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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	USF-106XC1
First Inventor	Michael J. Zaworotko
Title	Multiple-Component Solid Phases Containing At Least One Active Pharmaceutical Ingredient
Express Mail Label No.	EU082846466US

10/378956 JC784 U.S. PTO 03/03/03

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Assistant Commissioner for Patents
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Washington, DC 20231

1. [X] Fee Transmittal Form (e.g. PTO/SB/17) *(Submit an original and a duplicate for fee processing)*
2. [X] Applicant claims small entity status. See 37 CFR 1.27
3. [X] Specification [Total Pages 42]
   (preferred arrangement set forth below)
   - Descriptive title of the invention
   - Cross Reference to Related Applications
   - Statement Regarding Fed Sponsored R & D
   - Reference to sequence listing, a table, or a computer program listing appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
4. [X] Drawing(s) (35 U.S.C. 113) [Total Sheets 22]
5. Oath or Declaration [Total Pages 3]
   a. [X] Newly executed (original or copy) (unsigned)
   b. [ ] Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional with Box 18 completed)*
      i. [ ] DELETION OF INVENTOR(S)
      Signed statement attached deleting inventor(s) named in the prior application, 37 CFR 1.63(d)(2) and 1.33(b).
6. [ ] Application Data Sheet. See 37 CFR 1.76
7. [ ] CD-ROM or CD-R in duplicate, large table or Computer Program *(Appendix)*
8. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. [ ] Computer Readable Form (CRF)
   b. Specification Sequence Listing on:
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ACCOMPANYING APPLICATION PARTS

9. [ ] Assignment Papers (cover sheet & document(s))
10. [ ] 37 CFR 3.73(b) Statement [ ] Power of Attorney *(when there is an assignee)*
11. [ ] English Translation Document *(if applicable)*
12. [ ] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copies of IDS Citations
13. [ ] Preliminary Amendment
14. [X] Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
15. [ ] Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
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Signature	Glenn P. Ladwig	Date	March 3, 2003

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FEE TRANSMITTAL FORM

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Sir:

Transmitted herewith for filing is the patent application of:

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

Entitled: Multiple-Component Solid Phases Containing At Least One Active Pharmaceutical Ingredient

☒ A Utility Patent Application Transmittal Form accompanies this Fee Transmittal Form.
☒ The Filing Fee is calculated below:

CLAIMS AS FILED

	Number filed		Number Extra	Rate	Fee
Basic Fee				$375.00	$375.00
Total Claims	36	– 20 =	16	x $9	$144.00
Independent Claims	9	– 3 =	6	x $42	$252.00
Presentation of Multiple Dependent Claim(s) ($140)					$ 0.00
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Glenn P. Ladwig
Attorney of Record

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DESCRIPTION

MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT

CROSS-REFERENCE TO RELATED APPLICATION

The present application claims the benefit of priority of U.S. Provisional Application Serial No. 60/360,768, filed March 1, 2002, which is hereby incorporated by reference herein in its entirety, including any figures, tables, or drawings.

BACKGROUND OF THE INVENTION

[0001] The last decade has witnessed tremendous advances in the understanding of, and the ability to manipulate, molecular and supramolecular assemblies (Moulton, B. *et al.*, *Chem. Rev.*, 2001, 101:1629-1658). There are new paradigms concerning the design and synthesis of a new generation of functional materials and molecules. Such advances are a consequence of the fundamental importance of intermolecular interactions, structure and cooperativity in many aspects of molecular science, from environmental science to molecular biology, to pharmacology, to materials science. Thus, the prospects for control and manipulation of materials at the molecular level, particularly in areas related to non-covalent bonding and nanotechnology, are now truly exceptional. However, whereas crystal structure determination has been a tool used by scientists since the 1920's, crystal structure prediction remains a largely unmet goal (Ball, P. *Nature*, 1996, 381:648-650; Gavezzotti, A. *Acc. Chem. Res.*, 1994, 27:309-314). Furthermore, the existence of more than one crystalline form of a given molecular compound, typically in the form of polymorphs or solvates, represents both a problem and an opportunity (Desiraju, G.R. *Science*, 1997, 278:404-405; Bernstein, J. *et al.*, *Angew. Chem., Int. Ed. Engl.*, 1999, 38:3441-3461). This is particularly true for the pharmaceutical industry.

[0002] Crystal engineering (Schmidt, G.M.J. *Pure Appl. Chem.*, 1971, 27:647-678; Desiraju, G.R. *Crystal Engineering: the Design of Organic Solids*, 1989, Elsevier: Amsterdam) is predicated on the assumption that crystals are *de facto* examples of self-assembly, *i.e.* crystals are comprised from a series of molecular recognition events or *supramolecular synthons*

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(Desiraju, G.R. *Angew. Chem., Int. Ed. Engl.*, 1995, 34:2311-2327). It also offers a more realizable goal than crystal structure prediction since it relies on design and allows for careful selection of substrates, *i.e.* substrates that are predisposed to form predictable self-assembled superstructures can be targeted for study. Furthermore, the prototypal molecules used in crystal engineering contain exofunctional molecular recognition sites and they can be complementary with themselves (self-assembly) (Boucher, E. *et al.*, *J. Org. Chem.*, 1995, 60:1408-1412) or with other molecules (modular self-assembly) (Zaworotko, M.J. *Chem. Soc. Rev.*, 1994, 23:283-288; Sharma, C.V.K. and M.J. Zaworotko *Chem. Commun.*, 1996, 2655-2656). Coincidentally, most pharmaceutical molecules also contain exterior molecular recognition sites and, although this makes them susceptible to polymorphism and solvate formation, it also makes them attractive candidates for crystal engineering studies.

[0003] The ability of crystalline self-assemblies to be built from a bottom-up approach (Feynman, R. *Engineering and Science*, 1960, 22-36) could provide an exceptional control of the design of new phases at a molecular level. This contrasts with the current state-of-the-art: "The number of forms known for a given compound is proportional to the time and money spent in research on that compound" (McCrone, W.C. *Polymorphism in Physics and Chemistry of the Organic Solid-State*, pp. 726, Fox *et al.* Eds., Interscience: New York, 1965). This statement summarizes the predicaments and opportunities that one faces when dealing with a need to assert control over the composition and structure of pharmaceutical compounds in the solid state. Specifically, physical properties of crystalline solids are critically dependent on the internal arrangement of molecules or ions, making prediction of composition, crystal structure and morphology from knowledge of molecular structure a scientific challenge of the highest order. However, crystal structure prediction and even prediction of composition remains a largely unmet goal. Nonetheless, crystal engineering offers the intriguing possibility of using molecular components for their ability to impart functional characteristics (such as solubility, dissolution rate and stability) for the development of new delivery systems.

[0004] Undesirable physicochemical properties, physiological barriers, or issues of toxicity often limit the therapeutic benefit of drugs. This has motivated research in drug delivery systems for poorly soluble, poorly absorbed and labile substances. Crystalline self-assemblies represent a promising delivery modality for improving drug solubility, dissolution rate, stability and bioavailability. In addition, enhancement of drug activity can be achieved by means of

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inclusion complexation or molecular encapsulation. These systems offer various advantages over amorphous polymeric delivery systems both from design and stability perspectives. In this context, the existence of more than one crystalline form of a given compound, typically in the form of polymorphs or solvates, represents both a problem and an opportunity. Several factors further complicate the situation. For example, the Food and Drug Administration's (FDA's) strict purity requirements effectively mean that a particular crystalline phase of a drug must be selected and that its composition must be established. This has typically meant that a consistent X-ray powder diffraction (XPD) pattern is required (Federal Drug Administration *Fed. Regist.*, 1997, 62:62893-62894). The need to ensure that processing produces both purity and ease of processing is problematic because many drug molecules are prone to form multiple phases, and crystal size and morphology can vary for a given phase. The commercial and public image costs of not ensuring that processing is reliable and reproducible is at best very high, as demonstrated by the recent pull back and reformulation of NORVIR by ABBOTT LABORATORIES).

[0005] That XPD patterns have been relied on for quality control is convenient but is in many ways unfortunate since XPD is not as foolproof as single crystal X-ray crystallography (*e.g.* similar patterns can be obtained for different phases, composition is not unambiguously determined), and XPD does not determine crystal packing. Knowledge of crystal packing is important because it helps explain the solubility and composition of a particular phase and provides other valuable information. However, the materials properties of pharmaceuticals and the existence of polymorphs are generally investigated at the tail end of the drug development process.

[0006] Accordingly, it would be advantageous to provide a wide range of novel solid phases having properties, such as melting point, solubility, dissolution rate, chemical stability, thermodynamic stability, and/or bioavailability, which are different from existing solid forms of the pharmaceutical molecule upon which they are based.

BRIEF SUMMARY OF THE INVENTION

[0007] The subject invention relates to the application of the concepts of crystal engineering towards the design of new pharmaceutical phases that contain more than one molecular component.

[redacted]

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[0008] The subject invention concerns multiple-component solids having at least one active pharmaceutical ingredient. Examples of pharmaceutical molecules that may be utilized as active pharmaceutical ingredients in the multiple-component solids of the subject invention include, but are not limited to, aspirin, one or more members of the profen series (*e.g.*, ibuprofen and flurbiprofen), carbamazepine, phenytoin, and acetaminophen. Multiple-component solids, such as multiple-component crystals, containing these pharmaceutical ingredients and complementary molecules (hereafter referred to as "cocrystal formers") have been characterized by various techniques and can exhibit physical and/or chemical properties that are the same or different from the parent pharmaceutical ingredient as a direct result of alternative molecular recognition patterns. These novel crystalline assemblies can afford improved drug solubility, dissolution rate, stability and bioavailability.

[0009] The subject invention relates to the application of the concepts of crystal engineering towards the design of new pharmaceutical solid phases, such as multiple-component phases, using cocrystal formers that are complementary in the sense of supramolecular chemistry, *i.e.* they form supramolecular synthons with pharmaceutical molecules or ions. The cocrystal formers can be, but are not limited to, solvent molecules, other drug molecules, GRAS compounds, or approved food additives. Pharmaceutical molecules or ions are inherently predisposed for such crystal engineering studies since they already contain molecular recognition sites that bind selectively to biomolecules, and they are prone to supramolecular self-assembly. Examples of the groups commonly found in active pharmaceutical ingredients, and which are capable of forming supramolecular synthons include, but are not limited to, acids, amides, aliphatic nitrogen bases, unsaturated aromatic nitrogen bases (*e.g.* pyridines, imidazoles), amines, alcohols, halogens, sulfones, nitro groups, S-heterocycles, N-heterocycles (saturated or unsaturated), and O-heterocycles. Other examples include ethers, thioethers, thiols, esters, thioesters, thioketones, epoxides, acetonates, nitrils, oximes, and organohalides. Some of these groups can form supramolecular synthons with identical groups in similar or different molecules and are termed homosynthons, *e.g.* acids and amides. Other groups can form supramolecular synthons with different groups and are termed heterosynthons, *e.g.* acid/amide; pyridine/amide; alcohol/amine. Heterosynthons are particularly suitable for formation of multiple-component crystals whereas homosynthons can sometimes form multiple-component crystals.

[redacted]

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[0010] In one aspect, the subject invention concerns methods for identifying complementary chemical functionalities to form a desired supramolecular synthon, wherein the method comprises the steps of evaluating the structure of an active pharmaceutical ingredient (API), which can include determining its crystal structure; determining whether the API contains chemical functionalities capable of forming supramolecular synthons with itself; identifying from a plurality of chemical functionalities that are known to form a supramolecular synthon at least one chemical functionality that will form a further supramolecular synthon to the supramolecular synthon formed by the API, wherein the identified chemical functionality is not capable of disrupting non-covalent bonding within the supramolecular synthon formed by the supramolecular synthon formed by the API, and wherein the selected chemical functionality is capable of forming a noncovalent bond to the supramolecular synthon formed by the API; and identifying co-crystal formers having chemical functionalities that are complementary with the API.

[0011] In another aspect, the subject invention concerns methods for identifying complementary chemical functionalities to form a desired supramolecular synthon, wherein the method comprises the steps of evaluating the structure of an API, which can include determining its crystal structure; determining whether the API contains chemical functionalities capable of forming supramolecular synthons with itself; identifying from a plurality of chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular synthon with the API, wherein the identified chemical functionality is capable of disrupting non-covalent bonding within the supramolecular synthon formed by the API, and wherein the selected chemical functionality is capable of forming a noncovalent bond to a complementary chemical functionality on the API; and identifying co-crystal formers having chemical functionalities that are complementary with the API. Thus, according to this method, the formation of homosynthons for the purpose of disrupting the intermolecular interactions between pharmaceutical moieties can be carried out.

In still another aspect, the subject invention concerns methods for identifying complementary chemical functionalities to form a desired supramolecular synthon, wherein the method comprises the steps of evaluating the structure of an API, which can include determining its crystal structure; determining whether the API contains chemical functionalities capable of forming supramolecular synthons with different molecules; identifying from a plurality of

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chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular synthon with the API, and wherein the selected chemical functionality is capable of forming a noncovalent bond to a complementary chemical functionality on the API; and identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient.

[0012] As indicated above, certain aspects of the subject invention can involve selecting a chemical functionality that is capable of disrupting the non-covalent bonding between identical functionalities (homosynthon) and form a non-covalent bond between different, yet complementary, functionalities (heterosynthon); selecting a plurality of molecular entities that comprise the complementary functionality (preferably GRAS compounds or approved food additives); identifying additional chemical features on the molecular entities that will not interfere with the formation of the desired supramolecular synthon and that will impart the desired physical properties to the target phase; and, optionally, preparing a new solid phase that is composed of the pharmaceutical moiety and the complementary molecular entity (such as a multiple-component phase or two component phase) by crystallization techniques comprising reactions in solvent, and/or solventless reactions, that afford crystalline materials. Optionally, the methods can further include at least one of the subsequent steps of determining the structure of the new solid phase formed; and analyzing the physical properties of the new solid phase.

[0013] The subject invention further concerns new solid phases identified or produced using the methods identified herein. The subject invention further pertains to a multiple-component phase composition comprising a solid material (phase) that is sustained by intermolecular interactions between two or more independent molecular entities, in any stoichiometric ratio, wherein at least one of the independent molecular entities is a pharmaceutical entity. The multiple-component phase composition can be, for example, a discrete supramolecular entity or a polymeric structure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] Figure 1 shows the chemical structure of ibuprofen. The external functionalities are an isopropyl group (encircled on the left, in cyan) and a carboxylic acid (encircled on the right, in magenta).

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[0015] Figure 2 shows a scheme with the synthon of pure ibuprofen on the left and the supramolecular entity containing the synthon on the right, demonstrating that pure phases of ibuprofen are sustained by carboxylic acid-carboxylic acid interactions. The standard chemical color correlation appears in all the figures where color is utilized (*e.g.*, red = oxygen; white = oxygen; dark blue = nitrogen; light blue = fluorene; yellow = sulfur).

[0016] Figure 3 shows a scheme wherein the carboxylic acid-carboxylic acid interactions of ibuprofen are disrupted by co-crystallization with an aromatic amine. Specifically, by using diamines, 2:1 multiple-component phases are produced.

[0017] Figures 4A–4B show an acetaminophen 1-D polymeric chain and an acetaminophen/4,4'-bipyridine/water crystal, respectively. Reported forms are monoclinic ($P2_1/n$) (Haisa, M. *et al.*, *Acta Crystallogr., Sect B*, 1974, 30:2510) and orthorhombic (*Pbca*) (Haisa, M. *et al.*, *Acta Crystallogr., Sect B*, 1976, 32:1283) polymorphs. The monoclinic polymorph forms pleated sheets with all hydrogen bonding donors and acceptors interacting. The orthorhombic polymorph forms form 1-D polymeric chains with all donors and acceptors interacting.

[0018] Figures 5A-5B show pure phenytoin and a phenytoin/pyridone co-crystal, respectively. Phenytoin has one known pure form (Carmerman, A. *et al.*, *Acta Crystallogr., Sect B*, 1971, 27:2207). The crystal structure reveals a two dimensional polymeric network formed by hydrogen bonds between both the carbonyl and 2° amine.

[0019] Figures 6A-6D show supramolecular entities containing synthons and corresponding crystal structures of pure aspirin and aspirin/4,4'-bipyridine. Figures 3A and 3B show the supramolecular entity containing the synthon of pure aspirin and corresponding crystal structure, respectively. Figures 6C and 6D show the supramolecular entity containing the synthon and corresponding co-crystal of aspirin/4,4'-bipyridine, respectively. The pure phase (Chiari, G. *et al.*, *Acta Crystallogr., Sect B*, 1981, 37:1623) of acetylsalicylic acid, has centrosymmetric carboxylic acid homodimers and crystallizes in the space group $P2_1/c$, packing in 2D polymeric sheets with hydrophobic planes.

[0020] Figures 7A-7D show supramolecular entities containing synthons and corresponding crystal structures of pure ibuprofen [2-(4-isobutylphenyl) propionic acid] and ibuprofen/4,4'-bipyridine. Figures 7A and 7B show the supramolecular entity containing the synthon of pure ibuprofen and corresponding crystal structure, respectively. Figures 7C and 7D

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show the supramolecular entity containing the synthon of ibuprofen/4,4'-bipyridine and corresponding co-crystal, respectively. The reported crystal structures of ibuprofen are racemic (McConnell, J.F. *Cryst. Strucut. Commun.*, 1974, 3:73) and S (+) forms (Freer, A.A. *et al.*, *Acta Crystallogr., Sect C (Cr. Str. Comm)*, 1993, 49:1378). Both contain hydrogen bonded carboxylic acid homodimers. Racemic dimers have centers of inversion across the dimer, which crystallize in the space group $P2_1/c$. The S (+) form contains asymmetric dimers, which crystallize in the space group $P2_1$. Both crystals pack in 2-D polymeric sheets sustained by π-π stacking and hydrophobic in-layer interactions.

[0021] Figures 8A-8D show supramolecular entities containing synthons and corresponding crystal structures of pure flurbiprofen [2-(2-fluror-4-biphenyl) propionic acid] and flurbiprofen/4,4'-bipyridine. Figures 8A and 8B show the supramolecular entity containing the synthon of pure flurbiprofen and corresponding crystal structure, respectively. Figures 5C and 5D show the supramolecular synthon of flurbiprofen/4,4'-bipyridine and corresponding co-crystal, respectively. Flurbiprofen has one reported pure form (Flippen, J.L. *et al.*, *Acta Crystallogr., Sect. B*, 1975, 31:926) and contain hydrogen bonded carboxylic acid homodimers with a center of inversion and crystallizes in the *P-1* space group. 2-D polymeric sheets are formed through π-π and hydrophobic interactions from the phenyl rings.

[0022] Figures 9A and 9B show the supramolecular entity containing the synthon of flurbiprofen/trans-1,2-bis(4-pyridyl)ethylene and the corresponding crystal structure, respectively.

[0023] Figures 10A and 10B show the crystal structures of pure carbamazepine and carbamazepine/*p*-phthalaldehyde, respectively. Carbamazepine [5H-Dibenz(b, f) azepine-5-carboxamide] (CBZ) has been shown to exist in at least three anhydrous forms and two solvated forms (a dihydrate and an acetonate) (Himes, V.L. *et al.*, *Acta Crystallogr.*, 1981, 37:2242-2245; Lowes, M.M.J. *et al.*, *J. Pharm. Sci.*, 1987, 76:744-752; Reck, G. *et al.*, *Cryst. Res. Technol.*, 1986, 21:1463-1468). The primary intermolecular interaction in these crystal forms is the dimer formed between the carboxamide moieties of each CBZ molecule forming centrosymmetric dimers. The anhydrous polymorphs are monoclinic, trigonal, and triclinic. The polymorphs are enantiotropically related with the monoclinic form being the most thermodynamically stable at room temperature.

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[0024] Figure 11 shows the crystal structure of carbamazepine/nicotinamide (vitamin B3).

[0025] Figure 12 shows the crystal structure of carbamazepine/saccharin, engineered using the carbamazepine/nicotinamide co-crystal as a model.

[0026] Figures 13A-13C show the chemical structures of ibuprofen, flurbiprofen, and aspirin, respectively.

[0027] Figures 14A and **14B** show the crystal structures of carbamazepine and carbamazepine/2,6-pyridinedicarboxylic acid, respectively.

[0028] Figures 15A and 15B show the crystal structures of carbamazepine and carbamazepine/5-nitroisophthalic acid, respectively.

[0029] Figures 16A and **16B** show the crystal structures of carbamazepine and carbamazepine/acetic acid.

[0030] Figures 17A and **17B** show the crystal structure of carbamazepine and carbamazepine/adamantanetetracarboxylic acid.

[0031] Figures 18A and **18B** show the crystal structure of carbamazepine and carbamazepine/benzoquinone.

[0032] Figures 19A and **19B** show the crystal structure of carbamazepine and carbamazepine/butyric acid.

[0033] Figures 20A and **20B** show the crystal structure of carbamazepine and carbamazepine/DMSO.

[0034] Figures 21A and **21B** show the crystal structure of carbamazepine and carbamazepine/formamide.

[0035] Figures 22A and **22B** show the crystal structure of carbamazepine and carbamazepine/formic acid.

[0036] Figures 23A and **23B** show the crystal structure of carbamazepine and carbamazepine/trimesic acid.

[0037] Figure 24 shows an exemplified scheme for preparing multiple-component phase compositions of the subject invention.

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DETAILED DISCLOSURE OF THE INVENTION

[0038] The subject invention relates to the application of the concepts of crystal engineering towards the design of new multiple-component solid phases, such as multiple-component crystals, having at least one active pharmaceutical component. Examples of multiple-component crystals of the subject invention include, but are not limited to, acetominophen/4,4'-bipyridine/water, phenytoin/pyridone, aspirin/4,4'-bipyridine, ibuprofen/4,4'-bipyridine, flurbiprofen/4,4'-bipyridine, flurbiprofen/trans-1,2-bis (4-pyridyl) ethylene, carbamazepine/*p*-phthalaldehyde, carbamazepine/nicotinamide (GRAs), carbamazepine/saccharin (GRAs), carbamazepine/2,6-pyridinedicarboxylic acid, carbamazepine/5-nitroisophthalic acid, carbamazepine/acetic acid, carbamazepine/1,3,5,7-adamantanetetracarboxylic acid, carbamazepine/benzoquinone, carbamazepine/butyric acid, carbamazepine/dimethyl sulfoxide (DMSO), carbamazepine/formamide, carbamazepine/formic acid, and carbamazepine/trimesic acid, which have been characterized by various techniques and exhibit physical properties different from the parent pharmaceutical ingredient as a direct result of hydrogen bonding interaction. These crystalline assemblies can afford improved drug solubility, dissolution rate, stability and bioavailability, for example.

[0039] In one aspect, the subject invention concerns methods for identifying complementary chemical functionalities to form a desired supramolecular synthon, wherein the method comprises the steps of evaluating the structure of an active pharmaceutical ingredient (API), which can include determining its crystal structure; determining whether the API contains chemical functionalities capable of forming supramolecular synthons with itself; identifying from a plurality of chemical functionalities that are known to form a supramolecular synthon at least one chemical functionality that will form a further supramolecular synthon to the supramolecular synthon formed by the API, wherein the identified chemical functionality is not capable of disrupting non-covalent bonding within the supramolecular synthon formed by the supramolecular synthon formed by the API, and wherein the selected chemical functionality is capable of forming a noncovalent bond to the supramolecular synthon formed by the API; and identifying co-crystal formers having chemical functionalities that are complementary with the API.

[0040] In another aspect, the subject invention concerns methods for identifying complementary chemical functionalities to form a desired supramolecular synthon, wherein the

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method comprises the steps of evaluating the structure of an API, which can include determining its crystal structure; determining whether the API contains chemical functionalities capable of forming supramolecular synthons with itself; identifying from a plurality of chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular synthon with the API, wherein the identified chemical functionality is capable of disrupting non-covalent bonding within the supramolecular synthon formed by the API, and wherein the selected chemical functionality is capable of forming a noncovalent bond to a complementary chemical functionality on the API; and identifying co-crystal formers having chemical functionalities that are complementary with the API. Thus, according to this method, the formation of homosynthons for the purpose of disrupting the intermolecular interactions between pharmaceutical moieties can be carried out.

[0041] In still another aspect, the subject invention concerns methods for identifying complementary chemical functionalities to form a desired supramolecular synthon, wherein the method comprises the steps of evaluating the structure of an API, which can include determining its crystal structure; determining whether the API contains chemical functionalities capable of forming supramolecular synthons with different molecules; identifying from a plurality of chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular synthon with the API, and wherein the selected chemical functionality is capable of forming a noncovalent bond to a complementary chemical functionality on the API; and identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient.

[0042] In each of the three aspects of the methods described above, the methods can further comprise preparing a multiple-component solid phase composition composed of the API and at least one of the identified co-crystal formers. The identified co-crystal former can be, for example, a different API, a GRAS compound, a food additive, a low toxicity organic, or a metal-organic complex. Various methods can be utilized for preparing the multiple-component solid phase composition, such as crystallization from solution, cooling the melt, sublimation and grinding. In addition, the methods of the subject invention can further comprise either or both of the following steps: determining the structure of the new multiple-component solid phase composition, and analyzing the physical and/or chemical properties of the new multiple-component solid phase composition.

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[0043] The subject invention further concerns new solid phases identified or produced using the methods identified herein. The subject invention further pertains to a multiple-component phase composition comprising a solid material (phase) that is sustained by intermolecular interactions between two or more independent molecular entities, in any stoichiometric ratio, wherein at least one of the independent molecular entities is a pharmaceutical entity. The multiple-component phase composition of the subject invention can be, for example, a discrete supramolecular entity or a polymeric structure. The multiple-component phase compositions of the subject invention can have properties, such as melting point, solubility, dissolution rate, stability, and/or bioavailability, which are different from the pharmaceutical compound, or compounds, upon which they are based.

[0044] By way of example, the external functionalities of ibuprofen are an isopropyl group and a carboxylic acid, as shown in Figure 1.

[0045] Using the methods of the subject invention, it has been determined that this interaction can be disrupted by co-crystallization with an aromatic amine, as shown in Figure 2. Specifically, by using diamines, 2:1 multiple-component phases of ibuprofen have been prepared, as shown in Figure 3, as well as other phases exemplified herein. Therefore, the methods of the subject invention can be used to identify complementary chemical functionalities and produce multiple-component phase compositions for a variety of pharmaceuticals, including those pharmaceutical compounds with structures very different those of ibuprofen, flurbiprofen, and aspirin, which are shown in Figures 13A-13C, respectively.

[0046] As used herein, the term "multiple-component phase" refers to any solid material (phase) that is sustained by intermolecular interactions between at least two independent molecular entities, in any stoichiometric ratio, wherein at least one of the independent molecular entities is a pharmaceutical entity. Examples of intermolecular interactions include, but are not limited to one or more of the following: hydrogen bonding (weak and/or strong), dipole interactions (induced and/or non-induced), stacking interactions, hydrophobic interactions, and other inter-static interactions. Each independent molecular entity can be a discrete supramolecular entity or polymeric structure, for example. Preferably, one or more of the independent molecular entities comprises a molecule of a "GRAS" compound, that is, a compound "Generally Regarded as Safe by the Food and Drug Administration (FDA)". More preferably, the GRAS compound is a non-pharmaceutical entity.

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[0047] The terms "pharmaceutical entity", "pharmaceutical moiety", "pharmaceutical component", "pharmaceutical molecule", and "active pharmaceutical ingredient (API)", and grammatical variations thereof, are used interchangeably herein to refer to any biologically active moiety having a therapeutic effect on a human or animal suffering from a given pathological condition, when administered in a given concentration. Therefore, pharmaceutical entities useful as the active pharmaceutical ingredients in the multiple phase solids of the subject invention can be administered to a human or animal, which may or may not be suffering from a pathological condition, and the pharmaceutical entity can have a prophylactic effect, a palliative effect, and/or be a curative intervention. As used herein, these pharmaceutical entities are intended to include pharmaceutically acceptable salts of a given pharmaceutical entity that retain all or a portion of their pharmaceutical activity. Pharmaceutical molecules or ions are inherently predisposed for such crystal engineering studies since they already contain molecular recognition sites that bind selectively to biomolecules, and they are prone to supramolecular self-assembly. Examples of the groups commonly found in active pharmaceutical ingredients, and which are capable of forming supramolecular synthons include, but are not limited to, acids, amides, aliphatic nitrogen bases, unsaturated aromatic nitrogen bases (*e.g.* pyridines, imidazoles), amines, alcohols, halogens, sulfones, nitro groups, S-heterocycles, N-heterocycles (saturated or unsaturated), and O-heterocycles. Other examples include ethers, thioethers, thiols, esters, thioesters, thioketones, epoxides, acetonates, nitrils, oximes, and organohalides. Other examples include ethers, thioethers, thiols, esters, thioesters, thioketones, epoxides, acetonates, nitrils, oximes, and organohalides. Some of these groups can form supramolecular synthons with identical groups in similar or different molecules and are termed homosynthons, *e.g.*, acids and amides. Other groups can form supramolecular synthons with different groups and are termed heterosynthons, *e.g.*, acid/amide; pyridine/amide; alcohol/amine. Heterosynthons are particularly suitable for formation of multiple-component crystals whereas homosynthons can sometimes form multiple-component crystals.

[0048] As used herein, the term "supramolecular synthon" refers to the sum of the components of a multi-component non-covalent interaction, wherein the non-covalent interaction contributes to the formation of a discrete supramolecular entity or polymeric structure, wherein each component is a chemical functionality. A supramolecular synthon can be a dimer, trimer, or *n*-mer, for example.

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[0049] The multiple-component phase compositions can be formulated according to known methods for preparing pharmaceutically useful compositions. Such pharmaceutical compositions can be adapted for various forms of administration, such as oral, parenteral, nasal, topical, transdermal, *etc.* The multiple-component phase solids of the subject invention can be made into solutions or amorphous compounds, as injections, pills, or inhalants, for example. Optionally, the pharmaceutical compositions can include a pharmaceutically acceptable carrier or diluent. Formulations are described in a number of sources which are well known and readily available to those skilled in the art. For example, *Remington's Pharmaceutical Science* (Martin EW [1995] Easton Pennsylvania, Mack Publishing Company, 19th ed.) describes formulations that can be used in connection with the subject invention. Formulations suitable for administration include, for example, aqueous sterile injection solutions, which may contain antioxidants, buffers, bacteriostats, and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and nonaqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the condition of the sterile liquid carrier, for example, water for injections, prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powder, granules, or tablets of the multiple-component phase compositions of the subject invention, for example. It should be understood that in addition to the ingredients particularly mentioned above, the formulations of the subject invention can include other agents conventional in the art having regard to the type of formulation in question.

[0050] In terms of superstructure, three general types of compounds generated by interaction of a pharmaceutical molecule with another molecule include: (1) multiple-component compounds, in which superstructure is generated by two or more molecules, both of which are integral components of the network and complementary; (2) clathrate inclusion compounds, in which the compounds' superstructure is generated by self-assembly of one or more molecules and a guest molecules is enclosed within the superstructure; and (3) porous inclusion compounds, in which the superstructure is open framework in nature.

[0051] The subject invention concerns multiple-component compositions, and it is demonstrated herein that the concepts of crystal engineering and supramolecular synthons can be applied to prepare a wide range of novel pharmaceutical materials that are based on rational

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design. Therefore, the multiple-component compounds of the subject invention can be generated in such a fashion that they have desirable composition, structure and properties. More specifically, an issue that is particularly relevant to pharmaceutical compositions of matter and processing is addressed by the subject invention: the diversity of compositions, superstructures and solubilities that can be generated when drug molecules form multiple-component phases with complementary molecules. Multiple-component phases involving the following drugs are exemplified herein: aspirin, acetaminophen, ibuprofen (and related compounds), phenytoin and carbamazepine and appropriate molecular additives. These novel phases include both "model multiple-component phases" that illustrate the concept of crystal engineering and multiple-component phases that incorporate pharmaceuticals with "GRAS" compounds, that is, compounds "Generally Regarded as Safe by the FDA", and/or food additives.

[0052] In the context of organic and pharmaceutical solids, the subject invention addresses these issues by demonstrating that crystal engineering offers a paradigm for the supramolecular synthesis (Chang, Y.L. *et al.*, *J. Am. Chem. Soc.*, 1993, 115:5991-6000) of a wide range of new multiple-component phases that have predetermined compositions and, in some instances, predetermined topology. Such an ability to build hierarchical structures from molecular or supramolecular modules facilitates precise control of structure and function of solid phases. These multiple-component phases have the following advantages over single component phases and traditional multiple-component phases (solid dispersions): high thermodynamic stability (thereby reducing problems associated with solid phase transformations), modified bioavailability (finely tunable solubility and delivery), and enhanced processability (crystal morphology, mechanical properties, hygroscopicity).

[0053] The subject invention has the following implications from a scientific perspective: (a) protocols are now available for the rational design of a new generation of pharmaceutical phases that contain at least two components that are sustained by supramolecular synthons; (b) correlation of structure and function of the new pharmaceutical phases via characterization of structure, crystal energy, solubility, dissolution rate, and stability is now possible; and (c) a new range of novel phases for the treatment of pathological conditions in humans and animals are available.

[0054] The subject invention extends the state-of-the-art in at least three ways: (1) by generating a rational, supramolecular strategy for the design of novel, multiple-component

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crystalline phases; (2) by extending this strategy to pharmaceutical phases; and (3) by using this strategy to control the delivery properties and stability of pharmaceutical compounds.

[0055] The following pages describe examples of multiple-component crystalline phases that have been characterized using single crystal X-ray crystallography and structure-sensitive analytical techniques: FT-IR, XRPD, DSC, TGA. They represent prototypal examples of the invention as they are all based upon pharmaceutical molecules that are inherently predisposed to form supramolecular synthons with other complementary functional groups. They were chosen for study because of well-known limitations in their solubility/bioavailibility. In each example, the nature of the pure phase is discussed and it is sustained by a supramolecular homosynthon (self-complementary functionalities). The multiple-component phases prepared confirm the ability to persistently and rationally disrupt the homosynthon by judicious choice of a second molecular component that is predisposed to form a supramolecular heterosynthon. That these new solid phases will have different solubility profiles than their pure phases is to be expected. Examples designated as GRAS are those in which second a component that is "Generally Regarded as Safe by the FDA" was used.

Example 1—Multi-Component Crystal of Acetaminophen: Acetominophen/4,4'-bipyridine/water (1:1:1 stoichiometry)

[0056] 50 mg (0.3307 mmol) acetaminophen and 52 mg (0.3329 mmol) 4,4'-bipyridine were dissolved in hot water and allowed to stand. Slow evaporation yielded colorless needles of a 1:1:1 acetaminophen/4,4'-bipyridine/water co-crystal, as shown in Figure 4B.

[0057] Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{36}H_{44}N_2O_4$, M=339.84, triclinic, space group $P\bar{1}$; a = 7.0534(8), b = 9.5955(12), c = 19.3649(2) Å, α = 86.326(2), β = 80.291(2), γ = 88.880(2)°, U = 1308.1(3) Å^3, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.090 mm^{-1}, D_c = 1.294 Mg/m^3, λ = 0.71073 Å^3, F(000) = 537, $2\theta_{max}$ = 25.02°; 6289 reflections measured, 4481 unique (R_{int} = 0.0261). Final residuals for 344 parameters were R_1 = 0.0751, wR_2 = 0.2082 for I>2σ(I), and R_1 = 0.1119, wR_2 = 0.2377 for all 4481data.

[0058] Crystal packing: The co-crystals contain bilayered sheets in which water molecules act as a hydrogen bonded bridge between the network bipyridine moieties and the acetaminophen. Bipyridine guests are sustained by π-π stacking interactions between two

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network bipyridines. The layers stack via π-π interactions between the phenyl groups of the acetaminophen moieties.

[0059] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 57.77° C (endotherm); m.p. = 58-60° C (MEL-TEMP); (acetaminophen m.p. = 169° C, 4,4'-bipyridine m.p. = 111-114° C).

Example 2—Multi-Component Crystal of Phenytoin: Phenytoin/Pyridone (1:1 stoichiometry)

[0060] 28 mg (0.1109 mmol) phenytoin and 11 mg (0.1156 mmol) 4-hydroxypyridone were dissolved in 2 mL acetone and 1 mL ethanol with heating and stirring. Slow evaporation yielded colorless needles of a 1:1 phenytoin/pyridone co-crystal, as shown in Figure 5B.

[0061] Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{20}H_{17}N_3O_3$, M = 347.37, monoclinic $P2_1/c$; a = 16.6583(19), b = 8.8478(10), c = 11.9546(14) Å, β = 96.618(2)°, U = 1750.2(3) Å^3, T = 200(2) K, Z = 4, μ(Mo-Kα) = 0.091 mm^{-1}, D_c = 1.318 Mg/m^3, λ = 0.71073 Å^3, F(000) = 728, $2\theta_{max}$ = 56.60°; 10605 reflections measured, 4154 unique (R_{int} = 0.0313). Final residuals for 247 parameters were R_1 = 0.0560, wR_2 = 0.1356 for I>2σ(I), and R_1 = 0.0816, wR_2 = 0.1559 for all 4154 data.

[0062] Crystal packing: The co-crystal is sustained by hydrogen bonding of adjacent phentoin molecules between the carbonyl and the amine closest to the tetrahedral carbon, and by hydrogen bonding between pyridone carbonyl functionalities and the amine not involved in phenytoin-phenytoin interactions. The pyridone carbonyl also hydrogen bonds with adjacent pyridone molecules forming a one-dimensional network.

[0063] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), characteristic peaks for the co-crystal were identified as: 2°amine found at 3311cm^{-1}, carbonyl (ketone) found at 1711cm^{-1}, olephin peak found at 1390cm^{-1}.

[0064] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 233.39° C (endotherm) and 271.33° C (endotherm); m.p. = 231-233° C (MEL-TEMP); (phenytoin m.p. = 295° C, pyridone m.p. = 148° C).

[0065] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), a 29.09% weight loss starting at 192.80° C, 48.72% weight loss starting at 238.27° C, and 18.38% loss starting at 260.17° C followed by complete decomposition.

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[0066] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. XRPD: Showed analogous peaks to the simulated XRPD derived from the single crystal data. In all cases of recrystallization and solid state reaction, experimental (calculated): 5.2 (5.3); 11.1 (11.3); 15.1 (15.2); 16.2 (16.4); 16.7 (17.0); 17.8 (17.9); 19.4 (19.4); 19.8 (19.7); 20.3 (20.1); 21.2 (21.4); 23.3 (23.7); 26.1 (26.4); 26.4 (26.6); 27.3 (27.6); 29.5 (29.9).

Example 3—Multi-Component Crystal of Aspirin (acetylsalicylic acid): Aspirin/4,4'-bipyridine (2:1 stoichiometry)

[0067] 50 mg (0.2775 mmol) aspirin and 22 mg (0.1388 mmol) 4,4'-bipyridine were dissolved in 4 mL hexane. 8 mL ether was added to the solution and allowed to stand for one hour, yielding colorless needles of a 2:1 aspirin/4,4'-bipyridine co-crystal, as shown in Figure 6D. Alternatively, aspirin/4,4'-bipyridine (2:1 stoichiometry) can be made by grinding the solid ingredients in a pestle and mortar.

[0068] Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{28}H_{24}N_2O_8$, M = 516.49, orthorhombic *Pbcn*; a = 28.831(3), b = 11.3861(12), c = 8.4144(9) Å, *U* = 2762.2(5) Å^3, T = 173(2) K, Z = 4, μ(Mo-Kα) = 0.092 mm^{-1}, D_c = 1.242 Mg/m^3, λ = 0.71073 Å^3, F(000) = 1080, $2\theta_{max}$ = 25.02°; 12431 reflections measured, 2433 unique (R_{int} = 0.0419). Final residuals for 202 parameters were R_1 = 0.0419, wR_2 = 0.1358 for I>2σ(I), and R_1 = 0.0541, wR_2 = 0.1482 for all 2433 data.

[0069] Crystal packing: The co-crystal contains the carboxylic acid-pyridine heterodimer that crystallizes in the *Pbcn* space group. The structure is an inclusion compound containing disordered solvent in the channels. In addition to the dominant hydrogen bonding interaction of the heterodimer, π-π stacking of the bipyridine and phenyl groups of the aspirin and hydrophobic interactions contribute to the overall packing interactions.

[0070] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), characteristic (-COOH) peak at 1679 cm^{-1} was shifted up and less intense at 1694cm^{-1}, where as the lactone peak is shifted down slightly from 1750cm^{-1} to 1744cm^{-1}.

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[0071] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 95.14° C (endotherm); m.p. = 91-96° C (MEL-TEMP); (aspirin m.p. = 1345° C, 4,4'-bipyridine m.p. = 111-114° C).

[0072] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), weight loss of 9% starting at 22.62° C, 49.06% weight loss starting at 102.97° C followed by complete decomposition starting at 209.37° C.

Example 4—Multi-Component Crystal of Ibuprofen: Ibuprofen/4,4'-Bipyridine (2:1 stoichiometry)

[0073] 50 mg (0.242 mmol) racemic ibuprofen and 18mg (0.0960 mmol) 4,4'-bipyridine were dissolved in 5 mL acetone. Slow evaporation of the solvent yielded colorless needles of a 2:1 ibuprofen/4,4'-bipyridine co-crystal, as shown in Figure 7D.

[0074] Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{36}H_{44}N_2O_4$, M = 568.73, triclinic, space group *P-1*; a = 5.759(3), b = 11.683(6), c = 24.705(11) Å, α = 93.674(11), β = 90.880(10), γ = 104.045(7)°, *U* = 1608.3(13) Å^3, T= 200(2) K, Z = 2, μ(Mo-Kα) = 0.076 mm^{-1}, D_c = 1.174 Mg/m^3, λ = 0.71073 Å^3, F(000) = 612, $2\theta_{max}$ = 23.29°; 5208 reflections measured, 3362 unique (R_{int} = 0.0826). Final residuals for 399 parameters were R_1 = 0.0964, wR_2 = 0.2510 for I>2σ(I), and R_1 = 0.1775, wR_2 = 0.2987 for all 3362 data.

[0075] Crystal packing: The co-crystal contains ibuprofen/bipyridine heterodimers, sustained by two hydrogen bonded carboxylic acidpyridine supramolecular synthons, arranged in a herringbone motif that packs in the space group *P-1*. The heterodimer is an extended version of the homodimer and packs to form a two-dimensional network sustained by π-π stacking of the bipyridine and phenyl groups of the ibuprofen and hydrophobic interactions from the ibuprofen tails.

[0076] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). Analysis observed stretching of aromatic C-H at 2899 cm^{-1}; N--H bending and scissoring at 1886 cm$_{-1}$; C=O stretching at 1679 cm^{-1}; C-H out-of-plane bending for both 4,4'-bipyridine and ibuprofen at 808 cm^{-1} and 628 cm^{-1}.

[0077] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 64.85° C (endotherm) and 118.79° C (endotherm); m.p. = 113-120° C (MEL-TEMP); (ibuprofen m.p. = 75-77° C, 4,4'-bipyridine m.p. = 111-114° C).

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[0078] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 13.28% weight loss between room temperature and 100.02° C immediately followed by complete decomposition.

[0079] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. XRPD derived from the single crystal data, experimental (calculated): 3.4 (3.6); 6.9 (7.2); 10.4 (10.8); 17.3 (17.5); 19.1 (19.7).

Example 5—Multi-Component Crystal of Flurbiprofen: Flurbiprofen/4,4'-bipyridine (2:1 stoichiometry)

[0080] 50 mg (0.2046 mmol) flurbiprofen and 15 mg (0.0960 mmol) 4,4'-bipyridine were dissolved in 3 mL acetone. Slow evaporation of the solvent yielded colorless needles of a 2:1 flurbiprofen/4,4'-bipyridine co-crystal, as shown in Figure 8D.

[0081] Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{40}H_{34}F_2N_2O_4$, M = 644.69, monoclinic $P2_1/n$; a = 5.860(4), b = 47.49(3), c = 5.928(4) Å, β = 107.382 (8)°, U = 1574.3(19) Å^3, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.096 mm^{-1}, D_c = 1.360 Mg/m^3, λ = 0.71073 Å^3, F(000) = 676, $2\theta_{max}$ = 21.69°; 4246 reflections measured, 1634 unique (R_{int} = 0.0677). Final residuals for 226 parameters were R_1 = 0.0908, wR_2 = 0.2065 for I>2σ(I), and R_1 = 0.1084, wR_2 = 0.2209 for all 1634 data.

[0082] Crystal packing: The co-crystal contains flurbiprofen/bipyridine heterodimers, sustained by two hydrogen bonded carboxylic acidpyridine supramolecular synthon, arranged in a herringbone motif that packs in the space group $P2_1/n$. The heterodimer is an extended version of the homodimer and packs to form a two-dimensional network sustained by π-π stacking and hydrophobic interactions of the bipyridine and phenyl groups of the flurbiprofen.

[0083] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), aromatic C-H stretching at 3057 cm^{-1} and 2981 cm^{-1}; N--H bending and scissoring at 1886 cm^{-1}; C=O stretching at 1690 cm^{-1}; C=C and C=N ring stretching at 1418 cm^{-1}.

[0084] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 162.47° C (endotherm); m.p. = 155-160° C (MEL-TEMP); (flurbiprofen m.p. = 110-111° C, 4,4'-bipyridine m.p. = 111-114° C).

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[0085] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 30.93% weight loss starting at 31.13° C and a 46.26% weight loss starting at 168.74° C followed by complete decomposition.

[0086] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα ($\lambda = 1.540562$), 30kV, 15mA), the powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. XRPD derived from the single crystal data: experimental (calculated): 16.8 (16.8); 17.1 (17.5); 18.1 (18.4); 19.0 (19.0); 20.0 (20.4); 21.3 (21.7); 22.7 (23.0); 25.0 (25.6); 26.0 (26.1); 26.0 (26.6); 26.1 (27.5); 28.2 (28.7); 29.1 (29.7).

Example 6—Multi-Component Crystal of Flurbiprofen: Flurbiprofen/trans-1,2-bis (4-pyridyl) ethylene (2:1 stoichiometry)

[0087] 25 mg (0.1023 mmol) flurbiprofen and 10 mg (0.0548 mmol) trans-1, 2-bis (4-pyridyl) ethylene were dissolved in 3 mL acetone. Slow evaporation of the solvent yielded colorless needles of a 2:1 flurbiprofen/1,2-bis (4-pyridyl) ethylene co-crystal, as shown in Figure 9B.

[0088] Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{42}H_{36}F_2N_2O_4$, $M = 670.73$, monoclinic $P2_1/n$; $a = 5.8697(9)$, $b = 47.357(7)$, $c = 6.3587(10)$ Å, $\beta = 109.492(3)°$, $U = 1666.2(4)$ Å^3, $T = 200(2)$ K, $Z = 2$, μ(Mo-Kα) = 0.093 mm^{-1}, $D_c = 1.337$ Mg/m^3, $\lambda = 0.71073$ Å^3, $F(000) = 704$, $2\theta_{max} = 21.69°$, 6977 reflections measured, 2383 unique ($R_{int} = 0.0383$). Final residuals for 238 parameters were $R_1 = 0.0686$, $wR_2 = 0.1395$ for $I>2\sigma(I)$, and $R_1 = 0.1403$, $wR_2 = 0.1709$ for all 2383 data.

