slightly

^a n.d. = Not determined.

methanesulfonate, and camphorsulfonate counterions. Aqueous solubility, particle size and shape, powder properties, and polymorphism profile were considered to be the key properties to permit a choice of salt to be made. In addition, it was recognised that the use of some counterions with high molecular weights, would require a large excess of drug substance to achieve the required doses.

Studies demonstrated that the solubility of RPR200765 depended on the amount of drug substance used for the study. This occurred because the counterion reduced the pH of solution and enhanced solubility of the drug base. The mesylate salt consistently produced a higher solubility than any of the other salt forms. The higher solubility resulted in

an enhanced dissolution rate of the mesylate salt compared to the other salt forms. The solubility and dissolution rate of the hydrobromide salt was particularly poor. Intrinsic dissolution rate studies on compressed disks could not be carried out because a good compact could not be obtained for most of the salts, and the studies were carried out using drug powder (equivalent to 50 mg free base) in capsules.

Hygroscopicity studies demonstrated that the hydrochloride and hydrobromide salts adsorbed large amounts of moisture on exposure to humidity, resulting in the formation of multiple hydrated forms. The methanesulfonate salt however, was a stable monohydrate form which lost moisture at very low humidity (<10% relative humidity (RH)) but

Table 7. Comparison of the physicochemical properties of RPR200765 salt forms

test	result for mesylate salt (RPR 200765A)	result for camphorsulfonate salt (RPR 200765C)	result for hydrochloride salt (RPR 200765D)	result for hydrobromide (RPR200765E)
appearance	off-white to cream, free-flowing powder	white to off-white, crystalline, free-flowing powder	white, free-flowing powder	white to off-white, crystalline, free-flowing powder
MW	566.61	684.79	524.98	569.43
melting range, °C	214	265–267	245–248	276–277
maximum aqueous solubility at 25 °C, mg/mL	39	19.95	16.68	3.29
pH of saturated solution in demineralized water at 20 °C, mg/mL	1.93	2.22	2.16	2.63
hygroscopicity (by DVS)	non-hygroscopic with a stable, monohydrate form	non-hygroscopic	hygroscopic with multiple hydrated forms	hygroscopic with multiple hydrated forms
crystal habit and appearance	individual platelike crystals with some agglomeration.	clusters of highly aggregated, platelike crystals	platelike crystals; individual crystals contain stress lines	loosely agglomerated, flaky material
particle size by microscopy	~45–200 μm in agglomerates of 200–350 μm	crystals ~20–50 μm , clusters ~80–200 μm -some larger clusters up to 500 μm	~30–100 μm particles	10–40 μm particles
dissolution studies, drug substance in capsule ($T_{90\%}$, min)				
at pH 2				
at pH 4	2.0	6.0	7.4	3.9
(in citrate buffer)	> 60% release	> 60% release	> 60% release	14% release

rapidly re-equilibrated to form the monohydrate form when the humidity was raised. These findings suggested that this salt would be amenable to solid dose formulation and there was little risk of changes in the hydration state on processing or storage under normal conditions. The camphorsulfonate was non-hygroscopic. The results of these studies are outlined in Table 7; in this case very little comparative work was undertaken on the free base due to the poor solubility and bioavailability.

Overall, the studies suggested that the mesylate salt was the favoured form on the basis of its low hygroscopicity, clean polymorphic profile in the preliminary screen, high solubility, and rapid dissolution rates. Another favourable factor supporting the selection of the mesylate salt proved to be the good flow properties which allowed very satisfactory capsule and tablet formulations to be developed.

The Next Steps?

Having evaluated several possible alternatives in the three cases above, using a relatively simple range of tests, a form of the drug substance has been chosen that should be possible to develop further. These simple studies have required 3–4 g of the free base and a similar quantity of each of the salts; the data for all forms normally can be generated in one month, or less. The next steps involve confirmation of the choice, by employing a further range of tests, followed by the optimisation of the form of the salt. A series of tests, analogous to those in Table 2, are used in this evaluation; these tests are given in Table 8.

Optimisation of the Drug Substance Form for Development

Having chosen what should be a reasonably stable form of the salt, free acid, or free base, one of the key activities is to start investigations into which other polymorphic or pseudopolymorphic forms exist. In the short development phase where preclinical administration occurs, only a preliminary screening of these different forms is considered necessary, as it is possible that the compound can be found too toxic for further study. Our team undertakes this on about 500 mg of sample; small portions are recrystallised from anhydrous and hydrated solvents of differing polarity. Any crystalline product recovered is examined by a variety of techniques to determine how many different forms are produced and whether any are hydrates or solvates. Preliminary information on the inter-relationships between the different forms can often be found, even at this early stage.