[0089] Crystal packing: The co-crystal contains flurbiprofen/1,2-bis (4-pyridyl) ethylene heterodimers, sustained by two hydrogen bonded carboxylic acid-pyridine supramolecular synthons, arranged in a herringbone motif that packs in the space group $P2_1/n$. The heterodimer from 1,2-bis (4-pyridyl) ethylene further extends the homodimer relative to example 5 and packs to form a two-dimensional network sustained by π-π stacking and hydrophobic interactions of the bipyridine and phenyl groups of the flurbiprofen.

[0090] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), aromatic C-H stretching at 2927 cm^{-1} and 2850 cm^{-1}; N--H bending and scissoring at 1875 cm^{-1}; C=O stretching at 1707 cm^{-1}; C=C and C=N ring stretching at 1483 cm^{-1}.

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[0091] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 100.01° C, 125.59° C and 163.54°C (endotherms); m.p. = 153-158° C (MEL-TEMP); (flurbiprofen m.p. = 110-111° C, trans-1, 2-bis (4-pyridyl) ethylene m.p. = 150-153° C).

[0092] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 91.79% weight loss starting at 133.18° C followed by complete decomposition.

[0093] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA), the powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. XRPD derived from the single crystal data, experimental (calculated): 3.6 (3.7); 17.3 (17.7); 18.1 (18.6); 18.4 (18.6); 19.1 (19.3); 22.3 (22.5); 23.8 (23.9); 25.9 (26.4); 28.1 (28.5).

Example 7—Multi-Component Crystal of Carbamazepine: Carbamazepine/*p*-Phthalaldehyde (1:1 stoichiometry)

[0094] 25 mg (0.1058 mmol) carbamazepine and 7 mg (0.0521 mmol) *p*-phthalaldehyde were dissolved in approximately 3 mL methanol. Slow evaporation of the solvent yielded colorless needles of a 1:1 carbamazepine/*p*-phthalaldehyde co-crystal, as shown in Figure 10B.

[0095] Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{38}H_{30}N_4O_4$, M = 606.66, monoclinic *C2/c*; a = 29.191(16), b = 4.962(3), c = 20.316(11) Å, β = 92.105(8)°, *U* = 2941(3) Å^3, T= 200(2) K, Z = 4, μ(Mo-Kα) = 0.090 mm^{-1}, D_c = 1.370 Mg/m^3, λ = 0.71073 Å^3, F(000) = 1272, $2\theta_{max}$ = 43.66°, 3831 reflections measured, 1559 unique (R_{int} = 0.0510). Final residuals for 268 parameters were R_1 = 0.0332, wR_2 = 0.0801 for I>2σ(I), and R_1 = 0.0403, wR_2 = 0.0831 for all 1559 data.

[0096] Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers that crystallize in the space group *C2/c*. The 1° amines of the homodimer are bifurcated to the carbonyl of the *p*-phthalaldehyde forming a chain with an adjacent homodimer. The chains pack in a crinkled tape motif sustained by π-π interactions between phenyl rings of the CBZ.

[0097] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). The 1° amine unsymmetrical and symmetrical stretching was shifted down to 3418 cm^{-1}; aliphatic aldehyde and 1° amide C=O stretching was shifted up to 1690 cm^{-1}; N-H in-plane bending at 1669 cm^{-1}; C-H aldehyde stretching at 2861 cm^{-1} and H-C=O bending at 1391 cm^{-1}.

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[0098] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 128.46° C (endotherm), m.p. = 121-124° C (MEL-TEMP), (carbamazepine m.p. = 190.2° C, *p*-phthalaldehyde m.p. = 116° C).

[0099] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 17.66% weight loss starting at 30.33° C then a 17.57% weight loss starting at 100.14° C followed by complete decomposition.

[00100] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. XRPD derived from the single crystal data, experimental (calculated): 8.5 (8.7); 10.6 (10.8); 11.9 (12.1); 14.4 (14.7) 15.1 (15.2); 18.0 (18.1); 18.5 (18.2); 19.8 (18.7); 23.7 (24.0); 24.2 (24.2); 26.4 (26.7); 27.6 (27.9); 27.8 (28.2); 28.7 (29.1); 29.3 (29.6); 29.4 (29.8).

Example 8—Multi-Component Crystal of Carbamazepine: Carbamazepine/nicotinamide (GRAs) (1:1 stoichiometry)

[00101] 25 mg (0.1058 mmol) carbamazepine and 12 mg (0.0982 mmol) nicotinamide were dissolved in 4 mL of DMSO, methanol or ethanol. Slow evaporation of the solvent yielded colorless needles of a 1:1 carbamazepine/nicotinamide co-crystal, as shown in Figure 11.

[00102] Using a separate method, 25 mg (0.1058 mmol) carbamazepine and 12 mg (0.0982mmol) nicotinamide were ground together with mortar and pestle. The solid was determined to be 1:1 carbamazepine/nicotinamide microcrystals (XPD).

[00103] Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{21}H_{18}N_4O_2$, M = 358.39, monoclinic $P2_1/n$; a = 5.0961(8), b = 17.595(3), c = 19.647(3) Å, β = 90.917(3)°, U = 1761.5(5) Å^3, T = 200(2) K, Z = 4, μ(Mo-Kα) = 0.090 mm^{-1}, D_c = 1.351 Mg/m^3, λ = 0.71073 Å^3, F(000) = 752, $2\theta_{max}$ = 56.60°, 10919 reflections measured, 4041 unique (R_{int} = 0.0514). Final residuals for 248 parameters were R_1 = 0.0732, wR_2 = 0.1268 for I>2σ(I), and R_1 = 0.1161, wR_2 = 0.1430 for all 4041 data.

[00104] Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers. The 1° amines are bifurcated to the carbonyl of the nicotinamide on each side of the dimer. The 1° amines of each nicotinamide are hydrogen bonded to the carbonyl of the

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adjoining dimer. The dimers form chains with π-π interactions from the phenyl groups of the CBZ.

[00105] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), unsymmetrical and symmetrical stretching shifts down to 3443 cm^{-1} and 3388 cm^{-1} accounting for 1° amines; 1° amide C=O stretching at 1690 cm^{-1}; N-H in-plane bending at 1614 cm^{-1}; C=C stretching shifted down to 1579 cm^{-1}; aromatic H's from 800 cm^{-1} to 500 cm^{-1} are present.

[00106] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 74.49° C (endotherm) and 59.05° C (endotherm), m.p. = 153-158° C (MEL-TEMP), (carbamazepine m.p. = 190.2° C, nicotinamide m.p. = 150-160° C).

[00107] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 57.94% weight loss starting at 205.43° C followed by complete decomposition.

[00108] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. XRPD: Showed analogous peaks to the simulated XRPD derived from the single crystal data. XRPD analysis experimental (calculated): 6.5 (6.7); 8.8 (9.0); 10.1 (10.3); 13.2 (13.5); 15.6 (15.8); 17.7 (17.9); 17.8 (18.1); 18.3 (18.6); 19.8 (20.1); 20.4 (20.7); 21.6 (22.); 22.6 (22.8); 22.9 (23.2); 26.4 (26.7); 26.7 (27.0); 28.0 (28.4).

Example 9—Multi-Component Crystal of Carbamazepine: Carbamazepine/saccharin (GRAs) (1:1 stoichiometry)

[00109] 25 mg (0.1058mmol) carbamazepine and 19 mg (0.1037 mmol) saccharin were dissolved in approximately 4 mL ethanol. Slow evaporation of the solvent yielded colorless needles of a 1:1 carbamazepine/saccharin cocrystal, as shown in Figure 12. Solubility measurements indicate that this multiple-component crystal of carbamazepine has improved solubility over previously known forms of carbamazepine (*e.g.*, increased molar solubility and longer solubility in aqueous solutions).

[00110] Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{22}H_{17}N_3O_4S_1$, M = 419.45, triclinic *P-1*; a = 7.5140(11), b = 10.4538(15), c = 12.6826(18) Å, α = 83.642(2)°, β = 85.697(2) °, γ = 75.411(2) °, *U* = 957.0(2) $Å^3$, T = 200(2) K, *Z* = 2, μ(Mo-Kα) = 0.206 mm^{-1}, D_c = 1.456 Mg/m^3, λ = 0.71073 $Å^3$, F(000) = 436, $2\theta_{max}$ = 56.20°; 8426 reflections measured,

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4372 unique (R_{int} = 0.0305). Final residuals for 283 parameters were R_1 = 0.0458, wR_2 = 0.1142 for I>2σ(I), and R_1 = 0.0562, wR_2 = 0.1204 for all 4372 data.

[00111] Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers. The 2° amines of the saccharin are hydrogen bonded to the carbonyl of the CBZ on each side forming a tetramer. The crystal has a space group of *P-1* with π-π interactions between the phenyl groups of the CBZ and the saccharin phenyl groups.

[00112] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), unsymmetrical and symmetrical stretching shifts up to 3495 cm^{-1} accounting for 1° amines; C=O aliphatic stretching was shifted up to 1726 cm^{-1}; N-H in-plane bending at 1649 cm^{-1}; C=C stretching shifted down to 1561 cm^{-1}; (O=S=O) sulfonyl peak at 1330 cm^{-1} C-N aliphatic stretching 1175 cm^{-1}.

[00113] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 75.31° C (endotherm) and 177.32° C (endotherm), m.p. = 148-155°C (MEL-TEMP); (carbamazepine m.p. = 190.2° C, saccharin m.p. = 228.8° C).

[00114] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 3.342% weight loss starting at 67.03° C and a 55.09% weight loss starting at 118.71° C followed by complete decomposition.

[00115] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. XRPD derived from the single crystal data, experimental (calculated): 6.9 (7.0); 12.2 (12.2); 13.6 (13.8); 14.0 (14.1); 14.1 (14.4); 15.3 (15.6); 15.9 (15.9); 18.1 (18.2); 18.7 (18.8); 20.2 (20.3); 21.3 (21.5); 23.7 (23.9); 26.3 (26.4); 28.3 (28.3).

Example 10—Multi-Component Crystal of Carbamazepine: Carbamazepine/2,6-pyridinedicarboxylic acid (2:3 stoichiometry)

[00116] 36 mg (0.1524 mmol) carbamazepine and 26 mg (0.1556 mmol) 2,6-pyridinedicarboxylic acid were dissolved in approximately 2 mL ethanol. Slow evaporation of the solvent yielded clear needles of a 1:1 carbamazepine/2,6-pyridinedicarboxylic acid co-crystal, as shown in Figure 14B.

[00117] Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{22}H_{17}N_3O_5$, M=403.39, orthorhombic P2(1)2(1)2(1); a=7.2122, b=14.6491, c=17.5864 Å,α=90°, β=90°,

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γ=90°, V=1858.0(2) Å^3, T=100 K, Z=4, μ(MO-Kα)=0.104 mm^{-1}, D_c=1.442 Mg/m^3, λ=0.71073Å^3 , F(000)840, $2\theta_{max}$=28.3. 16641 reflections measured, 4466 unique (R_{int}=0.093). Final residuals for 271 parameters were R_1=0.0425 and wR_2=0.0944 for I>2σ(I).

[00118] Crystal packing: Each hydrogen on the CBZ 1° amine is hydrogen bonded to a carbonyl group of a different 2,6-pyridinedicarboxylic acid moiety. The carbonyl of the CBZ carboxamide is hydrogen bonded to two hydroxide groups of one 2,6-pyridinedicarboxylic acid moitey.

[00119] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3439 cm^{-1}, (N-H stretch, 1° amine, CBZ); 1734 cm^{-1}, (C=O); 1649 cm^{-1}, (C=C).

[00120] Melting Point: 214-216°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, 2,6-pyridinedicarboxylic acid m.p. = 248-250°C).

[00121] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 69% weight loss starting at 215° C and a 17% weight loss starting at 392° followed by complete decomposition.

Example 11—Multi-Component Crystal of Carbamazepine: Carbamazepine/5-nitroisophthalic acid (1:1 stoichiometry)

[00122] 40 mg (0.1693 mmol) carbamazepine and 30 mg (0.1421 mmol) 5-nitroisophthalic acid were dissolved in approximately 3 mL methanol or ethanol. Slow evaporation of the solvent yielded yellow needles of a 1:1 carbamazepine/5-nitroisophthalic acid co-crystal, as shown in Figure 15B.

[00123] Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{47}H_{40}N_6O_{16}$, M=944.85, monoclinic C2/c; a=34.355(8), b=5.3795(13), c=23.654(6) Å,α=90°, β=93.952(6)°, γ=90°, V=4361.2(18)Å^3, T=200(2) K, Z=4, μ(MO-Kα)=0.110 mm^{-1}, D_c=1.439 Mg/m^3, λ=0.71073Å^3 , F(000)1968, $2\theta_{max}$=26.43°. 11581 reflections measured, 4459 unique (R_{int}=0.0611). Final residuals for 311 parameters were R_1=0.0725, wR_2=0.1801 for I>2σ(I), and R_1=0.1441, wR_2=0.1204 for all 4459 data.

[00124] Crystal packing: The co-crystals are sustained by hydrogen bonded carboxylic acid homodimers between the two 5-nitroisophthalic acid moieties and hydrogen bonded

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carboxy-amide heterodimers between the carbamazepine and 5-nitroisophthalic acid moiety. There is solvent hydrogen bonded to an additional N-H donor from the carbamazepine moiety.

[00125] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3470 cm^{-1}, (N-H stretch, 1° amine, CBZ); 3178 cm^{-1}, (C-H stretch, alkene); 1688 cm^{-1}, (C=O); 1602 cm^{-1}, (C=C).

[00126] Differential Scanning Calorimetry: (TA Instruments 2920 DSC). 190.51°C (endotherm). m.p. = NA (decomposes at 197-200°C) (MEL-TEMP). (carbamazepine m.p. = 191-192°C, 5-nitroisophthalic acid m.p. = 260-261°C).

[00127] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 32.02% weight loss starting at 202°, a 12.12% weight loss starting at 224° and a 17.94% weight loss starting at 285° followed by complete decomposition.

[00128] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using CuKα (λ=1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3 to 40 2 in continuous scan mode using a step size of 0.02 2 and a scan speed of 2.0 /min. XRPD: Showed analogous peaks to the simulated XRPD derived from the single crystal data. XRPD analysis experimental (calculated): 10.138 (10.283), 15.291 (15.607), 17.438 (17.791), 21.166 (21.685), 31.407 (31.738), 32.650 (32.729).

Example 12—Multi-Component Crystal of Carbamazepine: Carbamazepine/acetic acid (1:1 stoichiometry)

[00129] 25 mg (0.1058 mmol) carbamazepine was dissolved in approximately 2 mL acetic acid. Slow evaporation of the solvent yielded yellow needles of a 1:1 carbamazepine/acetic acid co-crystal, as shown in Figure 16B.

[00130] Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{17}H_{16}N_2O_3$, M=296.32, monoclinic P2(1)/c; a=5.1206(4), b=15.7136(13), c=18.4986(15) Å,α=90°, β=96.5460(10)°, γ=90°, V=1478.8(2)$Å^3$, T=100(2) K, Z=4, μ(MO-Kα)=0.093 mm^{-1}, D_c=1.331 Mg/m^3, λ=0.71073$Å^3$, F(000)624, $2\theta_{max}$=28.4°. 12951 reflections measured, 3529 unique (R_{int}=0.076). Final residuals for 203 parameters were R_1=0.0492, wR_2=0.1335 for I>2σ(I).

[00131] Crystal packing: The co-crystal is sustained by hydrogen bonded carboxamide-carboxylic heterodimers. The second 1° amine hydrogen from each CBZ joins 2 heterodimers side by side forming a tetramer.

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[00132] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3462 cm^{-1}, (N-H stretch, 1° amine, CBZ); 1699 cm^{-1}, (C=O); 1629 cm^{-1}, (C=C, CBZ); 1419 cm^{-1}, (COOH, acetic acid).

[00133] Melting Point: 187°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, acetic acid m.p. = 16.6°C).

[00134] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 20.62% weight loss starting at 104° and a 77.05% weight loss starting at 200° followed by complete decomposition.

Example 13—Multi-Component Crystal of Carbamazepine: Carbamazepine/1,3,5,7-adamantanetetracarboxylic acid (1:1 stoichiometry)

[00135] 15 mg (0.1524 mmol) carbamazepine and 20 mg (0.1556 mmol) 1,3,5,7-adamantanetetracarboxylic acid were dissolved in approximately 1 mL methanol or 1 mL ethanol. Slow evaporation of the solvent yields clear plates of a 2:1 carbamazepine/1,3,5,7-adamantanetetracarboxylic acid co-crystal, as shown in Figure 17B.

[00136] Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{44}H_{40}N_2O_{10}$, M=784.80, monoclinicC2/c; a=18.388(4), b=12.682(3), c=16.429(3) Å, β=100.491(6)°, V=3767.1(14) $Å^3$, T=100(2) K, Z=4, μ(MO-Kα)=0.099 mm^{-1}, D_c=1.384 Mg/m^3, λ=0.71073$Å^3$, F(000)1648, $2\theta_{max}$=28.20°. 16499 reflections measured, 4481 unique (R_{int}=0.052). Final residuals for 263 parameters were R_1=0.0433 and wR_2=0.0913 for I>2σ(I).

[00137] Crystal packing: The co-crystals form a single 3D network of four tetrahedron, linked by square planes similar to the *PtS* topology. The crystals are sustained by hydrogen bonding.

[00138] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3431 cm^{-1}, (N-H stretch, 1° amine, CBZ); 3123 cm^{-1}, (C-H stretch, alkene); 1723 cm^{-1}, (C=O); 1649 cm^{-1}, (C=C).

[00139] Melting Point: (MEL-TEMP). 258-260°C (carbamazepine m.p. = 191-192°C, adamantanetetracarboxylic acid m.p. = >390°C).

[00140] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 9% weight loss starting at 189°C, a 52% weight loss starting at 251°C and a 31% weight loss starting at 374°C followed by complete decomposition.

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Example 14—Multi-Component Crystal of Carbamazepine: Carbamazepine/benzoquinone (1:1 stoichiometry)

[00141] 25 mg (0.1058 mmol) carbamazepine and 11 mg (0.1018 mmol) benzoquinone was dissolved in 2 mL methanol or THF. Slow evaporation of the solvent produced an average yield of yellow crystals of a 1:1 carbamazepine/benzoquinone co-crystal, as shown in Figure 18B.

[00142] Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{21}H_{16}N_2O_3$, M=344.36, monoclinic P2(1)/c; a=10.3335(18), b=27.611(5), c=4.9960(9) Å, β=102.275(3)°, V=1392.9(4) $Å^3$, T=100(2) K, Z=3, D_c=1.232 Mg/m^3, μ(MO-Kα)=0.084 mm^{-1}, λ=0.71073$Å^3$, F(000)540, $2\theta_{max}$=28.24°. 8392 reflections measured, 3223 unique (R_{int}=0.1136). Final residuals for 199 parameters were R_1=0.0545 and wR_2=0.1358 for I>2σ(I), and R_1=0.0659 and wR_2=0.1427 for all 3223 data.

[00143] Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers. Each 1° amine on the CBZ is bifurcated to a carbonyl group of a benzoquinone moiety. The dimers form infinite chains.

[00144] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3420 cm^{-1}, (N-H stretch, 1° amine, CBZ); 2750 cm^{-1}, (aldehyde stretch); 1672 cm^{-1}, (C=O); 1637 cm^{-1}, (C=C, CBZ).

[00145] Melting Point: 170°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, benzoquinone m.p. = 115.7°C).

[00146] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 20.62% weight loss starting at 168° and a 78% weight loss starting at 223° followed by complete decomposition.

Example 15—Multi-Component Crystal of Carbamazepine: Carbamazepine/butyric acid (1:1 stoichiometry)

[00147] 10 mg (0.0423 mmol) carbamazepine was dissolved in approximately 1 mL butyric acid. Slow evaporation of the solvent mixture produced an average yield of yellow/brown crystals of a 1:1 carbamazepine/butyric acid co-crystal, as shown in Figure 19B.

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[00148] Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{19}H_{20}N_2O_3$, M=324.37, triclinic P-1; a=9.1567, b=10.1745, c=10.5116 Å,α=72.850°, β=70.288°, γ=67.269°, V=832.17 $Å^3$, T=100° K, Z=2, μ(MO-Kα)=0.088 mm^{-1}, D_c=1.290 Mg/m^3, λ=0.71073$Å^3$, F(000)344, $2\theta_{max}$=28.28°. 5315 reflections measured, 3686 unique (R_{int}=0.0552). Final residuals for 217 parameters were R_1=0.0499, wR_2=0.1137 for I>2σ(I), and R_1=0.0678, wR_2=0.1213 for all 3686 data.

[00149] Crystal packing: The co-crystals are sustained by hydrogen bonded carboxamide-carboxylic heterodimers between the carbamazepine moieties and the butyric acid moieties. The second 1° amine hydrogen from each CBZ joins 2 heterodimers side by side forming a tetramer.

[00150] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3486 cm^{-1}, (N-H stretch, 1° amine, CBZ); 3307 cm^{-1}, (C-H stretch, alkene); 1684 cm^{-1}, (C=O); 1540 cm^{-1}, (C=C).

[00151] Melting Point: 63-64°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, butyric acid m.p. = -94°C).

[00152] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA).16 % weight loss starting at 54°, a 16% weight loss starting at 134° and a 49% weight loss starting at 174° followed by complete decomposition.

Example 16—Multi-Component Crystal of Carbamazepine: Carbamazepine/DMSO (1:1 stoichiometry)

[00153] 25 mg (0.1058 mmol) carbamazepine was dissolved in approximately 1.5 mL DMSO. Slow evaporation of the solvent yielded colorless plates of a 1:1 carbamazepine/ DMSO co-crystal, as shown in Figure 20B.

[00154] Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{34}H_{36}N_4O_4S_2$, M=628.79, triclinic P-1; a=7.3254(19), b=8.889(2), c=12.208(3) Å,α=94.840(5)°, β=94.926(5)°, γ=100.048(5)°, V=775.8(3)$Å^3$, T=200(2) K, Z=2, μ(MO-Kα)=0.216 mm^{-1}, D_c=1.320 Mg/m^3, λ=0.71073$Å^3$, F(000)320, $2\theta_{max}$=28.3°. 4648 reflections measured, 3390 unique (R_{int}=0.0459). Final residuals for 209 parameters were R_1=0.0929, wR_2=0.3043 for I>2σ(I).

[00155] Crystal packing: The co-crystals are sustained by the hydrogen bonded carboxamide homosynthon. The 1° amines are hydrogen bonded to the sulfoxide of the DMSO

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on each side of the homosynthon. The crystal is stabilized by π-π interactions from the tricyclic azepine ring system groups of the CBZ.

[00156] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3369 cm^{-1} (N-H stretch, 1° amine, CBZ); 1665 cm^{-1} (C=O stretching); 1481cm^{-1} (C=C).

[00157] Differential Scanning Calorimetry: (TA Instruments 2920 DSC). 100°C, 193°C (endotherms). m.p. = 189°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, DMSO m.p. = 18.45°C)

[00158] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 26% weight loss starting at 102°, a 64% weight loss starting at 212° followed by complete decomposition.

Example 17—Multi-Component Crystal of Carbamazepine: Carbamazepine/formamide (1:1 stoichiometry)

[00159] 10 mg (0.0423 mmol) carbamazepine was dissolved in a mixture of approximately 1 mL formamide/1 mL THF or 1 mL formamide/1 mL methanol. Slow evaporation of the solvent mixture produced an average yield of clear needles of a 1:1 carbamazepine/formamide co-crystal, as shown in Figure 21B.

[00160] Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{16}H_{15}N_3O_2$, M=281.31, triclinic P-1; a=5.1077(11), b=16.057(3), c=17.752(4) Å,α=73.711(3)°, β=89.350(3)°, γ=88.636(3)°, V=1397.1(5) $Å^3$, T=100° K, Z=4, μ(MO-Kα)=0.091 mm^{-1}, D_c=1.337 Mg/m^3, λ=0.71073$Å^3$, F(000)592, $2\theta_{max}$=28.33°. 11132 reflections measured, 6272 unique (R_{int}=0.1916). Final residuals for 379 parameters were R_1=0.0766 and wR_2=0.1633 for I>2σ(I).

[00161] Crystal packing: The co-crystals are sustained by hydrogen bonded carboxamide homodimers between two carbamazepine moieties and carboxylic acid homodimers between two formamide moieties. Infinite chains are formed by the homodimers linked side by side, with every other set of CBZ molecules attached on the sides of the chain but not bonded to form a dimer.

[00162] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3392 cm^{-1}, (N-H stretch, 1° amine, CBZ); 2875 cm^{-1}, (C-H stretch, alkene); 1653 cm^{-1}, (C=O); 1590 cm^{-1} , (C=C).

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[00163] Melting Point: 142-144°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, formamide m.p. = -94°C).

[00164] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 27% weight loss starting at 138°, a 67% weight loss starting at 195° followed by complete decomposition.

Example 18—Multi-Component Crystal of Carbamazepine: Carbamazepine/formic acid (1:1 stoichiometry)

[00165] 40 mg (0.1693 mmol) carbamazepine was dissolved in approximately 2 mL formic acid. Slow evaporation of the solvent yielded off-white starbursts of a 1:1 carbamazepine/formic acid co-crystal, as shown in Figure 22B.

[00166] Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{16}H_{14}N_2O_3$, M=282.29, monoclinic P21/c; a=5.2031(9), b=14.741(2), c=17.882(3) Å,α=90°, β=98.132(3)°, γ=90°, V=1357.7(4)Å^3, T= 100 K, Z=4, μ(MO-Kα)=0.097 mm^{-1}, D_c=1.381 Mg/m^3, λ=0.71073Å^3 , F(000)592, $2\theta_{max}$=28.3. 9402 reflections measured, 3191 unique (R_{int}=0.111). Final residuals for 190 parameters were R_1=0.0533 and wR_2=0.1268 for I>2σ(I).

[00167] Crystal packing: The co-crystals are sustained by hydrogen bonded carboxylic acid-amine heterodimers arranged in centrosymmetric tetramers.

[00168] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3439 cm^{-1}, (1° amine stretch,CBZ); 3026 cm^{-1} (C-H stretch, CBZ); 1692 cm^{-1}, (1° amide, C=O stretch).

[00169] Melting Point: 187°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, formic acid m.p. = 8.4°C).

[00170] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 14.60% weight loss starting at 123° and a 68.91% weight loss starting at 196° followed by complete decomposition.

Example 19—Multi-Component Crystal of Carbamazepine: Carbamazepine/trimesic acid (1:1 stoichiometry)

[00171] 36 mg (0.1524 mmol) carbamazepine and 31 mg (0.1475 mmol) trimesic acid were dissolved in a solvent mixture of approximately 2 mL methanol and 2mL dichloromethane.

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Slow evaporation of the solvent mixture yielded white starbursts of a 1:1 carbamazepine/trimesic acid co-crystal, as shown in Figure 23B.

[00172] Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{24}H_{18}N_2O_7$, M=446.26, monoclinic C2/c; a=32.5312(50), b=5.2697(8), c=24.1594(37) Å,α=90°, β=98.191(3)°, γ=90°, V=4099.39(37) Å^3, T=-173 K, Z=8, μ(MO-Kα)=0.110 mm^{-1}, D_c=1.439 Mg/m^3, λ=0.71073Å^3, F(000)1968, $2\theta_{max}$=26.43°. 11581 reflections measured, 4459 unique (R_{int}=0.0611). Final residuals for 2777 parameters were R_1=0.1563, wR_2=0.1887 for I>2σ(I), and R_1=0.1441, wR_2=0.1204 for all 3601 data.

[00173] Crystal packing: The co-crystals are sustained by hydrogen bonded carboxylic acid homodimers between carbamazepine and trimesic acid moieties and hydrogen bonded carboxylic acid-amine heterodimers between two trimesic acid moieties arranged in a stacked ladder formation.

[00174] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3486 cm^{-1}(N-H stretch, 1° amine, CBZ); 1688 cm^{-1} (C=O, 1° amide stretch, CBZ); 1602 cm^{-1} (C=C, CBZ).

[00175] Differential Scanning Calorimetry: (TA Instruments 2920 DSC). 273°C (endotherm). m.p. = NA, decomposes at 278°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, trimesic acid m.p. = 380°C)

[00176] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 62.83% weight loss starting at 253° and a 30.20% weight loss starting at 278° followed by complete decomposition.

[00177] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using CuKα (λ=1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3 to 40 2 in continuous scan mode using a step size of 0.02 2 and a scan speed of 2.0 /min. XRPD analysis experimental: 10.736, 12.087, 16.857, 24.857, 27.857.

[00178] All patents, patent applications, provisional applications, and publications referred to or cited herein are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

[00179] It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will

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be suggested to persons skilled in the art and are to be included within the spirit and purview of this application.

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Claims

1. 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.

2. The multiple-component phase composition of claim 1, wherein said multiple-component phase composition is a discrete supramolecular entity.

3. The multiple-component phase composition of claim 1, wherein said multiple-component phase composition is a polymeric structure.

4. The multiple-component phase composition of claim 1, wherein said pharmaceutical molecule is sustained by a supramolecular homosynthon when said pharmaceutical molecule is in its pure phase.

5. The multiple-component phase composition of claim 1, wherein said multiple-component phase composition has at least one physical property or chemical property that is different from that of said pharmaceutical when said pharmaceutical molecule is in its pure phase.

6. The multiple-component phase composition of claim 1, wherein said multiple-component phase composition has at least one physical or chemical property that is the same as that of said pharmaceutical molecule when said pharmaceutical molecule is in its pure phase.

7. The multiple-component phase composition of claim 5, wherein said at least one physical or chemical property is selected from the group consisting of chemical stability, thermodynamic stability, solubility, dissolution, bioavailability, crystal morphology, and hygroscopicity.

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8. The multiple-component phase composition of claim 6, wherein said at least one physical or chemical property is selected from the group consisting of chemical stability, thermodynamic stability, solubility, dissolution, bioavailability, crystal morphology, and hygroscopicity.

9. The multiple-component phase composition of claim 1, wherein said pharmaceutical molecule is selected from the group consisting of aspirin, acetaminophen, profen, phenytoin, and carbamazepine.

10. The multiple-component phase composition of claim 1, wherein said two or more independent molecular entities are selected from the group consisting of: acetaminophen, 4,4'-bipyridine, and water; phenytoin and pyridine; aspirin and 4,4'-bipyridine; ibuprofen and 4,4'-bipyridine; flurbiprofen and 4,4'-bipyridine; flurbiprofen, trans-1,2-bis (4-pyridyl) ethylene; carbamazepine, *p*-phthalaldehyde; carbamazepine and nicotinamide; carbamazepine and saccharin; carbamazepine and 2,6-pyridinedicarboxylic acid; carbamazepine and 5-nitroisophthalic acid; carbamazepine and acetic acid; carbamazepine and 1,3,5,7,-adamantanetetracarboxylic acid; carbamazepine and benzoquinone; carbamazepine and butyric acid; carbamazepine and dimethyl sulfoxide; carbamazepine and formamide; carbamazepine and formic acid; and carbamazepine and trimesic acid.

11. The multiple-component phase composition of claim 1, wherein said intermolecular interactions are selected from the group consisting of hydrogen bonding (weak and/or strong), dipole interactions (induced and/or non-induced), stacking interactions, hydrophobic interactions, and other inter-static interactions.

12. The multiple-component phase composition of claim 1, wherein said intermolecular interactions are between complementary chemical functionalities on said two or more independent molecular entities.

13. The multiple-component phase composition of claim 15, wherein said complementary chemical functionalities include at least one chemical functionality selected from

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the group consisting of acids, amides, aliphatic nitrogen bases, unsaturated aromatic nitrogen bases, amines, alcohols, halogens, sulfones, nitro groups, S-heterocycles, N-heterocycles, O-heterocycles, ethers thioethers, thiols, esters, thioesters, thioketones, epoxides, acetonates, nitrils, oximes, and organohalides.

14. The multiple-component phase composition of claim 12, wherein said complementary chemical functionalities on said two or more independent molecular entities are the same.

15. The multiple-component phase composition of claim 14, wherein said complementary chemical functionalities are acids.

16. The multiple-component phase composition of claim 14, wherein said complementary chemical functionalities are amides.

17. The multiple-component phase composition of claim 12, wherein said complementary chemical functionalities on said two or more independent molecular entities are not the same.

18. The multiple-component phase composition of claim 17, wherein said complementary chemical functionalities on said two or more independent molecular entities are selected from the group consisting of acids and amides; pyridines and amides; and alcohols and amines.

19. The multiple-component phase composition of claim 1, wherein two or more of said independent molecular entities is a pharmaceutical molecule.

20. A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between aspirin and at least one independent molecular entity.

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21. A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between acetaminophen and at least one independent molecular entity.

22. A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between a profen and at least one independent molecular entity.

23. A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between phenytoin and at least one independent molecular entity.

24. A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between carbamazepine and at least one independent molecular entity.

25. 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;

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

(d) identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient.

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26. The method of claim 25, wherein said method further comprises preparing a multiple-component solid phase composition, wherein the multiple-component solid phase composition comprises the active pharmaceutical ingredient and at least one of the identified co-crystal formers.

27. The method of claim 26, 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. The method of claim 26, 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. 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;

(c) identifying from a plurality of chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular synthon with the active pharmaceutical ingredient, wherein the identified chemical functionality is 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 a complementary chemical functionality on the active pharmaceutical ingredient; and

(d) identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient.

30. The method of claim 29, wherein said method further comprises preparing a multiple-component solid phase composition, wherein the multiple-component solid phase

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composition comprises the active pharmaceutical ingredient and at least one of the identified co-crystal formers.

31. The method of claim 30, 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.

32. The method of claim 30, 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.

33. 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 different molecules;

(c) identifying from a plurality of chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular synthon with the active pharmaceutical ingredient, and wherein the selected chemical functionality is capable of forming a noncovalent bond to a complementary chemical functionality on the active pharmaceutical ingredient; and

(d) identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient.

34. The method of claim 33, wherein said method further comprises preparing a multiple-component solid phase composition, wherein the multiple-component solid phase composition comprises the active pharmaceutical ingredient and at least one of the identified co-crystal formers.

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35. The method of claim 34, 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.

36. The method of claim 34, 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.

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Abstract

The subject invention concerns a method for identifying complementary chemical functionalities to form a desired supramolecular synthon. The subject invention also pertains to multiple-component phase compositions comprising one or more pharmaceutical entities and methods for producing such compositions.

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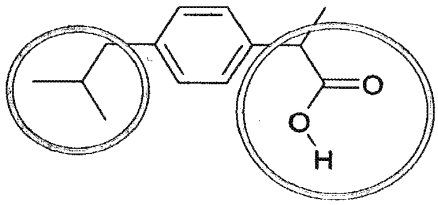


FIG. 1



FIG. 2

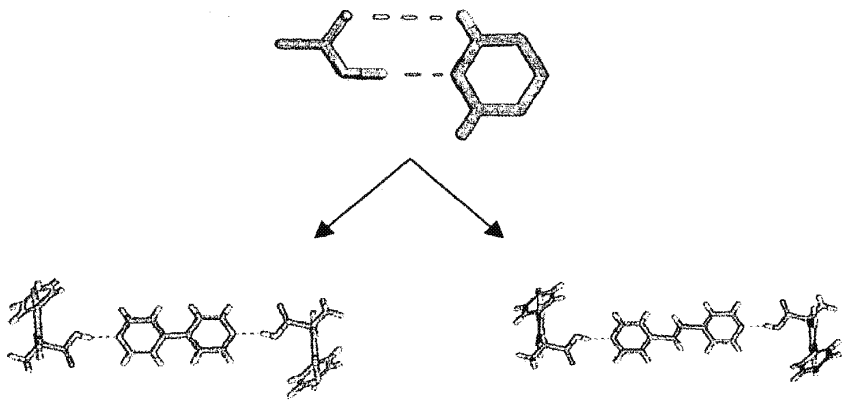


FIG. 3

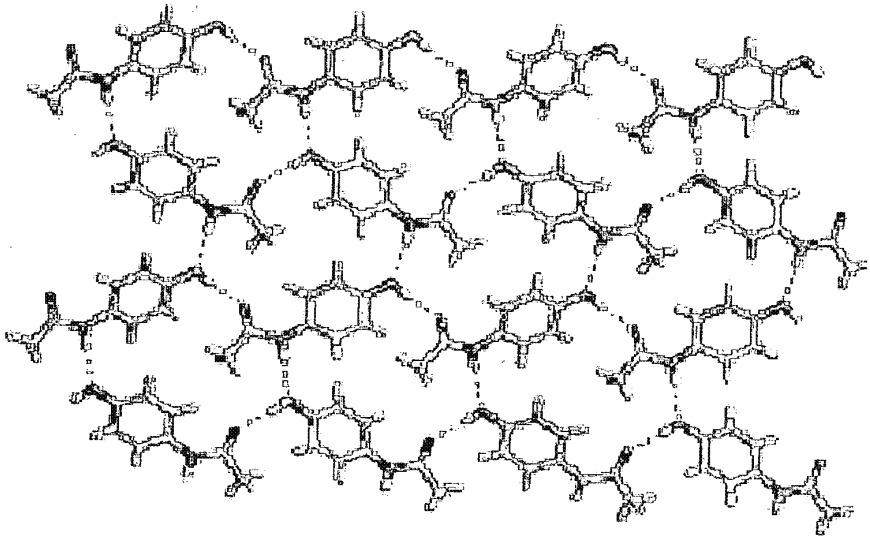


FIG. 4A

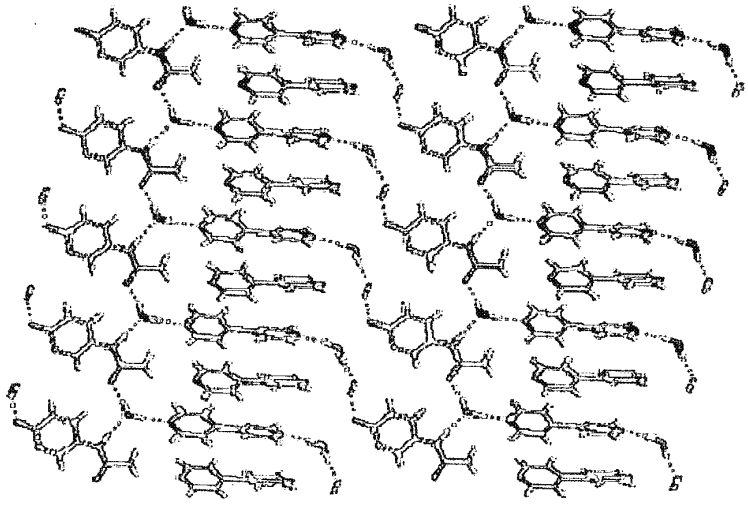


FIG. 4B

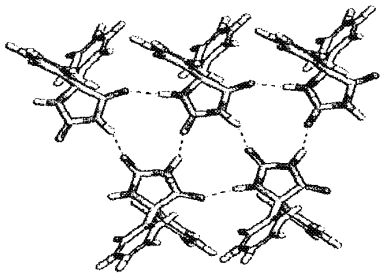


FIG. 5A

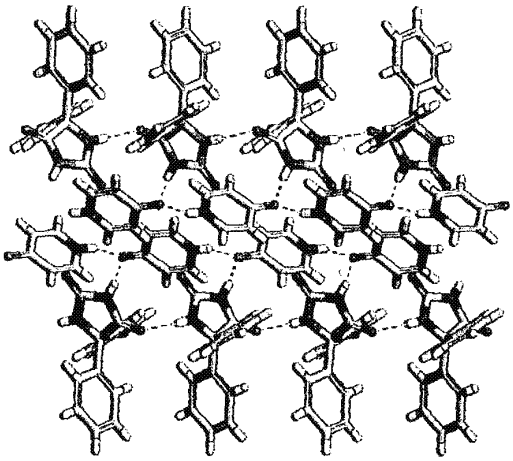


FIG. 5B

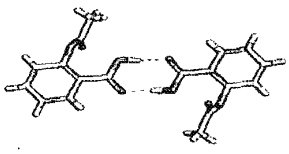


FIG. 6A

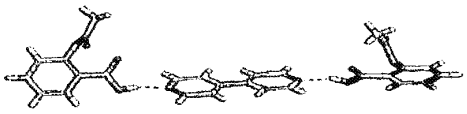


FIG. 6C

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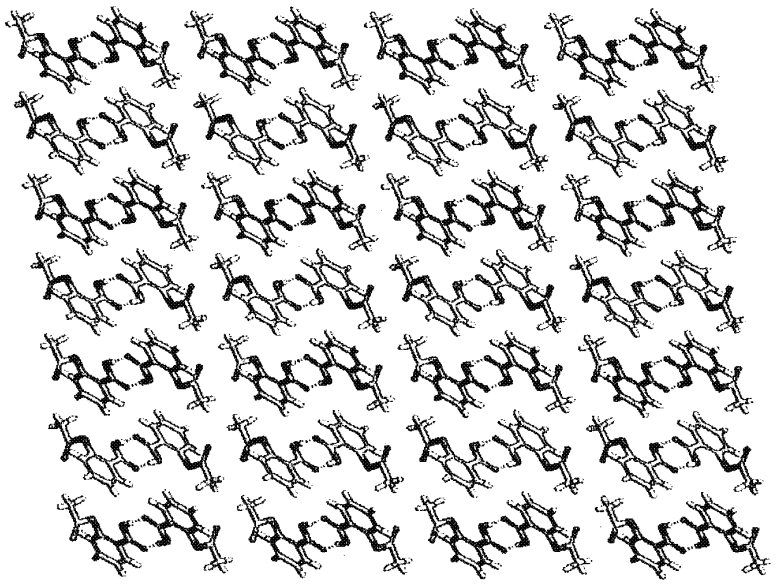


FIG. 6B

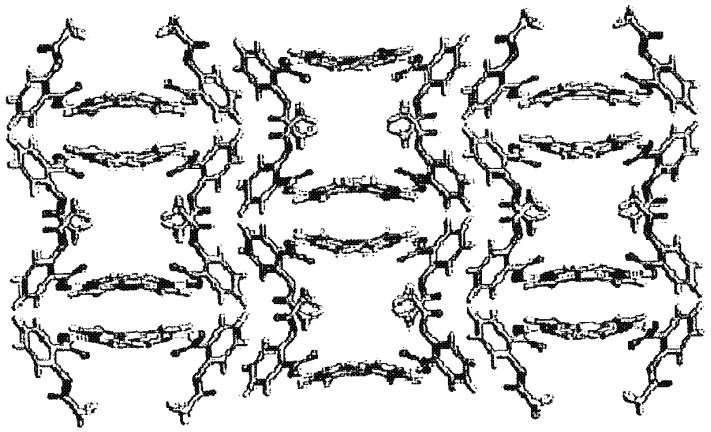


FIG. 6D

FIG. 7A

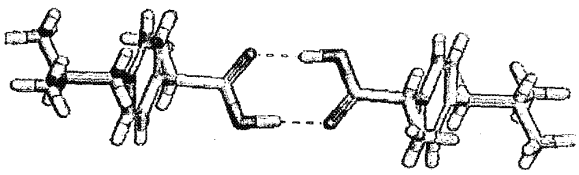
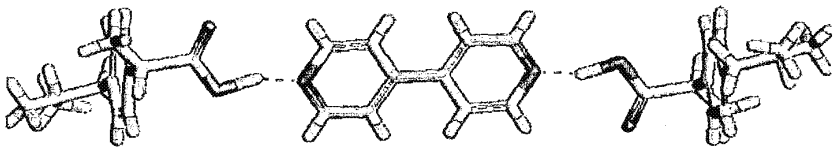


FIG. 7C



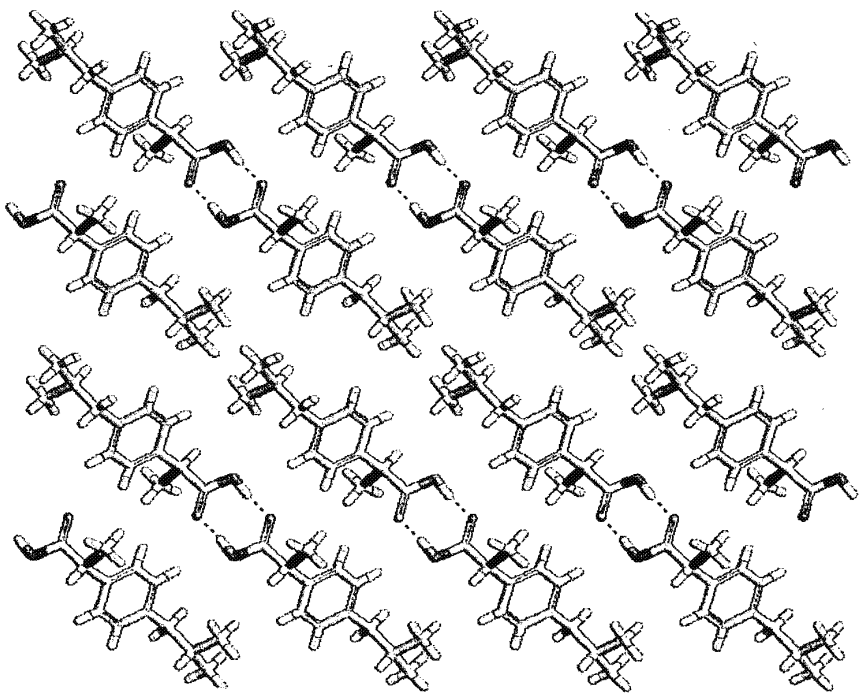


FIG. 7B

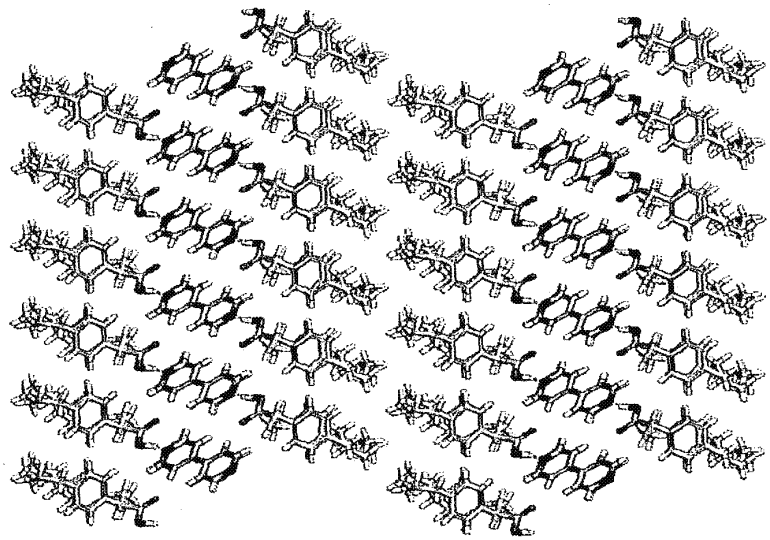


FIG. 7D

FIG. 8A

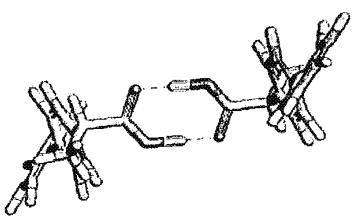
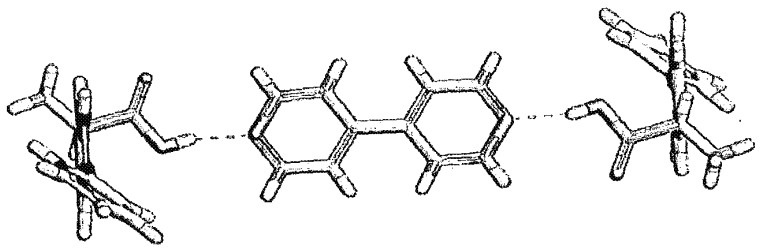


FIG. 8C



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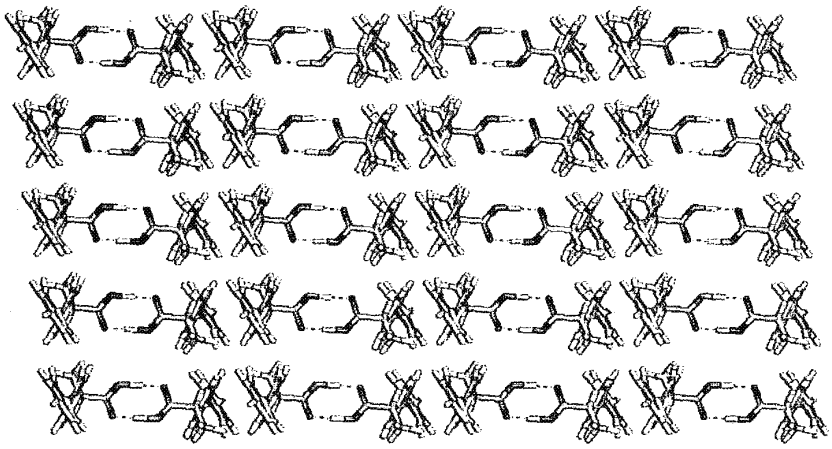


FIG. 8B

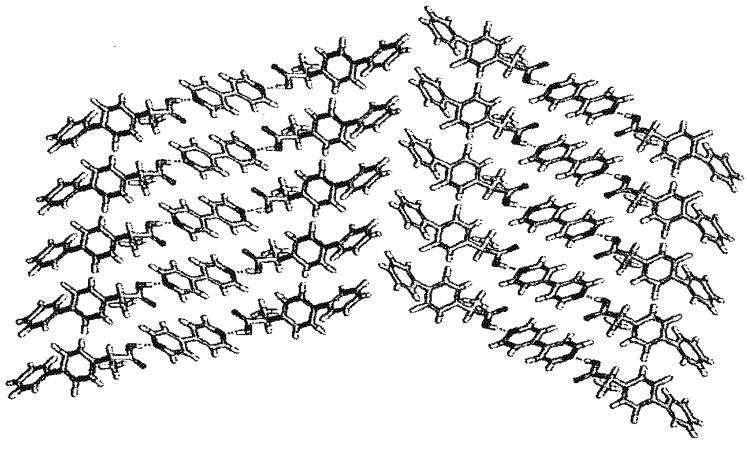


FIG. 8D

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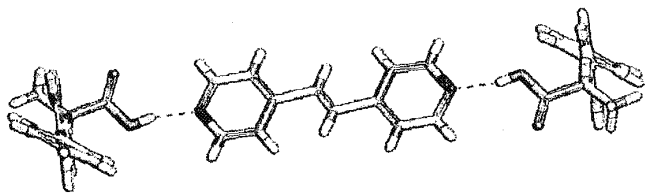


FIG. 9A

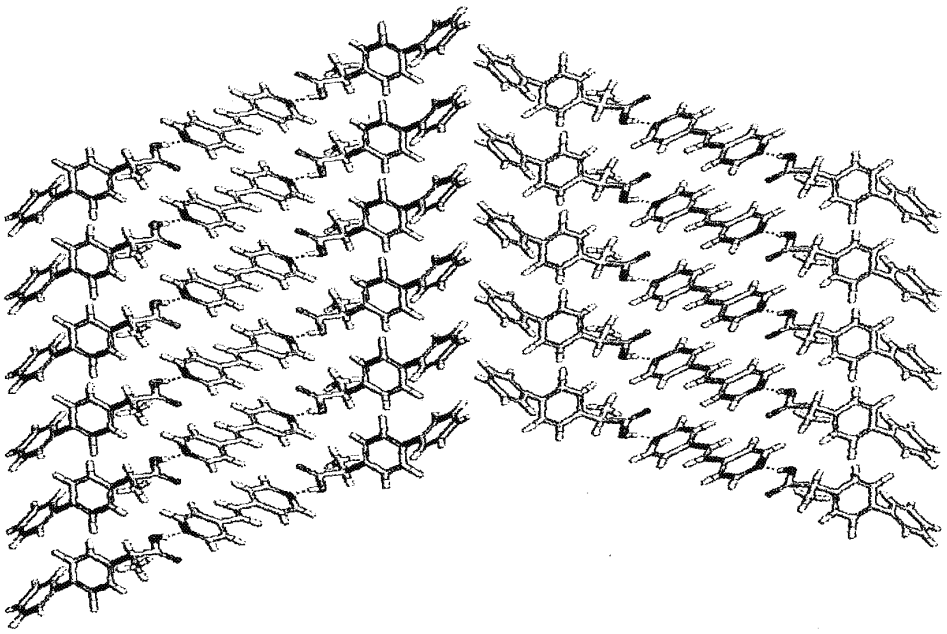


FIG. 9B

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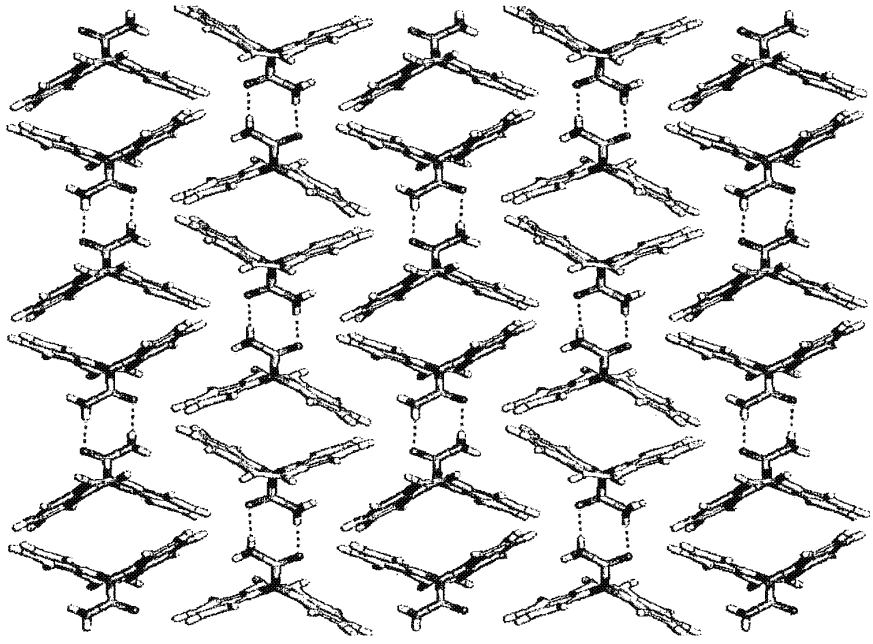


FIG. 10A

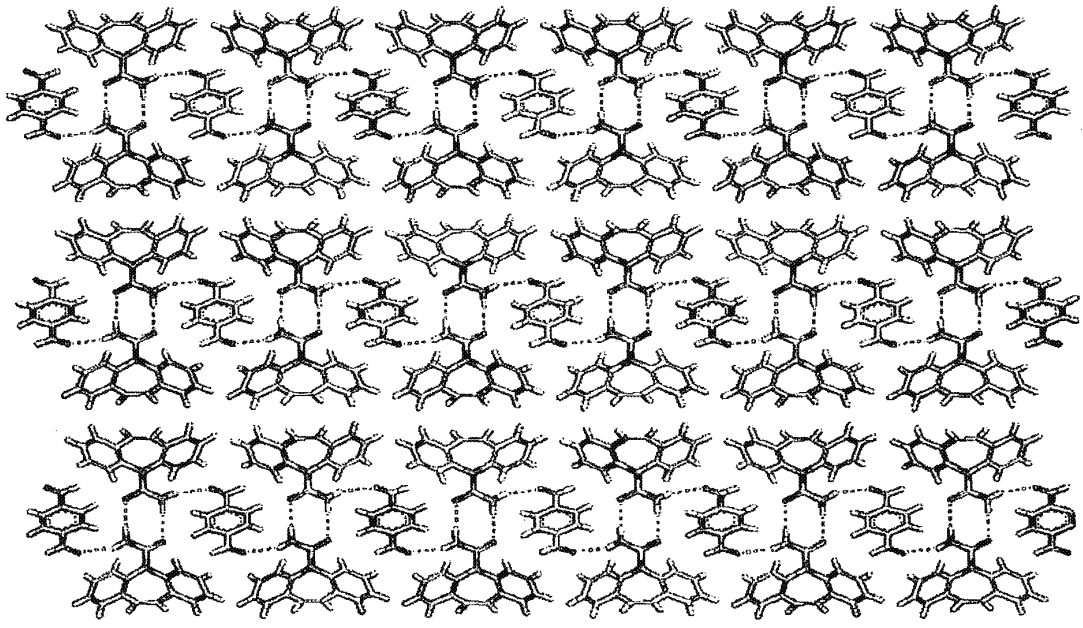


FIG. 10B

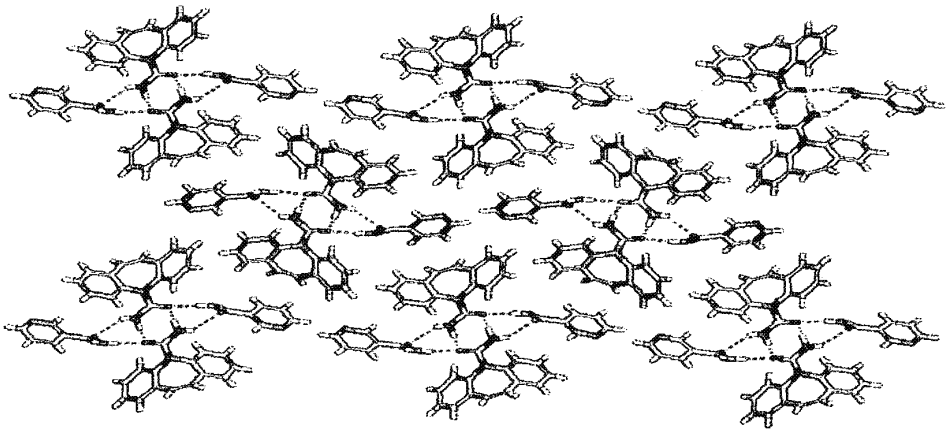


FIG. 11

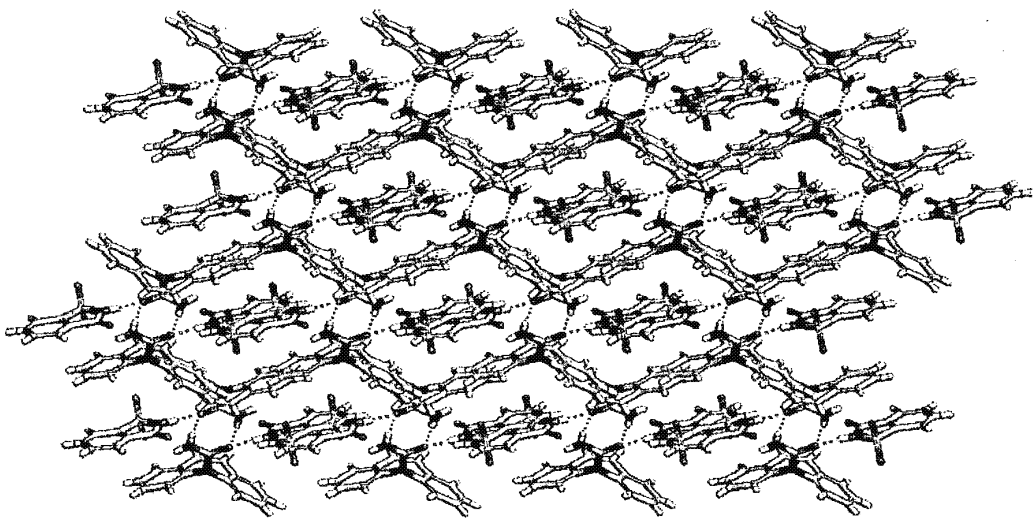


FIG. 12

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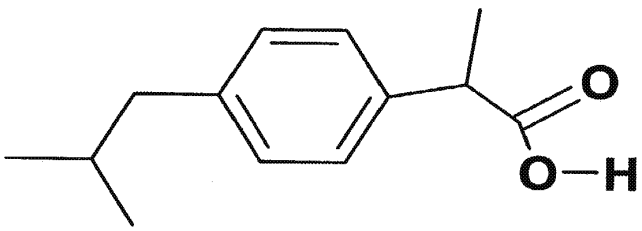


FIG. 13A

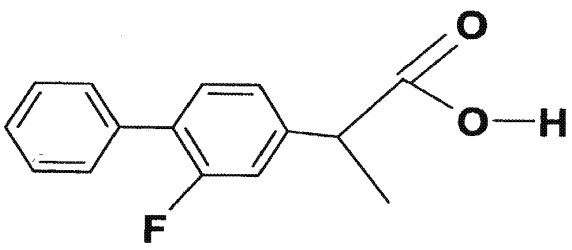


FIG. 13B

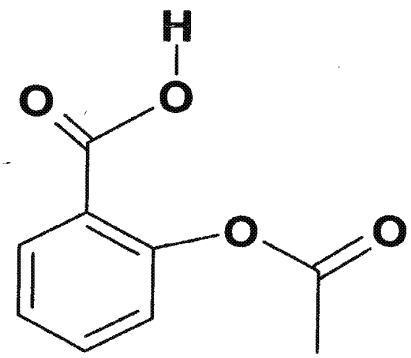


FIG. 13C

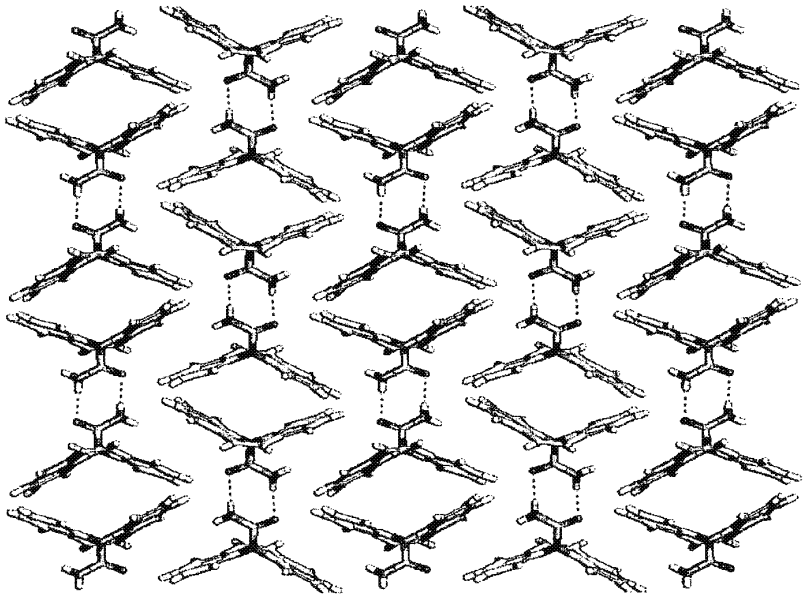


FIG. 14A

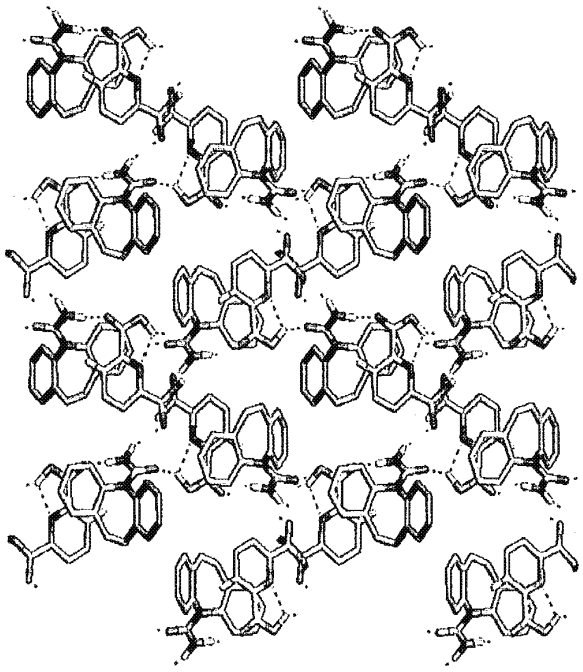


FIG. 14B

10378956 .030303

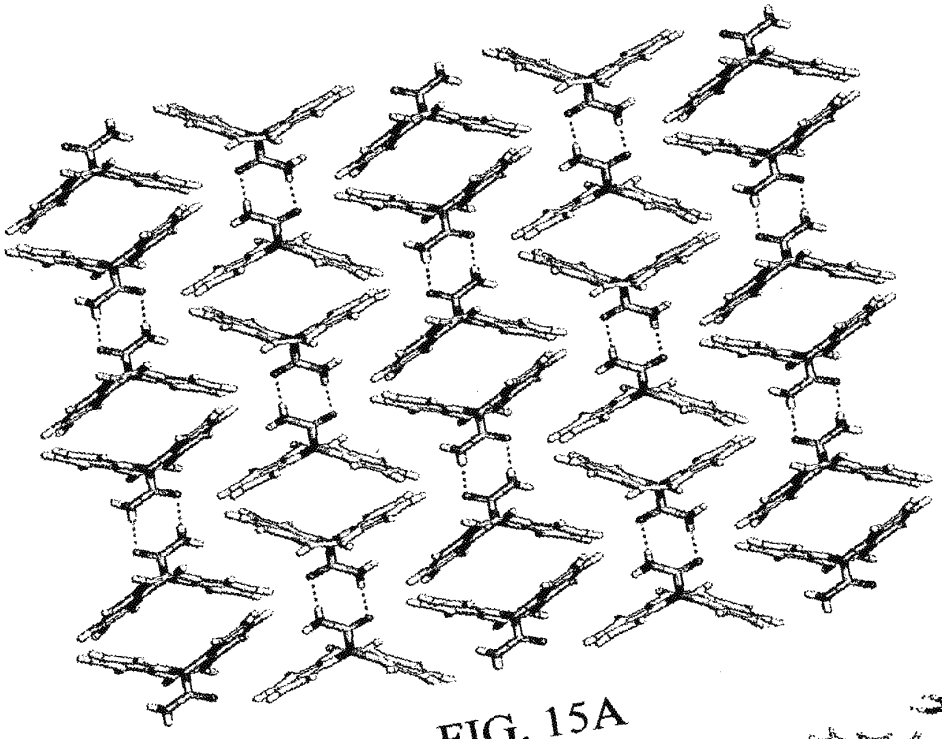


FIG. 15A

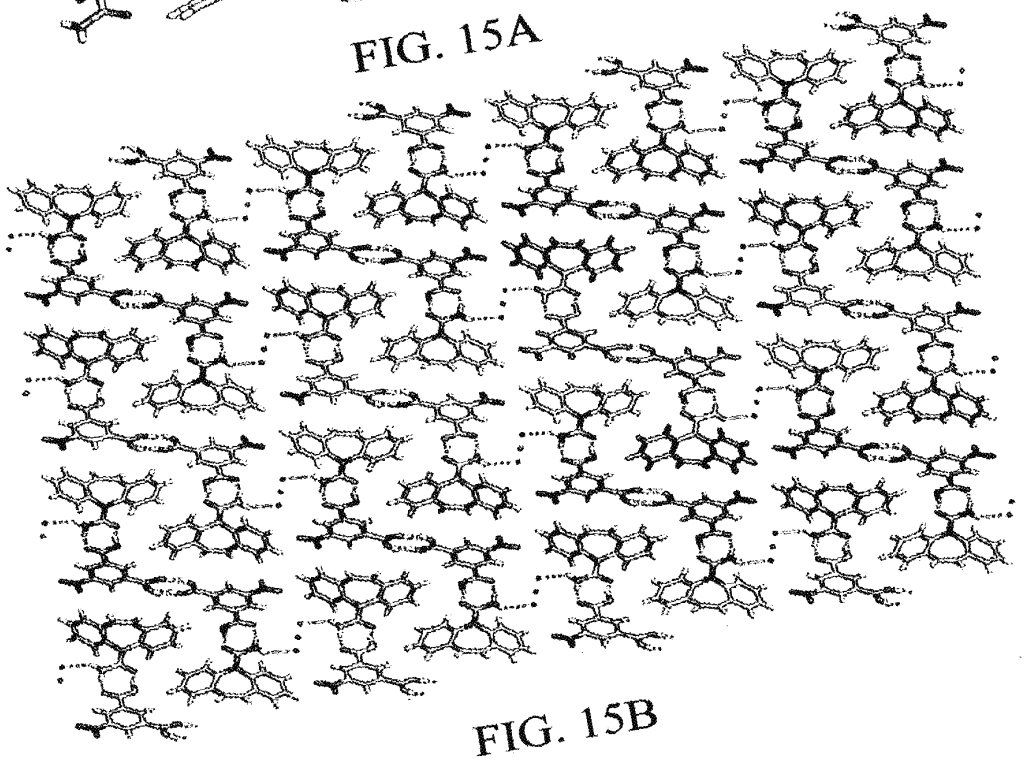


FIG. 15B

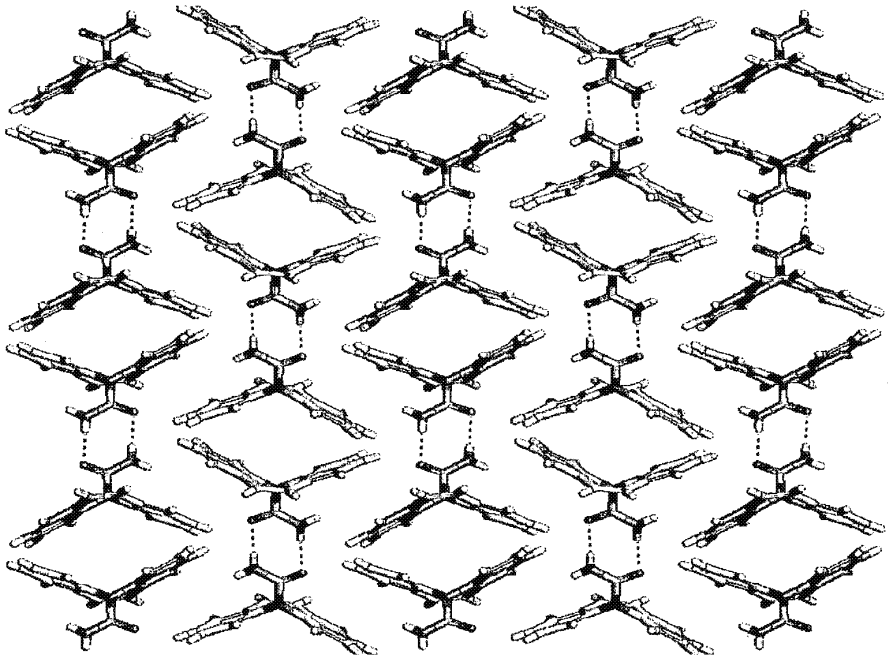


FIG. 16A

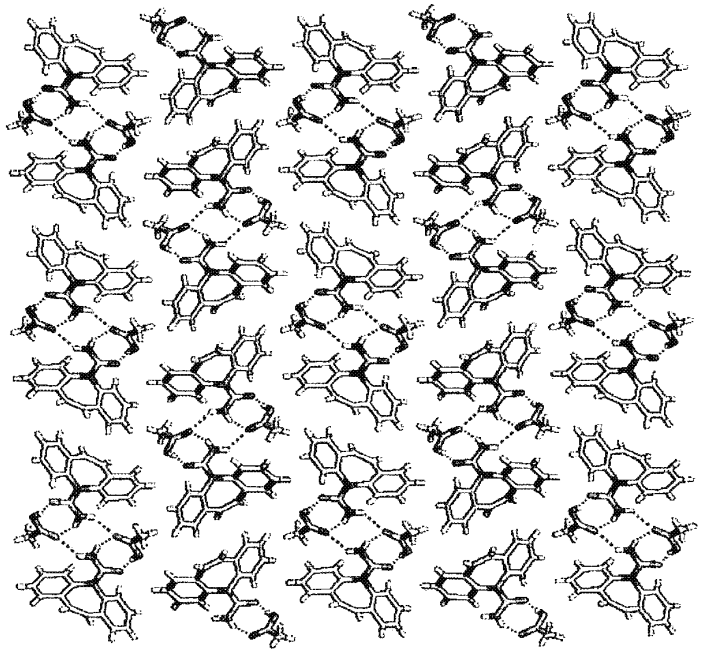


FIG. 16B

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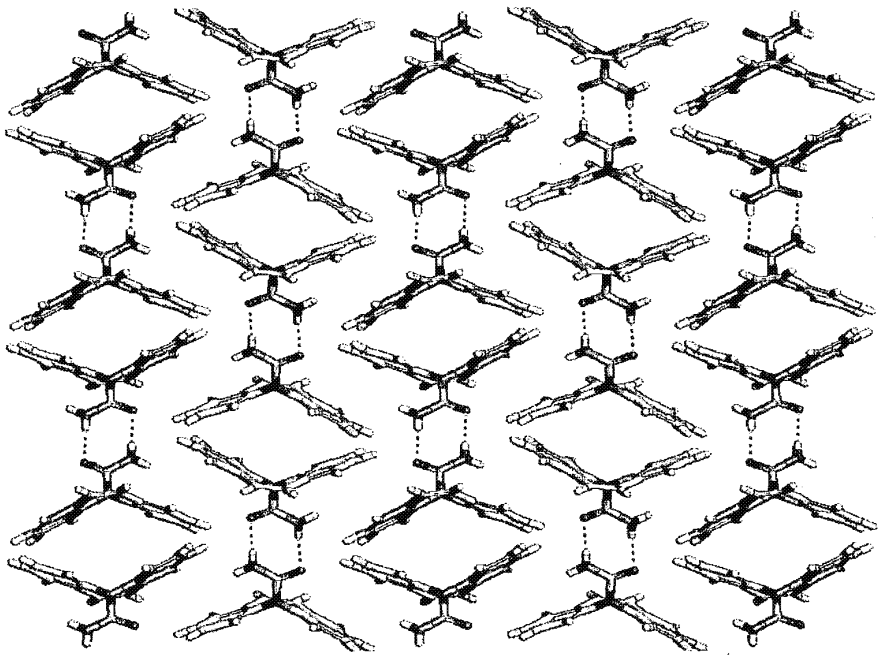


FIG. 17A

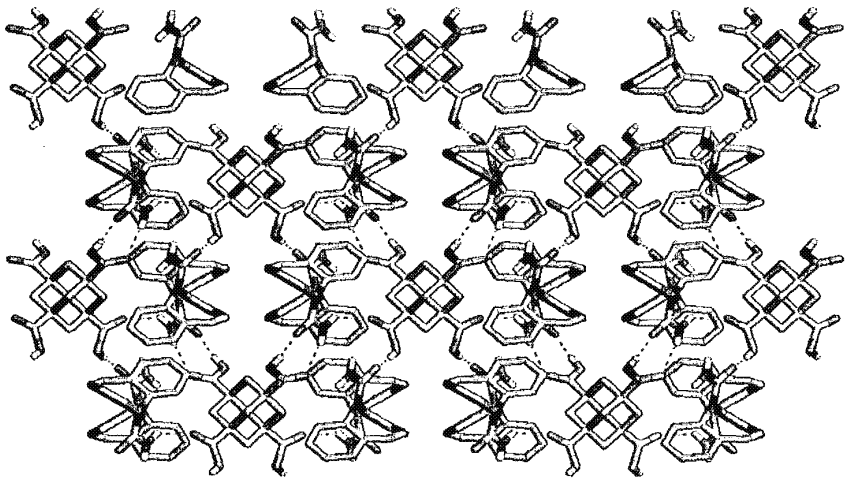


FIG. 17B

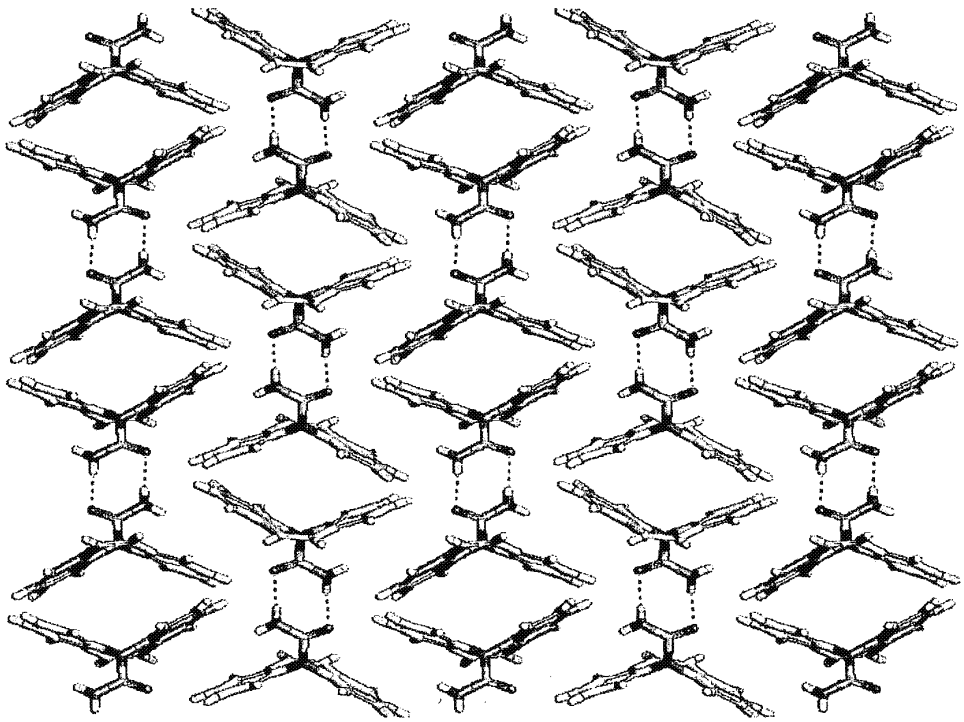


FIG. 18A

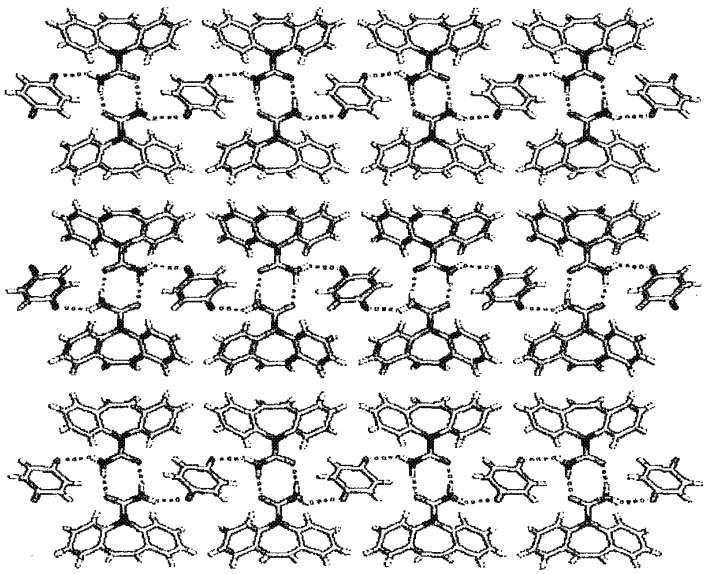


FIG. 18B

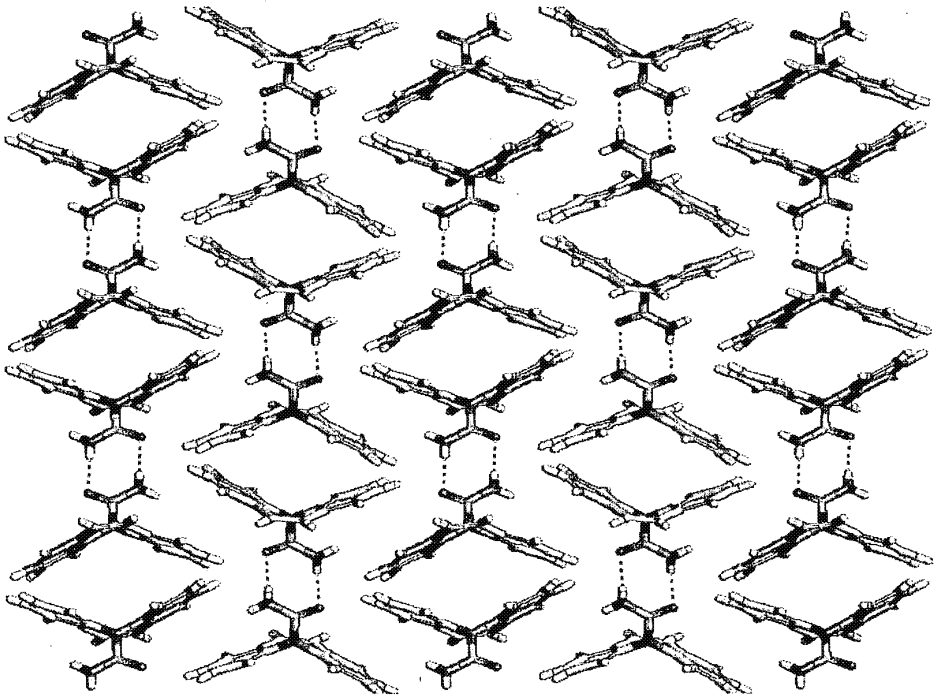


FIG. 19A

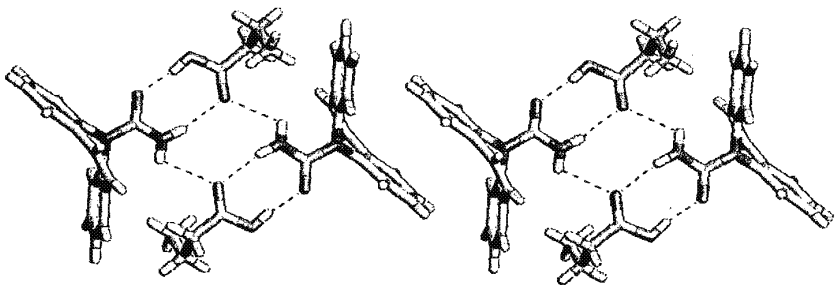


FIG. 19B

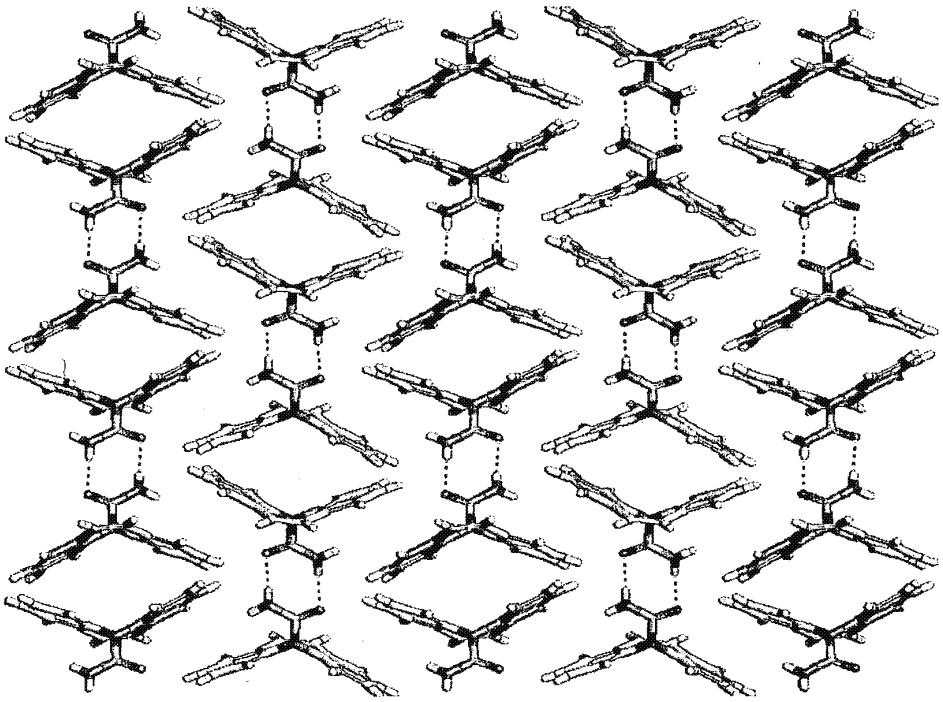


FIG. 20A

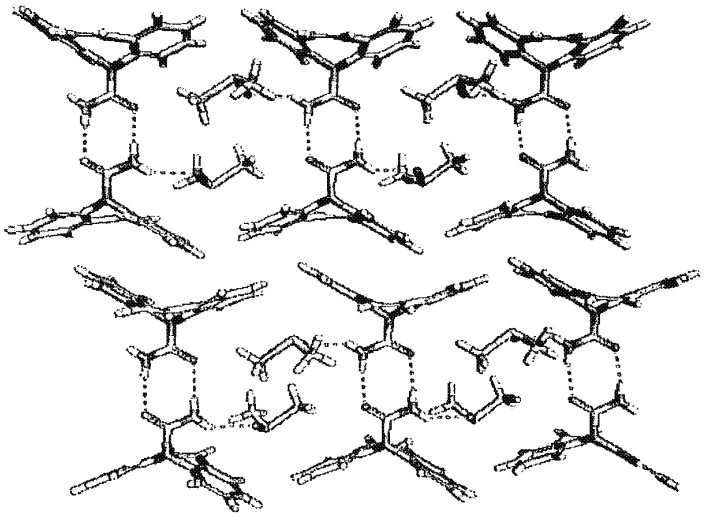


FIG. 20B

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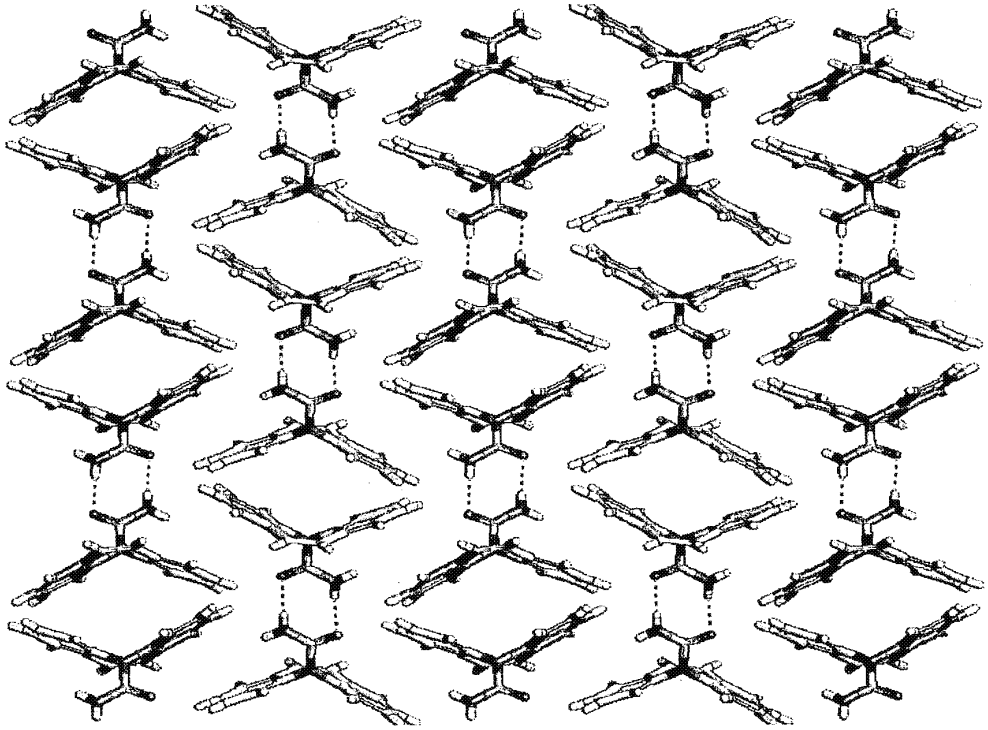


FIG. 21A

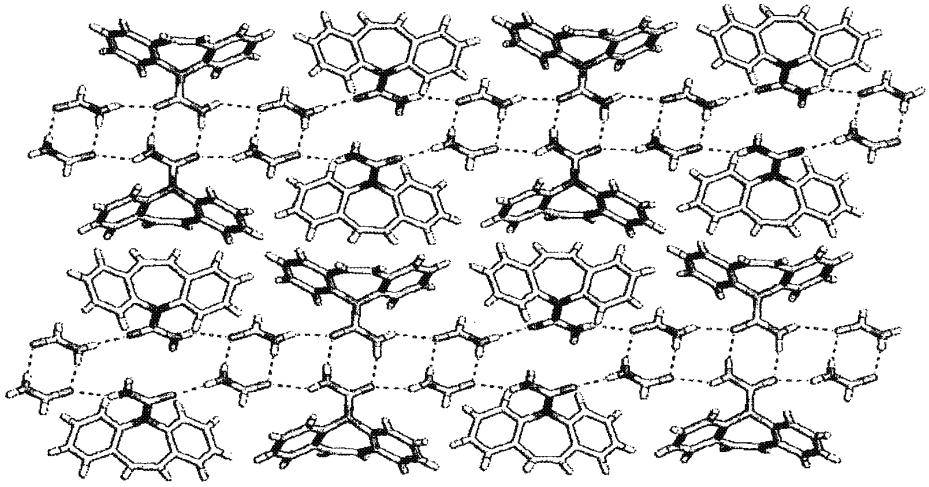


FIG. 21B

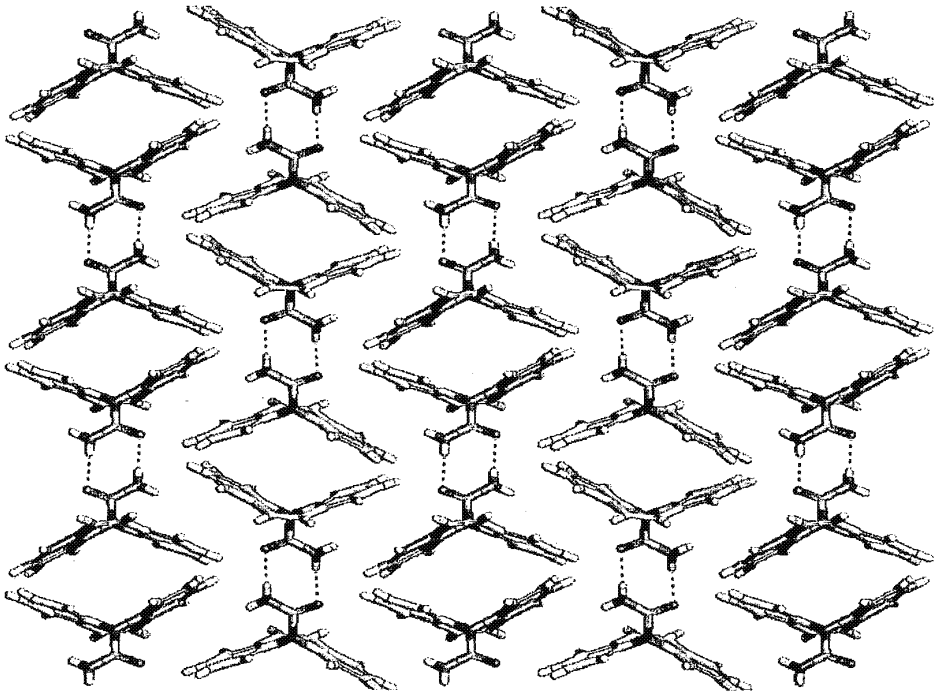


FIG. 22A

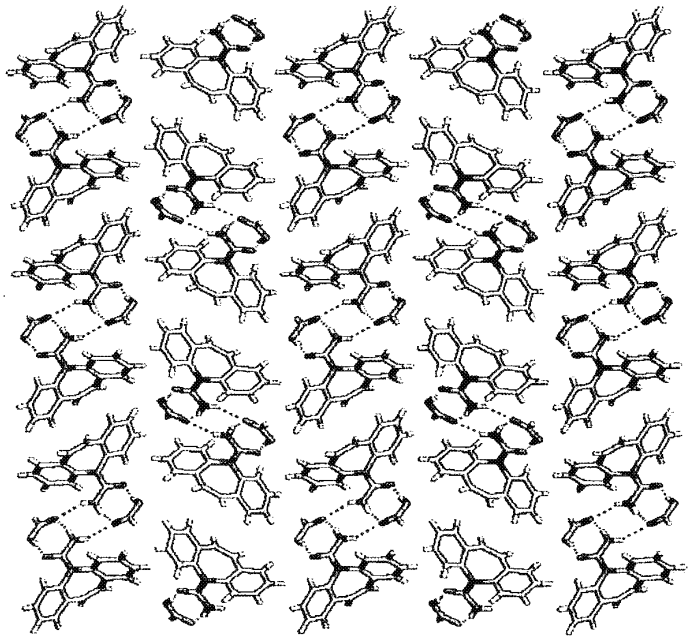


FIG. 22B

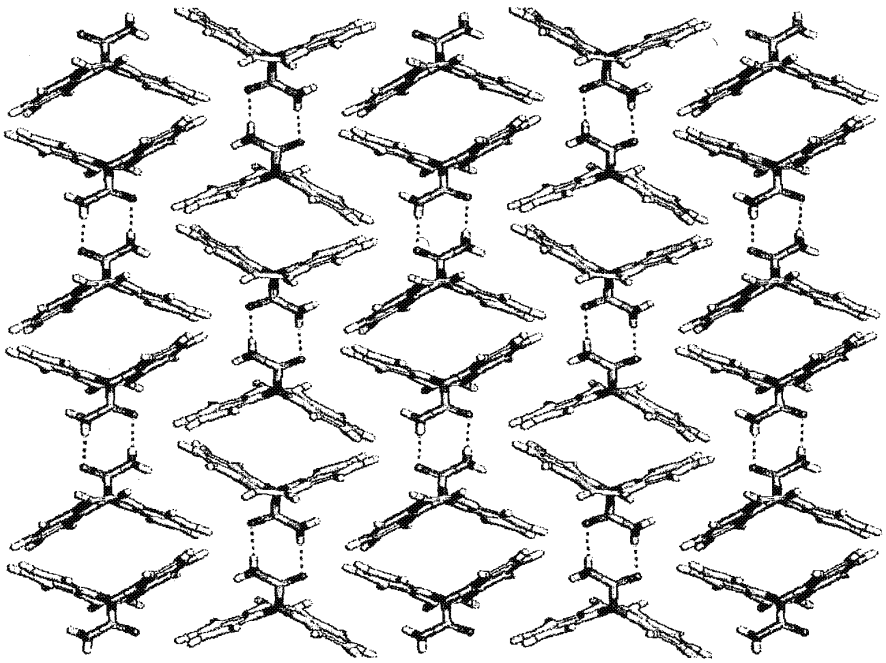


FIG. 23A

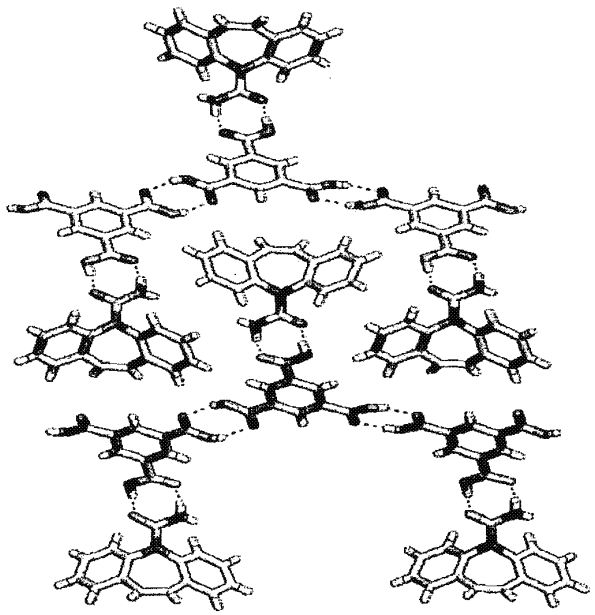


FIG. 23B

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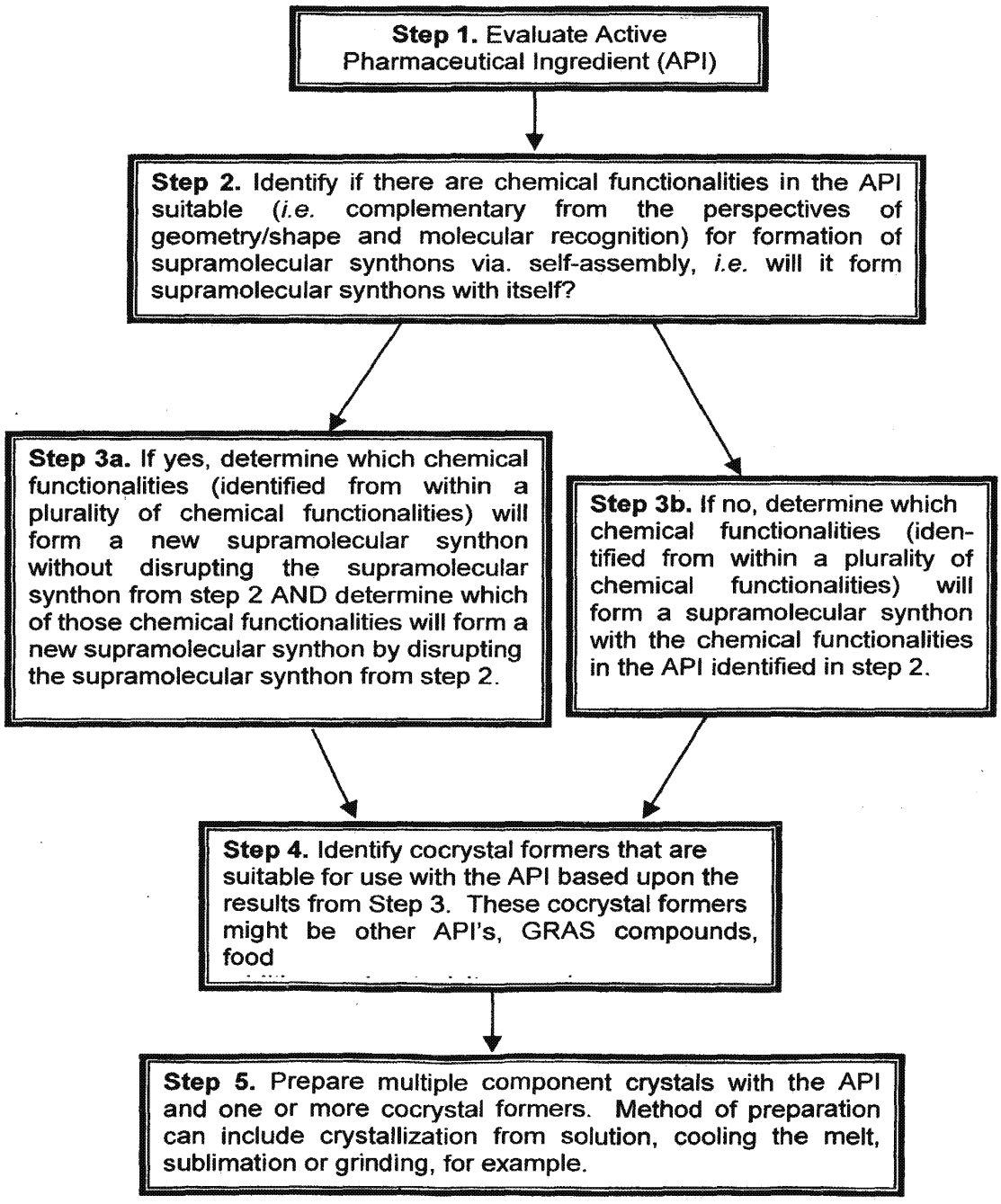


FIG. 24

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DECLARATION (37 C.F.R. § 1.63) AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name; and

I believe that I am the original, first, and sole inventor (if only one name is listed below), or an original, first, and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT**, specification for which

☐ is attached hereto.
☒ was filed **March 3, 2003**, Serial No. _____.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, § 1.56 (a).