The remainder of the tests are designed for two main purposes:

To define the various preclinical formulations that are required, to devise analytical methods for these, to determine their stability, and establish shelf lives.

To establish a database for the chosen form and to give an indication of the possibilities for clinical formulations.

To accomplish this, it is normal to request a minimum of 25 g of drug substance, although occasionally more may be needed if the drug substance is intended for inhalation and there are difficulties with micronisation.

Table 8. Tests to be considered for “preclinical phase” (column 2) and in preparation for initial clinical investigation (column 3) for compounds intended for use in oral, injection and inhalation products

test to be considered	amount required, mg or g	amount required, mg or g
Physicochemical Properties		
melting range	50 mg	50 mg
optical rotation		1 g
polymorphism	500 mg	25–50 g
X-ray diffraction	20 mg	20 mg
intrinsic aqueous solubility	400 mg	
cosolvent solubilities ^a	500 mg	2 g
propellant solubility ^b		2 g
Physical Properties		
hygroscopicity	800 mg	-
microscopy (SEM/optical)	100 mg	100 mg
particle size (Laser)	200 mg	200 mg
micronisation	5 g	
specific surface area	2 g (R)	4 g (R)
true density	200 mg (R)	200 mg (R)
bulk powder density	2.5 g (R)	10 g (R)
wettability		1 g
Impurities (HPLC)		
related substances	10 mg	10 mg
degradation products	10 mg	10 mg
chiral purity	10 mg	10 mg
electrophoresis/TLC	10 mg	
Stability Studies		
hydrolytic profile (identify degradants)	100 mg	
bulk drug powder		2 g
Excipient Compatibility		
HPLC, XRPD, and DSC	50 mg	250 mg
Compression Properties		
for dry powder inhaler only		5 g
Preclinical Formulation Development		
intra-tracheal suspensions	2 g	
oral solutions/suspensions	2 g	
solutions for nebulization	2 g	
IV solutions	2 g	
other routes (ip/sc)	1 g	-
Clinical Formulation Development		
	predict suitable dosage forms	Phase I–IIa ^c 250–1200 g
	3 g	
microbiological controls		^d
total substance requirements	20–25 g	depends on form and dose

^a Also solubilities in complexing agents/surfactant systems where appropriate. ^b Propellants and propellant/cosolvent systems for inhalation dosage forms. ^c Develop and specify Phase I formulation – commence stability/compatibility studies. ^d Dependent on drug availability; (R) possible to recycle drug substance for certain other tests.

Once the drug substance is shown to be nontoxic, studies leading to the definition of a suitable series of clinical formulations can begin. For this, we normally expect to have a reasonably clear picture of the inter-relationships between the different forms of the drug substance and should have started to define the most stable form. As more batches are manufactured at increasing scale by Process Chemistry, they are examined using some of the key tests to add information to the database. Also, with the increased availability of drug substance, it is possible to initiate maturation studies as an additional technique to assist in the definition of polymorphism. If the structure of the drug substance has been determined by single crystal X-ray, under certain circumstances it may be possible at this stage to initiate the theoretical search for other polymorphic forms. This is achieved using the Polymorph Predictor software (Molecular

Simulations Inc.). This software has been used successfully on several small molecules (molecular weight <500) and predicts theoretical crystal structures and their relative energies. The most stable form has the lowest energy; increasing energy signifies lower stabilities.

As larger quantities of drug substance and samples from different batches become available it is imperative that the variation in basic physical properties (e.g., crystal size and shape, specific surface area, powder flow properties, bulk and tapped density etc.) are studied for each batch. By close liaison with Process Chemistry, it is normally possible to modify the recrystallisation conditions such that greater batch-to-batch uniformity of these physical characteristics can be achieved. Also, these characteristics can often be modified such that they are closer to ideal.

The Negative Aspects of Salt Formation

One of the negative aspects of salt formation is that the percentage active content decreases markedly as higher-molecular weight counterions are used. If the free acid or base has only moderate or low activity, it may be necessary for the patient to have a relatively high dose for a clinical effect. If 20–50% of the weight of the drug substance is due to inactive counterion, the addition of suitable excipients for encapsulation or tableting may result in a powder volume that is too great, even after granulation, to fit successfully into even the largest acceptable capsule shell. This forces the formulator towards a tablet. Even with these formulations, a large tablet (or even multiple, smaller tablets) may be necessary; these do not aid patient compliance.