I hereby claim foreign priority benefits under Title 35, United States Code §119 and/or §365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Application Serial No.	Country	Filing Date	Priority Claimed

I hereby claim priority benefits under Title 35, United States Code §119 of any provisional application(s) for patent listed below:

Application Serial No.	Filing Date	Priority Claimed

I hereby claim the benefit under Title 35, United States Code, §120 and/or §365 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (Patented, Pending, Abandoned)
60/360,768	March 1, 2002	Pending

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

UM00009777
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I hereby appoint the following persons registered to practice before the Patent and Trademark Office as my attorneys with full power of substitution and revocation to prosecute this application and all divisions and continuations thereof and to transact all business in the Patent and Trademark Office connected therewith: David R. Saliwanchik, Reg. No. 31,794; Jeff Lloyd, Reg. No. 35,589; Doran R. Pace, Reg. No. 38,261; Jay M. Sanders, Reg. No. 39,355; Jean Kyle, Reg. No. 36,987; James S. Parker, Reg. No. 40,119; Frank C. Eisenschenk, Reg. No. 45,332; Glenn P. Ladwig, Reg. No. 46,853; Margaret Efron, Reg. No. 47,545; and Gwendolyn L. Daniels, Reg. No. 51,594.

I request that all correspondence be sent to:

Glenn P. Ladwig
Saliwanchik, Lloyd & Saliwanchik
A Professional Association
2421 N.W. 41st Street, Suite A-1
Gainesville, FL 32606-6669

I further request that all telephone communications be directed to:

Glenn P. Ladwig
352-375-8100

UM00009778
NOVARTIS EXHIBIT 1517
Novartis v. Regents, IPR2023-01347
Page 69 of 4460

Name of First or Sole Inventor Michael J. Zaworotko

Residence Tampa, FL Citizenship British/Canadian

Post Office Address 4202 E. Fowler Ave. (USF30244)

Tampa, FL 33620

Date

Signature of First or Sole Inventor

Name of Second Joint Inventor Brian Moulton

Residence Temple Terrace, FL Citizenship Canadian

Post Office Address 13455 Century Cove Dr. #325

Temple Terrace, FL 33637

Date

Signature of Second Joint Inventor

Name of Third Joint Inventor Nair Rodriguez-Hornedo

Residence Ann Arbor, MI Citizenship U.S.

Post Office Address 1690 Northbrook Dr.

Ann Arbor, MI 48103

Date

Signature of Third Joint Inventor

Name of Fourth Joint Inventor

Residence Citizenship

Post Office Address

Date

Signature of Fourth Joint Inventor

UM00009779
NOVARTIS EXHIBIT 1517
Novartis v. Regents, IPR2023-01347
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Special Instructions for Evidence
Copy Box Identification

Documents in this patent application scanned prior to the scan date of this document may not have a box number present in the database. The documents are in the same box as this paper. If the patent application documents that do not have a box number are stored in more than one box, a copy of this form is placed in each box. Check the database box number for each copy of this form to identify all of the evidence copy box numbers for documents that do not have a box number.

[✓] The documents stored in this box are original application papers scanned and endorsed by PACR and imported into IFW.

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Indexer, place an X in only one box above to indicate the documents placed in this box that were previously scanned in PACR or IFW and will not be scanned again.

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

03/10/2003 HTECKLU1 00000004 190065 10378956

01 FC:2001 375.00 CH
02 FC:2202 144.00 CH
03 FC:2201 252.00 CH

PTO-1556
(5/87)

*U.S. Government Printing Office: 2001 — 481-697/59173

PATENT APPLICATION FEE DETERMINATION RECORD
Effective January 1, 2003

Application or Docket Number: 10378986

CLAIMS AS FILED - PART I

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

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

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

CLAIMS AS AMENDED - PART II

AMENDMENT A

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

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

AMENDMENT B

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

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

AMENDMENT C

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

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

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

FORM PTO-875 (Rev. 1/03) — Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
Washington, DC 20231
www.uspto.gov

APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
10/378,956	03/03/2003	Michael J. Zaworotko	USF-106XC1

CONFIRMATION NO. 4742

23557
SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
2421 N.W. 41ST STREET
SUITE A-1
GAINESVILLE, FL 326066669

FORMALITIES LETTER

OC000000009893028

Date Mailed: 04/23/2003

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is unsigned.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(e) of $65 for a small entity in compliance with 37 CFR 1.27, must be submitted with the missing items identified in this letter.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **$65** for a Small Entity

- **$65** Late oath or declaration Surcharge.

A copy of this notice MUST be returned with the reply.

Customer Service Center
Initial Patent Examination Division (703) 308-1202

PART 3 - OFFICE COPY

OIPE JC40
JUN 20 2003
PATENT & TRADEMARK OFFICE

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450
on June 17, 2003.

Frank C Eisenschenk

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

Examining Group 1765
Patent Application
Docket No. USF-106XC1
Serial No. 10/378,956

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	(Not yet assigned)
Art Unit	:	1765
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 MISSING PARTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Sir:

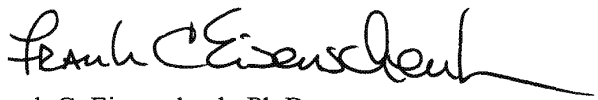
The applicants received a Notice to File Missing Parts of Nonprovisional Application in the subject application dated April 23, 2003. A copy of that Notice is enclosed.

In response to the Notice to File Missing Parts of Nonprovisional Application is an executed Declaration (37 CFR 1.63) and Power of Attorney form for the above-identified patent application.

J:\USF\106XC1\Amend-Resp\NTFMP response.doc/DNB/mv

Please charge the small entity surcharge of $65.00 to Deposit Account No. 19-0065. The Commissioner is hereby authorized to charge any additional fees that may be required to Deposit Account No. 19-0065. Two copies of this transmittal letter are enclosed.

Respectfully submitted,



Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: Saliwanchik, Lloyd & Saliwanchik
A Professional Association
2421 NW 41st Street, Suite A-1
Gainesville, FL 32606-6669

FCE/mv

Enclosures: Executed Declaration and Power of Attorney
Copy of Notice to File Missing Parts
Two copies of this Transmittal Letter

J:\USF\106XC1\Amend-Resp\NTFMP response.doc/DNB/mv

#3

MP/8

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
Washington, DC 20231
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APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
10/378,956	03/03/2003	Michael J. Zaworotko	USF-106XC1

CONFIRMATION NO. 4742

23557
SALIWANCHIK LLOYD & SALIWANCHIK
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2421 N.W. 41ST STREET
SUITE A-1
GAINESVILLE, FL 326066669

OIPE JC10 JUN 20 2003 PATENT & TRADEMARK OFFICE

FORMALITIES LETTER

OC000000009893028

Date Mailed: 04/23/2003

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is unsigned.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(e) of $65 for a small entity in compliance with 37 CFR 1.27, must be submitted with the missing items identified in this letter.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **$65** for a Small Entity

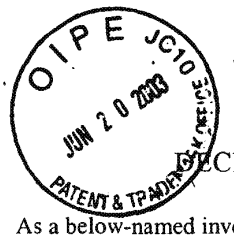
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#3

Docket No. USF-106XC1

DECLARATION (37 C.F.R. § 1.63) AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name; and

I believe that I am the original, first, and sole inventor (if only one name is listed below), or an original, first, and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT**, specification for which

☐ is attached hereto.
☒ was filed **March 3, 2003**, Serial No. 10/378,956 .

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, § 1.56 (a).

I hereby claim foreign priority benefits under Title 35, United States Code §119 and/or §365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Application Serial No.	Country	Filing Date	Priority Claimed

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Application Serial No.	Filing Date	Priority Claimed

I hereby claim the benefit under Title 35, United States Code, §120 and/or §365 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (Patented, Pending, Abandoned)
60/360,768	March 1, 2002	Pending

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

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Page 78 of 4460

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Page 79 of 4460

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Docket No. USF-106XC1

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Page 81 of 4460

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Page 82 of 4460

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Name of Second Joint Inventor Brian Moulton

Residence Temple Terrace, FL Citizenship Canadian

Post Office Address 13455 Century Cove Dr. #325

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Signature of Second Joint Inventor Date

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Signature of Third Joint Inventor

Name of Fourth Joint Inventor

Residence Citizenship

Post Office Address

Signature of Fourth Joint Inventor Date

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Page 83 of 4460

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Frank C Eisenschenk

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

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1765

INFORMATION DISCLOSURE STATEMENT
Examining Group 1765
Patent Application
Docket No. USF-106XC1
Serial No. 10/378,956

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

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

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §§1.97 AND 1.98

Sir:

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

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

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

Respectfully submitted,

Frank C Eisenschenk

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
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Address: 2421 N.W. 41st Street, Suite A-1
Gainesville, FL 32606-6669

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

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Sheet 1 of 2

Complete if Known	
Application Number	10/378,956
Filing Date	March 3, 2003
First Named Inventor	Michael J. Zaworotko
Art Unit	1765
Examiner Name	
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
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	F1	GB 1 297 261 A	11-22-1972 (22 Nov 1972)	E.R. Squibb & Sons, Inc.	whole document	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 2

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Application Numb r	10/378,956
Filing Date	March 3, 2003
First Named Inventor	Michael J. Zaworotko
Group Art Unit	1765
Examiner Name	
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	BRADER, M.L. *et al. Nature Biotechnol.*, 2002, 20 :800-804.	
	R2	EL-NAHHAS, S.A. *Pharmazie*, 1996, 51(12):960-963.	
	R3	FLEISCHMAN, S.G. *et al. Crystal Growth & Design.*, 2003, 3(6): 909-919.	
	R4	OSWALD, I.D.H. *et al. Acta Cryst.*, 2002, B58:1057-1066.	
	R5	REYNOLDS, J.E.F. (ed). Martindale, The Extra Pharmacopoeia, 1993, The Pharmaceutical Press, London, England, 13th Edition, pp. 1431 (e.g., Acetaminophen, Aspirin, and Caffeine Tablets), 1465 (e.g., Aspirin plus C), 1521 (Codafen Continus), 1610 (Gaboril Complex).	
	R6	WALSH, R.D. Bailey *et al. Chem. Commun.*, 2003, 2003:186-187.	
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Hybrid insulin cocrystals for controlled release delivery

Mark L. Brader[1]*, Muppalla Sukumar[1], Allen H. Pekar[1], David S. McClellan[2], Ronald E. Chance[3], David B. Flora[3], Amy L. Cox[4], Lynnie Irwin[4], and Sharon R. Myers[4]*

Published online: 22 July 2002, doi:10.1038/nbt722

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^{ε}-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.

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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 manufacture[4]. 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 mellitus[5]. This approach revolutionized diabetes therapy[6] and led to the development of a microcrystalline suspension formulation known as NPH insulin[7], 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 insulin[12].

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 crystals[13] including NPH insulin[14]. C8-HI most likely meets this requirement because previous studies have shown that hexadecanoyl-N^{ε}-LysB29–human insulin forms a zinc hexamer in solution[15]. 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 hexamer[16].

[1]*Bioproduct Pharmaceutical Development,* [2]*Physical and Structural Characterization,* [3]*Bio Research Technologies and Proteins, and* [4]*Endocrine Research, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285. *Corresponding authors (m.brader@lilly.com and s.r.myers@lilly.com).*

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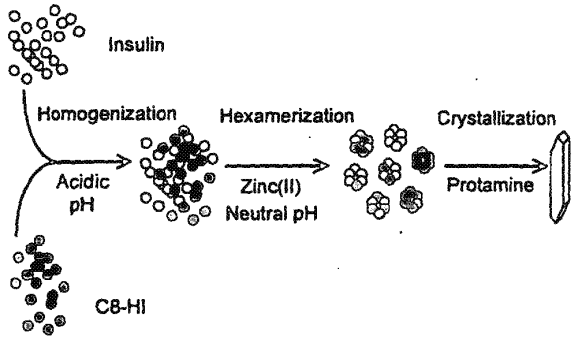


Figure 1. Schematic representation of cocrystal formation. Insulin and C8-HI are combined initially as solutions to facilitate homogeneous mixing of the two species. Adjustment to neutral pH in the presence of zinc forms a mixture of hybrid zinc hexamers, which complex with protamine to form homogeneous microcrystals (~5 μm long) with the distinctive NPH crystal morphology shown.

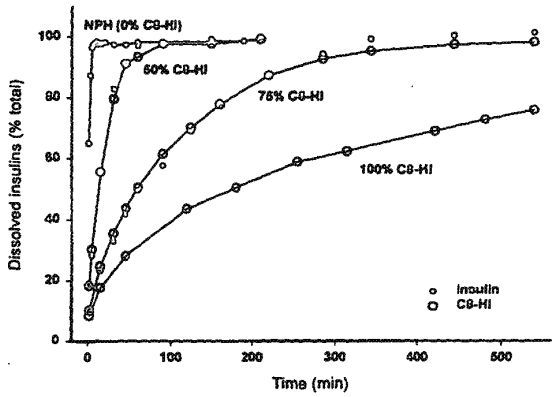


Figure 3. *In vitro* dissolution curves showing the relationship between the C8-HI content of the cocrystal and dissolution rate. The ordinate represents dissolved insulins expressed as a percentage of the total dissolved and undissolved insulins. (See Experimental Protocol for dissolution protocol.)

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 extension[19]. 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 substantially[22], thus retaining full biopotency of the insulin derivative. In addition, the LysB29 residue is not required for receptor activity[23]. 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 pH[7]. 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 gentle 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 effectiveness[29]. 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 hexamers[14].

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 states[30]. 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 cocrystals 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 states[31]. 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 hexamers[32]. The hexamers subsequently dissociate in the interstitial fluid

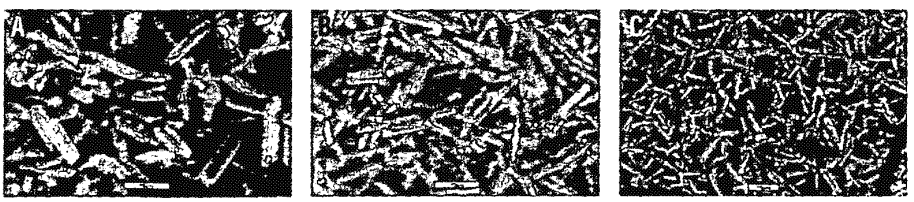


Figure 2. Environmental scanning electron microscope (ESEM) images. (A) NPH-like crystals formed from 100% C8-HI. (B) NPH insulin. (C) 75% C8-HI cocrystals. Images were taken of the microcrystalline samples deposited directly from the mother liquor onto a filter surface. Scale bars, 5 μm.

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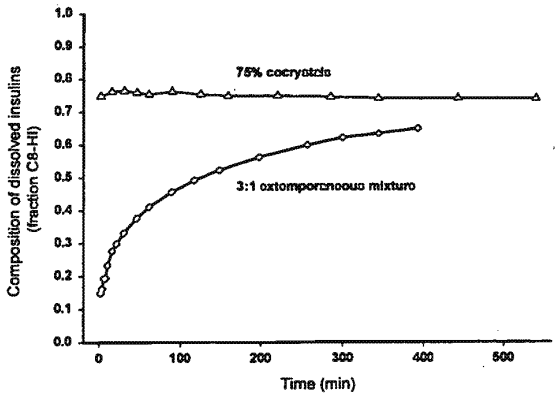


Figure 4. *In vitro* dissolution homogeneity. Homogeneous release of C8-HI occurs from a 75% C8-HI cocrystal (△) in contrast to the non-homogeneous dissolution behavior of an extemporaneous mixture of 100% C8-HI and NPH (0% C8-HI) mixed in a 3:1 ratio (◇). The ordinate represents the C8-HI dissolved 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 bloodstream[33]. 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 incorporation 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 ± 1% vs. 59 ± 1% for 58% and 75% C8-HI, respectively; $P < 0.01$) or bioavailability (area under

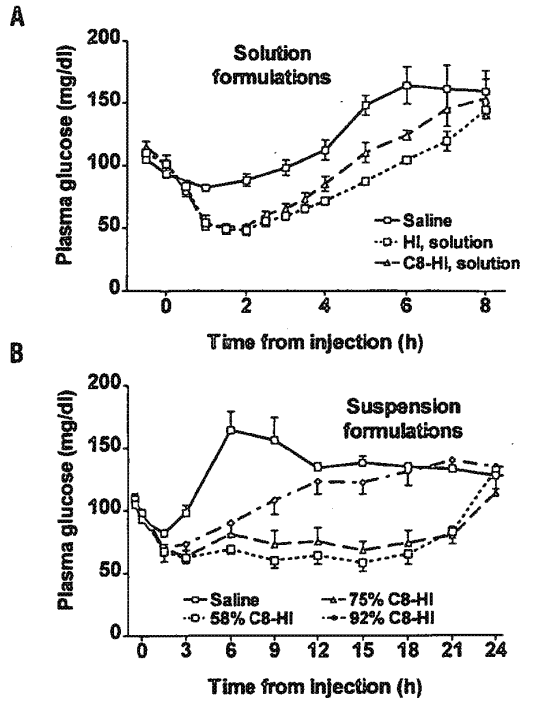


Figure 5. Time-action profiles of insulin formulations administered to somatostatin-treated dogs by subcutaneous injection. (A) Saline, HI, and C8-HI solution formulations (0.75 nmol/kg, $n = 5$). (B) C8-HI cocrystal suspension formulations (2 nmol/kg, $n = 6$). Values represent mean ± s.e.m.

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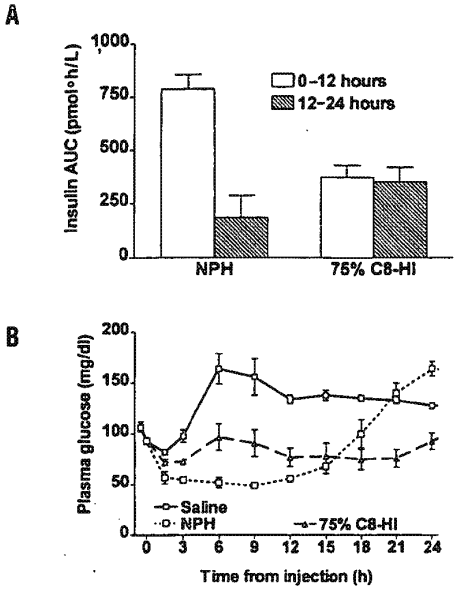


Figure 6. Pharmacokinetics and glucodynamics of 75% C8-HI cocrystal and NPH in somatostatin-treated dogs (2 nmol/kg, subcutaneous, $n = 6$; values represent mean ± s.e.m.). The pharmacokinetics (A) show that the 0–12 h area under curve (AUC) for 75% C8-HI cocrystal is significantly less than that of 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 proinsulin[34], and has recently been shown to form hybrid zinc hexamers with fluorescently labeled N^{ε}-LysB29-modified insulin derivatives[35] 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 screening[37], 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 µl of 10 mg/ml $ZnCl_2$ 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× 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, Altex 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 $CaCl_2$ and $MgCl_2$ (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 µm 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 × 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 µg/kg per min) of cyclic somatostatin (Bachem, Torrence, 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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Crystal Engineering of the Composition of Pharmaceutical Phases: Multiple-Component Crystalline Solids Involving Carbamazepine

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ABSTRACT: The crystal engineering design strategy facilitates supramolecular synthesis of 13 new crystalline phases of carbamazepine (CBZ), an analgesic and anticonvulsant with known problems related to solubility and polymorphism. CBZ forms supramolecular complexes with the following molecules, all of which are complementary to CBZ in terms of hydrogen bonding and can therefore act as cocrystal formers: acetone (**1a**); DMSO (**1b**); benzoquinone (**1c**); terephthalaldehyde (**1d**); saccharin (**1e**); nicotinamide (**1f**); acetic acid (**1g**); formic acid (**1h**); butyric acid (**1i**); trimesic acid (**1j**); 5-nitroisophthalic acid (**1k**); adamantane-1,3,5,7-tetracarboxylic acid (**1l**); and formamide (**1m**). Two distinct strategies based upon selection of complementary hydrogen-bond functionalities and previously known supramolecular synthons were utilized: strategy I exploits the exofunctional nature of the carboxamide dimer as either a hydrogen-bond donor or a hydrogen-bond acceptor and thereby retains the carboxamide dimer that is present in all previously isolated forms of CBZ; strategy II perturbs the carboxamide homosynthon by forming a heterosynthon between the carboxamide moiety of CBZ and the carboxylic acid moieties. The latter approach profoundly modifies crystal packing and should therefore affect the physical and pharmaceutical properties of CBZ. A full analysis of crystal packing and a discussion of what these results might mean in the broader context of crystal engineering and pharmaceutical solids is presented.

Introduction

The concept of crystal engineering was introduced by Pepinsky in 1955[1] and was first applied by Schmidt in the context of covalent bond formation in the solid state (i.e., topochemical reactions).[2] The concept continues to attract interest in this context;[3] however, more recent developments have expanded it into areas as diverse as supramolecular synthesis, crystal structure analysis and prediction,[4] and functional materials.[5] Supramolecular synthesis offers a paradigm for the facile design and isolation of supramolecular complexes using self-assembly of different but complementary supramolecular synthons. The subsequent ability to generate a diverse range of multiple-component crystalline solids affords new compositions of matter and an ability to engage in systematic analysis of the factors that control structure/function relationships in the solid state.

Active pharmaceutical ingredients (APIs) represent a particularly great challenge to crystal engineers because of both fundamental and applied reasons. APIs are inherently predisposed for self-assembly since their utility is normally the result of the presence of one or more exofunctional supramolecular synthons. However, the crystal packing of APIs tends to be even less predictable than that of other organics because they often have multiple avenues for self-assembly and are therefore predisposed to exhibit polymorphism.[6] The presence of torsional flexibility further exacerbates matters as it can result in conformational polymorphism.[7] Such issues are of more than academic interest since intellectual property implications are considerable, and physical properties and bioavailability are often critically dependent upon crystal packing.[8] In this paper, we address how the concepts of crystal engineering and supramolecular synthons can be applied to the design of new compositions of matter that are based upon existing APIs and complementary molecules that might be called cocrystal formers. The new compositions that are thereby generated are expected to offer desirable components, structures, and of course, properties.

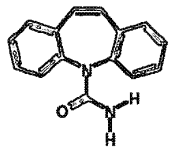
It should be noted that this approach represents a complementary strategy to the use of techniques such as high throughput crystallization[9] or polymer nucleation[10] for control of polymorphs. Furthermore, in principle it offers a much wider range of possible pharmaceutical compositions without the need for covalent modification of APIs.

The pharmaceutically active molecule carbamazepine (CBZ) [5*H*-dibenz(b,f) azepine-5-carboxamide] was of interest to us because of its limited bioavailability[11] and its eight reported polymorphs[12,13] and pseudopolymorphs.[13] It is an important drug for the treatment of epilepsy and trigeminal neuralgia, and pure CBZ crystallizes as one of four polymorphs: tri-

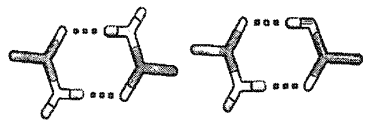
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clinic (form I); trigonal (form II); and monoclinic (forms III and IV). Its relevance, limited solubility, and the fact that it exists in multiple crystalline forms therefore makes CBZ an ideal candidate for a crystal engineering case study.



The primary supramolecular synthon in CBZ is the carboxamide moiety, which has already proven to be a reliable supramolecular synthon for the generation of supramolecular architectures.[14] It most commonly forms the cyclic homosynthon[15] I using the syn-oriented N−H group.[16] The anti-oriented N−H group of the carboxamide typically forms either a 5.1 Å translation related hydrogen-bonded tape or a glide or 2_1-screw pattern. In either case, the additional hydrogen-bond acceptor is the amide carbonyl group of the adjacent carboxamide moiety. This centrosymmetric homosynthon is the primary supramolecular synthon observed in crystalline solids that contain carboxamide moieties.

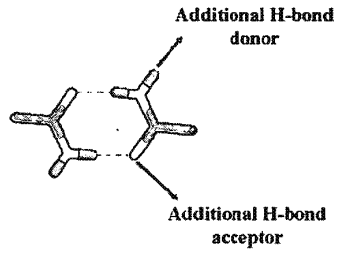


I II

A survey of the Cambridge Structural Database (CSD)[17] and a review of the literature indicated that only five of the eight forms of CBZ isolated thus far have been reported with full structural data (polymorphs II[13b] and III,[13c] a hydrate[14a] with an *R* factor of ~10%, and two multiple-component phases[14]), although the cell parameters of an acetone solvate have also been reported.[13d] Analysis of crystal packing in these structures reveals that the supramolecular homosynthon I generates CBZ dimers in all compounds and that the azepine ring adopts a boat conformation. Form II is trigonal, and form III is a monoclinic phase that contains cavities. The syn-oriented N−H of the carboxamide group forms the expected dimers, while the anti-oriented N−H does not engage in intermolecular interactions. A search of the CSD revealed 440 structures containing an amide homodimer (organics only, NH···O contact is 0−3.3 Å). Of those 440 structures, 30% have an anti-oriented N−H that is not involved in hydrogen bonding, most commonly because of steric hindrance.

As revealed later, the presence of unused hydrogen bond donor and acceptor sites is an important issue in the context of crystal engineering. Furthermore, the different crystal packing motifs in the polymorphs of CBZ might be attributed to the molecular shape of the CBZ dimer and its inability to efficiently pack or utilize the inactivated anti N−H group. Interestingly, an isostructural crystal packing with the trigonal form II was identified from the CSD. *N*-Acetyl-dibenz(b,f)-azepine [CSD REFCODE: BOWWAL] is an analogue of CBZ in which the amide NH_2 group in CBZ is replaced with a CH_3 group; therefore, the supramolecular synthon is the result of a C−H···O=C mediated homosynthon instead of a N−H···O=C homosynthon.[18] Form III has been reported to be the most thermodynamically stable phase at room temperature and the one selected for use herein.[19] Interestingly, the hydrate structure of CBZ forms N−H···O hydrogen bonds via the anti-oriented N−H of the amide group in addition to the homosynthon I and is even less soluble in water than the pure forms.[12] It is this low solubility of CBZ in water that makes it difficult to further extend its utility as a pharmaceutical and justifies CBZ as a candidate for a search for more crystalline phases.

In this contribution, we present two basic strategies for such a search, both of which might be generally applicable to APIs that contain carboxamide moieties. Strategy 1 maintains the carboxamide homosynthon but exploits the exterior H-bond donor and acceptor sites of the carboxamide homosynthon with a nonacid co-crystal former. Strategy 2 breaks the carboxamide homosynthon with carboxylic acid moieties, thereby generating the heterosynthon II.[20]



Strategy 1

As revealed herein, both strategies are fruitful, and we report full structural information on the acetone solvate of CBZ along with full structural data on 12 other multiple-component phases of CBZ. All 13 of these phases contain a cocrystal former, which are illustrated schematically in Scheme 1. Those generated from strategy 1 retain the carboxamide dimer motif, but there are three modes by which they exploit their remaining H-bonding sites: H-bond donor of CBZ to the H-bond acceptor of cocrystal former (CBZ/acetone, **1a**, Figure 1; CBZ/DMSO, **1b**, Figure 1; CBZ/benzoquinone, **1c**, Figure 2; and CBZ/terephthalaldehyde, **1d**, Figure 2); H-bond donor of the cocrystal former to the H-bond acceptor in CBZ (CBZ/saccharin, **1e**, Figure 3); and both H-bond donor and H-bond acceptors of the CBZ interacting with the cocrystal former (CBZ/nicotinamide, **1f**, Figure 4). Strategy 2 affords six new phases: CBZ/acetic acid, **1g**, Figure 5; CBZ/formic acid, **1h**, Figure 5; CBZ/butyric acid, **1i**, Figure 5; CBZ/trimesic acid, **1j**, Figure 6; CBZ/5-nitroisophthalic acid, **1k**, Figure 6; and CBZ/adamantane-1,3,5,7-tetracarboxylic acid, **1l**, Figure 7. Understanding the structural packing in these compounds allowed us to generate one more compound that is based upon extending the amide hydrogen-bond pattern with the use of the cocrystal former formamide, **1m**. Throughout the remainder of this paper we refer to **1a**−**1m** as supramolecular complexes and do not separately identify the solvated CBZ structures as peusodopolymorphs.[21]

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Table 1. Crystallographic Data for the Supramolecular Complexes 1a–1m

	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j	1k	1l	1m
formula	$C_{18}H_{18}N_2O_2$	$C_{17}H_{18}N_2O_2S_1$	$C_{18}H_{14}N_2O_2$	$C_{19}H_{15}N_2O_2$	$C_{22}H_{17}N_3O_4S_1$	$C_{21}H_{18}N_4O_2$	$C_{17}H_{16}N_2O_3$	$C_{16}H_{14}N_2O_3$	$C_{19}H_{20}N_2O_3$	$C_{24}H_{18}N_2O_7$	$C_{23.5}H_{20}N_3O_8$	$C_{44}H_{40}N_4O_{10}$	$C_{16}H_{15}N_3O_2$
stoichiometry	1:1	1:1	1:0.5	1:0.5	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:0.5	1:1
mol. wt.	294.34	308.36	290.31	303.33	419.46	358.39	296.32	282.29	324.37	446.40	472.42	784.80	281.31
crystal system	triclinic	triclinic	monoclinic	monoclinic	triclinic	monoclinic	monoclinic	monoclinic	triclinic	monoclinic	monoclinic	monoclinic	triclinic
space group	$P\bar{1}$	$P\bar{1}$	$P2_1/c$	$C2/c$	$P\bar{1}$	$P2_1/n$	$P2_1/c$	$P2_1/c$	$P\bar{1}$	$C2/c$	$C2/c$	$C2/c$	$P\bar{1}$
a (Å)	7.3985(15)	7.3254(19)	10.3335(15)	29.191(16)	7.5140(11)	5.0961(8)	5.1206(4)	5.2031(9)	9.1567(12)	32.531(5)	34.355(8)	18.388(4)	5.1077(11)
b (Å)	8.9054(18)	8.889(2)	27.611(5)	4.962(3)	10.4538(15)	17.595(3)	15.7136(13)	14.741(2)	10.1745(13)	5.2697(8)	5.3795(13)	12.682(3)	16.057(3)
c (Å)	11.873(2)	12.208(3)	4.9960(9)	20.316(11)	12.6826(18)	19.647(3)	18.4986(15)	17.882(3)	10.5116(14)	24.159(4)	23.654(6)	16.429(3)	17.752(4)
α (deg)	95.809(3)	94.840(5)	90	90	83.642(2)	90	90	98.132(3)	72.850(2)	90	90	90	73.711(3)
β (deg)	93.401(4)	94.926(5)	102.275(3)	92.105(8)	85.697(2)	90.917(3)	96.546(1)	90	70.288(2)	98.191(3)	93.952(6)	100.491(6)	89.350(3)
γ (deg)	101.362(3)	100.048(5)	90	90	75.411(2)	90	90	90	67.269(2)	90	90	90	88.636(3)
volume (Å^3)	760.5	775.8(3)	1392.9(4)	2941(3)	957.0(2)	1761.4(5)	1478.8(2)	1357.7(4)	834.91(19)	4099.3(11)	4361.2(2)	3767.1(1)	1397.1(5)
calc density (g cm^{-3})	1.285	1.346	1.232	1.370	1.456	1.352	1.331	1.381	1.290	1.450	1.408	1.384	1.337
Z	2	2	4	8	2	4	4	4	2	8	8	8	4
θ range	1.7–25.0	1.7–25.0	2.02–28.24	1.4–21.8	1.6–28.2	1.5–25.0	1.7–28.4	1.7–28.3	2.1–28.28	1.3–25.0	1.2–25.0	2.0–28.2	1.2–28.33
no. data/params	2449/202	2674/211	2707/199	1559/208	4372/283	3033/244	3529/203	3191/190	2684/217	3601/303	3839/310	4481/263	4610/379
T (K)	100	200	100	200	200	200	100	100	100	100	200	100	100
solvent	acetone	DMSO	methanol	methanol	ethanol	DMSO-methanol	acetic acid	formic acid	butyric acid	methanol	DMSO-methanol	ethanol	methanol
R1	0.0768	0.0795	0.0545	0.0351	0.0458	0.0522	0.0492	0.0533	0.0499	0.1556	0.0619	0.0433	0.0766
wR2	0.2669	0.2376	0.1358	0.0931	0.1204	0.1124	0.1335	0.1268	0.1137	0.3607	0.1763	0.0913	0.1633

Experimental Procedures

Crystals of **1c**, **1d**, **1e**, **1f**, **1j**, **1k**, **1l**, and **1m** were obtained via slow evaporation of 1:1 molar ratio of CBZ and cocrystal formers in an appropriate solvent. Solutions were not allowed to go to dryness. The remaining crystals were obtained by recrystallization from their respective solvents, which also acted as cocrystal formers. All crystallization experiments were conducted in an unmodified atmosphere, and solvents were dried by standard methods prior to use. All chemicals used are commercially available and were purchased from Aldrich. Melting points for **1a**–**1m** are given in Table 3.

Infrared spectroscopy was conducted using a Nicolet Avatar 320 FTIR. Differential scanning calorimetry was conducted on TA Instruments 2920 DSC. Thermogravimetric analysis was conducted using a TA Instruments 2950 Hi-Resolution TGA. X-ray powder diffraction was conducted on a Rigaku Miniflex Diffractometer using CuKα (λ = 1.540562, 30 kV, 15 mA). The powder data were collected over an angular range of 3–40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/min, and melting points were determined on a Mel-temp.

X-ray Crystallography. All single-crystal X-ray data were collected on a Bruker SMART-APEX CCD diffractometer. Lattice parameters were determined from least-squares analysis, and the reflection data were integrated using the program SAINT. Structures were solved by direct methods and refined by full matrix least-squares based on F^2 using SHELXTL.[22] Crystallographic data for **1a**–**1m** are presented in Table 1.

Results and Discussion

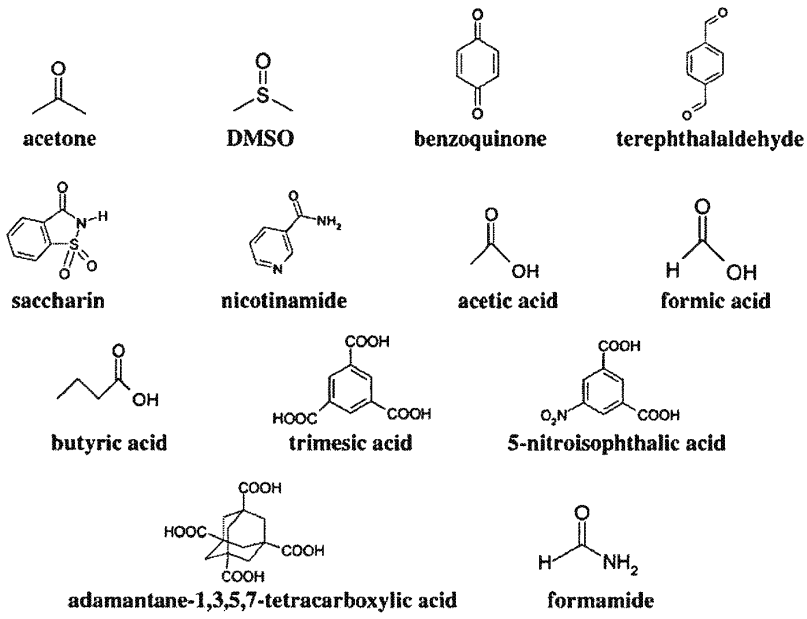
1a–**1m** form X-ray quality single crystals via a reaction between CBZ and cocrystal formers as described above. For the 10 new cocrystals reported, approximately 50 cocrystal formers were used with CBZ, giving a success ratio of 20%. The crystal structures of these supramolecular complexes are now described. In all crystal structures reported herein, **1a**–**1m**, the CBZ azepine ring adopts a boat conformation. **1a**–**1e** are related in that they contain the CBZ dimers that are sustained by the robust cyclic carboxamide homosynthon I and pack roughly in an eclipsed manner. This packing mode facilitates the formation of a cavity in which cocrystal formers can exist. Indeed, **1a** and **1b** are isostructural, and the asymmetric unit contains one molecule of CBZ and one solvent molecule.

The CBZ molecules in **1a** and **1b** form homosynthon I, and the voids that exist between adjacent CBZ dimers lie around crystallographic inversion centers. The salient hydrogen-bond distances for **1a** and **1b** are summarized in Table 2 and are within expected ranges for these types of hydrogen bonds.[23] The cocrystal formers interact with the anti N–H of the CBZ dimers to form N–H···O=C/S hydrogen bonds (Figure 1).

1c and **1d** exhibit a similar supramolecular structure to that of **1a** and **1b**, and benzoquinone and terephthalaldehyde molecules lie around crystallographic inversion centers. The asymmetric unit of **1c** and **1d** consists of one molecule of CBZ and a half molecule of benzoquinone and terephthalaldehyde, respectively. The difference between the crystal structures of **1c** and **1d** lies with the symmetry of homosynthon I. In supramolecular complex **1c**, homosynthon I was observed between inversion related CBZ molecules; however, in **1d** a 2_1-screw relates the CBZ molecules. As a result of the two different symmetry operations, the orientation of the CBZ azepine ring changes between **1c** and **1d** and influences the overall crystal packing. In short, the

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Scheme 1. Cocrystal Former Structures



benzoquinone and terephthalaldehyde molecules in **1c** and **1d** provide complementary molecular recognition sites for CBZ dimers in a similar way to those that exist in the acetone and DMSO solvates. However, the net result is a 1-D ribbon because of the presence of two acceptor sites (Figure 2).

In **1e**, homosynthon I is generated by inversion related CBZ molecules. The saccharin molecule acts as both H-bond donor and acceptor. An N−H···O hydrogen bond with the O=C group of the carboxamide is formed, while the anti N−H of the CBZ forms a weak N−H··· O=S hydrogen bond with weak metrics (d = 2.47 Å, D = 3.007(2) Å, θ = 113°). The inversion related saccharin molecules form auxiliary C−H···O hydrogen bonds (d = 2.21 Å, D = 3.196(2) Å, θ = 150°), and the overall hydrogen-bonding pattern can therefore be described as a 1-D array (Figure 3). The crystal packing of **1a**−**1e** can all be described as crinkled tape motifs with a zigzag arrangement along the hydrophobic regions of the CBZ azepine ring system.

Given these observations, one might ask what drives the CBZ molecule in the pure forms to adopt crystal

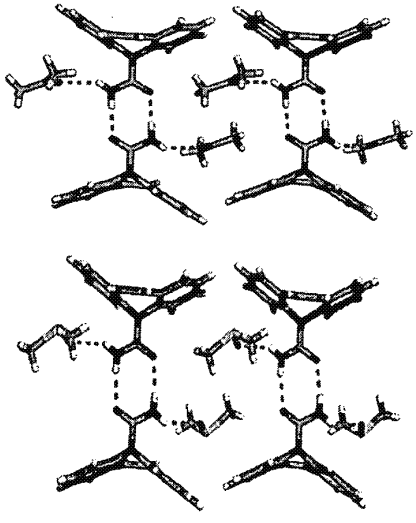


Figure 1. Illustration of the interactions between CBZ dimers and acetone (**1a**) or DMSO (**1b**). The cocrystal formers in these isostructural compounds are held by the anti N−H···O hydrogen bond of the CBZ dimers and thereby generate a void space between the CBZ dimers that is not present in the pure forms of CBZ.

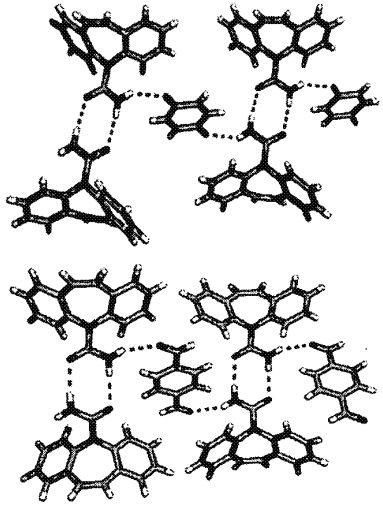


Figure 2. Interaction of CBZ dimers with cocrystal formers in structures **1c** and **1d**. The cocrystal formers are held by the anti N−H···O hydrogen bond of the CBZ dimers and not only generate a void space between the CBZ dimers but also sustain a 1-D hydrogen-bonded network.

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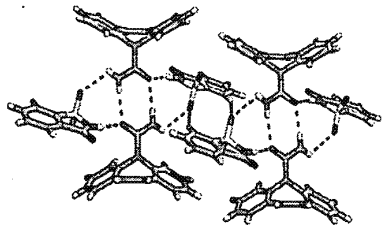


Figure 3. Illustration of the interaction between CBZ dimers and saccharin (**1e**). The cocrystal former in this structure is held by C=O···H–N hydrogen bonds with the CBZ dimers and is elongated into a 1-D network by C–H···O interactions between saccharin molecules.

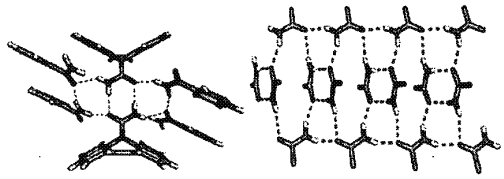


Figure 4. Cocrystal former, nicotinamide, links the CBZ homosynthon by forming a hydrogen-bonded strip in **1e**. For clarity, unwanted atoms are removed, and the hydrogen-bonded strip is shown in the adjacent figure.

packing with unsatisfied amide N–H moieties? Comparison of the supramolecular complexes **1a**–**1e** with the pure forms suggests that approach of two molecules of CBZ via the anti N–H···O=C is sterically disfavored because of the shape of the CBZ dimers. However, the supramolecular complexes satisfy these N–H moieties and facilitate a more open crystal packing (i.e., eclipsed with large cavities in **1a**–**1e** vs staggered with no large cavities but unsatisfied N–H moieties in **1**).

1f also exhibits an inversion related homosynthon I between CBZ molecules. However, an unexpected exterior hydrogen-bonded pattern that is translation related exists between cocrystal former, nicotinamide, and CBZ molecules (Figure 4). In this way, the donors and acceptors of both amide groups are fulfilled. However, the nitrogen atom within the ring structure of the nicotinamide does not form any strong hydrogen bonds. The crystal packing illustrates hydrophobic interlocking rows with $\pi\cdots\pi$ interactions between the CBZ hoods and the nicotinamide rings.

In summary, structures **1a**–**1f** retain the carboxamide homosynthon, I. We now turn our attention to exploitation of heterosynthon II (i.e., strategy 2). One would expect heterosynthon formation to be preferred over homosynthon formation if there is an appropriate complementarity between the two components of the heterosynthon. In the case of carboxamide/carboxylic acid heterosynthons, the strongest hydrogen-bond donor (acid O–H) should hydrogen bond with the best acceptor atom (amide C=O).[24] This leaves the slightly weaker donor (amide N–H) to hydrogen bond to the weaker acceptor group (acid C=O). It should be noted that this heterosynthon minimizes intermolecular lone-pair repulsions that would occur between the acid O–H and carbonyl moieties in hydrogen-bonded chains constructed from the homosynthon and N–H···O hydrogen bonds.[18,23]

X-ray quality single crystals of **1g** were grown from

Table 2. Geometric Parameters of Intermolecular Interactions[a]

	interaction	*d* (Å)	*D* (Å)	*θ* (deg)
1a	$N-H_s\cdots O$	1.98	2.928(4)	156
	$N-H_a\cdots O$	2.17	3.018(4)	140
1b	$N-H_s\cdots O$	1.98	2.960(6)	164
	$N-H_a\cdots O$	2.11	2.966(6)	141
1c	$N-H_s\cdots O$	1.90	2.899(2)	171
	$N-H_a\cdots O$	2.21	3.116(2)	148
1d	$N-H_s\cdots O$	2.07	2.947(3)	144
	$N-H_a\cdots O$	2.15	3.079(3)	152
1e	$N-H_s\cdots O$	1.95	2.954(2)	174
	$N-H\cdots O=C$	1.75	2.724(2)	161
1f	$N-H_s\cdots O$	1.90	2.868(2)	160
	$N-H_a\cdots O$	2.30	3.040(2)	129
	$N-H\cdots O=C$	1.95	2.871(2)	150
	$N-H_a\cdots O$	2.06	2.986(3)	152
1g	$N-H_s\cdots O$	2.09	3.016(2)	151
	$N-H_a\cdots O$	2.25	2.919(2)	122
	$O-H\cdots O=C$	1.59	2.553(2)	167
1h	$N-H_s\cdots O$	2.02	2.939(3)	150
	$N-H_a\cdots O$	2.06	2.894(2)	139
	$O-H\cdots O=C$	1.58	2.548(2)	167
1i	$N-H_s\cdots O$	2.04	2.963(2)	152
	$N-H_a\cdots O$	2.44	2.929(2)	109
	$O-H\cdots O=C$	1.62	2.589(2)	170
1j	$N-H_s\cdots O$	1.95	2.864(10)	149
	$O-H\cdots O=C$	1.57	2.542(10)	169
	$O-H\cdots O$		2.590(9)	
	$O-H\cdots O$	1.63	2.607(9)	171
1k	$N-H_s\cdots O$	1.96	2.898(4)	153
	$O-H\cdots O=C$	1.53	2.489(3)	163
	$O-H\cdots O$	1.63	2.599(3)	166
1l	$N-H_s\cdots O$	1.91	2.895(2)	164
	$N-H_a\cdots O$	2.09	2.899(2)	136
	$O-H\cdots O=C$	1.66	2.637(2)	170
	$O-H\cdots O=C$	1.69	2.675(2)	178
1m	$N-H_s\cdots O$	1.94	2.922(2)	164
	$N-H_a\cdots O$	2.11	2.974(3)	142
	$N-H_s\cdots O$	1.87	2.872(3)	171
	$N-H_a\cdots O$	2.04	2.911(3)	144
	$N-H_s\cdots O$	1.94	2.947(3)	172
	$N-H_s\cdots O$	1.94	2.941(3)	172
	$N-H_s\cdots O$	1.89	2.889(3)	170
	$N-H_a\cdots O$	1.95	2.875(3)	150

[a] The syn and anti N–H groups of the carboxamides are referred with subscript s and a, respectively. Neutron normalized hydrogen atom position are used for the intermolecular calculations.

Table 3. Melting Points of CBZ Cocrystals (°C)

carbamazepine (CBZ)	**1**	190–192°
CBZ.acetone (1:1)	**1a**	189°
CBZ.DMSO (1:1)	**1b**	189°
CBZ.benzoquinone (2:1)	**1c**	170°
CBZ.terephthalaldehyde (2:1)	**1d**	124°
CBZ.saccharin (1:1)	**1e**	174°
CBZ.nicotinamide (1:1)	**1f**	151–161°
CBZ.acetic acid (1:1)	**1g**	187°
CBZ.formic acid (1:1)	**1h**	187°
CBZ.butyric acid (1:1)	**1i**	120°
CBZ.trimesic acid (1:1)	**1j**	278° (dec)
CBZ.5-nitroisophthalic acid (1:1)	**1k**	190° (dec)
CBZ.adamantane-1,3,5,7-tetracarboxylic acid (2:1)1	**1l**	258–260°
CBZ.formamide (1:1)	**1m**	142–144°

acetic acid and exhibit the expected heterosynthon II. The anti N–H of the amide moiety forms an N–H···O hydrogen bond with the acetic acid carbonyl group instead of its own amide carbonyl group. However, an inversion center relates two adjacent heterosynthons, thereby generating a four-component supramolecular complex (Figure 5). These supramolecular complexes are connected to adjacent supramolecular complexes through C–H···O hydrogen bonds (d = 2.32 Å, D = 3.368(2) Å,

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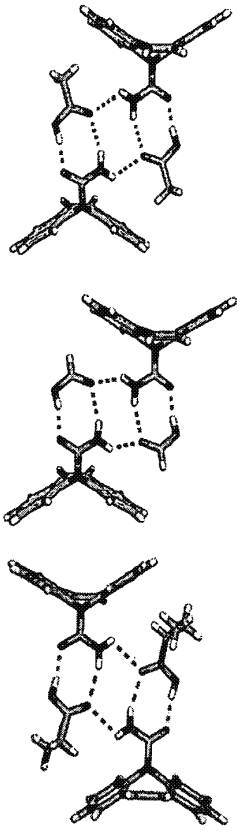


Figure 5. Heterosynthon **II** formed with cocrystal formers, acetic acid (**1g**), formic acid (**1h**), and butyric acid (**1i**). The anti-N−H group of CBZ is utilized to form the inversion related N−H···O hydrogen bond with carboxylic acid C=O of the cocrystal former, thereby generating a four-component supramolecular complex rather than a tape.

θ = 163°) that are glide related. The CBZ azepine ringsorient above and below the hydrogen-bonded patterns and thereby form a hydrophobic region.

Crystallization from formic acid afforded an isostructural four-component supramolecular complex, **1h** (Figure 5). The C−H moiety of the formic acid does not form any strong intermolecular interactions. Crystallization of CBZ from butyric acid resulted in **1i**, which exhibits a similar hydrogen-bonded motif (Figure 5). The butyric alkyl groups fold to facilitate formation of the four-component motif. The anti N−H···O hydrogen bond is bent, presumably because of the relative size of the alkyl group (matrix for the anti N−H···O in structure **1g**: d = 2.25 Å, D = 2.919(2) Å, θ = 122°; **1h**: d = 2.06 Å, D = 2.894(2) Å, θ = 139°; **1i**: d = 2.44 Å, D = 2.929(2) Å, θ = 109°).

The structures presented in Figure 5 suggest that the four-component supramolecular complex would be sterically disfavored if sterically bulky carboxylic acids were to be utilized. The 1:1 supramolecular complex, **1j**, of CBZ and trimesic acid reveals this to be the case. The hydrogen-bonding pattern in the crystal structure of **1j** is 1-D and consists of both acid−acid homosynthons and acid−amide heterosynthons. Two carboxylic acid groups of the trimesic acid are free to form homosynthons; and

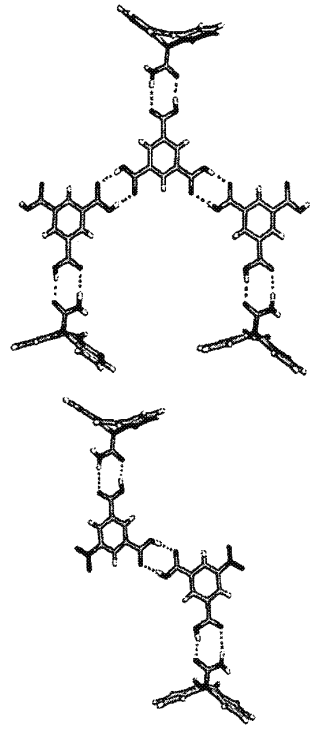


Figure 6. Illustration of portions of the structures observed in compounds **1j** and **1k**. One carboxylic acid group in the cocrystal former is utilized to form a heterosynthon, and the other carboxylic acid groups form homosynthons that propagate a 1-D hydrogen-bonded pattern in **1j** and a 0-D discrete pattern in **1k**.

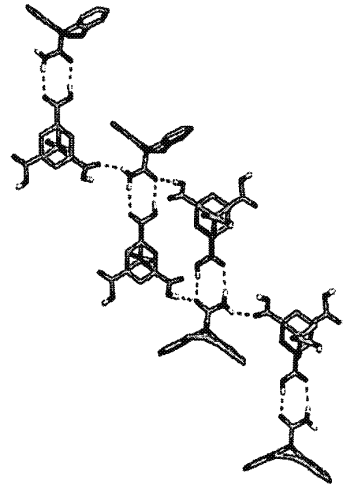


Figure 7. All the hydrogen-bonding sites of the cocrystal former are utilized in **1l**. Notice the heterosynthon **II** and absence of any carboxylic acid dimer homosynthons.

these sustain a 1-D zigzag array. The third carboxylic acid group bonds to CBZ molecules via heterosynthon II. Replacement of one carboxylic acid group in trimesic acid with a size matching nitro group, 5-nitroisophthalic acid, leads to a closely related structure in which a discrete four-component supramolecular complex is

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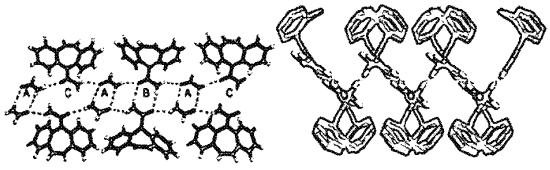


Figure 8. All the hydrogen-bonding sites of the CBZ molecule are utilized with the formamide cocrystal former in the supramolecular complex **1m**. Notice the homosynthon **I** formed by formamide molecules. The adjacent illustration represents the cross-section view of the hydrogen-bonded 2-D structure.

generated, **1k**. Indeed, **1k** is isostructural with **1j**, and its crystal structure consists of a carboxylic acid homosynthon and a heterosynthon (Figure 6). The anti N−H group of the carboxamide moieties forms N−H···O hydrogen bonds with disordered solvent molecules.

Adamantane-1,3,5,7-tetracarboxylic acid would be expected to increase the dimensionality further. Supramolecular complex **1l** was obtained when the cocrystallization was carried out with a 1:1 ratio of CBZ and adamantane-1,3,5,7-tetracarboxylic acid from either ethanol or methanol. The asymmetric unit of **1l** consists of one molecule of CBZ and a half molecule of adamantane-1,3,5,7-tetracarboxylic acid, which lies at a 2-fold rotation axis. The structure contains heterosynthon II and does not form acid−acid homosynthons (Figure 7). The two carboxylic acid groups of the cocrystal former generate heterosynthon II with two CBZ molecules, and the exterior hydrogen-bond acceptor/donor sites of the CBZ molecules interact with the remaining acid groups by means of anti N−H···O=C and acid O−H···O=C H bonds. In this fashion, all the hydrogen-bonding donor/acceptor sites of CBZ molecule and adamantane tetra acid are satisfied. The resulting H-bond network is 3-D in nature and free of solvent molecules.

Structures **1g**−**1l** confirm that heterosynthon II can indeed be formed reliably and that they can generate supramolecular structures and networks that are rational and prototypal for an even wider range of related structures.

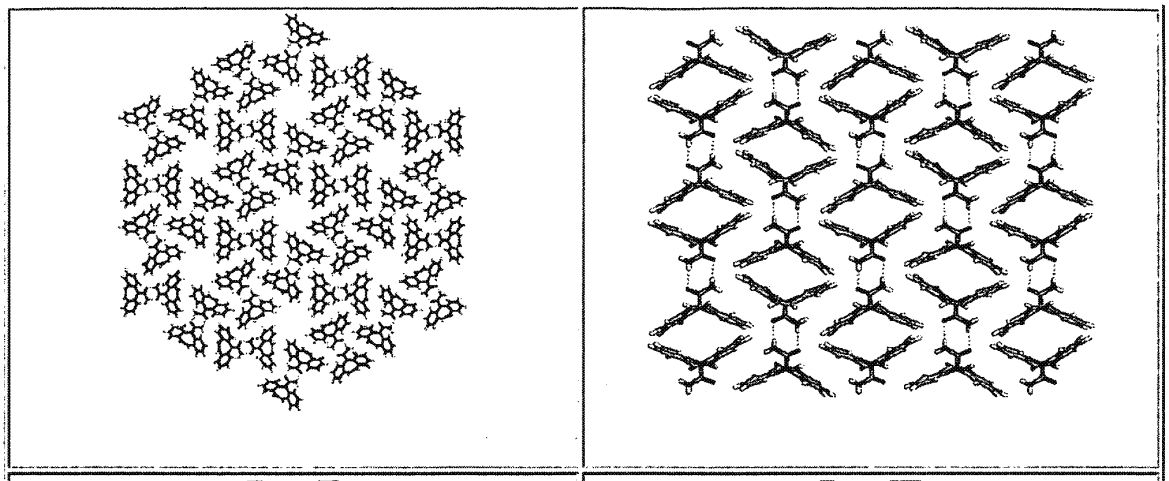
As revealed by Figure 9, there is a considerable degree of superstructural diversity in the crystal packing observed within compounds **1a**−**m**. Indeed, they also differ from the crystal packing exhibited by forms II and III of CBZ itself. An analysis of **1a**−**m** reveals that it is possible for the CBZ carboxamide group to form conventional translation or 2_1-screw/glide symmetry tapes that are commonly observed in amide hydrogen-bonding patterns. However, the conventional motif appears to be impossible in pure CBZ because of the boat shaped azepine ring that sterically blocks the exterior amide hydrogen-bond acceptor/donor. Analysis of the aliphatic acid phases **1g**−**1i** provides the hint that crystallizing CBZ with a simple aliphatic amide might extend the hydrogen-bonded pattern, using the exterior amide acceptor/donor in a manner similar to that observed in the approach as in **1g**−**1i**. Another viable pattern could utilize the exterior hydrogen-bond acceptor/donor of the CBZ homosynthon I with the exterior hydrogen-bond acceptor/donor sites of a carboxamide cocrystal former. A third possibility would be a structure similar to that of supramolecular complex **1f** that does not follow the conventional amide hydrogen-bonded pattern.

1m was prepared to test which of these possible structures occurs. **1m** forms when CBZ is crystallized with formamide in methanol.[25] The asymmetric unit of **1m** consists of two molecules of CBZ and two molecules of formamide in the triclinic space group $P\bar{1}$. Both formamide molecules in the asymmetric unit form homosynthon I, hereafter denoted as A. The two CBZ molecules form two different inversion related homosynthons, denoted B and C, respectively. The exterior of CBZ homosynthon B hydrogen bonds with the two pairs of A homosynthons to generate a six-component planar supramolecular complex, A-B-A. The exterior of the A-B-A supramolecular complex consists of two formamide anti N−H donor groups and two C=O acceptor groups. These donor/acceptor moieties hydrogen bond with the second CBZ dimer, C, of the asymmetric unit. In the hydrogen-bonding pattern, the formamide and the CBZ dimers alternate through exterior hydrogen bonding (Figure 8). In this fashion, a 2-D hydrogen-bonded pattern is generated. **1m** represents a rare example of a crystal structure that contains two chemically different amide groups. Previous examples include a urea-carboxamide cocrystal[26] and an amide-secondary amide cocrystal[27] that could be described as being examples of homosynthons between two different molecules (i.e., amide-amide′ homosynthons). However, **1m** is to our knowledge unprecedented in that it contains two different molecules, both of which form the amide-amide homosynthon, not the amide-amide′ homosynthon.

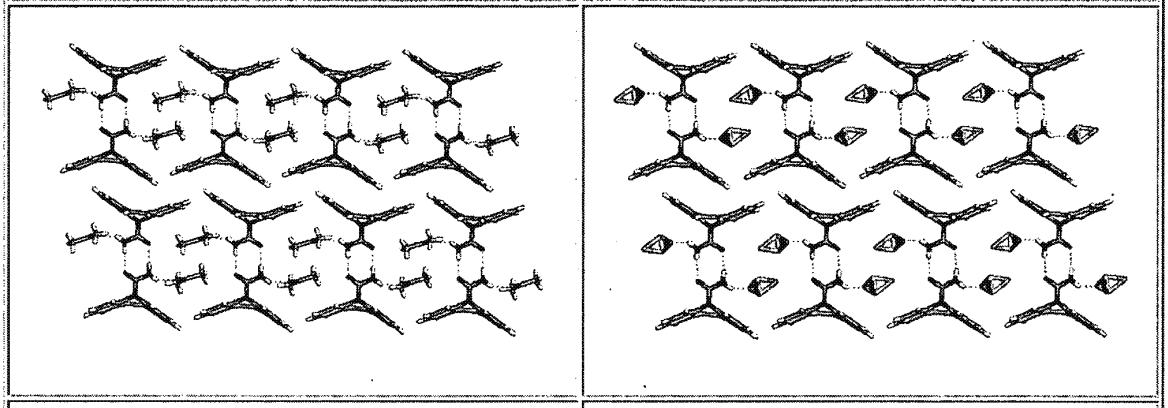
Conclusion

In summary, we have exercised a paradigm based on modular design in which cocrystal formers can be exploited for their ability to form supramolecular interactions with APIs. The result is a diverse range of multiple-component crystalline phases of a well-known API with previously documented solubility and polymorphism problems. Of particular note is that the multiple-component phases are formed in preference over a low solubility hydrate of CBZ (there were no attempts to eliminate adventitious moisture in our experiments). The immediate implication of our results is that it should be generally possible to exploit APIs that contain amide moieties for formation of a diverse range of new multiple-component crystalline phases if appropriate cocrystal formers are employed. The broader implications are that the cocrystal former strategy might be applied even more generally and that it could ultimately become an essential component in optimization of the drug design, processing, and delivery procedures. Indeed, we recently demonstrated that pyridinecarboxylic acid heterosynthons might be exploited in a similar fashion,[15] and there are numerous examples of other heterosynthons that will be expected to be suitable in the context of APIs. Most importantly, the cocrystal former approach means that the APIs are not covalently modified, and a diverse range of new compositions of matter with different physical properties is readily accessible. Simply put, we have applied new tricks to old procedures and molecules. Future work will concen-

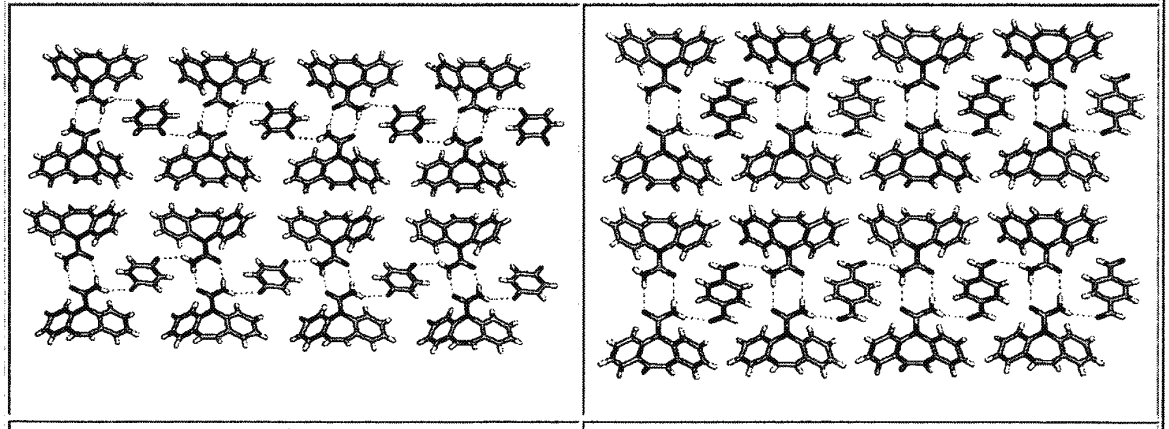
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Form II **Form III**

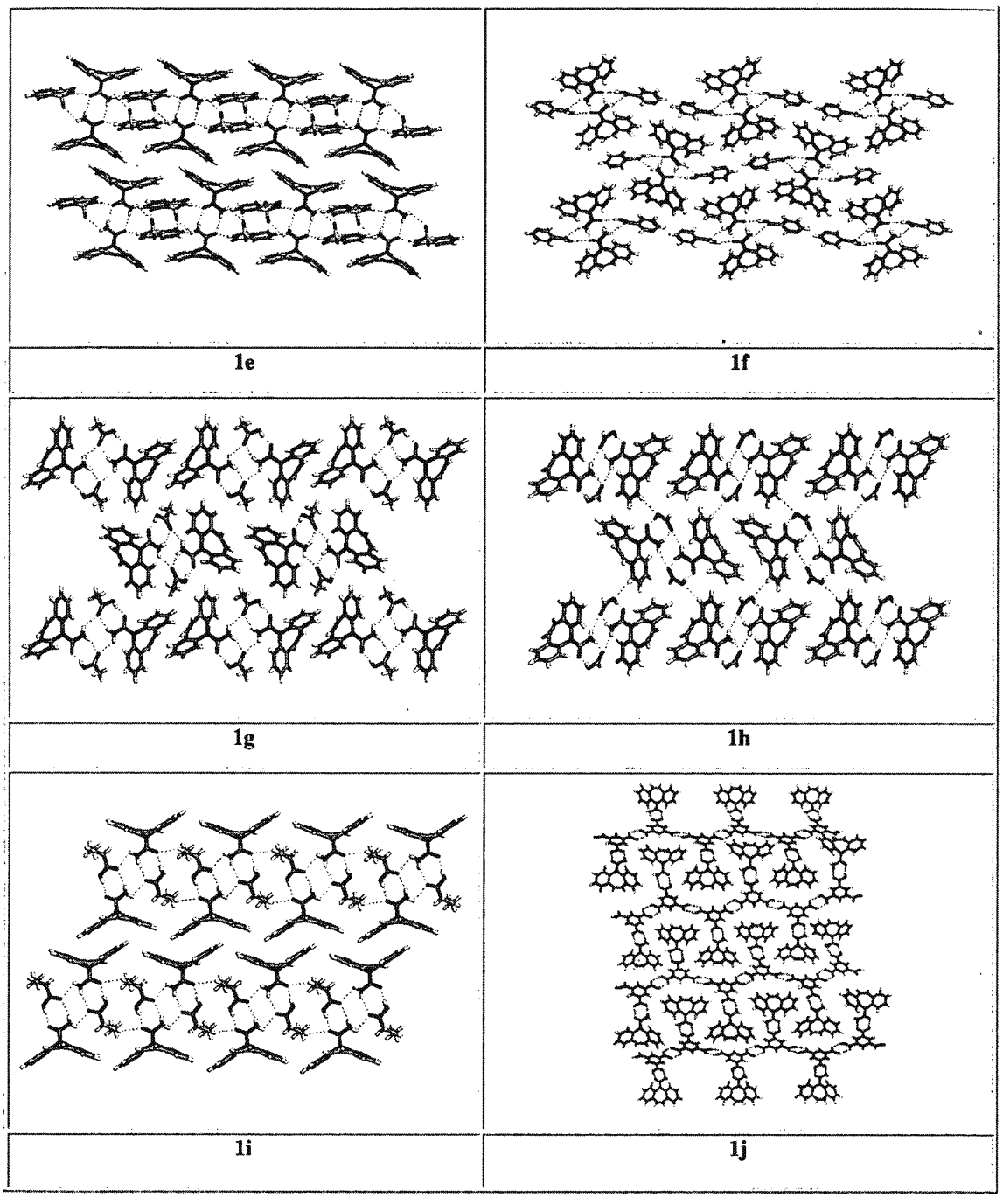


1a **1b**



1c **1d**

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1e 1f

1g 1h

1i 1j

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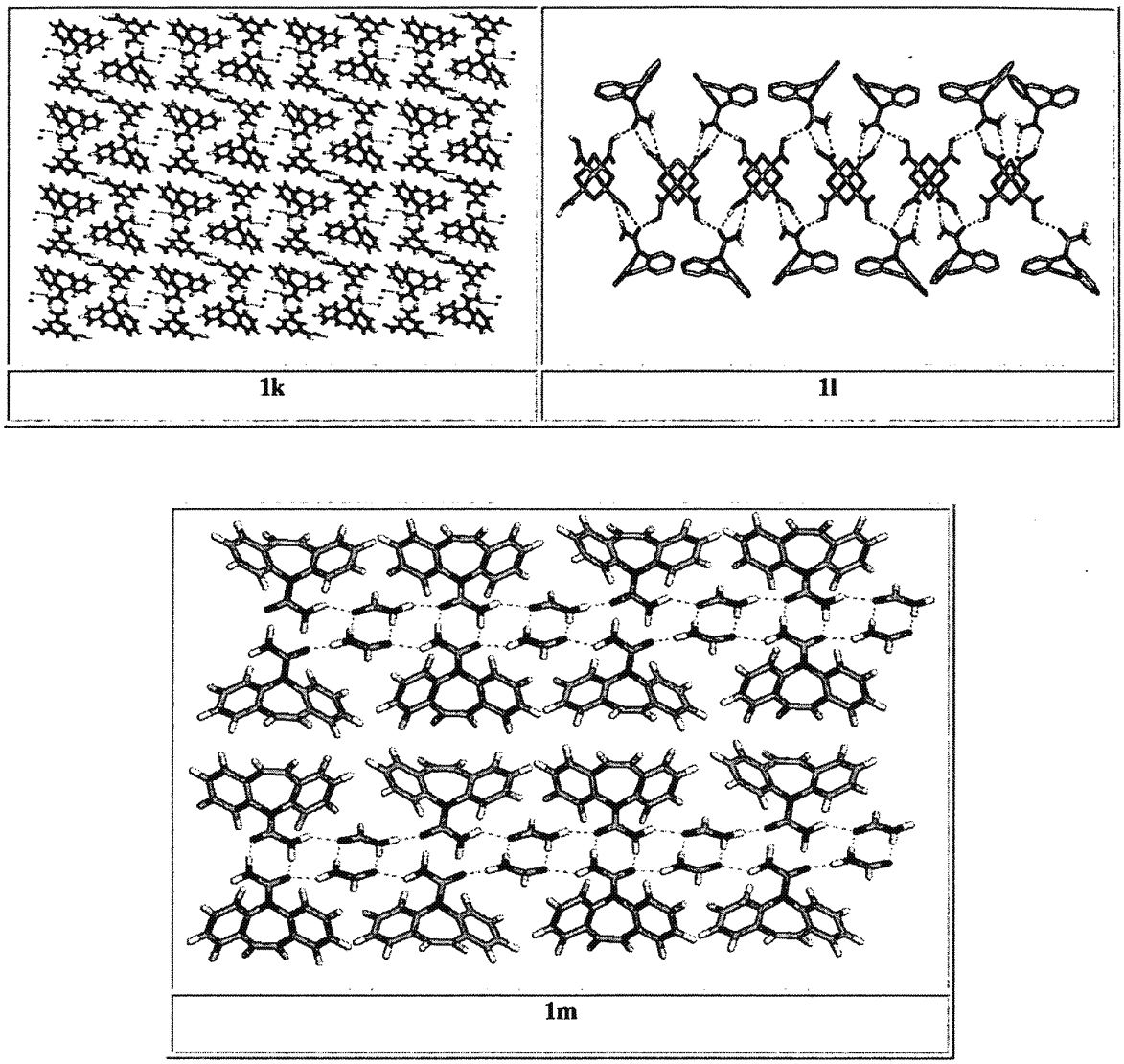


Figure 9. Crystal packing of pure CBZ (forms II and III) and supramolecular complexes **1a**−**1m**.

Ⓦ 3D rotatable images in PDB format of Ⓦ **1f** , Ⓦ **1g** , and Ⓦ **1m** are available.

trate upon other supramolecular synthons, the use ofGRAS[28] or food additives as cocrystal formers.[29] structure/functional property studies, and high-throughput crystallization experiments.

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Note Added after ASAP Posting

An earlier version of this paper was posted ASAP on the Web on June 17, 2003. Links to web-enhanced files were added to a new electronic version posted October 16, 2003.

Supporting Information Available: Crystallographic information files for compounds **1a**−**1m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) Saccharin, nicotinamide (vitamin B3), and acetic acid are appearing on the Generally Recognized As Safe (GRAS) list.[28] The list is maintained by the US Food and Drug Administration.

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The formation of paracetamol (acetaminophen) adducts with hydrogen-bond acceptors

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The crystal structures of five hemiadducts of paracetamol with 1,4-dioxane, *N*-methylmorpholine, morpholine, *N*,*N*-dimethylpiperazine and piperazine and a related 1:1 adduct of paracetamol with 4,4′-bipyridine are described. All structures are characterized by the formation of chains of paracetamol molecules, which are linked *via* either OH···O=C interactions [*C*(9) chains in graph-set notation] or NH···O=C interactions [*C*(4) chains], depending on the presence or absence of substituent groups on the guest molecule. In all cases except for the morpholine and bipyridine adducts these chains are connected by hydrogen-bond interactions with the guest molecules, which reside on crystallographic inversion centres. In the bipyridine adduct this linkage also involves a π-stacking interaction; in the morpholine adduct it is formed between the OH groups of two opposed paracetamol molecules. Most adducts (that with 4,4′-bipyridine is an exception) decompose on heating to give monoclinic paracetamol. This is the first systematic study of a series of co-crystals containing paracetamol.

1. Introduction

There have been a number of detailed studies on the polymorphic behaviour of paracetamol (acetaminophen, *p*-hydroxylacetanilide or Tylenol). Form I, which is monoclinic, was first characterized by Haisa *et al.* (1976), and has since been shown to be the thermodynamically more stable form. Form II is orthorhombic and was also described by Haisa *et al.* in 1974 (Haisa *et al.*, 1974). The orthorhombic form can be grown using a single orthorhombic crystal as a seed from a super-saturated aqueous solution of paracetamol. This method, however, can result in the crystals changing to the monoclinic form if left in contact with the solution for any length of time (Nichols & Frampton, 1998). The same authors showed that the only method that gives the orthorhombic polymorph reproducibly is growth from the melt. They also showed that this form is stable if dried and stored in a stoppered vial and that neither grinding nor compression induces a transition to the monoclinic form. In a very careful study, Boldyreva *et al.* (2000) have shown that application of hydrostatic pressures up to 4.2 GPa does not induce a transition from the monoclinic to the orthorhombic form. The behaviour of the orthorhombic form is of interest for its ability to undergo plastic deformation when compressed, thereby facilitating the production of tablets of paracetamol.

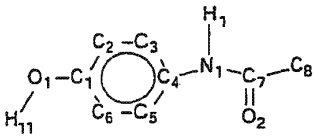
With the exception of our own recent report of paracetamol trihydrate (McGregor *et al.*, 2002), little structural work appears to have been carried out on solvates or other co-crystals of paracetamol, although a thermochemical study showed the existence of a hemisolvate of paracetamol with

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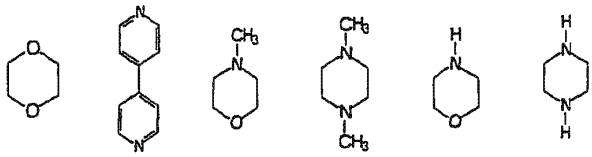
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1,4-dioxane (Fachaux *et al.*, 1995). In this report, we describe the preparation and characterization of six new adducts of paracetamol with 1,4-dioxane, 4,4′-bipyridine, *N*-methylmorpholine, *N*,*N*-dimethylpiperazine, morpholine and piperazine (these are referred to as *guest molecules* below; see Schemes). All these molecules, except for morpholine, can be considered to be at least pseudo-centrosymmetric with respect to their hydrogen-bonding properties.



Paracetamol, with atomic numbering scheme.



Guest molecules used to form adducts with paracetamol. Left to right: dioxane, bipyridine, *N*-methylmorpholine, *N*,*N*-dimethylpiperazine, morpholine and piperazine.

2. Experimental

2.1. Synthesis

All starting materials were obtained from Sigma-Aldrich except for 1,4-dioxane (May & Baker) and were used as received.

Paracetamol:0.5 1,4-dioxane. A saturated solution of paracetamol (1.51 g, 10 mmol) in 1,4-dioxane (2 cm^3, 23 mmol) was refluxed and allowed to cool. Colourless crystals were formed overnight at 293 K according to the published procedure (Fachaux *et al.*, 1995).

Paracetamol:4,4′-bipyridine. Paracetamol (0.51 g, 3.40 mmol) was refluxed with an equimolar amount of 4,4′-bipyridine (0.52 g, 3.33 mmol) in ethanol (1 cm^3). Pale-yellow needle-like crystals were formed on standing overnight at room temperature.

Paracetamol:0.5 N-methylmorpholine. Paracetamol (0.43 g, 2.85 mmol) and *N*-methylmorpholine (1 cm^3, 9.11 mmol) were refluxed and allowed to cool. The flask was maintained at 277 K, leading to the formation of colourless rod-shaped crystals.

Paracetamol:0.5 N,N-dimethylpiperazine. Paracetamol (0.55 g, 3.64 mmol) and *N*,*N*-dimethylpiperazine (3 cm^3, 22.2 mmol) were refluxed together and allowed to cool. A large excess of dimethylpiperazine was required to dissolve the paracetamol completely. The flask was maintained at 277 K leading to the formation of colourless rod-shaped crystals.

Paracetamol: 0.5 piperazine. Paracetamol (0.62 g, 4.1 mmol) was refluxed together with piperazine (0.35 g, 4.1 mmol) in ethanol (1 cm^3). Colourless crystals formed on cooling to 293 K.

Paracetamol:0.5 morpholine. Paracetamol (0.57 g, 3.8 mmol) was refluxed with morpholine (0.37 g, 4.3 mmol). Colourless crystals formed directly from the reaction mixture after a week at 277 K.

Ethanol was required in the reactions of paracetamol with piperazine and 4,4′-bipyridine because these compounds are both solids at room temperature.

2.2. Differential scanning calorimetry (DSC)

DSC traces were recorded using a Perkin Elmer Pyris DSC 1. Samples were contained in open aluminium pans and purged with helium during the temperature scans to facilitate the removal of any volatile products of thermal decomposition. Samples were heated from 298 K to 453 K at a rate of 10 K min^{-1}.

2.3. Crystallography

X-ray diffraction intensities were collected on either a Stoe Stadi-4 diffractometer with Cu $K\alpha$ radiation or a Bruker SMART APEX CCD diffractometer with Mo $K\alpha$ radiation. Both instruments were equipped with Oxford Cryosystems low-temperature devices. An absorption correction for the four-circle data was applied using ψ scans [*SHELXTL* (Sheldrick, 1997*a*), based on the procedure described by North *et al.* (1968)]; the multiscan procedure *SADABS* [(Sheldrick, 1997*b*), based on the procedure described by Blessing (1995)] was applied to the CCD data sets. All structures were in space group $P2_1/c$, except the morpholine adduct, which formed in $P2_12_12_1$. All structures were solved by direct methods and refined by full-matrix least squares against F^2 using all data (*SHELXTL*). H atoms were placed in calculated positions and allowed to ride on their parent atoms; methyl groups were treated with the Sheldrick (1997) rotating rigid group model. H atoms involved in hydrogen bonding were located in difference maps and refined freely. All non-H atoms were modelled with anisotropic displacement parameters.

One of the two crystallographically independent dioxane molecules in the 1,4-dioxane adduct was disordered over two orientations about a crystallographic inversion centre. The occupancies of the two components were fixed at 0.75 and 0.25 after competitive refinement. Similarity restraints were applied to the geometries and displacement parameters of the two components. The program *ROTAX* (Cooper *et al.*, 2002) suggested that the crystal may have been twinned by a twofold rotation about the [100] direct lattice direction. Incorporation of this into the model reduced *R*1 slightly from 7.02% to 6.86%, with a twin scale factor of 2.6 (3)%. This is barely significant, and the twinning is omitted in the model presented here.

In the *N*-methylmorpholine adduct, the *N*-methylmorpholine is disordered over a crystallographic inversion centre with

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Table 1
Experimental details.

All data were collected at 150 K.

	1,4-Dioxane adduct	Dimethylpiperazine adduct	*N*-methylmorpholine adduct
Crystal data			
Chemical formula	$2[C_6H_9O_2N][C_4H_8O_2]$	$2[C_8H_9NO_2][C_6H_{14}N_2]$	$2[C_8H_9NO_2][C_5H_{11}NO]$
Chemical formula weight	390.43	416.52	403.47
Cell setting, space group	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/c$
a, b, c (Å)	12.421 (5), 12.056 (4), 13.396 (3)	10.6970 (9), 11.0240 (9), 9.4896 (8)	10.5749 (8), 11.0221 (8), 9.3894 (7)
β (°)	91.51 (3)	100.684 (2)	101.145 (2)
V (Å^3)	2005.4 (11)	1099.65 (16)	1073.77 (14)
Z	4	2	2
D_x (Mg m^{-3})	1.293	1.258	1.248
D_m (Mg m^{-3})	Not measured	Not measured	Not measured
Radiation type	Cu $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
No. of reflections for cell parameters	80	3488	2729
θ range (°)	20–22	2.5–29	2.5–27.5
μ (mm^{-1})	0.795	0.088	0.090
Temperature (K)	220 (2)	150 (2)	150 (2)
Crystal form, colour	Lath, colourless	Plate, colourless	Rod, colourless
Crystal size (mm)	0.78 × 0.19 × 0.16	0.56 × 0.18 × 0.08	0.34 × 0.09 × 0.07
Data collection			
Diffractometer	Stoe Stadi-4	Bruker SMART APEX CCD	Bruker SMART APEX CCD
Data collection method	ω–θ scans	φ and ω scans	φ and ω scans
Absorption correction	Empirical	Multiscan	Multiscan
T_{min}	0.602	0.833	0.792
T_{max}	0.826	1	0.962
No. of measured, independent and observed reflections	4865, 3499, 2508	7034, 2724, 2512	6517, 2444, 1890
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.0532	0.0164	0.0221
θ_{max} (°)	69.79	29.08	27.49
Range of h, k, l	$-15 \rightarrow h \rightarrow 15$ $0 \rightarrow k \rightarrow 14$ $0 \rightarrow l \rightarrow 15$	$-8 \rightarrow h \rightarrow 14$ $-15 \rightarrow k \rightarrow 14$ $-12 \rightarrow l \rightarrow 12$	$-13 \rightarrow h \rightarrow 13$ $-14 \rightarrow k \rightarrow 14$ $-11 \rightarrow l \rightarrow 12$
No. and frequency of standard reflections	3 every 60 min	Not measured	Not measured
Intensity decay (%)	10.9	0	0
Refinement			
Refinement on	F^2	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.0702, 0.2243, 1.078	0.0525, 0.1339, 1.059	0.0408, 0.1082, 0.973
No. of reflections and parameters used in refinement	3499, 285	2724, 146	2444, 147
H-atom treatment	Riding	Riding/All H-atom parameters refined	Riding/All H-atom parameters refined
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.125P)^2 + 1.1494P]$ where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.069P)^2 + 0.4625P]$ where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0658P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.002	0.009	0.000
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.503, −0.260	0.401, −0.193	0.216, −0.220
Extinction method	*SHELXL*	None	*SHELXL*
Extinction coefficient	0.0019 (6)	0	0.008 (3)

	Piperazine adduct	4,4′-Bipyridine adduct	Morpholine adduct
Crystal data			
Chemical formula	$2[C_8H_9NO_2][C_4H_{10}N_2]$	$[C_8H_9NO_2][C_{10}H_8N_2]$	$2[C_8H_9NO_2][C_4H_9O]$
Chemical formula weight	388.46	307.35	389.45
Cell setting, space group	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/c$	Orthorhombic, $P2_12_12_1$
a, b, c (Å)	15.893 (5), 5.1664 (17), 12.993 (4)	11.2906 (10), 24.103 (2), 11.5526 (10)	7.2791 (9), 14.6277 (18), 18.303 (2)

the N and O atoms sharing an equivalent site. A composite scattering factor $[0.5f(N) + 0.5f(O)]$ was used for this site; the occupancy of the methyl group was fixed at 0.5.

A consistent numbering scheme was used for the paracetamol molecules in all structures and this is shown in the schemes above. Where there is more than one paracetamol molecule in the asymmetric unit the labels in the schemes are augmented with the letters *A* and *B*. Labels for atoms forming part of the guest molecules carry the letters *S*, *T etc*. A full listing of crystal, data collection and refinement parameters is given in Table 1; a set of hydrogen-bonding parameters is given in Table 2.[1] The figures were produced using *CAMERON* (Watkin *et al.*, 1993). Other analyses utilized the PC version of the program *PLATON* (Spek, 2002; Farrugia, 1999).

3. Results

3.1. Paracetamol

Crystal structures of the monoclinic and orthorhombic polymorphs of paracetamol have been reported several times, but here we have used the structures reported by Nichols & Frampton (1998) [Cambridge Structural Database (CSD; Allen *et al.*, 1983) reference codes HXACAN07 and HXACAN08]. Our motive for discussing them here is to highlight certain features of their graph sets that enable structural relationships to be drawn between them and the adducts that form the subject of the rest of this paper.

Packing in both polymorphs is dominated by the formation of NH···OH and OH···O=C hydrogen bonds (Fig. 1) giving rise to layered two-dimensional networks. Both polymorphs of paracetamol have identical graph sets (Bernstein *et al.*, 1995), in which the

[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: AN0622). Services for accessing these data are described at the back of the journal.

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Table 1 (continued)

	Piperazine adduct	4,4'-Bipyridine adduct	Morpholine adduct
β (°)	113.633 (5)	96.1484 (16)	90
V (Å^3)	977.4 (6)	3125.8 (5)	1948.9 (4)
Z	2	8	4
D_x (Mg m^{-3})	1.320	1.306	1.327
D_m (Mg m^{-3})	Not measured	Not measured	Not measured
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
No. of reflections for cell parameters	1227	5375	3801
θ range (°)	2.5–29	2–28.5	2.5–24.5
μ (mm^{-1})	0.093	0.087	0.096
Temperature (K)	150 (2)	150 (2)	150 (2)
Crystal form, colour	Plate, colourless	Block, colourless	Block, colourless
Crystal size (mm)	0.77 × 0.28 × 0.11	0.46 × 0.28 × 0.18	0.54 × 0.52 × 0.28
Data collection			
Diffractometer	Bruker Smart Apex CCD	Bruker SMART APEX CCD	Bruker SMART APEX CCD
Data collection method	ω and φ scans	ω and φ scans	φ and ω scans
Absorption correction	Multiscan	Multiscan	Multiscan
T_{min}	0.690	0.830	0.868
T_{max}	1	1	1
No. of measured, independent and observed reflections	5628, 2309, 1778	20270, 7766, 6044	12312, 4733, 4265
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.0458	0.0220	0.0308
θ_{max} (°)	28.55	29.18	28.97
Range of h, k, l	$-17 \rightarrow h \rightarrow 21$ $-6 \rightarrow k \rightarrow 6$ $-17 \rightarrow l \rightarrow 16$	$-14 \rightarrow h \rightarrow 14$ $-19 \rightarrow k \rightarrow 31$ $-15 \rightarrow l \rightarrow 15$	$-9 \rightarrow h \rightarrow 7$ $-19 \rightarrow k \rightarrow 18$ $-24 \rightarrow l \rightarrow 22$
No. and frequency of standard reflections	Not measured	Not measured	Not measured
Intensity decay (%)	0	0	0
Refinement			
Refinement on	F^2	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.0779, 0.1652, 1.179	0.0471, 0.128, 1.038	0.0462, 0.1028, 1.066
No. of reflections and parameters used in refinement	2309, 140	7766, 433	4733, 276
H-atom treatment	Riding/All H-atom parameters refined	Riding/All H-atom parameters refined	Riding/All H-atom parameters refined
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.052P)^2 + 0.5663P]$ where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0676P)^2 + 0.569P]$ where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.049P)^2 + 0.2716P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.002	0.001	0.001
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.336, −0.447	0.357, −0.246	0.256, −0.270
Extinction method	None	None	*SHELXL*
Extinction coefficient	0	0	0.0031 (7)

Computer programs used: Stoe *DIF4* (Stoe & Cie, 1990*a*), Stoe *RED U4* (Stoe & Cie, 1990*b*), Bruker *SMART* (Bruker, 2001), Bruker *SAINT* (Bruker, 2002), *SHELXTL* (Sheldrick, 1997*a*).

OH···O=C and NH···OH hydrogen bonds, respectively, form $C(9)$ and $C(7)$ motifs at the unitary level.[2] In both polymorphs, these are disposed about crystallographic glide planes. In the monoclinic form, the hydrogen-bonded layers are arranged parallel to the (010) planes, which means that the layers are polar: in Fig. 1(*a*) all the molecules have the methyl group on the left. This polarity is reversed in neighbouring layers by crystallographic inversion centres. In the orthorhombic form, glide planes run perpendicular to the layers, so that the layers are non-polar: in Fig. 1(*b*) the methyl groups lie on the left- and right-hand sides of the molecules in alternate $C(9)$ chains.

The angles between mean planes of the amide and phenyl groups in orthorhombic and monoclinic paracetamol are 17.7° and 20.5°, respectively. Analogous angles observed in this work are given in the figure captions and range from 3.03° to 41.72°. pπ-pπ bonding between the phenyl ring and the amide group favours a dihedral angle of zero, and some correlation between this angle and the N—C(phenyl) bond length might have been expected, though none is evident at the precision of these structure determinations. This angle is evidently a rather easily deformed structural parameter, and is presumably at the mercy of crystal-packing forces. As we show in the following sections, hydrogen bonding is the dominant feature in these structures, and the torsion observed is presumably a consequence of the optimization of these interactions.

3.2. The paracetamol:1,4-dioxane adduct

The asymmetric unit in the crystal structure of the dioxane adduct of paracetamol consists of two paracetamol molecules and two half molecules of dioxane. The latter both reside on crystallographic inversion centres. One of the dioxane molecules (labelled *T*/*U* in the tables and supplemental data) is disordered, although both components participate in hydrogen bonding. The occupancy ratio is 0.75:0.25 and in the discussion that follows we have ignored the minor component (*U*). There is some evidence from electron-density difference maps that the other dioxane molecule (labelled *S*) is disordered as well, although, if present, the distinction between the components is at the limit of the resolution of our data set. An ordered model for this part of the structure is therefore presented here. The structure is depicted in Fig. 2. Primary bond lengths and angles are normal and have been deposited; hydrogen-bonding parameters are listed in Table 2.