Other problems that are frequently created, or exacerbated, by salt formation are an increased tendency for the existence or formation of hydrates and polymorphs. Hydrates may be produced in formulations by interaction with water bound to excipients, water in capsule shells, etc.

Final Definition of the Form

As the candidate passes through initial clinical evaluation (Phases Ia and Ib), additional characterisation and refinement of the drug substance form continues in parallel with the

finalisation of studies on the drug substance manufacturing process. Close liaison and teamwork between the Process Chemist and the Preformulation Scientist in an exploration of the various possible recrystallisation solvents can often result in further refinement of the crystal properties. An excellent scheme for the final characterisation of solid drug substances, prior to the final regulatory submission, has been described recently.¹² The aim of both the Preformulation and Process Chemistry teams is to finalise the definition of all of the characteristics of the drug substance in readiness for the initiation of Phase IIa clinical trials

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Hybrid insulin cocrystals for controlled release delivery

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The ability to tailor the release profile of a drug by manipulating its formulation matrix offers important therapeutic advantages. We show here that human insulin can be cocrystallized at preselected ratios with the fully active lipophilically modified insulin derivative octanoyl-*N*-LysB29-human insulin (C8-HI). The cocrystal is analogous to the NPH (neutral protamine Hagedorn) crystalline complex formed with human insulin, which is commonly used as the long-acting insulin component of diabetes therapy. The *in vitro* and *in vivo* release rates of the cocrystal can be controlled by adjusting the relative proportions of the two insulin components. We identified a cocrystal composition comprising 75% C8-HI and 25% human insulin that exhibits near-ideal basal pharmacodynamics in somatostatin-treated beagle dogs. The dependence of release rate on cocrystal ratio provides a robust mechanism for modulating insulin pharmacodynamics. These findings show that a crystalline protein matrix may accommodate a chemical modification that alters the dissolution rate of the crystal in a therapeutically useful way, yet that is structurally innocuous enough to preserve the pharmaceutical integrity of the original microcrystalline entity and the pharmacological activity of the parent molecule.

Controlled release methods for the injectable delivery of therapeutic proteins use exogenous matrices to encapsulate the protein and thereby slow its absorption from the site of injection. Such systems include hydrogels, liposomes, microspheres, and polymer depots^{1–3}, and are typically physicochemically complex, making the predictable modulation of *in vivo* protein-release rate difficult and presenting formidable challenges for protein stabilization and commercial manufacture⁴. The oldest and simplest approach to prolonging the time action of a therapeutic protein is to inject it in the form of a suspension of amorphous or microcrystalline particles that dissolve slowly in the interstitial fluid before absorption into the microvasculature of the subcutaneous or intramuscular tissue. This approach is limited because the dissolution process governing bioavailability and pharmacokinetics is dictated largely by the intrinsic solubility of the protein particle.

The concept of combining insulin with zinc and protamine was developed in the 1930s to meet the medical need for an insulin preparation with sustained action for the treatment of diabetes mellitus⁵. This approach revolutionized diabetes therapy⁶ and led to the development of a microcrystalline suspension formulation known as NPH insulin⁷, which is still the most widely used insulin product today. However, recent studies have established that tight glycemic control dramatically diminishes serious long-term diabetic complications^{8,9}. NPH insulin has clinical limitations in this respect, as the duration of action of this formulation is too short to provide basal therapy with a single injection per day, and it has a pharmacodynamic profile exhibiting a large peak^{10,11}. These characteristics cause continual deviations from normoglycemia. Despite these clinical shortcomings, NPH insulin is a time-proven, robust biopharmaceutical platform that has been applied commercially to a variety of insulin

molecules including beef insulin, pork insulin, biosynthetic human insulin, and the insulin analog LysB28,ProB29-human insulin¹².

Here we sought an approach that could retain the favorable pharmaceutical properties of NPH yet correct its pharmacokinetic shortcomings. To explore the possibility of manipulating the release rate of an NPH-like formulation, we cocrystallized insulin with a lipophilically modified insulin derivative (Fig. 1). We report a method whereby the dissolution rate of the resulting microcrystalline suspension may be systematically adjusted to allow manipulation of insulin absorption kinetics. These findings show that a protein drug itself can form the scaffold of a controlled release matrix, allowing the fine tuning of the absorption kinetics of biopharmaceutical suspensions.