[2] Note that where no sub- and superscripts appear in the graph-set descriptor, one donor and one acceptor are implied.

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The $C(9)$ chains formed by hydrogen bonding between OH···O=C moieties of neighbouring molecules described above with regard to the crystal structures of paracetamol are also observed in the structure of the 1,4-dioxane adduct. In order to accommodate the dioxane molecules these chains are sinusoidal, with the two crystallographically independent paracetamol molecules alternating along the chain. The NH groups point towards the O atoms of dioxane molecules forming NH···O hydrogen bonds. Since both dioxane molecules reside on inversion centres, the space-group symmetry builds up two-dimensional sheets in which chains of paracetamol are linked by dioxane bridges (Fig. 2). In graph-set notation, the bridges can be described as $D_2^2(6)$. The two-dimensional sheets are parallel to the (210) lattice planes, and the rather open structure depicted in Fig. 2 is 'filled in' by symmetry-equivalent sheets parallel to $(2\bar{1}0)$.

Table 2
Hydrogen-bonding parameters.

Standard uncertainties are omitted in the case of the dioxane adduct because the H-atom positions were calculated and not refined. N—H and O—H distances were normalized to 1.009 Å and 0.983 Å, respectively, to aid comparison with Cambridge Structural Database search results (Fig. 7).

Adduct	Donor	Acceptor	Observed distance (Å)	Normalized distance (Å)	Typical normalized distance (Å)
1,4-Dioxane	N1*A*—H1*A*	O1*S*	2.03	1.90	1.96
	O1*A*—H1*A*	O2*B*	1.82	1.67	1.78
	O1*B*—H1*B*	O2*A*^{i}	1.86	1.71	1.78
	N1*B*—H1*B*	O1*U*	1.92	1.77	1.96
	N1*B*—H1*B*	O1*T*	2.13	2.00	1.96
4,4′-Bipyridine	O1*A*—H1*A*	O2*B*	1.755 (19)	1.68	1.78
	N1*A*—H1*A*	N10*S*	2.047 (18)	1.92	1.96
	O1*B*—H1*B*	O2*A*^{ii}	1.81 (2)	1.71	1.78
	N1*B*—H1*B*	N17^{iii}	2.100 (18)	2.01	1.96
N,*N*-dimethylpiperazine	N1—H1	O2^{iv}	1.98 (2)	1.84	1.92
	O1—H11	N1*S*^{v}	1.81 (2)	1.82	1.82
N-methylmorpholine	O1—H11	O1*S*/N1*S*^{vi}	1.88 (2)	1.81	1.81/1.82
	N1—H1	O2^{vii}	1.925 (16)	1.80	1.92
Piperazine	O1—H11	N1*S*	1.79 (3)	1.74	1.82
	N1—H1	O2^{viii}	2.14 (3)	2.06	1.92
	N1*S*—H1*S*	O1^{viii}	2.30 (3)	2.21	2.03
Morpholine	O1*A*—H1*A*	O1*B*^{ix}	1.97 (2)	1.76	1.87
	N1*A*—H1*A*	O2*B*^{x}	2.033 (18)	1.87	1.92
	O1*B*—H1*B*	N4*S*^{xi}	1.79 (3)	1.69	1.82
	N1*B*—H1*B*	O2*A*^{xii}	2.061 (19)	1.86	1.92

(i) $x, y, z+1$; (ii) $x-1, y, z-1$; (iii) $-x, y-\frac{1}{2}, -z+\frac{1}{2}$; (iv) $x, -y+\frac{1}{2}, z-\frac{1}{2}$; (v) $-x+1, -y, -z$; (vi) $-x+1, -y+2, -z$; (vii) $x, -y+\frac{1}{2}, z-\frac{1}{2}$; (viii) $x, y+1, z$; (ix) $x+\frac{1}{2}, -y+\frac{1}{2}, -z$; (x) $x+\frac{1}{2}, -y+\frac{1}{2}, -z$; (xi) $-x+1, y+\frac{1}{2}, -z+\frac{1}{2}$; (xii) $-x+1, y-\frac{1}{2}, -z+\frac{1}{2}$.

3.3. The paracetamol:4,4′-bipyridine adduct

The O atoms in 1,4-dioxane formally have two lone pairs of electrons, each of which could potentially act as a hydrogen-bond acceptor. In practice, however, motifs in which ethers act as double hydrogen-bond acceptors occur rarely, and so for practical crystal-packing purposes it can be considered to be a centrosymmetric molecule containing two hydrogen-bond acceptors. 4,4′-Bipyridine is similar, although a torsion about the central C—C bond breaks the inversion symmetry. Recrystallization of paracetamol from a solution of 4,4′-bipyridine in ethanol yields a 1:1 co-crystal rather than the hemisolvate obtained with dioxane, a possible effect of the greater basicity of bipyridine.

The crystal structure of paracetamol:bipyridine contains two independent molecules each of paracetamol and bipyridine. Primary bond lengths and angles are normal and have been deposited; hydrogen-bonding parameters are listed in Table 2. As in the dioxane adduct, the paracetamol molecules form $C(9)$ chains through OH···O=C hydrogen bonds (Fig. 3). The two crystallographically independent paracetamol molecules alternate along the chain. The disposition of the molecules within the chains is rather similar to that in orthorhombic paracetamol, except that alternate molecules are rotated through 180° about the chain axis in order to accommodate the bipyridine molecules.

The NH bonds of paracetamol act as hydrogen-bond donors to the aromatic N atoms of the bipyridine molecules, forming a discrete (D) graph set. However, since this crystal is a 1:1 adduct there are insufficient hydrogen-bond donors for the number of acceptors present, and only one of the two N atoms in each bipyridine acts as an acceptor. The result is that there are no hydrogen-bonded pathways connecting the $C(9)$ paracetamol chains. The structure thus consists of a paracetamol backbone with attached bipyridine molecules. These motifs are interconnected by π-stacking between the bipyridine molecules, building up sheets than run parallel to the $(10\bar{1})$ planes.

3.4. The paracetamol adducts with *N*-methylmorpholine and *N*,*N*-dimethylpiperazine

N,*N*-dimethylpiperazine and *N*-methylmorpholine are closely related to 1,4-dioxane by the substitution of one or both O atoms by N—Me; paracetamol forms 2:1 adducts with both compounds, as it does with dioxane. The *N*,*N*-dimethylpiperazine adduct consists of one crystallographically independent paracetamol molecule with the *N*,*N*-dimethylpiperazine residing on a crystallographic inversion centre. The *N*-methylmorpholine adduct is isostructural with this, with the guest molecule disordered about the inversion centre. Primary bond lengths and angles are unremarkable and have been deposited; hydrogen-bonding parameters are listed in Table 2

The crystal structures are similar to those of the dioxane and bipyridine adducts in that the packing can be described with reference to chains of paracetamol molecules. However, rather than $C(9)$ motifs formed through OH···O=C H bonds, the paracetamol molecules define a $C(4)$ graph set through NH···O=C bonds (Fig. 4). The NH moiety of the para-

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cetamol now fulfils the role of the OH groups in the dioxane structure, and *N*,*N*-dimethylpiperazine and *N*-methylmorpholine are similar to dioxane with regard to their hydrogen-bonding properties. Therefore, alth ugh the nature of the paracetamol chain differs from that of the dioxane adduct, the roles of the *N*-methylmorpholine and dimethylpiperazine molecules are similar, and both act to link paracetamol chains *via* the $D_2^2(6)$ graph set. Overall, this structure consists of a two-dimensional network, although the sheets formed have a corrugated or zigzag appearance in cross section. Alternate regions of the network are approximately parallel to the (310) and (3$\bar{1}$0) planes. Just as in the dioxane adduct, the open structure of Fig. 4 is filled in by symmetry-equivalent networks.

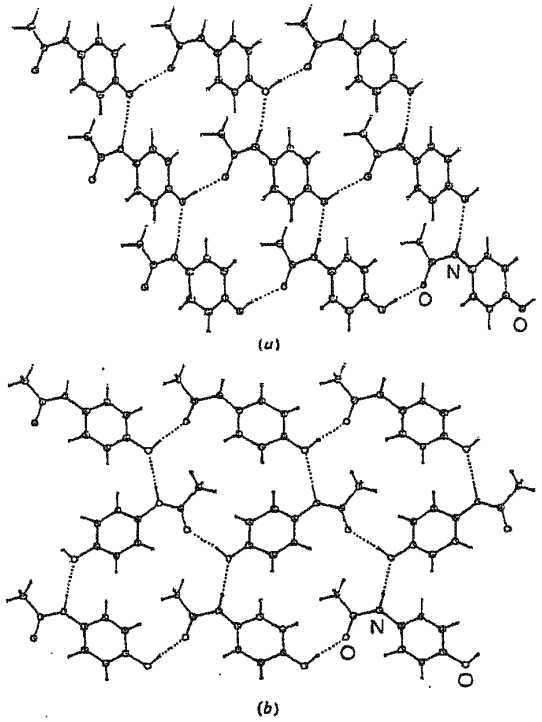


Figure 1
(*a*) Monoclinic paracetamol (Form I) viewed along the *b* axis; the *c* axis runs diagonally from top left to bottom right, so that the *C*(9) chains are established by the *n*-glide. (*b*) Orthorhombic paracetamol (Form II) viewed along the *c* axis; the *a* axis runs horizontally, the *b* axis runs from top to bottom. The *C*(9) chains referred to in the text run from left to right and the *C*(7) chains run approximately vertically. [Colour versions of this and the other figures are available in the online edition of this journal.]

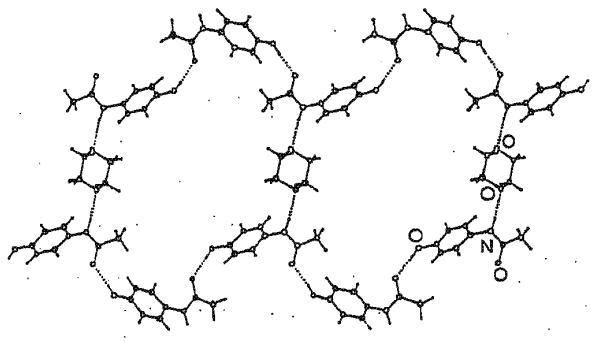


Figure 2
Paracetamol:1,4-dioxane adduct viewed perpendicular to (210); the *c* axis runs horizontally. The *C*(9) chains referred to in the text run from left to right and are linked together by dioxane molecules. The dihedral angles between the amide and phenyl mean planes in the two independent paracetamol molecules are 41.72 (15)° and 39.37 (14)° for molecules *A* and *B*, respectively.

3.5. The paracetamol:morpholine adduct

Morpholine is related to *N*-methylmorpholine by the substitution of the methyl group for hydrogen, and it is unique in this series because the hydrogen-bonding characteristics of the two hetero-centres are not the same: the NH group is a donor and acceptor, the ether O atom potentially a double, but more usually a single, acceptor. The asymmetric unit of the morpholine hemiadduct consists of two crystallographically independent paracetamol molecules (labelled *A* and *B*) and one molecule of morpholine (labelled *S* in the tables). Primary bond lengths and angles are normal and have been deposited; hydrogen-bonding parameters are listed in Table 2.

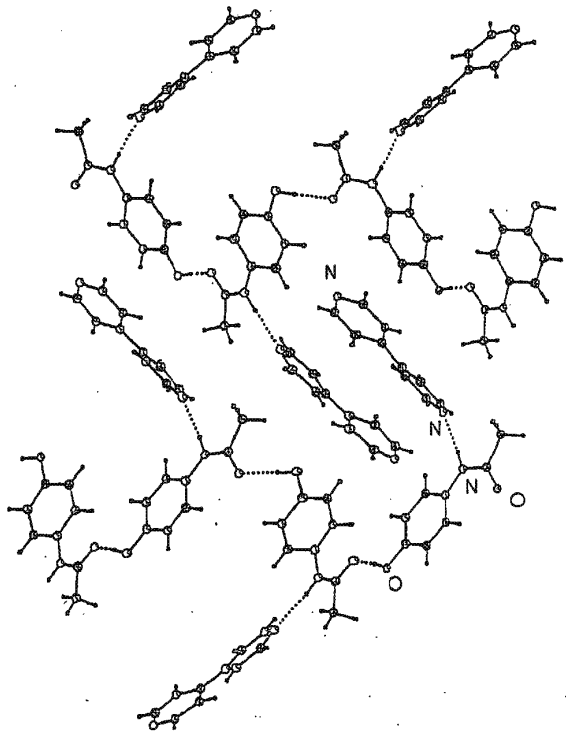


Figure 3
Paracetamol:4,4-bipyridine viewed perpendicular to (10$\bar{1}$); the *b* axis runs from top to bottom. The *C*(9) chains referred to in the text run from left to right and are linked together by a pair of π-stacked bipyridine molecules. The dihedral angles between the amide and phenyl mean planes in the two independent paracetamol molecules are 14.68 (8)° and 13.27 (9)° for molecules *A* and *B*, respectively.

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The crystallographically independent paracetamol molecules alternate in the pattern ...*ABABAB*... along a chain formed by ···HNCO···NHCO··· linkages between neighbouring amide groups. Because these molecules are crystallographically independent, these hydrogen bonds formally constitute discrete graphs at the unitary level, although it is clear from Fig. 5 that they are closely related to the *C*(4) graphs observed in the crystal structures of the *N*-methylmorpholine and *N*,*N*-dimethylpiperazine adducts described above. For consistency we continue to use this designation, although it is not formally correct [the binary graph $C_2^2(8)$ takes proper account of symmetry].

The chains are formed by 2_1 operations parallel to *c*, leading to a pairwise alternation of the centres of the paracetamol molecules above and below the chain. This pattern is reminiscent of the structures of the *N*-methylmorpholine and *N*,*N*-dimethylpiperazine adducts, except that in these cases the alternation applies to single molecules. The potential for this arrangement to lead to some steric hindrance between the phenyl groups of neighbouring molecules is avoided by adjacent molecules veering slightly away from each other and an increase in the torsional angle between the phenyl group and amide group from 3.04 (3)° in molecule *B* to 36.03 (6)° in molecule *A*.

Lattice translation along the *b* direction generates further *C*(4) chains, and these are linked together by discrete [*D*] hydrogen bonds in which an OH group from an '*A*' molecule in one chain acts as a donor to an OH group of a '*B*' molecule in a neighbouring chain. This is the only structure in the series in which pairs of paracetamol molecules interact *via* their hydroxyl moieties.

The two sets of hydrogen bonds described above – the *C*(4) chains and the *D* links between chains – form a grid-like network parallel to the (100) planes. The morpholine molecules fit into the cavities of the grid. As in the *N*-methylmorpholine adduct, the amine N atom acts as an acceptor to the OH group of one of the paracetamol molecules (*B*), but this is the only hydrogen-bonding interaction formed by the morpholine. The NH group of the morpholine is in an axial position to accommodate this interaction.

This scheme satisfies all the hydrogen-bonding potential of the two paracetamol molecules, with the exception of the hydroxyl acceptor of molecule *A*. The weakest acceptor in the system (the ether function of the morpholine) does not

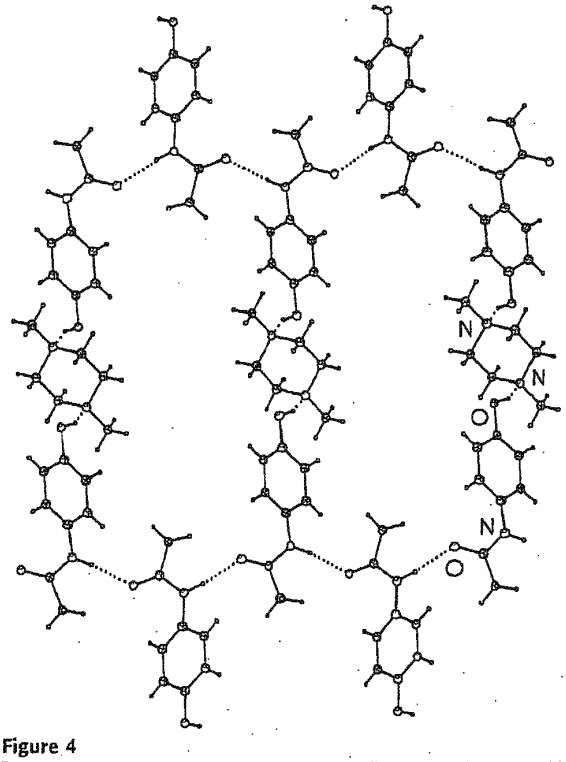


Figure 4
Paracetamol:*N*,*N*-dimethylpiperazine adduct (isostructural to the *N*-methylmorpholine adduct) viewed along the *a* axis; the *c* axis runs from left to right and the *b* axis from top to bottom. The *C*(4) chains referred to in the text run from left to right and are linked together by *N*,*N*-dimethylpiperazine molecules. The dihedral angles between the amide and phenyl mean planes in the paracetamol molecules are 33.75 (7)° and 34.11 (6)° in the *N*,*N*-dimethylpiperazine and *N*-methylmorpholine adducts, respectively.

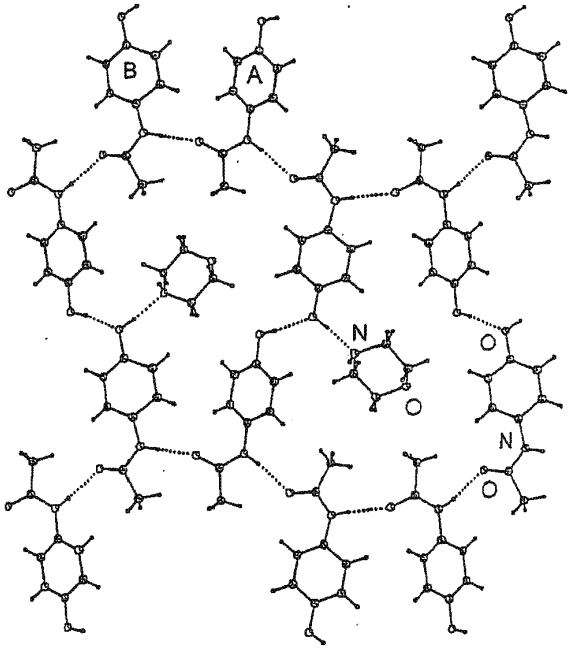


Figure 5
Paracetamol:morpholine adduct viewed along the *a* axis. The *c* direction runs from left to right, the *b* direction up and down. The labels *A* and *B* refer to the crystallographically independent paracetamol molecules referred to in the text. The *C*(4) chains referred to in the text run from left to right and are linked together by hydrogen bonds between opposed OH groups. This forms a grid-like array with the morpholine molecules residing in the grid cavities. The dihedral angles between the amide and phenyl mean planes in the two independent paracetamol molecules are 36.03 (6)° and 3.04 (3)° for molecules *A* and *B*, respectively.

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participate in hydrogen bonding at all. A rather surprising feature of this structure, given the excess of acceptors present, is that the NH donor functionality of the morpholine amine moiety is also unsatisfied. However, this is consistent with the relatively long NH···OH hydrogen bonds observed in the piperazine adduct (which is described in the next section) and the generally poor hydrogen-bond-donor ability of secondary amines (see below).

3.6. The paracetamol:piperazine adduct

Piperazine is related to *N,N*-dimethylpiperazine by substitution of the two methyl groups by hydrogen. The asymmetric unit of the piperazine adduct, in common with the *N,N*-dimethylpiperazine adduct, consists of one paracetamol molecule and a molecule of piperazine on a crystallographic inversion centre. Primary bond lengths and angles are normal and have been deposited: hydrogen-bonding parameters are listed in Table 2. There are $C(4)$ chains, consisting of NH···O=C hydrogen bonds, linked *via* $D_2^2(6)$ motifs consisting of OH···N bonds (Fig. 6). Piperazine is a weak hydrogen-bond donor as well as an acceptor, and the extra NH-donor moiety is satisfied by rotating alternate paracetamol molecules about the $C(4)$ chain axis, leading to *D*-type NH···OH hydrogen bonds. This rotation produces ribbons that run parallel to the *b* axis rather than the infinite two-dimensional networks.

3.7. Differential scanning calorimetry

Decomposition of a co-crystal of paracetamol is a potential strategy for the production of the orthorhombic polymorph. In all cases except for the 4,4′-bipyridine adduct, DSC traces exhibited thermal events attributable to loss of the guest molecule followed by a strong endotherm, corresponding to melting, at 438–444 K. The melting point of monoclinic paracetamol is 442 K (Nichols & Frampton, 1998). The same authors showed that DSC traces for orthorhombic paracetamol show either melting at 430 K or a phase transition to the monoclinic form at the same temperature, depending on the method of preparation. The DSC traces observed in this study can therefore be interpreted in terms of decomposition leading to formation of the monoclinic polymorph.

Thermal decomposition temperatures follow the trend that might be predicted on the basis of the boiling points of 1,4-dioxane (374 K), *N*-methylmorpholine (388 K), morpholine (401 K), *N,N*-dimethylpiperazine (404 K) and piperazine (419 K). Two exotherms were observed for the dioxane solvate at 299 K and 338 K, in agreement with the previous study (Fachaux *et al.*, 1995). This is plausibly interpreted as sequential loss of the two crystallographically independent dioxane molecules. Dioxane is readily lost at room temperature from a crystalline sample of this adduct, and the DSC trace of a sample that had been allowed to stand for 10 min showed only one exotherm with an onset temperature of 330 K. Decomposition of the morpholine, *N*-methylmorpholine and *N,N*-dimethylpiperazine adducts occur as broad exotherms with onsets at approximately 327, 335 and 373 K, respectively. The DSC trace of the piperazine adduct showed one endotherm at 413 K.

4,4′-Bipyridine sublimes at 578 K under ambient pressure, and it is the least volatile compound to have been studied in this work. The DSC trace of the co-crystal exhibits a weak endotherm at 399 K followed by a strong endotherm at 402 K; no thermal event attributable to the melting of pure paracetamol was observed. The strong endotherm occurs at a similar temperature to the decomposition events observed for the other adducts, and it is likely to correspond to a melting process forming paracetamol solvated by liquid bipyridine (m.p. 374–377 K). Unlike the other solvents studied here, bipyridine is not lost to leave pure paracetamol, because its boiling point is well beyond the temperature of adduct decomposition. It is likely that the small peak corresponds to a phase transition.

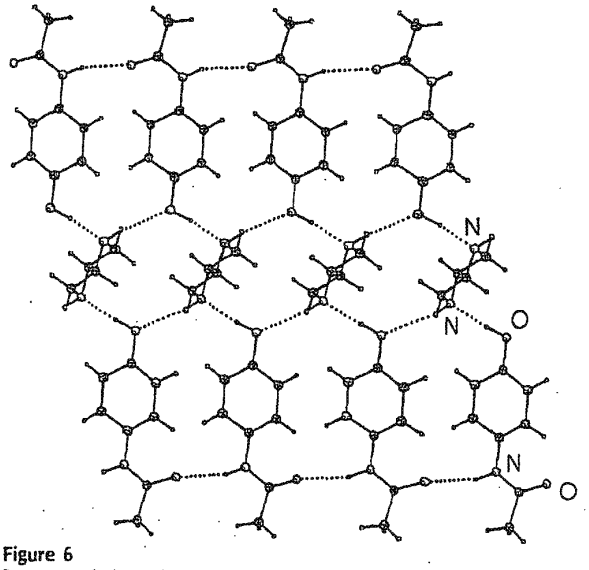


Figure 6
Paracetamol:piperazine adduct viewed perpendicular to (302); the *b* axis runs from left to right. The $C(4)$ chains referred to in the text run from left to right and are linked together by piperazine molecules. The latter also act as weak hydrogen-bond donors. The dihedral angles between the amide and phenyl mean planes in the paracetamol molecule is 33.21 (14)°.

4. Discussion and conclusions

This paper has described the formation of five new paracetamol hemiadducts with 1,4-dioxane, *N,N*-dimethylpiperazine, *N*-methylmorpholine, morpholine and piperazine and a 1:1 adduct with 4,4′-bipyridine. This is the first such systematic study of paracetamol co-crystals to have been undertaken. As is to be expected, the crystal structures of all adducts are dominated by hydrogen-bond formation, and comparisons between them were much facilitated by the use of graph-set analysis in the form described in the illuminating review by Bernstein *et al.* (1995).

Although ether oxygen can potentially act as a double acceptor, it rarely does so, and so with the exception of

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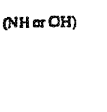
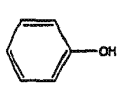
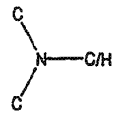
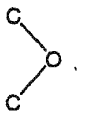
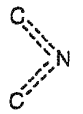
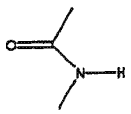
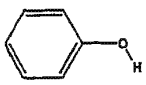
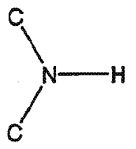
	Acceptor (O or N in each case)					
Donor (NH or OH)						
	Sample size	1250	14	11	31	40
	Max NH..A /Å	(2.2) *	2.14	2.17	2.19	2.19
	Min NH..A /Å	1.73	1.79	1.80	1.83	1.81
	Mean NH..A /Å	1.92	2.01	1.96	2.03	1.96
	Sample size	49	256	49	53	76
	Max OH..A /Å	2.19	2.20	2.19	2.20	2.18
	Min OH..A /Å	1.60	1.67	1.66	1.62	1.53
	Mean OH..A /Å	1.78	1.87	1.82	1.90	1.81
	Sample size	5	1 (HOLZOD)	12	4	Not applicable
	Max NH..A /Å	2.17	-	2.20	2.18	
	Min NH..A /Å	2.08	-	2.00	2.11	
	Mean NH..A /Å	2.13	2.03	2.14	2.13	

Figure 7
Summary of the results of searches of the CSD (Version 5.23, April 2002) for typical distances (in Å) in hydrogen-bonded systems containing identical functional groups to the paracetamol adducts studied. The distances to H atoms were normalized to typical neutron distances (C—H 1.803, N—H 1.009 and O—H 0.983 Å). Only 'organic' structures where the *R* factor is less than 0.05 with no errors or disorder were included, and ionic or polymeric structures were excluded. The C atoms attached to the amine moieties were specified to be sp^3 hybridized. The donor-H-to-acceptor distance was specified to be 1.50–2.20 Å. The asterisk denotes the limit of search.

morpholine all the guest molecules studied are at least pseudo-centrosymmetric with respect to their hydrogen-bonding properties. The dioxane, *N*-methylmorpholine, *N*,*N*-dimethylpiperazine and piperazine adducts all consist of hydrogen-bonded chains of paracetamol molecules linked together by the guest molecules, which all reside on crystallographic inversion centres. In the bipyridine adduct the chains are linked *via* a pair of π-stacked pyridine rings, though the structure as a whole is still centrosymmetric. The morpholine adduct does not conform to this pattern, although chains of paracetamol are still present. The arrangements of paracetamol chains described in this paper tend to lend themselves to the formation of centrosymmetric crystal structures, and this seems to favour adduct formation in the centrosymmetric guest molecules. It is perhaps significant that we have been unable to prepare an adduct with 1,3,5-trioxane, a molecule closely related to dioxane but which lacks inversion symmetry.

The donor groups that appear in this series are amidic NH, phenol OH and secondary amine NH; the acceptors are amidic O, phenolic O, secondary or tertiary amine N, ether O, and pyridine N. The results of searches of the CSD for typical hydrogen-bond geometries involving these functionalities are shown in Fig. 7; searching criteria are given in the legend to that figure. The pattern of adduct formation observed in this study is quite consistent with the data in Fig. 7 if the reasonable assumption is made that the hydrogen-bond strength is related to the average donor-hydrogen—acceptor distance. The donor group O—H or N—H to acceptor distances observed in this study were normalized to typical neutron values (O—H 0.983 Å and N—H 1.009 Å) to aid ready comparison with typical H-to-acceptor distances derived from our CSD search, and this comparison is made in Table 2. Our hydrogen-bond distances agree tolerably well with typical values; they are often on the short side, as might be expected with low-temperature data.

The strongest hydrogen bonds in Fig. 7 are formed between phenolic OH (as donor) and amide O (as acceptor). These are observed in the *C*(9) chains formed in structures of both polymorphs of paracetamol. In pure paracetamol, hydrogen bonds are formed between the remaining NH donor and OH acceptor to form *C*(7) chains, but on adduct formation with 1,4-dioxane and 4,4′-bipyridine it is these, weaker, interactions that break to accommodate the guest molecules, preserving the strongly bound *C*(9) chains and forming hydrogen bonds between the amide NH of paracetamol and either the ether O or the pyridyl N atoms of the guest molecule. These observations are consistent with the results obtained in the variable-pressure study of monoclinic paracetamol by Boldyreva *et al.* (2000), where the NH···O contacts were found to be more compressible than the OH···O contacts.

Neither dioxane nor bipyridine has any group attached to the donor O or N atoms. All of the other molecules studied carry either hydrogen or methyl groups in these positions, and reference to Fig. 2 or Fig. 3 shows that a structure based on the *C*(9) paracetamol chains would suffer some steric crowding

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between these groups and either the phenyl or the methyl group attached to the amide moiety. In order to avoid steric overcrowding in the morpholine, piperazine, *N*,*N*-dimethylpiperazine and *N*-methylmorpholine adducts, the paracetamol utilizes its NH group as a donor. Fig. 7 shows that the most effective acceptor for this group is amide CO and this explains the formation of *C*(4) paracetamol chains in all four of these structures.

In the structures of *N*-methylmorpholine and *N*,*N*-dimethypiperazine, hydrogen bonds are formed between the OH group of paracetamol and the N or O of the guest molecule. In morpholine and piperazine, both the OH group of paracetamol and the NH group(s) of the guest could act as either donors or acceptors. Fig. 7 shows that secondary aliphatic amines are particularly poor hydrogen-bond donors, and so the hydroxyl group acts as the donor in both cases. In fact, so poor a donor is secondary amine NH that it is left unsatisfied in the morpholine adduct, even in the presence of excess acceptor functions. The weakness of these NH···N hydr gen bonds relative to OH···O or NH···O systems may be a consequence of the size of N relative to O, a feature recently emphasized by Brown (2002). However, in piperazine the NH groups do act as weak donors, and this induces a change in conformation of these *C*(4) chains relative to the *N*,*N*-dimethylpiperazine adduct that condenses the sheets into ribbons.

In the case of morpholine, the *C*(4) chains are linked by the OH group of a paracetamol molecule in one chain acting as a hydrogen-bond donor to a similar group in a neighbouring chain. On the basis of the structures of the other adducts, the role might have been expected to be fulfilled by the ether moiety of the morpholine. Fig. 7 shows that these interactions are of rather similar strength, and this might explain the apparently anomalous behaviour observed in this adduct.

In the 1,4-dioxane adduct, alternate *C*(9) paracetamol chains have reversed polarity. In the adducts based on *C*(4) chains, the resemblance to orthorhombic paracetamol is less obvious, although inspection of Fig. 1(*b*) shows that removal of alternat molecules along the *C*(7) graph followed by a small displacement would yield NH···O=C *C*(4) chains. Viewed in this light, desolvation might have been predicted to yield the orthorhombic polymorph of paracetamol, although in practice it was shown by DSC that in all cases except for paracetamol:bipyridine (for which we did not observe desolvation at all) the thermodynamically more stable monoclinic polymorph was formed.

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cepress *(Guidotti, Ital.).*
aptopril.
ypertension; congestive heart failure.

cepril *(Squibb, UK).*
aptopril.
ypertension; congestive heart failure.

cequin *(Recordati, Ital.).*
uinapril hydrochloride.
ypertension.

cerbine† *(Millot-Solac, Fr.).*
enzoic acid; salicylic acid; malic acid; opylene glycol.
'ounds; bedsores.

cerbine *(Lucchini, Switz.).*
intment: Benzoic acid; malic acid; salicyl- acid; propylene glycol; propylene glycol alate; hexachlorophane.
'ounds; burns.

cerbine *(Lucchini, Switz.).*
opical solution; topical gel: Benzoic acid; alic acid; salicylic acid; propylene glycol; opylene glycol malate.
ounds; burns.

cerbiol *(Vitapharm, Spain).*
enzyl alcohol; benzoic acid; malic acid; opylene glycol malate; propylene glycol; licylic acid.
ounds; burns.

cerbon *(ICI, Ger.; Rhein-Pharma, Ger.).*
sinopril.
ypertension.

cerola Complex *(Suisse, Austral.).*
scorbic acid; hesperidin-rutin-buckwheat- trus bioflavonoid complex.
tamin C deficiency.

certol *(Lacer, Spain).*
uracetamol.
iin; fever.

cesal *(Manzoni, Ital.).*
spirin.
iin; fever.

cesistem *(Sigma-Tau, Ital.).*
ialapril maleate; hydrochlorothiazide.
ypertension.

cetaco *(Legere, USA).*
uracetamol; codeine phosphate.

cetadeps *(Westbrook, UK).*
cetylated wool fat.

cétalgine *(Streuli, Switz.).*
uracetamol.
iin; fever.

cet-Am *(Organon, Canad.).*
eophylline calcium glycinate.
onchodilator.

cet-Am Expectorant *(Organon, Canad.).*
eophylline sodium glycinate; guaiphenes-

onchodilator; expectorant.

cetaminophen, Aspirin, and Caffeine Capsules *(U.S.P. XXII).*
uracetamol; aspirin; caffeine.

cetaminophen, Aspirin, and Caffeine Tablets *(U.S.P. XXII).*
uracetamol; aspirin; caffeine.

cetaminophen and Aspirin Tablets *I.S.P. XXII).*
uracetamol; aspirin.

cetaminophen and Caffeine Capules *(U.S.P. XXII).*
uracetamol; caffeine.

cetaminophen and Caffeine Tablets *I.S.P. XXII).*
uracetamol; caffeine.

cetaminophen Capsules *(U.S.P. XII).*
uracetamol.

cetaminophen with Codeine *(Pharmas- nce, Canad.; Stanley, Canad.).*
uracetamol; caffeine; codeine phosphate.
ain; fever; coughs.

cetaminophen and Codeine Phos- hate Capsules *(U.S.P. XXII).*
uracetamol; codeine phosphate hemihy- ate.

Acetaminophen and Codeine Phosphate Elixir *(U.S.P. XXII).*
Paracetamol; codeine phosphate hemihydrate.

Acetaminophen and Codeine Phosphate Tablets *(U.S.P. XXII).*
Paracetamol; codeine phosphate hemihydrate.

Acetaminophen and Diphenhydramine Citrate Tablets *(U.S.P. XXII).*
Paracetamol; diphenhydramine citrate.

Acetaminophen for Effervescent Oral Solution *(U.S.P. XXII).*
Paracetamol.

Acetaminophen Oral Solution *(U.S.P. XXII).*
Paracetamol.

Acetaminophen Oral Suspension *(U.S.P. XXII).*
Paracetamol.

Acetaminophen and Pseudoephedrine Hydrochloride Tablets *(U.S.P. XXII).*
Paracetamol; pseudoephedrine hydrochloride.

Acetaminophen Suppositories *(U.S.P. XXII).*
Paracetamol.

Acetaminophen Tablets *(U.S.P. XXII).*
Paracetamol.

Acetamol *(Gentili, Ital.).*
Paracetamol.
Pain.

Acetard *(Benzon, Swed.).*
Aspirin.
Pain; inflammation; fever.

Acetazolamide Tablets *(B.P. 1988).*

Acetazolamide Tablets *(U.S.P. XXII).*

Acetazone Forte *(Technilab, Canad.).*
Chlorzoxazone; paracetamol.
Pain; muscle spasm.

Acetazone Forte C8 *(Technilab, Canad.).*
Chlorzoxazone; paracetamol; codeine phosphate.
Pain; muscle spasm.

Acetensil *(Andromaco, Spain).*
Enalapril maleate.
Hypertension; heart failure.

Acétest *(Ames, Fr.).*
Test for ketones in urine.

Acetest *(Ames, UK).*
Test for ketones in urine, plasma, or serum. In the *UK* these are described in the Drug Tariff as Nitroprusside Reagent Tablets (Rothera's Tablets).

Acethropan *(Hoechst, Ger.).*
Corticotrophin (porcine).
Stimulation of the adrenal glands; multiple sclerosis; glucocorticoid therapy.

Acetic Acid Irrigation *(U.S.P. XXII).*
Glacial acetic acid 0.25%.

Acetic Acid Otic Solution *(U.S.P. XXII).*
Glacial acetic acid.

Acétocaustine *(Asta, Switz.).*
Monochloroacetic acid.
Warts.

Acetohexamide Tablets *(B.P. 1988).*

Acetohexamide Tablets *(U.S.P. XXII).*

Acetohydroxamic Acid Tablets *(U.S.P. XXII).*

Acetolyt *(Madaus, Ger.).*
Hexacalcium-hexasodium-heptacitrate-hydrate complex.
Metabolic acidosis.

Acetonal *(Athenstaedt, Ger.).*
Aluminium subacetate tartrate; (2,2,2-trichlor-1,1-dimethylethyl)-salicylate.
Anorectal disorders.

Acetonal Vaginale *(Athenstaedt, Ger.).*
Aluminium acetotartrate; (2,2,2-trichlor-1,1-dimethylethyl)-salicylate; oestradiol benzoate; sulphanilamide.
Vaginitis; vaginal infections.

Acetophenazine Maleate Tablets *(U.S.P. XXII).*

Acetopt *(Sigma, Austral.).*
Sulphacetamide sodium.
Conjunctival infections.

Acetoxyl *(Stiefel, Canad.).*
Benzoyl peroxide.
Acne vulgaris.

Acetoxyl *(Stiefel, UK).*
Benzoyl peroxide.
Acne vulgaris.

Acetuber *(Hubber, Spain).*
Injection: Pituitary extract.
Acetonaemia; vomiting in pregnancy.

Acetuber *(Hubber, Spain).*
Suppositories: Cocarboxylase; dimenhydrinate; glucose; pyridoxine; potassium chloride; dibasic sodium phosphate.
Acetonaemia; vomiting in pregnancy.

Acetylcholine Chloride for Ophthalmic Solution *(U.S.P. XXII).*

Acetylcysteine and Isoproterenol Hydrochloride Inhalation Solution *(U.S.P. XXII).*
Acetylcysteine; isoprenaline hydrochloride.

Acetylcysteine Solution *(U.S.P. XXII).*

Acetylin *(Squibb-Heyden, Ger.).*
Aspirin.
Pain; fever; rheumatism.

Acetyst *(Jossa-Arznei, Ger.).*
Acetylcysteine.
Respiratory-tract disorders associated with increased or viscous mucus; otitis media.

Acezide *(Squibb, UK).*
Captopril; hydrochlorothiazide.
Hypertension.

Acfol *(Torlan, Spain).*
Folic acid.
Folic acid deficiency.

Achrocidin *(Lederle, Canad.).*
Tetracycline hydrochloride; caffeine; salicylamide; chloropyrilene citrate.
Bacterial infections.

Achromycin *(Lederle, Austral.).*
Tetracycline hydrochloride.
Bacterial infections.

Achromycin *(Lederle, Canad.).*
Intramuscular injection: Tetracycline hydrochloride; procaine hydrochloride.
Bacterial infections.

Achromycin *(Lederle, Canad.).*
Intravenous injection; ointment; eye ointment: Tetracycline hydrochloride.
Bacterial infections.

Achromycin *(Lederle, Ger.).*
Capsules; ointment; tablets: Tetracycline hydrochloride.
Bacterial infections.

Achromycin *(Lederle, Ger.).*
Eye ointment: Tetracycline hydrochloride; hydrocortisone.
Allergic and inflammatory disorders of the eye.

Achromycin *(Lederle, Swed.).*
Tetracycline hydrochloride.
Bacterial infections.

Achromycin *(Lederle, UK).*
Capsules; tablets; ointment; eye and ear ointment; intravenous injection: Tetracycline hydrochloride.
Bacterial infections.

Achromycin *(Lederle, UK).*
Intramuscular injection: Tetracycline hydrochloride; procaine hydrochloride.
Bacterial infections.

Achromycin† *(Lederle, USA).*
Intramuscular injection: Tetracycline hydrochloride; procaine hydrochloride.
Bacterial infections.

Achromycin *(Lederle, USA).*
Intravenous injection; ophthalmic suspension; ophthalmic ointment; ointment; capsules: Tetracycline hydrochloride.
Bacterial infections.

Achromycin V *(Lederle, Austral.).*
Tetracycline hydrochloride.
Bacterial infections.

Achromycin V *(Lederle, Canad.).*
Tetracycline hydrochloride.
Bacterial infections.

Achromycin V *(Lederle, S.Afr.).*
Tetracycline hydrochloride.
Bacterial infections.

Achromycin V† *(Lederle, UK).*
Tetracycline.
Bacterial infections.

Achromycin V *(Lederle, USA).*
Capsules: Tetracycline hydrochloride.
Bacterial infections.

Achromycin V *(Lederle, USA).*
Oral suspension: Tetracycline.
Bacterial infections.

Achromycine *(Lederle, Switz.).*
Tetracycline hydrochloride.
Bacterial infections.

Achrostatin *(Lederle, Austral.).*
Tetracycline hydrochloride; nystatin.
Bacterial infections.

Aci Kestomal *(Boizot, Spain).*
Aluminium hydroxide; dimethicone; magnesium carbonate; magnesium oxide; metoclopramide hydrochloride.
Gastro-intestinal disorders.

Acicloftal *(Bruschettini, Ital.).*
Acyclovir.
Herpes simplex keratitis.

Acid A Vit *(Roche, Neth.).*
Tretinoin.
Acne vulgaris.

Acid Citrate Dextrose Solution (ACD) *(B.P. 1988).*
Formula A: sodium citrate 2.2 g; citric acid monohydrate 0.8 g; glucose monohydrate 2.45 g or anhydrous glucose 2.24 g; water for injections to 100 mL. Formula B: sodium citrate 1.32 g; citric acid monohydrate 0.48 g; glucose monohydrate 1.47 g or anhydrous glucose 1.34 g; water for injections to 100 mL.
15 mL of formula A and 25 mL of formula B are used for the collection of 100 mL of blood.

Acid Gentian Mixture *(B.P. 1988).*
Concentrated Compound Gentian Infusion *(B.P.)* 10% v/v; dilute hydrochloric acid 5% v/v.
For extemporaneous preparation the *B.P.* specifies Concentrated Compound Gentian Infusion *(B.P.)* 10 mL; dilute hydrochloric acid 5 mL; Double-strength Chloroform Water *(B.P.)* 50 mL; water to 100 mL.

Acid Insulin Injection *(B.P. 1988)*
Acid Insulin.
A sterile solution of Insulin *(B.P.)* pH 3.0 to 3.5.

Acid Mantle *(Miles, Canad.).*
Aluminium acetate.
Skin irritation.

Acid Mantle *(Sandoz Consumer, USA).*
Aluminium acetate.
Minor skin disorders; pharmaceutical vehicle.

Acidac *(Alonga, Spain).*
Aluminium hydroxide; dimethicone; magnesium carbonate; magnesium hydroxide.
Hyperchlorhydria; flatulence.

Acidion *(Dibios, Spain).*
Aluminium hydroxide; dimethicone; magnesium carbonate; magnesium hydroxide.
Gastro-intestinal disorders.

Acidion Solucion *(Dibios, Spain).*
Aluminium hydroxide; magnesium hydroxide.
Hyperchlorhydria.

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Asmaven *(Approved Prescription Services, UK).*
Salbutamol sulphate.
Bronchospasm; premature labour.

Asmaxen *(Doetsch, Grether, Switz.).*
Salbutamol.
Bronchospasm.

Asmetil *(Benvegna, Ital.).*
Protokylol hydrochloride.
Respiratory-system disorders.

Asmisul *(Inibsa, Spain).*
Eprozinol dihydrochloride.
Asthmatic and dyspnoeic disorders.

Asmo *(Hubber, Spain).*
Theophylline.
Obstructive airways disease; paroxysmal dyspnoea; heart failure.

Asmobacterial† *(Leti, Spain).*
Escherichia coli; Haemophilus influenzae; Klebsiella pneumoniae; Staphylococcus pyogenes; Moraxella (Branhamella) catarrhalis; Streptococcus sp.; Proteus vulgaris.
Respiratory-tract infections.

Asorec *(Radiumfarma, Ital.).*
Sulphaguanole.
Infective diarrhoea.

Aspac *(Inexfa, Spain).*
Paracetamol.
Pain; fever.

Aspalgin *(Fawns & McAllan, Austral.).*
Aspirin; codeine phosphate.
Pain; fever.

Aspalox *(Rorer, Ger.).*
Aspirin.
Pain; fever; rheumatism; arthritis; thrombo-embolic disorders.

Aspam *(RP-LABO, Fr.).*
Aspartame.
Sugar substitute.

Asparagin (Röwo-119) *(Pharmakon, Ger.).*
Vitamin and electrolyte preparation with rutin.
Tonic.

Asparagus-P *(Plantina, Ger.).*
Rhiz. asparagi off. pulv.; herb. petroselini sat. pulv.
Oedema; urinary tract stones.

Aspartatol *(Eagle, Austral.).*
Potassium aspartate; magnesium aspartate; levoglutamide.
Tonic.

Aspartina *(Vick International, Ital.).*
Aspartame.
Sugar substitute.

Aspartono *(Medix, Spain).*
Adenosine triphosphate; glucose; magnesium aspartate; potassium aspartate.
Tonic; cardiopathies; liver disorders; muscular dystrophies.

Aspaserine B6 Tranq *(Roger, Spain).*
Diazepam; pyridoxine.
Anxiety; insomnia; febrile convulsions; muscle spasm; alcohol withdrawal.

Aspasmon N *(Norgine, Ger.).*
Peppermint oil; anise oil; caraway oil.
Gastro-intestinal disorders; asthma.

Aspav *(Rousxel, UK).*
Aspirin; papaveretum.
Pain.
Formerly known as Soluble Aspirin and Papaveretum Tablets.

Aspecton *(Krewel, Ger.).*
Rad. liquiritiae; anise oil; greek sage oil; eucalyptus oil; fennel oil; thyme oil.
Coughs; catarrh.

Aspecton N *(Krewel, Ger.).*
Thyme; saponins from gypsophila spp.
Respiratory-tract disorders.

Aspecton-Balsam *(Krewel, Ger.).*
Camphor; ol. thymi; ol. eucalypti.
Coughs; cold symptoms.

Aspectonetten *(Krewel, Ger.).*
Butethamate citrate.
Coughs and associated respiratory-tract disorders.

Aspégic *(Synthelabo, Fr.).*
Lysine aspirin.
Pain; fever; rheumatism.

Aspegic *(Lirca, Ital.).*
Lysine aspirin.
Pain; fever; inflammation.

Aspegic *(Lorex, Neth.).*
Lysine aspirin.
Pain; fever; inflammation.

Aspegic *(Cantabria, Spain).*
Lysine aspirin.
Pain; fever; inflammation; thrombo-embolic disorders.

Aspégic *(Synthelabo, Switz.).*
Lysine aspirin; glycine.
Pain; fever.

Aspellin *(Fisons, UK).*
Methyl salicylate; ethyl salicylate; ammonium salicylate; menthol; camphor.
Pain.