Results and discussion

Rational selection of C8-HI. We hypothesized that it may be possible to reduce the dissolution rate of NPH crystals by “doping” a less soluble insulin derivative into the lattice. The octanoyl moiety at LysB29 was incorporated in order to lower aqueous solubility by enhancing the hydrophobicity of the insulin molecule while having minimal steric and pharmacological impact. A key steric requirement of the derivative is that it must retain its ability to form a zinc hexamer, the crystallizing unit of insulin crystals¹³ including NPH insulin¹⁴. C8-HI most likely meets this requirement because previous studies have shown that hexadecanoyl-*N*-LysB29-human insulin forms a zinc hexamer in solution¹⁵. Furthermore, an X-ray crystal structure of LysB29-tetradecanoyl, des(B30) human insulin shows that this molecule forms rhombohedral crystals in which the C14 chains are oriented on the exterior of the hexamer¹⁶.

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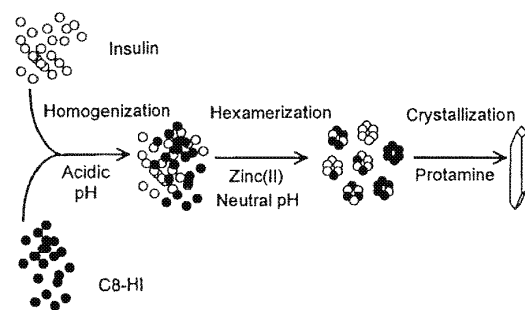


Figure 1. Schematic representation of cocystal formation. Insulin and C8-HI are combined initially as solutions to facilitate homogeneous mixing of the two species. Adjustment to neutral pH in the presence of zinc forms a mixture of hybrid zinc hexamers, which complex with protamine to form homogeneous microcrystals (~5 μm long) with the distinctive NPH crystal morphology shown.

Insulins acylated with fatty acids at the ϵ -amino group of LysB29 have been explored as potential soluble protracted-acting candidates^{17,18}. The basis for their protraction is a substantially enhanced albumin-binding affinity conferred by the fatty acid extension¹⁹. The C14 and C16 derivatives produce time-action profiles comparable to NPH insulin, although the enhanced albumin binding seems responsible for diminished biopotencies in humans^{20,21}. The C8 derivative was selected for this study, as the relatively short fatty acid is not expected to increase albumin-binding affinity of the insulin derivative substantially²², thus retaining full biopotency of the insulin derivative. In addition, the LysB29 residue is not required for receptor activity²³. Thus, the octanoylation at LysB29 is likely a relatively benign modification to the insulin molecule.

C8-HI forms NPH-like crystals. Several crystalline varieties of insulin have been characterized since Abel first prepared rhombohedral zinc insulin crystals in 1925 (ref. 24). Insulin forms a zinc hexamer that can crystallize in various ligand-bound forms depending on the crystallization conditions and complexing agents present^{14,25–27}. NPH crystallization is based on a complexation reaction between zinc insulin hexamers and protamine at neutral pH⁷. The combination of stoichiometric quantities of zinc insulin and protamine results in the quantitative formation of a precipitate that gradually transforms into microcrystals over ~24 hours. The rod-like, bipyramidally-tipped tetragonal crystals are characteristic of NPH insulin and are morphologically distinct from other crystalline forms of insulin^{14,25,28}. This crystallization process results in an aqueous phase devoid of soluble insulin and a stable microcrystalline phase that forms a uniform injectable suspension upon gen-

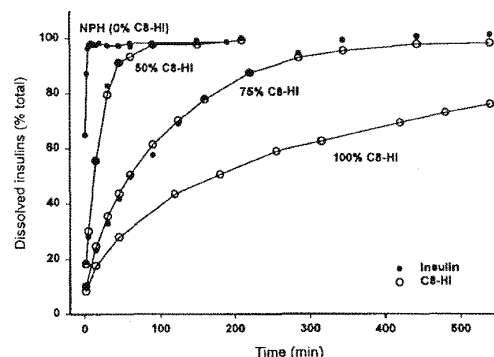


Figure 3. *In vitro* dissolution curves showing the relationship between the C8-HI content of the cocystal and dissolution rate. The ordinate represents dissolved insulins expressed as a percentage of the total dissolved and undissolved insulins. (See Experimental Protocol for dissolution protocol.)

tle agitation. The crystallization mother liquor also provides ingredients facilitating pharmaceutical use, specifically: phosphate for pH buffering, glycerol for subcutaneous isotonicity, and phenol and *m*-cresol for antimicrobial effectiveness²⁹. The NPH X-ray crystal structure shows that the protamine molecules are accommodated in the interstices of the lattice formed by *m*-cresol-bound zinc insulin hexamers¹⁴.