Aspenil *(Chemil, Ital.).*
Amoxycillin.
Bacterial infections.

Aspercreme *(Roche, Ital.).*
Diethylamine salicylate; methyl nicotinate.
Musculoskeletal disorders.

Aspergum† *(Plough, UK).*
Aspirin.
Pain; fever.

Aspidol *(Piam, Ital.).*
Lysine aspirin.
Pain; fever.

Aspiglicina *(Antoneto, Ital.).*
Glycine; aspirin.
Neuralgia.

Aspinfantil *(Lasa, Spain).*
Aspirin.
Pain; fever.

Aspirin, Alumina, and Magnesia Tablets *(U.S.P. XXII).*
Aspirin; aluminium hydroxide; magnesium hydroxide.

Aspirin, Alumina, and Magnesium Oxide Tablets *(U.S.P. XXII).*
Aspirin; aluminium hydroxide; magnesium oxide.

Aspirin, Caffeine, and Dihydrocodeine Capsules *(U.S.P. XXII).*
Aspirin; caffeine; dihydrocodeine tartrate.

Aspirin and Caffeine Tablets *(B.P. 1988).*
Aspirin 350 mg; caffeine 30 mg.

Aspirin Capsules *(U.S.P. XXII).*
They may be enteric-coated.

Aspirin, Codeine Phosphate, Alumina, and Magnesia Tablets *(U.S.P. XXII).*
Aspirin; codeine phosphate hemihydrate; aluminium hydroxide; magnesium hydroxide.

Aspirin, Codeine Phosphate, and Caffeine Capsules *(U.S.P. XXII).*
Aspirin; codeine phosphate hemihydrate; caffeine.

Aspirin, Codeine Phosphate, and Caffeine Tablets *(U.S.P. XXII).*
Aspirin; codeine phosphate hemihydrate; caffeine.

Aspirin and Codeine Phosphate Tablets *(U.S.P. XXII)* Co-codaprin Tablets.
Aspirin; codeine phosphate hemihydrate.

Aspirin Delayed-release Capsules *(U.S.P. XXII).*
Enteric-coated aspirin.

Aspirin Delayed-release Tablets *(U.S.P. XXII).*
Enteric-coated aspirin.

Aspirin Effervescent Tablets for Oral Solution *(U.S.P. XXII).*

Aspirin Extended-release Tablets *(U.S.P. XXII).*

Aspirin forte *(Bayer, Ger.).*
Aspirin; caffeine.
Pain; inflammation.

Aspirin plus C *(Bayer, Ger.).*
Aspirin; ascorbic acid.
Light to moderate pain; fever; cold symptoms.

Aspirin Suppositories *(U.S.P. XXII).*

Aspirin Tablets *(B.P. 1988)* Acetylsalicylic Acid Tablets.

Aspirin Tablets *(U.S.P. XXII).*
They may be enteric-coated.

Aspirina *(Bayer, Ital.).*
Aspirin.
Pain; fever; inflammation.

Aspiriha C *(Bayer, Ital.).*
Aspirin; ascorbic acid.
Pain; fever; inflammation.

Aspirina C *(Bayer, Spain).*
Aspirin; ascorbic acid.
Pain; fever; musculoskeletal disorders.

Aspirine C *(Bayer, Neth.).*
Aspirin; ascorbic acid.
Pain; fever.

Aspirinetta *(Bayer, Ital.).*
Aspirin.
Pain; fever; inflammation.

Aspirinetta C *(Bayer, Ital.).*
Aspirin; ascorbic acid.
Pain; fever; inflammation.

Aspisol *(Bayer, Ger.).*
Lysine aspirin.
Pain; fever; rheumatism; thrombo-embolic disorders.

Asplin *(Roger, Spain).*
Paracetamol.
Pain; fever.

Asporin 0.25 *(MC, Ital.).*
Sodium phenolate; glutaraldehyde.
Instrument sterilisation.

Asporin 2 *(MC, Ital.).*
Glutaraldehyde.
Instrument sterilisation.

Aspro *(Nicholas, Austral.).*
Aspirin.
Pain; fever.

Aspro *(Nicholas, Ger.).*
Aspirin.
Pain; inflammation.

Aspro *(Bouty, Ital.).*
Aspirin.
Pain; fever.

Aspro *(Nicholas, Neth.).*
Aspirin.
Pain; fever.

Aspro *(Pan Quimica, Spain).*
Aspirin.
Pain; fever; inflammation; thrombo-embolism prophylaxis.

Aspro *(Nicholas, Switz.).*
Aspirin.
Pain; fever.

Aspro *(Nicholas, UK).*
Aspirin.
Pain; fever.

Aspro C *(Bouty, Ital.).*
Aspirin; ascorbic acid.
Pain; fever.

Aspro Paraclear *(Nicholas, UK).*
Paracetamol.

Asprodeine *(Nicholas, Austral.).*
Aspirin; codeine phosphate.

Asprol *(Nicholas, Austral.).*
Paracetamol.
Pain; fever.

ASS *(Stada, Ger.; Durachemie, Ger.; Woelm, Ger.; Ratiopharm, Ger.).*
Aspirin.
Pain; inflammation; fever; rheumatism; thrombo-embolic disorders.

ASS + C *(Ratiopharm, Ger.).*
Aspirin; ascorbic acid.
Pain; cold symptoms.

Assagix *(Pierre Fabre, Fr.).*
Tilia; calcium bromolactobionate.
Insomnia; irritability.

Assan *(Permamed, Switz.).*
Flufenamic acid; glycol salicylate; heparin sodium.
Musculoskeletal and joint pain; peripheral vascular disorders.

Assan-Thermo *(Permamed, Switz.).*
Flufenamic acid; glycol salicylate; benzyl nicotinate; heparin sodium.
Musculoskeletal and joint pain.

Assist Energetico *(Farmasport, Ital.).*
Vitamin preparation.

Assist Reintegratore *(Farmasport, Ital.).*
Nutritional supplement.
Fluid and electrolyte imbalance.

ASS-Kombi *(Ratiopharm, Ger.).*
Paracetamol; aspirin; ascorbic acid.
Pain.

Assocort *(Squibb, Ital.).*
Triamcinolone acetonide; neomycin sulphate; gramicidin; nystatin.
Skin disorders.

Assoral *(Glaxo, Ital.).*
Roxithromycin.
Bacterial infections.

Assugrin *(Pan Quimica, Spain).*
Sodium cyclamate; saccharin sodium; sodium bicarbonate; tartaric acid.
Sugar substitute.

Assur *(Delagrange, Fr.).*
Moroxydine hydrochloride; aspirin.
Viral infections.

Astenile *(Recordati, Ital.).*
Prasterone sodium sulphate.
Asthenia.

Astenolit *(Elmu, Spain).*
Vitamin, mineral and amino-acid preparation.
Tonic.

Aster C *(Corvi, Ital.).*
Ascorbic acid.
Vitamin C deficiency.

Asthénal *(Grossmann, Switz.).*
Sodium dimethyl aminophenylphosphinate; glutamic acid; thiamine hydrochloride; ascorbic acid.
Tonic.

Asthenopin *(Mann, Ger.).*
Pilocarpine hydrochloride.
Ophthalmic disorders.

Asthma 6 *(Hobein, Ger.).*
Ephedrine hydrochloride; caffeine; khellin; potassium iodide; potassium guaiacolsulfonate; sodium benzoate; tinct. herb. grindel.; tinct. herb. hyoscyami; rad. senegae; polysorbate 20; rad. liquiritiae.
Obstructive airways disease.

Asthma-Bisolvon *(Thomae, Ger.).*
Bromhexine hydrochloride; ephedrine hydrochloride; theophylline.
Bronchitis; emphysema; asthma.

Asthma-Bomint *(Pfluger, Ger.).*
Ambra; ammi visnaga; arnica; blatta or.; cactus; carduus mar.; cetraria isl.; chamomilla; crataegus; dracontium foet.; drosera; dulcamara; echinacea ang.; ephedrinum; eriodictyon calif.; gelsemium; grindelia rob.; ipecacuanha; menthol; mercurius cyan.; sodium sulphate; pulsatilla; spigelia; spongia; stramonium.
Homoeopathic preparation.

Asthmacolat *(Galenika, Ger.).*
Etofylline; ephedrine hydrochloride; sem. stramonii; herb. adonidis; flor. arnicae; fol. belladonnae.
Asthma; bronchitis; adjunct in whooping cough.

The symbol † denotes a preparation no longer actively marketed

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Coalgan *(Brothier, Fr.).*
Calcium alginate.
Haemorrhage.

Coalgel *(Ducray, Fr.).*
Coal tar; salicylic acid.
Dandruff.

Coalip *(ISF, Ital.).*
Coenzyme A.
Metabolic disorders.

Co-amilozide Oral Solution *(B.P. 1988)* Amiloride and Hydrochlorothiazide Oral Solution.
Anhydrous amiloride hydrochloride 1 part by weight; hydrochlorothiazide 10 parts by weight.

Co-amilozide Tablets *(B.P. 1988)* Amiloride and Hydrochlorothiazide Tablets.
Anhydrous amiloride hydrochloride 1 part by weight; hydrochlorothiazide 10 parts by weight.

CO-B1 *(Bruco, Ital.).*
Cocarboxylase.
Metabolic disorders.

CO-B12 (Cobidodici) *(Bruco, Ital.).*
Cocarboxylase; thiamine monophosphate; cyanocobalamin.
Neuralgia symptoms.

Coba-12 *(Nordic, Canad.).*
Vitamin B substances; lysine hydrochloride; lignocaine hydrochloride.
Vitamin B deficiency.

Cobadex *(Cox, UK).*
Hydrocortisone; dimethicones.
Skin disorders.

Cobaforte *(Roussel, Ital.).*
Cobamamide.
Vitamin B_{12} deficiency.

Cobalatec *(Caps, S.Afr.).*
Cyanocobalamin.
Vitamin B_{12} deficiency.

Cobaldocemetil *(Clariana, Spain).*
Mecobalamin.
Vitamin B_{12} deficiency.

Cobalin-H *(Paines & Byrne, UK).*
Hydroxocobalamin.
Anaemia due to B_{12} deficiency; tobacco amblyopia; Leber's atrophy.

Cobalparen† *(Saarstickstoff-Faiol, Ger.).*
Cyanocobalamin.
Vitamin B deficiency.

Cobalparen-Depot† *(Saarstickstoff-Faiol, Ger.).*
Hydroxocobalamin.
Vitamin B deficiency.

Cobalton *(Lagap, Ital.).*
Cocarboxylase; cyanocobalamin; sodium glycerophosphate.
Neuralgia symptoms.

Cobamas *(Tafir, Spain).*
Cyproheptadine hydrochloride; amino acids and vitamins.
Anorexia; weight loss; tonic.

Cobamide *(UCB, Ital.).*
Hydroxocobalamin.
Anaemias; neurological symptoms.

Cobantril *(Pfizer, Switz.).*
Pyrantel hydrogen embonate.
Nematode infections.

Cobanzyme *(Bouchara, Fr.).*
Cobamamide.
Debilitated states.

Cobazymase *(Bouchara, Switz.).*
Cobamamide.
Vitamin B_{12} deficiency.

Cobed *(Merrell, Ger.).*
Drops; syrup: Guaiphenesin; sodium camsylate.
Bronchitis; tracheobronchitis.

Cobed *(Merrell, Ger.).*
Gel: Camphor; guaiacol ethylglycolate; turpentine oil; peppermint oil; menthol; rosemary oil; thymol; methyl nicotinate.
Bronchitis; bronchopneumonia.

Cobergon *(Mendelejeff, Ital.).*
Cobamamide.
Tonic.

Co-Betaloc *(Astra, Eire).*
Metoprolol tartrate; hydrochlorothiazide.
Hypertension.

Co-Betaloc *(Astra, UK).*
Metoprolol tartrate; hydrochlorothiazide.
Hypertension.

Cobeton *(Propan, S.Afr.).*
Vitamin B substances.

cobidec n *(Parke, Davis, Ger.).*
Multivitamin and mineral preparation.

Cobiona *(Esteve, Spain).*
Oxatomide.
Hypersensitivity reactions.

Cobolin-M *(Legere, USA).*
Cyanocobalamin.

Cobutolin† *(Cox, UK).*
Inhalation: Salbutamol.
Asthma; bronchospasm.

Cobutolin† *(Cox, UK).*
Tablets: Salbutamol sulphate.
Asthma; bronchospasm.

Cocaine Eye-drops *(B.P.C. 1973).*
Cocaine hydrochloride.

Cocaine and Homatropine Eye-drops *(B.P.C. 1973).*
Cocaine hydrochloride; homatropine hydrobromide.

Cocaine Hydrochloride Tablets for Topical Solution *(U.S.P. XXII).*

Cocardoce *(Hortel, Spain).*
Cyanocobalamin; cocarboxylase.
Vitamin B deficiency; nausea and vomiting in pregnancy; tonic; alcoholism.

Cocardoce A M P *(Hortel, Spain).*
Adenosine phosphate; cyanocobalamin; cocarboxylase.
Tonic.

Co-careldopa Tablets *(B.P. 1988)* Levodopa and Carbidopa Tablets.
Levodopa; carbidopa.

Co-Carnetina B12 *(Sigma-Tau, Ital.).*
Cobamamide; L-carniitine.
Tonic.

Cocarvit *(CT, Ital.).*
Cocarboxylase.

Coccidioidin *(U.S.P. XXII).*
Contains the antigens obtained from the by-products of mycelial growth or from the spherules of the fungus *Coccidioides immitis.*

Cocculine *(Boiron, Fr.).*
Cocculus; tabacum; nux vomica; petroleum.
Homoeopathic preparation.

Cocilix *(Vernleigh, S.Afr.).*
Cocillana; senega; squill; guaiacol; terpin hydrate; menthol; codeine phosphate.
Coughs.

Cocillana Liquid Extract *(B.P.C. 1973).*

Cocillana-etyfin *(Kabi, Swed.).*
Ethylmorphine hydrochloride; senega; cocillana; cascara.
Coughs.

Co-Cillin *(Compu, S.Afr.).*
Ampicillin trihydrate.
Bacterial infections.

Cocktail Reale *(Sella, Ital.).*
Honey; pollen; ginseng; royal jelly; propolis.
Nutritional supplement.

Co-codamol Tablets *(B.P. 1988)* Codeine Phosphate and Paracetamol Tablets.
Codeine phosphate 2 parts by weight; paracetamol 125 parts by weight.

Co-codaprin Tablets *(B.P. 1988)* Aspirin and Codeine Tablets.
Codeine phosphate 1 part by weight; aspirin 50 parts by weight.

Cocois *(Bioglan, UK).*
Coal tar solution; salicylic acid; precipitated sulphur; coconut oil.
Dry scalp conditions.

Cocresol *(Areu, Spain).*
Feprazone.
Pain; fever; inflammation.

Codafen Continus *(Napp, UK).*
Ibuprofen; codeine phosphate.
Pain; inflammation.

Codalan *(Lannett, USA).*
Codeine phosphate; paracetamol; caffeine.

Codalax *(Regent Laboratories, UK).*
Danthron; poloxamer 188.
Constipation.
These ingredients are present in such proportion that together they can be described by the British Approved Name Co-danthramer.

Codalgin *(Fawns & McAllan, Austral.).*
Paracetamol; codeine phosphate.
Pain; fever.

Codalgina Retard *(Faes, Spain).*
Aspirin.
Pain; inflammation; fever; thrombo-embolism prophylaxis.

Coda-Med *(Broad, UK).*
Paracetamol; codeine phosphate; caffeine citrate.

Codamine *(Barre-National, USA).*
Phenylpropanolamine hydrochloride; hydrocodone tartrate.

Codan *(Warner Chilcott, USA).*
Hydrocodone tartrate; homatropine methobromide.

Codanin *(Whitehall, UK).*
Codeine phosphate; paracetamol.
Pain; fever.

Co-danthrusate Capsules *(B.P. 1988)*
Danthron and Docusate Sodium Capsules.
Danthron 5 parts by weight; docusate sodium 6 parts by weight.

Codaphen *(Roxane, USA).*
Codeine phosphate; paracetamol.

Codate *(Rorer, Austral.).*
Codeine phosphate.
Pain; diarrhoea; coughs.

Code Vin† *(Vinsi, Spain).*
Suppositories: Codeine phosphate; ephedrine hydrochloride; propyphenazone.
Influenza and cold symptoms.

Code Vin† *(Vinsi, Spain).*
Tablets: Codeine phosphate; ephedrine hydrochloride.
Coughs.

Codefilona† *(Lasa, Spain).*
Aminophylline; codeine.
Coughs; bronchospasm.

Codegest Expectorant *(Great Southern, USA).*
Phenylpropanolamine hydrochloride; codeine phosphate; guaiphenesin.

Codeine Linctus *(B.P. 1988).*
Codeine phosphate hemihydrate 0.3% w/v or an equivalent concentration of the sesquihydrate.
Diabetic Codeine Linctus *(B.P.)* is formulated with a vehicle appropriate for administration to diabetics and complies with the requirements for Codeine Linctus *(B.P.).*

Codeine Phosphate Injection *(U.S.P. XXII).*
Codeine phosphate hemihydrate.

Codeine Phosphate Oral Solution *(B.P. 1988)* Codeine Phosphate Syrup.
Codeine phosphate hemihydrate 0.5% w/v or an equivalent concentration of the sesquihydrate.
This preparation replaces Codeine Phosphate Syrup *B.P.C. 1973.* For extemporaneous preparation the *B.P.* specifies codeine phosphate hemihydrate 0.5 g, water 1.5 mL, chloroform spirit 2.5 mL, and syrup to 100 mL.

Codeine Phosphate Tablets *(B.P. 1988).*
Codeine phosphate or codeine phosphate sesquihydrate.

Codeine Phosphate Tablets *(U.S.P. XXII).*
Codeine phosphate hemihydrate.

Codeine Sulfate Tablets *(U.S.P. XXII).*
Codeine sulphate trihydrate.

Codeinol *(Saba, Ital.).*
Codeine hydrochloride; ephedrine hydrochloride.
Respiratory-tract symptoms with cough.

Codeisan *(Abello, Spain).*
Syrup: Codeine phosphate; ephedrine hydrochloride; Primula veris; sodium benzoate.
Respiratory-tract disorders.

Codeisan *(Abello, Spain).*
Tablets; suppositories: Codeine phosphate.
Coughs; pain; diarrhoea.

Codelasa *(Lasa, Spain).*
Codeine; ephedrine hydrochloride; potassium guaiacolsulfonate.
Respiratory-tract disorders.

Codelasa Infantil† *(Lasa, Spain).*
Cineole; codeine; ephedrine hydrochloride.
Respiratory-tract disorders.

Codelix *(Drug Houses Austral., Austral.).*
Codeine phosphate.
Coughs; pain; diarrhoea.

Codella *(Napp, UK).*
Glycerol; kaolin; povidone-iodine.
Dry skin.

Co-dergocrine Tablets *(B.P. 1988)* Codergocrine Mesylate Tablets.

Coderma *(Biotrading, Ital.).*
Fluocinolone acetonide.
Skin disorders.

Codetilina *(Promesa, Spain).*
Cineole; ethylmorphine.
Respiratory-tract disorders.

Codetilina-Eucaliptolo Houdé *(Lirca, Ital.).*
Ethylmorphine hydrochloride; eucalyptus oil.
Coughs.

Codex DNB *(Smith Kline & French, Ital.).*
Saccharomyces boulardii.
Gastro-intestinal disorders.

Codicaps *(Thiemann, Ger.).*
Capsules: Codeine; chlorpheniramine maleate.
Coughs and associated respiratory-tract disorders.

Codicaps *(Thiemann, Ger.).*
Oral liquid: Codeine polistirex; chlorpheniramine polistirex.
Coughs and associated respiratory-tract disorders.

Codicaps B *(Thiemann, Ger.).*
Codeine; chlorpheniramine maleate; bromhexine hydrochloride.
Coughs and associated respiratory-tract disorders.

codicept *(Sanol, Ger.).*
Codeine.
Coughs.

Codiclear DH *(Central Pharmaceuticals, USA).*
Hydrocodone tartrate; guaiphenesin.
Coughs.

Codicompren *(Cascan, Ger.).*
Codeine phosphate hemihydrate.
Coughs.

Codidoxal *(Muck, Illert., Ger.).*
Doxycycline hydrochloride; codeine polistirex.
Coughs associated with infections of the respiratory-tract.

Codimal DH *(Central Pharmaceuticals, USA).*
Hydrocodone tartrate; phenylephrine hydrochloride; mepyramine maleate.
Coughs.

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Furo-Puren *(Klinge-Nanermann, 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.

Furunkulosin *(Diabetylin, 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; lynoestrenol.
Biphasic oral contraceptive; dysmenorrhoea.

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

G 1000 Record *(Pierrel, Ital.).*
Carbohydrate, multivitamin, and mineral preparation.

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

Gabacet *(Carrion, Fr.).*
Piracetam.
Cerebral vascular disorders.

Gabakalm *(Contassium 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 *(Biotekfarma, Ital.).*
Niperotidine hydrochloride.
Gastro-intestinal disorders.

Gaiarsol *(Chanteaud, Fr.).*
Methylarsinic acid; guaiacol; 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.

Galactoquin *(Mundipharma, Ger.).*
Quinidine polygalacturonate.
Arrhythmias.

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

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

Galantase *(Noristan, S.Afr.).*
Tilactase.
Lactose intolerance.

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

Galenamet *(Galen, UK).*
Cimetidine.

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

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

Galenavowen-N *(Weber & Weber, Ger.).*
Oral drops: Ammi visnaga; boldo; curcuma long.; cynara scolymus; frangula; syzygium jambolanum.
Homoeopathic preparation.

Galénic *(Galenic, Fr.).*
Ruscus aculeatus; dextran sulphate; melilot.
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-Clevenot, Fr.).*
Calcium bromide; calcium lactate pentahydrate.
Insomnia; nervous disorders.

Galium Complex *(Blackmores, Austral.).*
Galium 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).*

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

Galleb *(Hoyer, Ger.).*
Tinct. herb. chelidonii; tinct. rhiz. curcumae xanth.; 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. curcumae xanth.; herb. virgaureae; fruct. ammeos visnagae; rad. taraxaci c. herb.; rad. echinaceae purpur.; fol. menthae pip.; fruct. cardui mariae; cort. frangulae; aescin.
Biliary disorders.

Gallemolan N *(Redel, Ger.).*
Herb. chelidon.; herb. absinth.; fol. boldo; rad. taraxaci c. herba; rhiz. rhei; flor. chamomiliae; fel tauri.
Biliary disorders; gall stones; liver disorders.

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

Gallensteinkapseln *(Evers, Ger.).*
Herb. hederae terrestr.
Gall stones.

Gallexier *(Salushaus, Ger.).*
Tablets: Rhiz. curcumae xanthor.; fol. cynarae scolym.; fruct. cardui mariae; rad. taraxaci c. herb.; flor. chamomiliae; fol. menthae pip.
Biliary disorders.

Gallexier *(Salushaus, Ger.).*
Tea: Fol. cynarae scolym.; herb. taraxaci; rhiz. curcumae xanth.; fruct. cardui mariae; herb. cardui benedicti; fol. trifolii fibrini; herb. millefolii; rad. gentianae; herb. absinthii; rhiz. calami; flor. chamomillae; fruct. foeniculi; fructose.
Herbal tea.

Galliagène T.C.M. *(Gallia, Fr.).*
Infant feed; food for special diets.
Milk-protein intolerance; malabsorption syndromes.

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. sennae angust.; fol. betul.; herb. chelidon.; herb. equiset.; herb. card. bened.; fruct. card. mar.; flor. chamomill.; herb. nastur.; 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.

Gallium(^{67}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. curcumae.
Gastro-intestinal disorders.

Gallo-Merz Spasmolyticum† *(Merz, Ger.).*
Ethaverine hydrochloride; dehydrocholic acid; pancreatin; cellulase; dimethicone; rhiz. curcumae.
Biliary disorders; gastro-intestinal spasm.

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

Galloselect *(Dreluso, Ger.).*
Chamomilla; carduus marianus; lycopodium; menth. pip.; chelidonium; belladonna; natrum sulfuricum; taraxacum.
Homoeopathic 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.

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

Gamanil *(E. Merck, UK).*
Lofepramine hydrochloride.
Depression.

Gamastan *(Cutter, Canad.).*
A normal immunoglobulin.
Passive immunisation.

Gamastan *(Cutter, USA).*
A normal immunoglobulin.

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Crystal engineering of the composition of pharmaceutical phases

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The carboxylic acid–pyridine supramolecular heterosynthon can be exploited to predictably generate binary crystalline phases involving *rac*-ibuprofen, *rac*-flurbiprofen or aspirin.

The concept of crystal engineering was originally introduced in the context of stereochemical control of photochemical reactions,[1] but it has subsequently been shown to have wider implications for materials science. In the context of pharmaceuticals, there are important process and intellectual property implications related to control and reproducibility of composition and polymorphism.[2,3] In this contribution, we focus upon how crystal engineering can be applied towards small organic molecules and generation of novel pharmaceutical compositions. This study is premised on the assumption that pharmaceutical molecules are inherently predisposed for such studies since they contain exofunctional supramolecular synthons.[4]

Supramolecular synthons that are based upon hydrogen bonds represent a prototypal tool for crystal engineering[5] and can be readily categorized as illustrated in Scheme 1: 'supramolecular homosynthons' from self-complementary moieties, *e.g.* the dimer formed by carboxylic acids, **I**; 'supramolecular heterosynthons' from two or more components, *e.g.* the dimer formed by pyridines with single or multiple carboxylic acids,[6–10] **II**.

Heterosynthon **II** has previously been exploited for liquid-crystalline materials,[7] two-dimensional beta networks,[7] two-dimensional corrugated sheets[9] and 'ternary supermolecules'[10] and similar heterosynthons have been used as templates for control of solid-state reactions.[11] We herein extend its use to the realm of pharmaceutical molecules by forming novel compositions of ibuprofen,[12] flurbiprofen,[13] and aspirin.[14]

Supramolecular complexes **A–D** form when *rac*-ibuprofen, *rac*-flurbiprofen or aspirin are crystallized in the presence of dipyridyls: (ibuprofen)$_2$(4,4′-bipyridine), **A** (Fig. 1); (flurbiprofen)$_2$(4,4′-bipyridine), **B**, (Fig. 2); (flurbiprofen)$_2$ (trans-1,2-bis(4-pyridyl)ethylene), **C** (Fig. 2); (aspirin)$_2$(4,4′-bipyridine), **D** (Fig. 3); **A–D** were characterized by FT-IR spectroscopy, XRPD, DSC, TGA and single crystal X-ray diffraction† . The crystal structures of **A–D** exhibit the expected 2 : 1 stoichiometries because of heterosynthon **II**. The resulting 3-component adducts are centrosymmetric for **A–C** and exhibit herringbone packing patterns of the type seen in the pure phases.[12,13] All hydrogen bonds in **A–C** are consistent with expected values,[15–18] including the C–H···O interaction[19,20] that affords rigidity to this supramolecular heterosynthon and helps to explain the similarity between the crystal packing of **A–C** and the pure pharmaceutical phases.

The 3-component supramolecular adduct formed between aspirin and 4,4-bipyridine differs from **A–C** in that the 4,4′-bipyridine molecules are twisted with a torsion angle of 39° rather than planar and the planes of the C_6 rings in the aspirin molecules are oriented with a torsion angle of *ca.* 54°. This precludes formation of a centrosymmetric supramolecular adduct and results in dramatically different crystal packing. The crystal packing of adducts of **D** results in a channel inclusion

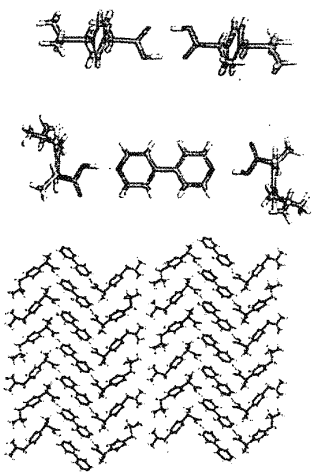


Fig. 1 The 3-component adducts present in pure ibuprofen and **A** (above); the herringbone crystal-packing pattern seen in **A** (below).

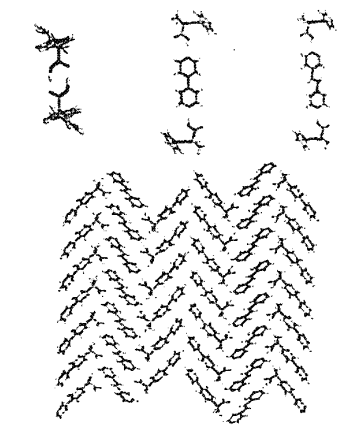
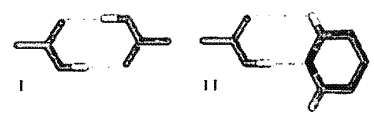
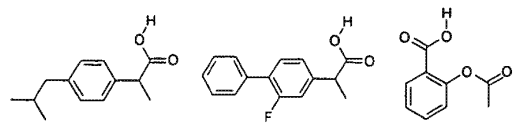


Fig. 2 The 3-component adducts present in pure flurbiprofen, **B** and **C** (above); the herringbone crystal-packing pattern seen in **C**, which is isostructural with **B** (below).



Scheme 1



ibuprofen flurbiprofen aspirin

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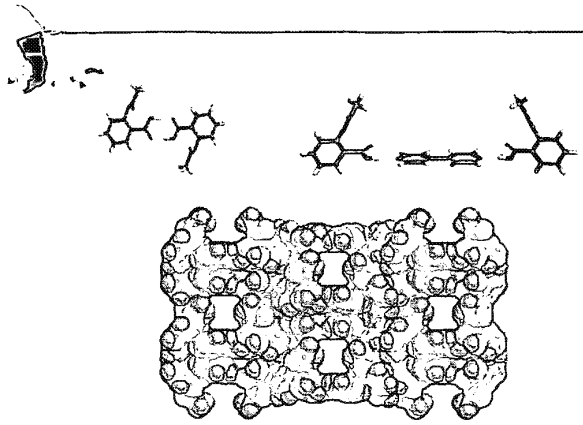


Fig. 3 The 3-component adducts present in pure aspirin and **D** (above); the open framework crystal packing pattern seen in **D** (below). The hourglass channels have effective dimensions as follows: 4.7 Å in height; 2.4 Å wide at the narrowest point (middle); 2.7 Å wide at the widest point (top & bottom).

compound, presumably templated by the presence of hexane during crystallization (Fig. 3). A review of the crystallographic literature revealed that 4,4-bipyridine moieties exhibit torsional flexibility in other circumstances.[15]

In conclusion, supramolecular heterosynthons can be exploited for generation of binary crystals that contain pharmaceutical components and, furthermore, the nature of the non-pharmaceutical component can dramatically affect crystal packing and, therefore, physical properties. For example, the melting points for **A–C** are higher than their pure individual components, and the melting point of **D**, a phase that exhibits dramatically different crystal packing, has a lower melting point than its pure individual components.‡

Whereas **A–D** should only be regarded as model compounds, we believe that the observations reported herein could have broad implications for the formulation of pharmaceuticals since control of composition can in appropriate circumstances now be regarded as being addressable *via* a supramolecular retrosynthetic[21] approach. Further studies will focus upon multiple component crystalline phases that will be designed and optimized for improved pharmaceutical performance and contain components that are generally regarded as safe (GRAS) by the FDA.[22]

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Notes and references

† *Synthesis and data:* A–C were prepared by dissolving the pharmaceutical and bipyridine molecules in a 2 : 1 ratio in acetone and slow evaporation. D was prepared by dissolving aspirin and 4,4′-dipyridyl (2 : 1) in hexane and addition of diethyl ether. FT-IR spectra confirmed that deprotonation did not occur. Single crystal X-ray diffraction data for A–D were collected on a Bruker SMART-APEX CCD Diffractometer. Diffracted data were corrected for absorption using the SADABS[23] program. SHELXTL[24] was used for the structure solution and refinement was based on $|F|^2$. All non-hydrogen atoms were refined anisotropically. Carboxylic acid protons were located and refined with isotropic thermal parameters whereas the remaining hydrogen atoms were fixed in idealized positions and refined isotropically with thermal parameters based upon the corresponding carbon atoms [U(H) = 1.2 Ueq (C)]. In B and C the fluorine atom was disordered between the 2 and 6 positions of the benzene ring with the major component having ~70% occupancy. Calculated and experimental XRPD patterns for A–D are consistent with single crystals being representative of the bulk phases.

Crystal data for **A**: $C_{36}H_{44}N_2O_4$, M = 568.73, triclinic, space group $P\bar{1}$; a = 5.759(3), b = 11.683(6), c = 24.705(11) Å, α = 93.674(11), β = 90.880(10), γ = 104.045(7)°, U = 1608.3(13) Å^3, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.076 mm^{-1}, D_c = 1.174 Mg m^{-3}, λ = 0.71073 Å^3, F(000) = 612, $2\theta_{max}$ = 23.29°. 5208 reflections measured, 3362 unique (R_{int} = 0.0826). Final residuals for 399 parameters were R_1 = 0.0964, wR_2 = 0.2510 for $I > 2\sigma(I)$, and R_1 = 0.1775, wR_2 = 0.2987 for all 3362 data

Crystal data for **B**: $C_{40}H_{34}F_2N_2O_4$, M = 644.69, monoclinic $P2_1/n$; a = 5.860(4), b = 47.49(3), c = 5.928(4) Å, β = 107.382 (8)°, U = 1574.3(19) Å^3, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.096 mm^{-1}, D_c = 1.360 Mg m^{-3}, λ = 0.71073 Å^3, F(000) = 676, $2\theta_{max}$ = 21.69°. 4246 reflections measured, 1634 unique (R_{int} = 0.0677). Final residuals for 226 parameters were R_1 = 0.0908, wR_2 = 0.2065 for $I > 2\sigma(I)$, and R_1 = 0.1084, wR_2 = 0.2209 for all 1634 data.

Crystal data for **C**: $C_{42}H_{36}F_2N_2O_4$, M = 670.73, monoclinic $P2_1/n$; a = 5.8697(9), b = 47.357(7), c = 6.3587(10) Å, β = 109.492(3)°, U = 1666.2(4) Å^3, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.093 mm^{-1}, D_c = 1.337 Mg m^{-3}, λ = 0.71073 Å^3, F(000) = 704, $2\theta_{max}$ = 21.69°. 6977 reflections measured, 2383 unique (R_{int} = 0.0383). Final residuals for 238 parameters were R_1 = 0.0686, wR_2 = 0.1395 for $I > 2\sigma(I)$, and R_1 = 0.1403, wR_2 = 0.1709 for all 2383 data.

Crystal data for **D**: $C_{28}H_{24}N_2O_8$, M = 516.49, orthorhombic $Pbcn$; a = 28.831(3), b = 11.3861(12), c = 8.4144(9) Å, U = 2762.2(5) Å^3, T = 173(2) K, Z = 4, μ(Mo-Kα) = 0.092 mm^{-1}, D_c = 1.242 Mg m^{-3}, λ = 0.71073 Å^3, F(000) = 1080, $2\theta_{max}$ = 25.02°. 12431 reflections measured, 2433 unique (R_{int} = 0.0419) Final residuals for 202 parameters were R_1 = 0.0419, wR_2 = 0.1358 for $I > 2\sigma(I)$, and R_1 = 0.0541, wR_2 = 0.1482 for all 2433 data.

CCDC 188913–188916. See http://www.rsc.org/suppdata/cc/b2/b208574g/ for crystallographic files in CIF or other electronic format.

‡ *Melting points* (°C): **A**: 117–120; **B**: 155–160; **C**: 153–158; **D**: 91–96; aspirin: 133–135; ibuprofen: 77–78; flurbiprofen: 113–114; 4,4′-bipyridine: 111–114; trans-1,2-bis(4-pyridyl)ethylene: 150–153.

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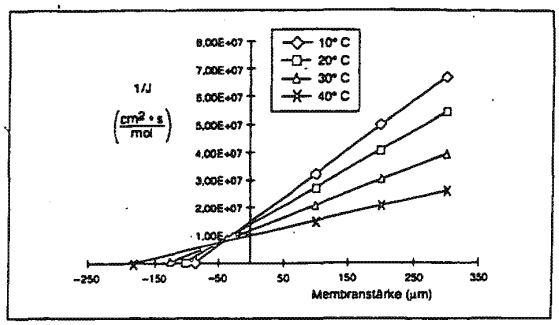


Abb. 7: Darstellung des reziproken Flusses gegen die Membranstärke für das Modell Kaliumchlorid/Wasser

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} cm² · s/mol)	J (10^{-8} mol/cm² · 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 Gesamtwiderstand bei der verwendeten Apparatur erhebliche 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 v n der Geometrie der Diffusionszelle k nnen 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 λ = 252 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 h 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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[PD. 00/12/96
p-960 - 963 = (4)]

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, coevoporate and inclusion complex demonstrated a faster dissolution rate of the inclusion complex compared to solid dispersions and CBZ alone.

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Physikochemische Charakteristiken v n 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

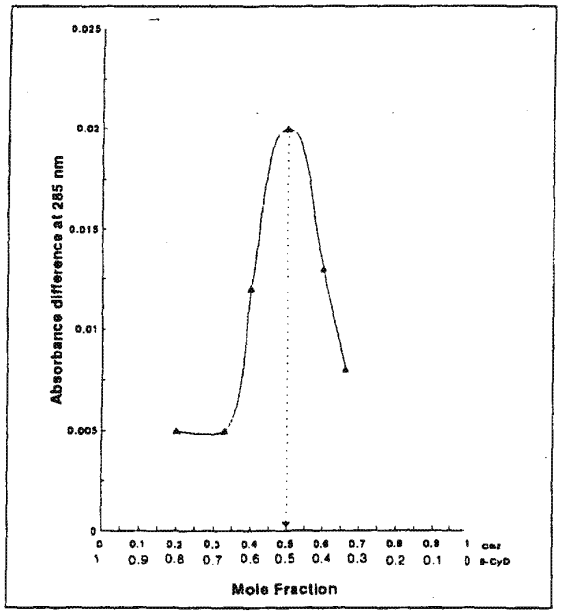


Fig. 1: Elucidation of the stoichiometric ratio of carbamazepine-β-cyclodextrin complex by the spectrophotometric method

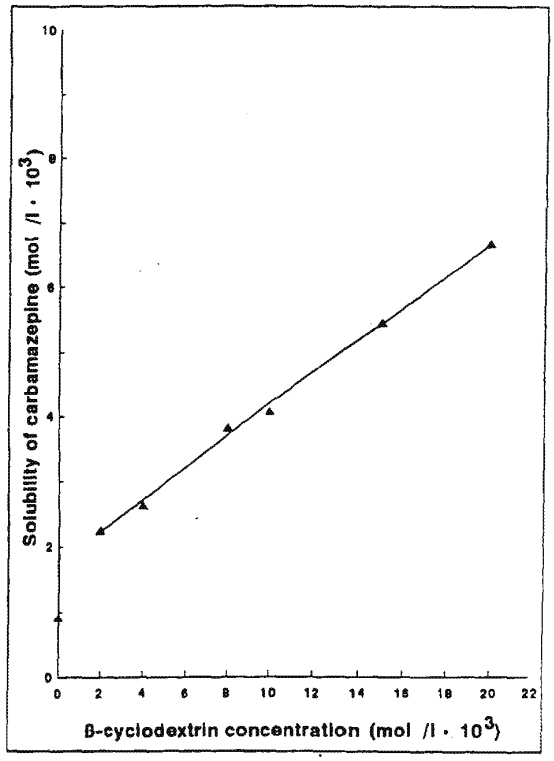


Fig. 2: Effect of β-cyclodextrin on the solubility of carbamazepine in water at 25 °C

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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 coevaprate		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.

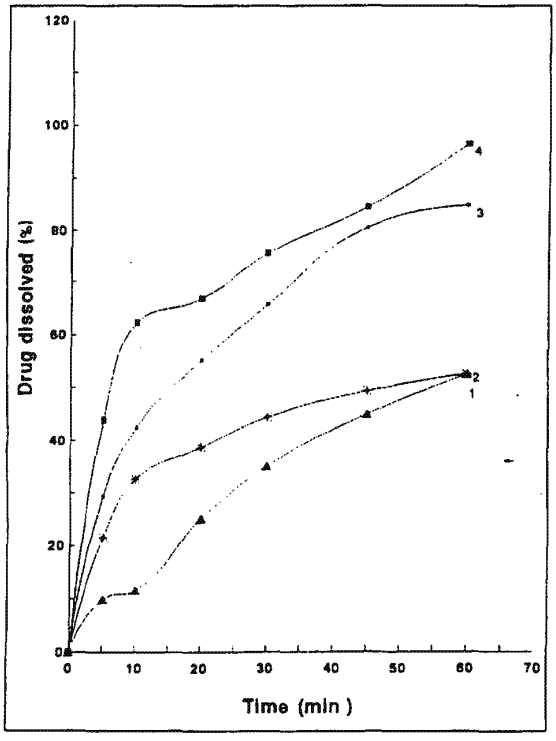


Fig. 3: Dissolution profiles of carbamazepine (1), carbamazepine – PEG 6000 coevaporate (2), carbamazepine – PEG 6000 comelt (3), and carbamazepine – β-cyclodextrin complex (4) in 0.1 N HCl at 37 °C

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 reagents and solvents were of analytical grade.

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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 µm). 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 µm 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 N_2 purging gas atmosphere (at a constant rate of 50 cm^3/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 ± 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 µm 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 C_{18} 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 used after 8 h at room temperature without protection from light.

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

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Applicants	:	Michael J. Zaworotko, Brian Moulton, Nair Rodriguez-Hornedo
Serial No.	:	10/378,956
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Conf. No.	:	4742
For	:	Multiple-Component Solid Phases Containing at Least One Active Pharmaceutical Ingredient

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

SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §§1.97 AND 1.98

Sir:

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

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

Respectfully submitted,

Frank C. Eisenschenk

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: 2421 N.W. 41st Street, Suite A-1
Gainesville, FL 32606-6669

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

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NOVARTIS EXHIBIT 1517
Novartis v. Regents, IPR2023-01347
Page 126 of 4460

OIPE JC116 JUL 0 2 2004 PATENT & TRADEMARK OFFICE

PTO/SB/08A (08-03)
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Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet	1	of	1

Complete if Known	
Application Number	10/378,956
Filing Date	March 3, 2003
First Named Inventor	Michael J. Zaworotko
Art Unit	1765
Examiner Name	
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-			
	U2	US-			
	U3	US-			
	U4	US-			
	U5	US-			
	U6	US-			
	U7	US-			
	U8	US-			
	U9	US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No. [1]	Foreign Patent Document Country Code [3] - Number [4] - Kind Code [5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T [6]
	F1	WO 02/056878 A2	07-25-2002	Pharmacia Corp.	All	
	F2	WO 01/41536 A2	06-14-2001	Pharmacia Corp.	All	
	F3	EP 1167355 A1	01-02-2002	Fako Ilaclari A.S.	All	
	F4					
	F5					
	F6					
	F7					

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard T.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

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MAY 2 4 2004
JC53
PATENT & TRADEMARK OFFICE

1765 JGW

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450
on May 20, 2004

Frank C Eisenschenk

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

SUPPLEMENTAL INFORMATION
DISCLOSURE STATEMENT
Examining Group 1765
Patent Application
Docket No. USF-106XC1
Serial No. 10/378,956

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

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

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR §§1.97 AND 1.98

Sir:

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

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

Respectfully submitted,

Frank C Eisenschenk

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 46,853
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: 2421 N.W. 41st Street, Suite A-1
Gainesville, FL 32606-6669

FCE/mv
Attachments: Form PTO/SB/08 (2 pages); copies of references cited therein.

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OIPE JC53 MAY 24 2004 PATENT & TRADEMARK OFFICE

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Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	10/378,956
Filing Date	March 3, 2003
First Named Inventor	Michael J. Zaworotko
Art Unit	1765
Examiner Name	
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
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	U6	US-			
	U7	US-			
	U8	US-			
	U9	US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No. [1]	Foreign Patent Document Country Code [3] - Number [4] - Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	F1	WO 03 074474 A2	09-12-2003	Univ. South Fla. et al.	All	
	F2	WO 03 033462 A2	04-23-2003	Regents of Univ. Mich.	All	
	F3	WO 01 51919 A2	07-19-2001	Transform Pharm. Inc.	All	
	F4	WO 01 42222 A1	06-14-2001	Pharmacia Corp.	All	
	F5					
	F6					
	F7					

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard T.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	10/378,956
Filing Date	March 3, 2003
First Named Inventor	Michael J. Zaworotko
Group Art Unit	1765
Examiner Name	
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	WEISSBUCH, I. *et al.* "Understanding and control of nucleation, growth, habit, dissolution and structure of two- and three-dimensional crystals using 'tailor-made' auxiliaries" *Acta Cryst.*, 1995, B51:115-148.	
	R2		
	R3		
	R4		
	R5		
	R6		
	R7		
	R8		
	R9		
	R10		
	R11		
	R12		
	R13		

Examiner Signature		Date Considered	

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[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

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UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	PATENT NUMBER	GROUP ART UNIT	FILE WRAPPER LOCATION
10/378,956		1617	0430

Change of Address/Power of Attorney

The following fields have been set to Customer Number 23557 on

- Correspondence Address
- Power of Attorney
- Maintenance Fee Address

The address of record for Customer Number 23557 is:
SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO BOX 142950
GAINESVILLE, FL 32614-2950

The Practitioners of record for Customer Number 23557 are:

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Please take the following action when the correspondence address has been changed to a customer number:
1) Add 'ADDRESS CHANGE TO CUSTOMER NUMBER' on the next available content line of the File Jacket.
2) Put a line through the old address on the File Jacket and enter the Customer Number as the new address.
3) File this Notice in the File Jacket.

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

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

23557 7590 10/12/2005

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

EXAMINER	
WILLIAMS, LEONARD M	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 10/12/2005

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

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	10/378,956	ZAWOROTKO ET AL.	
	Examiner	Art Unit	
	Leonard M. Williams	1617	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2003*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-36* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

UM00010445
NOVARTIS EXHIBIT 1517
Novartis v. Regents, IPR2023-01347
Page 133 of 4460

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-24, drawn to a multiple-component phase composition, classified in class 424, subclass 400.

II. Claims 25-28, drawn to a method of identifying complementary chemical functionalities wherein the identified chemical functionality is not capable of disrupting non-covalent bonding, classified in class 252, subclass 183.11.

III. Claims 29-32, drawn to a method of identifying complementary chemical functionalities wherein the identified chemical functionality is capable of disrupting non-covalent bonding, classified in class 252, subclass 183.11.

IV. Claims 33-36, drawn to a method of identifying complementary chemical functionalities wherein the selected chemical functionality is capable of forming a non-covalent bond to a complementary chemical functionality, classified in class 252, subclass 183.11.