To investigate whether the C8-HI derivative retains the ability to crystallize as an NPH-like complex, we applied a protocol to C8-HI (Experimental Protocol) similar to that of NPH insulin. This yielded rod-like microcrystals morphologically consistent with NPH as determined by environmental scanning electron microscopy (ESEM; Fig. 2A, B). Protein crystallization is related intimately to the delicate balance of parameters affecting the solubility limit of the protein and the relative energetics of the protein in the solution, amorphous, and crystalline states³⁰. The C8 group imparts a substantial modification to the physical properties of the insulin molecule as demonstrated by the substantial perturbation of the solubility of the resultant crystals (Fig. 3). Consequently, it is remarkable that C8-HI crystallizes in an analogous manner to NPH insulin under essentially identical crystallization conditions.

Cocrystallization of C8-HI with insulin. We prepared cocystals using a similar method to that of NPH crystallization, the principal difference being that the desired proportion of insulin derivative was dissolved together with the insulin fraction in acidic solution to facilitate complete mixing of the two molecules before crystallization (Fig. 1). The insulin hexamer dissociates in acidic solution, although it maintains a complex equilibrium of self-associated states³¹. Complete dissociation to monomers and random mixing of subunits would result theoretically in a statistical mixture of seven types of hexamers (Fig. 1). Upon injection, the process rate limiting to absorption is dissolution from the crystal lattice, which is believed to occur via the departure of intact zinc hexamers³². The hexamers subsequently dissociate in the interstitial fluid

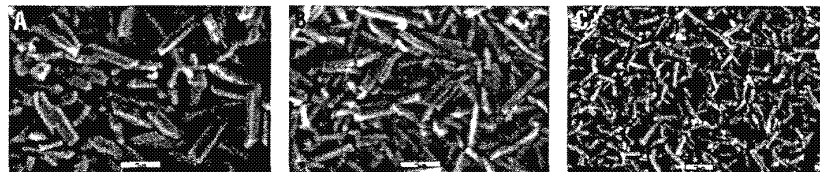


Figure 2. Environmental scanning electron microscope (ESEM) images. (A) NPH-like crystals formed from 100% C8-HI. (B) NPH insulin. (C) 75% C8-HI cocystals. Images were taken of the microcrystalline samples deposited directly from the mother liquor onto a filter surface. Scale bars, 5 μm .

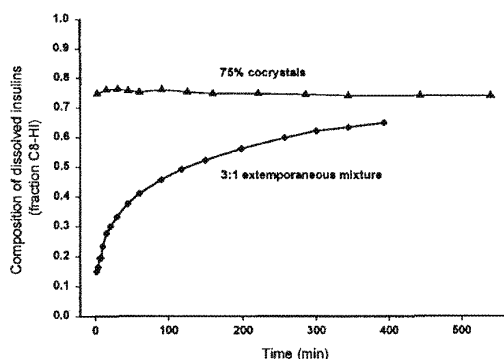


Figure 4. *In vitro* dissolution homogeneity. Homogeneous release of C8-HI occurs from a 75% C8-HI cocrystal ($\blacktriangle$) in contrast to the non-homogeneous dissolution behavior of an extemporaneous mixture of 100% C8-HI and NPH (0% C8-HI) mixed in a 3:1 ratio ($\blacklozenge$). The ordinate represents the C8-HI dissolved as a fraction of the total dissolved C8-HI and dissolved insulin as determined by reversed-phase HPLC. (See Experimental Protocol for dissolution protocol.)

before absorption into the bloodstream³³. Consequently, it is not the underlying distribution of hexamers per se, but the dissolution homogeneity of the cocrystal and the dependence of dissolution rate on composition, that are expected to be fundamental to its utility as a controlled-release drug matrix.

To explore the use of C8-HI cocrystals for controlled release, we prepared a cocrystal series incorporating different C8-HI proportions. We found a single preparative protocol (Experimental Protocol) to be effective for cocrystals containing C8-HI fractions across the entire 0–100% range. Specific C8-HI percentages could be targeted conveniently and accurately because the cocrystallization is quantitative and thus the C8-HI percentage in the cocrystal corresponds directly to the C8-HI percentage of the initial solution mixture. The morphology of the cocrystals was consistent with the 100% C8-HI crystals (Fig. 2A) and with NPH (Fig. 2B). An ESEM image of a representative 75% C8-HI cocrystal sample is shown in Figure 2C. Presumably the C8-HI and HI molecules are mutually replaceable within the crystal lattice because of the relatively minor steric modification, and thus retain the order of the crystal with the exception of the acyl moiety. For this reason we describe the preparations as cocrystals, although in the strictest crystallographic sense they would be considered mixed crystals.

Cocrystals are homogeneous and release rate is controllable. We investigated the *in vitro* dissolution behavior of the cocrystals as a function of C8-HI content for preparations containing 50%, 75%, and 100% C8-HI, and compared with that of NPH (Fig. 3). These data show that the cocrystals dissolve substantially more slowly than NPH and that there is a strong dependence of the dissolution rate on the proportion of C8-HI in the cocrystal. Equivalent rates of dissolution of C8-HI and insulin from the 50% and 75% cocrystals are evident (Fig. 3), consistent with homogeneous release of the two insulin components. This was confirmed by a control experiment comparing the dissolution behavior of the 75% cocrystal with a 3:1 extemporaneous mixture of 100% C8-HI and NPH (0% C8-HI) crystals. Dissolution of the 3:1 extemporaneous mixture exhibits the expected continuous change in the relative proportions of the two insulin components (Fig. 4), whereas the 75% cocrystal releases a constant 0.75 fraction of C8-HI over its entire dissolution duration. These results establish that the *in vitro* release rate of the cocrystal can be manipulated over a wide range by adjusting the level of C8-HI incor-

poration and that a constant rate of release of the two active molecules from the site of injection to the bloodstream is expected. The inverse relationship between dissolution rate and C8-HI percentage in the cocrystal is consistent with the hypothesis that the more hydrophobic C8-HI molecule confers a proportionate decrease in aqueous solubility to the cocrystal.

***In vivo* absorption and time action.** To explore the significance of the *in vitro* release findings in an *in vivo* system, we investigated the pharmacodynamics and pharmacokinetics of select C8-HI cocrystal formulations in somatostatin-treated beagle dogs, an animal model of acute insulin deficiency.

We initially carried out a control experiment to characterize the time action of the C8-HI molecule relative to that of insulin. In this experiment, each molecule was administered in identical solution formulations. The C8-HI molecule does not exhibit a protracted time action relative to insulin (Fig. 5A), and the glucose-lowering biopotencies of the two molecules are very similar. The C8-HI molecule thus does not exhibit an inherent protracted time action in this model.

Glucodynamic profiles of 58%, 75%, and 92% C8-HI cocrystals (Fig. 5B) suggest that the glucodynamic profile is influenced by the fraction of C8-HI in the cocrystal. However, the difference between the 92% and 75% formulations is substantially larger than between the 58% and 75% formulations, suggesting that the time action may arise in this model from a more complex relationship than a linear correlation with *in vitro* dissolution kinetics. As the proportion of C8-HI is increased, there is a trend toward a decrease in efficacy. We attribute this change to an alteration in the absorption pattern (fraction of total insulin absorbed during first 12 h: $64 \pm 1\%$ vs. $59 \pm 1\%$ for 58% and 75% C8-HI, respectively; $P < 0.01$) or bioavailability (area under

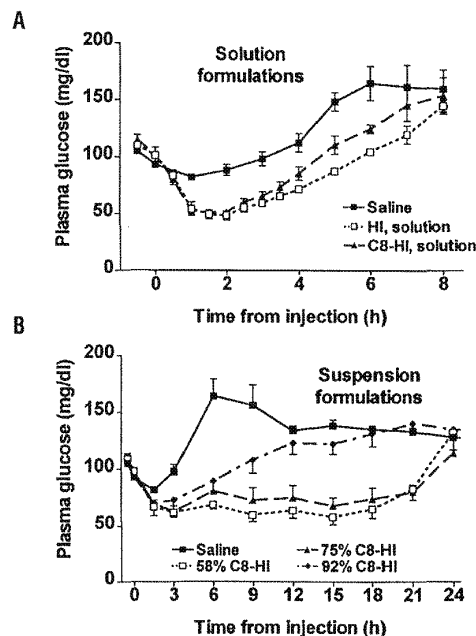


Figure 5. Time-action profiles of insulin formulations administered to somatostatin-treated dogs by subcutaneous injection. (A) Saline, HI, and C8-HI solution formulations (0.75 nmol/kg, $n = 5$). (B) C8-HI cocrystal suspension formulations (2 nmol/kg, $n = 6$). Values represent mean $\pm$ s.e.m.

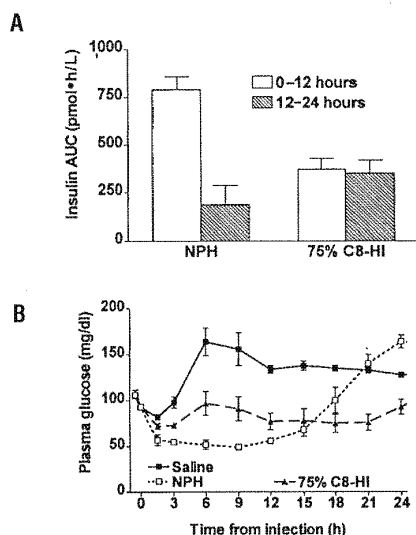


Figure 6. Pharmacokinetics and glucodynamics of 75% C8-HI cocrystal and NPH in somatostatin-treated dogs (2 nmol/kg, subcutaneous, $n = 6$; values represent mean $\pm$ s.e.m.). The pharmacokinetics (A) show that the 0–12 h area under curve (AUC) for 75% C8-HI cocrystal is significantly less than that of NPH ($P < 0.05$), and the 12–24 h AUC for 75% C8-HI cocrystal is significantly greater than that of NPH ($P < 0.05$). The release pattern of the 75% C8-HI cocrystal results in a flatter, more ideal basal pharmacokinetics and longer time action (B) than that of NPH.

the insulin curve (insulin AUC): 1.26 ± 0.27 nmol h/L vs. 0.80 ± 0.20 nmol h/L for 58% and 92% C8-HI, respectively; $P < 0.02$) of the formulations.

C8-HI (75%) cocrystals give improved basal glycemic control. In somatostatin-treated dogs injected with NPH human insulin or a 75% C8-HI cocrystal formulation, pharmacokinetics and pharmacodynamics results (Fig. 6) illustrate that inclusion of C8-HI in the crystalline lattice slows the initial absorption of insulin from the subcutaneous site (insulin AUC 0–12 h; Fig. 6A) and provides a more even insulin exposure throughout the 24 h test period (insulin AUC 0–12 h vs. 12–24 h; Fig. 6A). This change in insulin kinetics resulted in an extension of time action from 18 h (NPH) to 24 h (75% C8-HI cocrystal) in this animal model (Fig. 6B). The alteration in absorption kinetics and extension of time action relative to NPH are consistent with the slowed dissolution of insulin cocrystals observed in the *in vitro* dissolution experiments.

These findings suggest that it may be possible to improve the time action of NPH by incorporating an appropriate fraction of a less soluble insulin derivative that is structurally tolerated by the crystal lattice. We hypothesize that the crystallizing unit of the cocrystal is a mixture of hybrid zinc insulin hexamers (Fig. 1). Insulin cocrystallizes with proinsulin³⁴, and has recently been shown to form hybrid zinc hexamers with fluorescently labeled N⁶-LysB29-modified insulin derivatives³⁵ in solution.

Although the utility of protein crystals in formulation design has been recognized for some time^{29,36}, to our knowledge there have been no previous reports of the use of a hybrid protein cocrystal to tailor the biopharmaceutics of a therapeutic protein. The broader applicability of this approach will depend upon the ability to modify the parent protein in a way that retains its biological activity and crystallization propensity, yet alters its resultant solubility. The availability of X-ray crystal structures should help identify regions of proteins

that may tolerate a suitable modification without destroying contacts critical to lattice stability. In view of the unprecedented numbers of new therapeutic proteins entering clinical testing and rapidly advancing methods for protein crystallization screening³⁷, cocrystallization with a solubility-modified derivative may be useful in optimizing subcutaneous absorption kinetics.

Experimental protocol

Reagents. Biosynthetic human insulin (as zinc insulin crystals), protamine sulfate, NPH human insulin (Humulin N), and C8-HI (prepared and characterized as described previously^{15,18}) were supplied by Eli Lilly (Indianapolis, IN). All other materials were either US Pharmacopeia (USP) or analytical reagent grade.

Cocrystal preparation. Cocrystals were prepared using final formulation concentrations of 3.5 mg/ml total insulins, 0.025 mg/ml Zn(II), 16 mg/ml glycerol, 1.8 mg/ml *m*-cresol, 0.7 mg/ml phenol, 3.75 mg/ml dibasic sodium phosphate heptahydrate, 3 mg/ml trisodium citrate dihydrate, and 0.3 mg/ml protamine. Specific cocrystal ratios were achieved by initially mixing solutions of human insulin and C8-HI in a ratio corresponding to the target ratio of the cocrystal. The general protocol is exemplified here by a 10 ml preparation of the 75% C8-HI cocrystal as follows: 29.6 mg of C8-HI (88% protein content) was dissolved in 0.75 ml of 0.1 M HCl and mixed with a solution of 9.6 mg of human insulin (90% protein content) dissolved in 0.25 ml of 0.1 M HCl. To this solution was added 20 μ l of 10 mg/ml ZnCl₂ solution. To this solution was added 4 ml of a solution containing 40 mg/ml glycerol, 3.75 mg/ml trisodium citrate dihydrate, 1.8 mg/ml phenol, 4.4 mg/ml *m*-cresol, and 9.4 mg/ml dibasic sodium phosphate heptahydrate, pH 8. The resulting solution was adjusted to pH 7.6 using 1 M HCl and 1 M NaOH, then combined with an equal volume of a 0.6 mg/ml protamine solution prepared by dissolving protamine sulfate in water. A precipitate formed immediately, and was allowed to stand quiescent for one day at 25°C. Inspection using a Carl Zeiss Axioplan light microscope (München-Hallbergmoos, Germany) at 1,000 $\times$ magnification showed that the amorphous precipitate had converted completely to rod-like microcrystals. Analysis of the supernatant by reversed-phase high-performance liquid chromatography (HPLC; Beckman, Altech division, San Ramon, CA) showed that no protamine and <2% of the total insulins remained dissolved in solution.

Environmental scanning electron microscopy. An Electroscan model E3 instrument (Philips/FEI, Hillsboro, Oregon) was used.

Dissolution studies. Dissolution rates were characterized by placing a volume of formulation containing 1.80 mg of total insulins into 200 ml of Dulbecco's phosphate-buffered saline, without CaCl₂ and MgCl₂ (Life Technologies, Grand Island, NY), pH 7.4, containing 1 mg/ml BSA (Sigma, St. Louis, MO); the mixture was stirred at a fixed rate using a magnetic stirrer at 25°C. Aliquots withdrawn at regular intervals were filtered through a 0.2 μ m low-protein-binding filter (Pall Corporation, Ann Arbor, MI). The respective quantities of dissolved insulin and dissolved C8-HI were determined by reversed-phase HPLC analysis of the filtrate.

Time-action studies in somatostatin-treated dogs. Animal protocols were approved by the Institutional Animal Care and Use Committee, Eli Lilly and Company, and care and handling of the animals were in accordance with the guidelines of the American Association for the Accreditation of Laboratory Animal Care. Experiments were conducted in chronically cannulated (femoral artery and vein) conscious male and female beagles weighing 10–17 kg (Marshall Farms, North Rose, NY) which had fasted overnight. On the day of the experiment, indwelling vascular access ports (Access Technologies, Norfolk Medical, Skokie, IL) were accessed and cleared and the animals were placed in 3 ft $\times$ 3 ft study cages. Dogs were allowed at least 10 min to acclimate to the cage environment before an arterial blood sample was drawn for determination of fasting insulin and glucose concentrations (time = –30 min). At this time a continuous venous infusion (0.65 μ g/kg per min) of cyclic somatostatin (Bachem, Torrance, CA) was initiated and continued for the next 8.5–24.5 h. At 30 min after the start of the infusion (time = 0), an arterial sample was drawn and a subcutaneous bolus of saline or test substance was injected into the dorsal aspect of the neck. Arterial blood samples were taken periodically thereafter for the determination of plasma glucose and insulin concentrations. Plasma glucose concentrations were determined on the day of the study using a glucose oxidase method in a Beckman Glucose Analyzer II (Beckman Instruments,

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Brea, CA). Plasma samples were stored at -80°C until time for insulin analysis. Insulin concentrations were determined using a double-antibody radioimmunoassay (goat anti-guinea pig IgG, Jackson 106-006-008, Jackson ImmunoResearch Laboratories, Westgrove, PA; guinea pig anti-porcine insulin, Lot P5, Eli Lilly) sensitive to both human insulin and C8-HI.

Competing interests statement

The authors declare competing financial interests: see the Nature Biotechnology website (<http://biotech.nature.com>) for details.

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