The inventions are distinct, each from the other because of the following reasons:

Inventions II, III, IV and I are related as processes of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the processes as claimed can be used to make other and materially different products or (2) that the product as claimed can be made by another and materially different process

(MPEP § 806.05(f)). In the instant case the processes as described could be utilized to identify nearly anything. The processes differ by varying the chemical functionality on some unidentified molecule (or molecules) to either allow for non-disruption of non-covalent binding of some unspecified supramolecular synthon or disruption of non-covalent binding of some unspecified supramolecular synthon and subsequent forming or reforming of a non-covalent bond between the unidentified molecule with the unspecified supramolecular synthon and subsequent identification of the non-covalently bound unidentified molecule. The product made additionally could be nearly anything. The product could be found (synthesized) via differing traditional chemical techniques such as molecular modeling, combinatorial chemistry or rational compound design.

Inventions II, III and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions while being drawn to a method of identifying chemical functionalities in order to form a supramolecular synthon and being classified in the same class and subclass, the sheer number of different compounds, pharmaceutical ingredients, chemical functionalities, and physical characteristics covered by the claims require their designations as different inventions. Group II is different from Group III and IV as the chemical functionality (which is not specified) is required not to disrupt non-covalent bonding within the supramolecular structure (which is not specified). In group III the chemical functionality (which is not specified) is required to disrupt non-covalent bonding within the supramolecular structure (which is

not identified). In Group IV the chemical functionality (which is not specified) is required to form a non-covalent bond to a complementary chemical functionality (which is not specified) on the active pharmaceutical ingredient (which is not specified).

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, as exemplified by the different classes and subclasses. Further, a search for the invention of the 4 groups would not be coextensive because a search indicating the method is novel or unobvious would not extend to a holding that the product itself is novel or unobvious; similarly, a search indicating that the product is known or would have been obvious would not extend to a holding that the methods are known or would have been obvious. Therefore, restriction for examination purposes as indicated is proper.

If Group I is chosen a species election is required:

This application contains claims directed to the following patentably distinct species of the claimed invention:

Physical or Chemical Properties: chemical stability, thermodynamic stability, solubility, dissolution, bioavailability, crystal morphology and hygroscopicity.

Pharmaceutical Moieties: aspirin, acetaminophen, profen, phenytoin, and carbamazepine.

Molecular Entities: acetaminophen, 4,4'-bipyridine and water; phenytoin and pyridine; aspirin and 4,4'-bipyridine; ibuprofenand 4,4'-bipyridine; fluriprofen and 4,4'-bipyridine; flurbiprofen, trans-1,2-bis(4-pyridyl)ethylene; carbamazapine, p-

phthalaldehyde; carbamazepine and nicotinamide; carbamazepine and saccharin; carbamazepine and 2,6-pyridinedicarboxylic acid; carbamazepine and 5-nitroisopthalic acid; carbamazepine and acetic acid; carbamazepine and 1,3,5,7-adamantanetetracarboxylic acid; carbamazepine and bezoquinone; carbamazepine and butyric acid; carbamazepine and dimethyl sulfoxide; carbamazepine and formamide; carbamazepine and formic acid; and carbamazepine and trimesic acid.

Intermolecular Interactions: hydrogen bonding (weak and/or strong), dipole interactions (induced and/or non-induced), stacking interactions, hydrophobic interactions, and other inter-static interactions.

Complementary Chemical Functionalities: acids, amides, aliphatic nitrogen bases, unsaturated aromatic nitrogen bases, amines, alcohols, halogens, sulfones, nitro groups, S-heterocycles, N-heterocycles, O-heterocycles, ethers thioethers, thiols, esters, thioesters, thioketones, epoxides, acetonates, nitils, oximes, organohalides, acids and amides, pyridines and amides, and alcohols and amines.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for each bolded section above for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1-6 are generic.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim

is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Further restriction may be required.

A telephone call was not made due to the complexity of the restriction requirement.

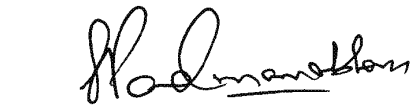
Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leonard M. Williams whose telephone number is 571-272-0685. The examiner can normally be reached on MF 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

LMW



SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER

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FACSIMILE COVER SHEET

SALIWANCHIK, LLOYD & SALIWANCHIK
A Professional Association
P.O. Box 142950
Gainesville, FL 32614-2950
Telephone (352) 375-8100
Facsimile (352) 372-5800

TO:	Examiner Leonard Williams	**FROM:**	Christopher Eisenschenk, Ph.D.
COMPANY:	U.S. Patent Office	**DATE:**	November 10, 2005
FAX NO.:	(571)273-8300	**NO. OF PAGES (INCLUDING COVER SHEET):**	2

SUBJECT/MESSAGE:

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

Attachment: Election Under 35 U.S.C. § 121 (1 page)

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NOVARTIS EXHIBIT 1517
Novartis v. Regents, IPR2023-01347
Page 140 of 4460

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I hereby certify that this correspondence is being facsimile transmitted to the United States Patent and Trademark Office on November 10, 2005.

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

ELECTION UNDER 35 U.S.C. § 121
Examining Group 1765
Patent Application
Docket No. USF-106XC1
Serial No. 10/378,956

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

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

ELECTION UNDER 35 U.S.C. § 121

Sir:

In response to the written Restriction Requirement dated October 12, 2005 in the above-identified patent application, Applicants hereby elect to prosecute the invention of Group II (claims 25-28), without traverse.

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

Respectfully submitted,

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
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Gainesville, FL 32614-2950

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

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

23557 7590 03/22/2006

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

EXAMINER	
WILLIAMS, LEONARD M	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 03/22/2006

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

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	10/378,956	ZAWOROTKO ET AL.	
	Examiner	Art Unit	
	Leonard M. Williams	1617	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *1-24 and 29-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Election/Restrictions

Applicant's election without traverse of Group II (claims 25-28) in the reply filed on 11/10/2005 is acknowledged.

Claims 1-24 and 29-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/10/2005.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 25 the applicant seems to be stating that the active pharmaceutical ingredient (API) must be capable of forming a supramolecular synthon by itself. The API must also have chemical functionalities capable of interacting non-covalently with a second component that will not disrupt the supermolecular synthon formed by the API. It is not clear if a second component is required to be present or if the claim is drawn solely to a homosupermolecular synthon containing "potential" chemical functionalities

capable of interacting with additional components. Further it is not clear that if an additional component is required, what interactions it would have that would not disrupt non-covalent bonding of the API supermolecular synthon already formed. It is not clear if the second component is added to an already preformed solid homosupermolecular API synthon and thus coats the API synthon, or if the second component spontaneously forms around the API supermolecular synthon, or perhaps it could be both. Additionally it is not clear if there can exist an API supermolecular synthon, an area wherein there exists a co-crystal-API supermolecular synthon structure, and then a co-crystal supermolecular synthon surronding the API and co-crystal-API supermolecular structure. Finally claim 25 does not seem to exclude the possibility that the API supermolecular synthon formed can then have a second supermolecular synthon formed, different from the first, that then aggregates with the first forming an heterosupermolecular synthon with homo-API ingredients. Clarification is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 25-28 are rejected under 35 U.S.C. 102(e) as being anticipated by Almarsson et al. (US Patent No. 6559293).

Almarsson et al., in the abstract, teach novel salts of topiramate, along with pharmaceutically acceptable polymorphs, solvates, hydrates, dehydrates, and co-crystals thereof as well as pharmaceutical compositions containing the same. The invention further encompasses novel co-crystals or complexes of topiramate and pharmaceutical compositions comprising them.

In col. 1 lines 15-65, Almarsson et al. teach that topiramate is a sulfamate-substituted monosaccharide which is a white crystalline powder. In col. 6 lines 1-12, Almarsson et al. teaches that specific co-crystals are complexes with caffeine. Almarsson et al. teach in col. 14 line 14 to col. 15 line 20 and example 7, methods of making a topiramate-caffeine co-crystal compositions. Almarrson et al. states:

"The present invention involves the unexpected discovery that the sulfamate (--OSO.sub.2 NH.sub.2) group of topiramate is slightly acidic and thus may be a handle for generation of salts, co-crystals, and complexes with basic compounds such as, but not limited to, caffeine, N-methyl pyrrolidine, nicotine, nicotinamide, and ethers such as PEGs (examples include but are not limited to PEG 200 and PEG 300). Salts are often associated with improved chemical stability and increased solubility of drugs leading to better delivery of drug to the body, by reducing unwanted degradation product exposure and increasing levels of drug in the body. Salt forms of drugs therefore constitute a useful set of options for development of drug formulations."

Further in col. 14 Almarrson et al. state:

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

Thus Almarsson et al. teach that topiramate has an acidic proton, the acidity can be exploited to make salts and/or co-crystals (such as when complexed with caffeine) and that such salts and/or co-crystals can be used to alter the structural and

pharmaceutical properties of the salts and/or co-crystals. In example 7 the synthesis and characterization of the topiramate-caffeine co-crystal is detailed wherein caffeine was melted, recrystallized between a glass slide and a cover slip, allowed to cool and then topiramate was placed on the glass slide in contact with the cover slip and melted wherein the melt came into contact with the recrystallized caffeine. The melted topiramate was then recrystalized overnite and the interfacial region of the topiramate and caffeine was determined to be crystalline and showed a different morphology than the pure caffeine and pure topiramate phases. The absence of multiple melt regions (eutectics) between the topiramate and caffeine indicated only one pure topiramate-caffeine co-crystalline phase anticipating the "...method for identifying complementary chemical functionalities in order to form a desired supramolecular synthon, said method comprising: (a) evaluating the structure of an active pharmaceutical ingredient; (b) determining whether the active pharmaceutical ingredient contains chemical functionalities capable of forming supramolecular synthons with itself; (c) identifying from a plurality of chemical functionalities that are known to form a supramolecular synthon at least one functionality that will form a further supramolecular synthon to the supramolecular synthon formed by the active pharmaceutical ingredient, wherein the identified chemical functionality is not capable of disrupting non-covalent bonding within the supramolecular synthon formed by the supramolecular synthon formed by the active pharmaceutical ingredient, and wherein the selected chemical functionality is capable of forming a noncovalent bond to the supramolecular synthon formed by the active pharmaceutical ingredient; and (d) identifying co-crystal formers having chemical

functionalities that are complementary with the active pharmaceutical ingredient" of claim 25, the "....method...wherein said method further comprises preparing a multiple-component solid phase composition, wherein the multiple-component solid phase composition comprises the active pharmaceutical ingredient and at least one of the identified cocrystal formers" of claim 26, the "...method...wherein the at least one co-crystal former is selected from the group consisting of a different active pharmaceutical ingredient, a GRAS compound, a food additive, a low toxicity organic, and a metal-organic complex" of claim 27, and the "....method...wherein the multiple-component solid phase composition is formed by one or more methods selected from the group consisting of crystallization from solution, cooling the melt, sublimation, and grinding" of claim 28.

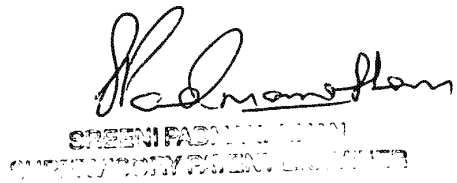
Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leonard M. Williams whose telephone number is 571-272-0685. The examiner can normally be reached on MF 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

LMW



Notice of References Cited	Application/Control No. 10/378,956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.	
	Examiner Leonard M. Williams	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-6,559,293	05-2003	Almarsson et al.	536/18.7
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

UM00010463
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Alexandria, Virginia 22313-1450
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Bib Data Sheet

CONFIRMATION NO. 4742

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/378,956	03/03/2003 RULE	424	1617	USF-106XC1

APPLICANTS

Michael J. Zaworotko, Tampa, FL;

Brian Moulton, Temple Terrace, FL;
Nair Rodriguez-Hornedo, Ann Arbor, MI;

** CONTINUING DATA **********
This appln claims benefit of 60/360,768 03/01/2002

** FOREIGN APPLICATIONS **********

IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** SMALL ENTITY **
** 04/23/2003

Foreign Priority claimed	STATE OR	SHEETS	TOTAL	INDEPENDENT
35 USC 119 (a-d) conditions met	COUNTRY	DRAWING	CLAIMS	CLAIMS
Verified and Acknowledged	FL	22	36	9

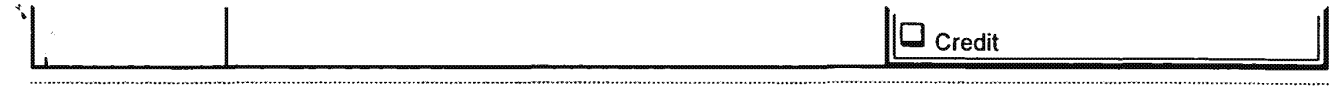
☐ yes ☒ no
☐ yes ☒ no ☐ Met after Allowance
Examiner's Signature Initials

ADDRESS
23557
SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO BOX 142950
GAINESVILLE , FL
32614-2950

TITLE
Multiple-component solid phases containing at least one active pharmaceutical ingredient

FILING FEE	FEES: Authority has been given in Paper	☐ All Fees
RECEIVED	No. _____ to charge/credit DEPOSIT ACCOUNT	☐ 1.16 Fees (Filing)
836	No. _____ for following:	☐ 1.17 Fees (Processing Ext. of time)
		☐ 1.18 Fees (Issue)
		☐ Other _____

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Index of Claims

Application/Control No.	Applicant(s)/Patent under Reexamination
10/378,956	ZAWOROTKO ET AL.
Examiner	**Art Unit**
Leonard M. Williams	1617

R	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date
Final	Original	3/9/06
	1	N
	2	N
	3	N
	4	N
	5	N
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Claim	
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Claim	
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Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination	
10/378,956	ZAWOROTKO ET AL.	
Examiner	**Art Unit**	
Leonard M. Williams	1617	

SEARCHED			
Class	Subclass	Date	Examiner
424	401	3/9/2006	LMW

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
PALM MICHAEL J. ZAWOROTKO BRIAN MOULTON NAIR RODRIGUEZ-HORNEDO	3/9/2006	LMW
EAST MICHAEL J. ZAWOROTKO BRIAN MOULTON NAIR RODRIGUEZ-HORNEDO	3/9/2006	LMW

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EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	2	"supramolecular synthon"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2006/03/09 10:25
S2	20682	aspirin	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2006/03/09 10:25
S3	5141	S2 and crystal	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2006/03/09 10:25
S4	49	S3 and co-crystal	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2006/03/09 11:23
S5	0	"PHENAZONE SALICYLATE"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2006/03/09 11:23
S6	265	phenazone	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2006/03/09 11:23
S7	41	S6 and aspirin	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2006/03/09 11:28
S8	65	S6 and salicylate	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2006/03/09 11:40
S9	71	S6 and paracetamol	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2006/03/09 11:46
S10	1	salipyrine	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2006/03/09 11:46
S11	0	salazolon	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2006/03/09 11:46

UM00010468
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EAST Search History

S12	70	"antipyrine salicylate"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2006/03/09 11:47

UM00010469
NOVARTIS EXHIBIT 1517
Novartis v. Regents, IPR2023-01347
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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313 on July 24, 2006.

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

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

OIPE IAP60 JUL 27 2006 PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

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

AMENDMENT UNDER 37 C.F.R. § 1.111

Sir:

A Petition and Fee for a one-month Extension of Time through and including July 24, 2006, accompanies this Amendment. In response to the Office Action dated March 22, 2006, please amend the above-identified patent application as follows:

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

In the Claims

1 (original). 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.

2 (original). The multiple-component phase composition of claim 1, wherein said multiple-component phase composition is a discrete supramolecular entity.

3 (original). The multiple-component phase composition of claim 1, wherein said multiple-component phase composition is a polymeric structure.

4 (original). The multiple-component phase composition of claim 1, wherein said pharmaceutical molecule is sustained by a supramolecular homosynthon when said pharmaceutical molecule is in its pure phase.

5 (original). The multiple-component phase composition of claim 1, wherein said multiple-component phase composition has at least one physical property or chemical property that is different from that of said pharmaceutical when said pharmaceutical molecule is in its pure phase.

6 (original). The multiple-component phase composition of claim 1, wherein said multiple-component phase composition has at least one physical or chemical property that is the same as that of said pharmaceutical molecule when said pharmaceutical molecule is in its pure phase.

7 (original). The multiple-component phase composition of claim 5, wherein said at least one physical or chemical property is selected from the group consisting of chemical stability,

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thermodynamic stability, solubility, dissolution, bioavailability, crystal morphology, and hygroscopicity.

8 (original). The multiple-component phase composition of claim 6, wherein said at least one physical or chemical property is selected from the group consisting of chemical stability, thermodynamic stability, solubility, dissolution, bioavailability, crystal morphology, and hygroscopicity.

9 (original). The multiple-component phase composition of claim 1, wherein said pharmaceutical molecule is selected from the group consisting of aspirin, acetaminophen, profen, phenytoin, and carbamazepine.

10 (original). The multiple-component phase composition of claim 1, wherein said two or more independent molecular entities are selected from the group consisting of: acetaminophen, 4,4'-bipyridine, and water; phenytoin and pyridine; aspirin and 4,4'-bipyridine; ibuprofen and 4,4'-bipyridine; flurbiprofen and 4,4'-bipyridine; flurbiprofen, trans-1,2-bis (4-pyridyl) ethylene; carbamazepine, *p*-phthalaldehyde; carbamazepine and nicotinamide; carbamazepine and saccharin; carbamazepine and 2,6-pyridinedicarboxylic acid; carbamazepine and 5-nitroisophthalic acid; carbamazepine and acetic acid; carbamazepine and 1,3,5,7,-adamantanetetracarboxylic acid; carbamazepine and benzoquinone; carbamazepine and butyric acid; carbamazepine and dimethyl sulfoxide; carbamazepine and formamide; carbamazepine and formic acid; and carbamazepine and trimesic acid.

11 (original). The multiple-component phase composition of claim 1, wherein said intermolecular interactions are selected from the group consisting of hydrogen bonding (weak and/or strong), dipole interactions (induced and/or non-induced), stacking interactions, hydrophobic interactions, and other inter-static interactions.

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12 (original). The multiple-component phase composition of claim 1, wherein said intermolecular interactions are between complementary chemical functionalities on said two or more independent molecular entities.

13 (original). The multiple-component phase composition of claim 15, wherein said complementary chemical functionalities include at least one chemical functionality selected from the group consisting of acids, amides, aliphatic nitrogen bases, unsaturated aromatic nitrogen bases, amines, alcohols, halogens, sulfones, nitro groups, S-heterocycles, N-heterocycles, O-heterocycles, ethers thioethers, thiols, esters, thioesters, thioketones, epoxides, acetonates, nitrils, oximes, and organohalides.

14 (original). The multiple-component phase composition of claim 12, wherein said complementary chemical functionalities on said two or more independent molecular entities are the same.

15 (original). The multiple-component phase composition of claim 14, wherein said complementary chemical functionalities are acids.

16 (original). The multiple-component phase composition of claim 14, wherein said complementary chemical functionalities are amides.

17 (original). The multiple-component phase composition of claim 12, wherein said complementary chemical functionalities on said two or more independent molecular entities are not the same.

18 (original). The multiple-component phase composition of claim 17, wherein said complementary chemical functionalities on said two or more independent molecular entities are selected from the group consisting of acids and amides; pyridines and amides; and alcohols and amines.

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19 (original). The multiple-component phase composition of claim 1, wherein two or more of said independent molecular entities is a pharmaceutical molecule.

20 (original). A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between aspirin and at least one independent molecular entity.

21 (original). A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between acetaminophen and at least one independent molecular entity.

22 (original). A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between a profen and at least one independent molecular entity.

23 (original). A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between phenytoin and at least one independent molecular entity.

24 (original). A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between carbamazepine and at least one independent molecular entity.

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;

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

(c) ~~identifying~~identifying, from a plurality of chemical functionalities that are known to form a supramolecular ~~synthon~~ synthon, at least one functionality that will form a ~~further~~second supramolecular synthon with~~to~~ 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 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; ~~and~~

(d) identifying co-crystal formers having at least one functionality identified in step (c); and~~chemical functionalities that are complementary with the active pharmaceutical ingredient~~

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

26 (canceled).

27 (currently amended). The method of claim 25 ~~claim 26~~, 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 (currently amended). The method of claim 25~~claim 26~~, 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 (original). A method for identifying complementary chemical functionalities in order to form a desired supramolecular synthon, said method comprising:

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

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

(c) identifying from a plurality of chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular synthon with the active pharmaceutical ingredient, wherein the identified chemical functionality is 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 a complementary chemical functionality on the active pharmaceutical ingredient; and

(d) identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient.

30 (original). The method of claim 29, wherein said method further comprises preparing a multiple-component solid phase composition, wherein the multiple-component solid phase composition comprises the active pharmaceutical ingredient and at least one of the identified co-crystal formers.

31 (original). The method of claim 30, 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.

32 (original). The method of claim 30, 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.

33 (original). 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;

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(b) determining whether the active pharmaceutical ingredient contains chemical functionalities capable of forming supramolecular synthons with different molecules;

(c) identifying from a plurality of chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular synthon with the active pharmaceutical ingredient, and wherein the selected chemical functionality is capable of forming a noncovalent bond to a complementary chemical functionality on the active pharmaceutical ingredient; and

(d) identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient.

34 (original). The method of claim 33, wherein said method further comprises preparing a multiple-component solid phase composition, wherein the multiple-component solid phase composition comprises the active pharmaceutical ingredient and at least one of the identified co-crystal formers.

35 (original). The method of claim 34, 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.

36 (original). The method of claim 34, 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.

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Remarks

Claims 1-36 are pending in the subject application and Applicants acknowledge that claims 1-24 and 29-36 stand withdrawn from further consideration as being drawn to a non-elected invention. By this Amendment, Applicant has amended claims 25, 27, and 28 and canceled claim 26. Support for the amendments can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-25 and 27-36 are currently before the Examiner with claims 1-24 and 29-36 standing withdrawn from consideration. Favorable consideration of the pending claims is respectfully requested.

As an initial matter, Applicants note that the Information Disclosure Statements previously filed in this matter on November 5, 2003 and May 20, 2004 have not been acknowledged by the Patent Office in the last Office Action. The undersigned respectfully requests that the Examiner consider the references cited in those papers and that intialed PTO/SB08A and SB08B forms be returned with the next Office Action.

Claims 25-28 are rejected under 35 U.S.C. §112, second paragraph, as indefinite. The Office Action argues:

> In claim 25 the applicant seems to be stating that the active pharmaceutical ingredient (API) must be capable of forming a supramolecular synthon by itself. The API must also have chemical functionalities capable of interacting non-covalently with a second component that will not disrupt the supermolecular synthon formed by the API. It is not clear if a second component is required to be present or if the claim is drawn solely to a homosupermolecular synthon containing "potential" chemical functionalities capable of interacting with additional components. Further it is not clear that if an additional component is required, what interactions it would have that would not disrupt non-covalent bonding of the API supermolecular synthon already formed. It is not clear if the second component is added to an already preformed solid homosupermolecular API synthon and thus coats the API synthon, or if the second component spontaneously forms around the API supermolecular synthon, or perhaps it could be both. Additionally it is not clear if there can exist an API supermolecular synthon, an area wherein there exists a co-crystal-API supermolecular synthon structure, and then a co-crystal supermolecular synthon surronding the API and co-crystal-API supermolecular structure. Finally claim 25 does not seem to exclude the possibility that the API supermolecular synthon formed can then have a second supermolecular synthon formed, different from the first, that then aggregates with the first forming an heterosupermolecular synthon with homo-API ingredients.

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Applicants believe that this rejection is being applied to element c) of the claims where it is stated "c) identifying from a plurality of chemical functionalities that are known to form a supramolecular synthon at least one functionality that will form a further supramolecular synthon to the supramolecular synthon formed by the active pharmaceutical ingredient, wherein the identified chemical functionality is not capable of disrupting non-covalent bonding within the supramolecular synthon formed by the supramolecular synthon formed by the active pharmaceutical ingredient, and wherein the selected chemical functionality is capable of forming a noncovalent bond to the supramolecular synthon formed by the active pharmaceutical ingredient;". Applicants respectfully submit that the claim is definite for the following reasons.

Applicants respectfully submit that figures illustrating the supramolecular complexes formed in this aspect of the invention illustrate the language recited within the claims. For example, Figures 10A and 10B, Figures 18A and 18B and Figures 20A and 20B illustrate supramolecular complexes exemplifying the concept of the invention. Figures 10A, 18A and 20A illustrate a supramolecular synthon formed by the chemical functionalities on a selected API. Figures 10B, 18B and 20B illustrate the formation of a second supramolecular synthon between the API molecules and a co-crystal former having functionalities capable of forming "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 supramolecular synthon formed by the active pharmaceutical ingredient". In these examples, the co-crystal former is interspersed amongst the supramolecular synthons formed by the API; however, it should be appreciated that the supramolecular synthons formed by the API and co-crystal formers is a function of the location of the chemical functionalities on the API and co-crystal former and that the supramolecular synthons arising from the interaction of the API and a co-crystal former can take a number of forms (non-limiting examples of which include supramolecular synthons where the co-crystal former is interspersed within supramolecular synthons formed by an API, supramolecular synthons where the co-crystal former surrounds a supramolecular synthons formed by an API, supramolecular synthons where the co-crystal former is present in a layer above and/or below a supramolecular synthon formed by an API). Applicants further respectfully submit that this concept is also illustrated in Fleischman *et al.*, 2003, *Crystal Design and Growth*, 3(6):909-

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919 and cited in the IDS filed November 5, 2003 and is referred to as "Scheme 1" (see page 910, column 2, paragraph 2). Figures 1a through 1f (pages 916-917 of the Fleischman *et al.* reference) show the formation of various supramolecular synthons formed by an API and various co-crystal formers wherein the co-crystal former is not capable of disrupting the supramolecular synthon formed by non-covalent bonding within the supramolecular synthon formed by the active pharmaceutical ingredient. Accordingly, it is respectfully submitted that the claims are definite and reconsideration and withdrawal of the rejection is respectfully requested.

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

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

The Office Action further states:

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

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and topiramate regions. The slide can then be heated to determined the melting point of the caffeine:topiramate co-crystal.

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

For example, the paragraph beginning at column 14, line 60, is not present in United States Provisional Patent Application 60/256,764 (filed February 15, 2002). Applicants respectfully submit that this passage is first disclosed in United States Provisional Patent Application 60/380,288 (filed May 15, 2002) at page 16, last paragraph of the priority document. With respect to the passage at column 14, lines 14-26, the language related to ", co-crystals, and complexes with basic compounds such as, but not limited to, caffeine, N-methyl pyrrolidine, nicotine, nicotinamide, and ethers such as PEGs (examples include but are not limited to PEG 200 and PEG 300)" is not found in the '764 application. The '288 patent application states this passage as "The present invention involves the unexpected discovery that the sulfamate ($-OSO_2NH_2$) group of topiramate is slightly acidic and thus may be a handle for generation of salts, or a co-crystal or complex with the basic compound caffeine. Salts are often associated with improved chemical stability and increased solubility of drugs leading to better delivery of drug to the body, by reducing unwanted degradation product exposure and increasing levels of drug in the body. Salt forms of drugs therefore constitute a useful set of options for development of drug formulations" (see page 15, line 29 through to page 16, line 2). The current version of this passage first appears in the paragraph bridging pages 15-16 of United States Provisional Patent Application 60/406,974 (filed August 30, 2002). Finally, Applicants respectfully submit that the Example relied upon in establishing this rejection is also not found in the earliest priority document for the '293 patent. Rather, Example 7 of the '293 patent is first disclosed as Example 6 in United States Provisional Patent Application 60/380,288 (filed May 15, 2002) at page 37. Accordingly it is respectfully submitted that the '293 patent is not prior art under 35 U.S.C. § 102(e) to the claimed invention and withdrawal of the rejection is respectfully requested.

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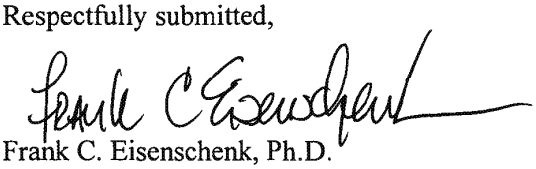
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right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

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

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

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

Respectfully submitted,



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1617 #
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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313 on July 24, 2006.

Frank C. Eisenschenk

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

PETITION AND FEE FOR EXTENSION OF TIME UNDER 37 CFR §1.136(a)
Examining Group 1617
Patent Application
Docket No. USF-106XC1
Serial No. 10/378,956



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

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

PETITION AND FEE FOR EXTENSION OF TIME
UNDER 37 CFR §1.136(a)

Sir:

Applicants request that the period for response be extended one month through and including July 24, 2006. An Amendment Under 37 C.F.R. § 1.111 accompanies this Petition. Please charge the fee of $60.00 to Deposit Account No. 19-0065.

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Any additional fees as required by 37 CFR §§1.16 or 1.17 should be charged to Deposit Account No. 19-0065. Two additional copies of this Petition are enclosed.

Respectfully submitted,

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Attachment: Amendment Under 37 C.F.R. § 1.111

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313 on July 24, 2006.

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

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT
Examining Group 1617
Patent Application
Docket No. USF-106XC1
Serial No. 10/378,956

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

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

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR §§1.97 AND 1.98

Sir:

In accordance with 37 CFR §1.56, the references listed on the attached form PTO/SB/08 are being brought to the attention of the Examiner for consideration in connection with the examination of the above-identified patent application. A copy of each cited reference is enclosed. However, Applicants have not submitted copies of the U.S. patents or published U.S. Patent Applications cited on attached Form PTO/SB/08 pursuant to 37 CFR 1.98(a)(2)(ii).

This information is being submitted subsequent to the later of three months after the filing date of the present application or the mailing of the first Office Action on the merits but before the mailing of a final action or the notice of allowance. Please charge the fee of $180.00 to Deposit Account No. 19-0065.

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

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

Respectfully submitted,

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Gainesville, FL 32614-2950

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

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 33

Complete if Known	
Application Number	10/378,956
Filing Date	March 3, 2003
First Named Inventor	Michael J. Zaworotko
Art Unit	1617
Examiner Name	Leonard Williams
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-2,711,411	06-21-1955	Holbert, *et al.*	All
	U2	US-4,198,507	04-15-1980	Barry, *et al.*	All
	U3	US-4,368,197	01-11-1983	Shefter, *et al.*	All
	U4	US-4,994,604	02-19-1991	Tung, *et al.*	All
	U5	US-5,177,262	01-15-1993	Taylor, *et al.*	All
	U6	US-5,332,834	07-26-1994	Bhattacharya, *et al.*	All
	U7	US-5,338,644	08-16-1994	Taylor, *et al.*	All
	U8	US-5,380,867	01-10-1995	Bhattacharya, *et al.*	All
	U9	US-5,412,094	05-02-1995	Amos, *et al.*	All
	U10	US-5,523,090	06-04-1996	Znaiden, *et al.*	All
	U11	US-5,614,342	03-25-1997	Molaire, *et al.*	All
	U12	US-5,998,413	12-07-1999	Heeres, *et al.*	All
	U13	US-6,001,996	12-14-1999	Amos, *et al.*	All
	U14	US-6,268,385	07-31-2001	Whittle, *et al.*	All
	U15	US-6,570,036	05-27-2003	Reuter	All
	U16	US-2003/0162226	08-28-2003	Cima, *et al.*	All
	U17	US-2003/0166581	09-04-2003	Almarsson, *et al.*	All
	U18	US-2003/0224006	12-04-2003	Zaworotko, *et al.*	All
	U19	US-2004/0019211	01-29-2004	Remenar, *et al.*	All
	U20	US-2004/0106052	06-03-2004	Molaire	All

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard T.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet	2	of	33

Complete if Known	
Application Number	10/378,956
Filing Date	March 3, 2003
First Named Inventor	Michael J. Zaworotko
Art Unit	1617
Examiner Name	Leonard Williams
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
	U21	US-2004/0106053	06-03-2004	Molaire, *et al.*	All
	U22	US-2004/0106055	06-03-2004	Molaire, *et al.*	All
	U23	US-2004/0171062	09-02-2004	Hirth, *et al.*	All
	U24	US-2004/0176335	09-09-2004	Childs	All
	U25	US-2005/0070551	03-31-1995	Remenar, *et al.*	All
	U26	US-2005/0181041	08-18-2005	Goldman	All
	U27	US-2005/0169982	08-04-2005	Almarsson, *et al.*	All
	U28	US-2005/0252649	11-17-2005	Chiu, *et al.*	All
	U29	US-2005/0256127	11-17-2005	Ku, *et al.*	All
	U30	US-6,559,293	05-06-2003	Almarsson, *et al.*	All
	U31	US-6,699,840	03-02-2004	Almarsson, *et al.*	All
	U32	US-2004-0053853	03-18-2004	Almarsson, *et al.*	All
	U33	US-2005/0070551 A1	03-31-2005	Remenar, *et al.*	All
	U34	US-2003/00224006	12-04-2003	Zaworotko *et al.*	All
	U35	US-3,536,809	04-09-1991	Schaller *et al.*	All
	U36	US-3,598,123	08-10-1971	Zaffaroni	All
	U37	US-3,845,770	11-05-1974	Theeuwes *et al.*	All
	U38	US-3,916,899	11-04-1975	Theeuwes *et al.*	All
	U39	US-4,008,719	02-22-1977	Theeuwes *et al.*	All
	U40	US-4,267,179	05-12-1981	Heeres *et al.*	All
	U41	US-4,764,604	08-16-1988	Muller	All

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet	3	of	33

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

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	U42	US-4,916,134	04-10-1990	Heeres *et al.*	All
	U43	US-5,006,513	04-09-1991	Hector *et al.*	All
	U44	US-5,059,595	10-22-1991	Le Grazie	All
	U45	US-5,073,543	12-17-1991	Marshall *et al.*	All
	U46	US-5,120,548	06-09-1992	McClelland *et al.*	All
	U47	US-5,354,556	10-11-1994	Sparks *et al.*	All
	U48	US-5,414,997	05-16-1995	Tailer	All
	U49	US-5,474,997	12-12-1995	Gray *et al.*	All
	U50	US-5,591,767	01-07-1997	Mohr *et al.*	All
	U51	US-5,633,015	05-27-1997	Gilis *et al.*	All
	U52	US-5,639,476	06-17-1997	Oshlack *et al.*	All
	U53	US-5,661,151	08-26-1997	Saksena *et al.*	All
	U54	US-5,674,533	10-07-1997	Santus *et al.*	All
	U55	US-5,707,975	01-13-1998	Francois *et al.*	All
	U56	US-5,733,566	03-31-1998	Lewis	All
	U57	US-2003/0096014	05-22-2003	Sherman	All
	U58				
	U59				
	U60				
	U61				

Examiner Signature		Date Considered	

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Sheet	4	of	33

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

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3] - Number[4] - Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	F1	EP 413528	11-15-1995	Yu, R. *et al.*	All	
	F2	EP 1364649	11-26-2003	Cilag AG	All	
	F3	WO 94/16733	08-04-1994	Chiesi Farmaceutici S.P.A.	All	
	F4	WO 96/07331	03-14-1996	Xyrofin Oy	All	
	F5	WO 98/57967	12-23-1998	Dong-A Pharmaceutical Co., Ltd.	All	
	F6	WO 2000/53283	09-14-2000	Reuter Chemische Apparatebau KG	All	
	F7	WO 2001/13904	03-01-2001	Ortho-McNeil Pharmaceutical, Inc.	All	
	F8	JP 54-16494	02-07-1979	Yamanouchi Pharmaceutical Co., Ltd.	All	X
	F9	WO 2001/42221	06-14-2001	Pharmacia Corporation	All	
	F10	FR 769,586	06-11-1934	Chemische Fabrik von Heyden	All	X
	F11	IT 01303251	11-06-2000	Industriale Chimica, S.R.L.	All	X
	F12	WO 2001/97853	12-27-2001	Biochemie Gesellschaft MBH	All	
	F13	EP 0310122	04-05-1989	Kaken Pharma	All	
	F14	WO 2002/062318	08-15-2002	DSM N.V.	All	
	F15	EP 0283992	09-16-1992	Janssen Pharma	All	
	F16	WO 2003/101392	12-11-2003	Transform Pharmaceuticals, Inc.	All	
	F17	WO 2004/054571	07-01-2004	Cilag AG	All	
	F18	WO 2004/078161 (CD-ROM)	09-16-2004	Transform Pharmaceuticals, Inc.	All	
	F19	WO 2004/078163 (CD-ROM)	09-16-2004	Transform Pharmaceuticals, Inc.	All	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 5 of 33

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

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No. [1]	Foreign Patent Document: Country Code [3] - Number [4] - Kind Code [5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T [6]
	F20	WO 2004/089313	10-21-2004	Transform Pharmaceuticals, Inc.	All	
	F21	WO 2005/023198 (CD-ROM)	03-17-2005	Transform Pharmaceuticals, Inc.	All	
	F22	WO 2005/037424	04-28-2005	Salvias AG	All	
	F23	WO 2005/055983	06-23-2005	Medcrystalforms, LCC	All	
	F24	WO 2005/060968 (CD-ROM)	07-07-2005	Sepracor, Inc.	All	
	F25	WO 2005/089375 (CD-ROM)	09-29-2005	S.S.C.I., Inc.	All	
	F26	WO 2005/094804	10-13-2005	The Regents of the University of Michigan	All	
	F27	WO 2006/024930	03-09-2006	Pharmacia and Upjohn Co., LCC	All	
	F28	WO 03/070738	08-28-2003	Transform Pharmaceuticals, Inc.	All	
	F29	WO 03/074474	09-12-2003	Univ. South Fl	All	
	F30	WO 95/17407	06-29-1995	Schering Corp	All	
	F31					
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	F41					
	F42					

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 6 of 33

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

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. [1]	Include name of the author (in CAPITAL LETTERS), title of the article, (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	R1	AAKERÖY, C. *et al.* "Crystal engineering of hydrogen-bonded assemblies- a progress report" *Aust. J. Chem.*, 2001, pp. 409-421, Vol. 54.	
	R2	BINGHAM, A. *et al.* "Over one hundred solvates of sulfathiazole" *Chem. Commun.*, 2001, pp. 603-604.	
	R3	BYRIEL, K., *et al.* "Molecular cocrystals of carboxylic acids. IX Carboxylic acid interactions with organic heterocyclic bases. The crystal structures of the adducts of (2,4-dichlorophenoxy) acetic acid with 3-hydroxypyridine, 2,4,6,-trinitrobenzoic acid with 2-aminopyrimidine, and 4-nitrobenzoic acid with 3-amino-1,2,4-triazole" *Aust. J. Chem.*, 1992, pp. 969-981, Vol. 45, No. 6.	
	R4	SALMON, J. *et al.* "Supramolecular chemistry of boronic acids (Abstract)" 38th Midwest Regional Meeting of the American Chemical Society in Columbia, MO., November 5-7, 2003, published by the American Chemical Society, Washington, D.C.	
	R5	URBINA, J. *et al.* "Supramolecular design of inorganic/organic networks using flexible ligands with self-complementary hydrogen bonds (Abstract)" 38th Midwest Regional Meeting of the American Chemical Society in Columbia, MO., November 5-7, 2003, published by the American Chemical Society, Washington, D.C.	

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Sheet	7	of	33

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

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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]
	R6	SMITH, D. *et al.* "Structure confirmation by single crystal X-ray diffraction of a series of new schiff bases and theoretical computations on 3-(N-2-α, α, α-triflourotoluylidene amino) tetrahydrothiophene-1, 1-dioxide (Abstract)" 216th ACS National Meeting in Boston, MA., August 23-27, 1998, published by the American Chemical Society, Washington, D.C.	
	R7	DESIRAJU, G. "Supramolecular synthons in crystal engineering- A new organic synthesis" *Angew. Chem. Int. Ed. Engl.*, 1995, pp. 2311-2327, Vol. 34.	
	R8	FRITCHIE, C. *et al.* "The configuration of phenothiazine in various molecular complexes" *Chem. Commun.*, 1968, pp. 833-834.	
	R9	HUANG, C.-M. *et al.* "Molecular packing modes. Part XI. Crystal structures of the 2:1 complexes of benzamide with succinic acid and furamide with oxalic acid" *J. Chem. Soc. Perkins Trans. 2: Physical Organic Chemistry*, 1973, pp. 503-508, Vol. 5.	
	R10	JACKISCH, M. *et al.* "Structures of three related biphenyl compounds: 4,4'-biphenyldiol, 3, 3',5,5'-tetra-*tert*-butyl-4,4'-biphenyldiol, and 3,3',5,5'- tetra-*tert*-butyl-1,1'-bicyclohexa-2,5-dienylidene-4,4'-dione" *Acta Cryst.*, 1990, pp. 919-922, Vol. C46.	
	R11	KIM, S. *et al.* "The structure of a crystalline complex containing one phenobarbital molecule and two adenine derivatives" *Proc. Natl. Acad. Sci. USA*, 1968, pp. 402-408, Vol. 60.	
	R12	KOBAYASHI, H. *et al.* "Sinusoidal structure of the 1:1 complex of phenothiazine and 7,7,8,8-tetracyanoquinodimethane, PTZ-TCNQ" *Acta Cryst.*, 1974, pp. 1010-1017, Vol. B30.	
	R13	ERMER, O. *et al.* "Molecular recognition among alcohols and amines: super-tetrahedral crystal architectures of linear diphenol-diamine complexes and aminophenols" *J. Chem. Soc. Perkins Trans. 2*, 1994, pp. 925-944.	
	R14	MARTIN, R. *et al.* "Polyphenal-caffeine complexation" *J. Chem. Soc., Chem. Commun.*, 1986, pp. 105-106.	
	R15	LEHN, J.-M. *et al.* "Molecular recognition directed self-assembly of ordered supramolecular strands by cocrystallization of complementary molecular components" *Chem. Soc., Chem. Commun.*, 1990, pp. 479-481.	

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Sheet 8 of 33

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First Named Inventor	Michael J. Zaworotko
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NON PATENT LITERATURE DOCUMENTS

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	R16	LYNCH, D. *et al.* "Molecular cocrystals of carboxylic acids. XV Preparation and characterization of heterocyclic base adducts with a series of carboxylic acids, and the crystal structures of the adducts of 2-aminopyrimidine with 2,6-dihydroxybenzoic acid, 4-aminobenzoic acid, phenoxyacetic acid, (2,4-dichlorophenoxy) acetic acid, (3,4-dichlorophenoxy)- acetic acid and salicylic acid, and 2-aminopyridmine with 2,6-dihydroxybenzoic acid" *Aust. J. Chem.*, 1994, pp. 1097-1115, Vol. 47.	
	R17	MCINTOSH, J. *et al.* "Chemotherapeutic drugs in anaerobic infections of wounds" *The Lancet*, June 26, 1943, pp. 793-795.	
	R18	MCINTOSH, J. *et al.* "Zinc peroxide, proflavine and penicillin in experimental *cl. welchii* infections" *The Lancet*, December 26, 1942, pp. 750-752.	
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Sheet 9 of 33

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

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	R25	NAKANISHI, I. *et al.* "X-ray structural studies on two forms of β-cyclodextrin barbital complexes" *Journal of Inclusion Phenomena*, 1984, pp. 689-699, Vol. 2.	
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Filing Date	March 3, 2003
First Named Inventor	Michael J. Zaworotko
Group Art Unit	1617
Examiner Name	Leonard Williams
Attorney Docket Number	USF-106XC1

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Filing Date	March 3, 2003
First Named Inventor	Michael J. Zaworotko
Group Art Unit	1617
Examiner Name	Leonard Williams
Attorney Docket Number	USF-106XC1

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Examiner Name	Leonard Williams
Attorney Docket Number	USF-106XC1

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Sheet	14	of	33

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

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. [1]	Include name of the author (in CAPITAL LETTERS), title of the article, (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	R78	ZERKOWSKI, J. *et al.* "Investigations into the robustness of secondary and tertiary architecture of hydrogen-bonded crystalline tapes" *Chem. Mater.*, 1994, pp. 1250-1257, Vol. 6.	
	R79	ZERKOWSKI, J. *et al.* "New varieties of crystalline architecture produced by small changes in molecular structure in tape complexes of melamines and barbiturates" *J. Am. Chem. Soc.*, 1994, pp. 4305-4315, Vol. 116.	
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	R84	AAKERÖY, C. *et al.* "Aromatic dicarboxylic acids as building blocks of extended hydrogen-bonded architectures" *Supramolecular Chemistry,* 1998, pp. 127-135, Vol. 9.	
	R85	AAKERÖY, C. *et al.* "Assembly of 2-D inorganic/organic lamellar structures through a combination of copper (I) coordination polymers and self-complimentary hydrogen bonds" *J. Chem. Soc., Dalton Trans.*, 2000, pp. 3869-3872.	
	R86	AAKERÖY, C. *et al.* "Building organic assemblies with 2-pyridone and dicarboxylic acids: relating molecular conformation and synthon stability to crystal structure" *Crystal Engineering*, 1998, pp. 225-241, Vol. 1, No. 3-4.	
	R87	AAKERÖY, C. *et al.* "The C-H•••C1 hydrogen bond: does it exist?" *New J. Chem.*, 1999, pp. 145-152.	
	R88	AAKERÖY, C. *et al.* "Crystal engineering of ionic solids" Modular Chemistry (ed. by Michl, J.), 1997, pp. 153-162, Kluwer Academic Publishers, The Netherlands.	

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Sheet 15 of 33

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First Named Inventor	Michael J. Zaworotko
Group Art Unit	1617
Examiner Name	Leonard Williams
Attorney Docket Number	USF-106XC1

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	R91	AAKERÖY, C. *et al.* "The crystal structure of the molecular cocrystal *L*-malic acid *L*-tartaric acid (1/1)" *Supramolecular Chemistry*, 1996, pp. 153-156, Vol. 7.	
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	R93	AAKERÖY, C. *et al.* "Di-hydroxy malonic acid as a building block of hydrogen-bonded 3-dimensional architectures" *Journal of Chemical Crystallography*, 1998, pp. 111-117, Vol. 28, No. 2.	
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	R96	AAKERÖY, C. *et al.* "A high-yielding supramolecular reaction" *J. Am. Chem. Soc.*, 2002, 14425-14432, Vol. 124.	
	R97	AAKERÖY, C. *et al.* "The hydrogen bond and crystal engineering" *Chemical Society Reviews*, 1993, pp. 397-407.	
	R98	AAKERÖY, C. *et al.* "Hydrogen-bond assisted assembly of organic and organic-inorganic solids" Crystal Engineering: From Molecules and Crystals to Materials, 1999, pp. 89-106, Kluwer Academic Publishers, The Netherlands.	
	R99	AAKERÖY, C. *et al.* "Hydrogen-bonding in solids" Crystal Engineering (ed. by Seddon, K. R. *et al.*), 1999, pp. 303-324, Kluwer Academic Publishers, The Netherlands.	

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First Named Inventor	Michael J. Zaworotko
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Attorney Docket Number	USF-106XC1

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	R100	AAKERÖY, C. *et al.* "Low-dimensional architectures of silver coordination compounds assembled *via* amide-amide hydrogen bonds" *Crystal Engineering*, 1998, pp. 39-49, Vol. 1, No. 1.	
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	R105	AAKERÖY, C. *et al.* "Pitfalls in the supramolecular assembly of silver(I) coordination compounds" *Journal of Molecular Structure*, 1999, pp. 91-101, Vol. 474.	
	R106	AAKERÖY, C. *et al.* "A structural study of 2-amino-5-nitropyridine and 2-amino-3-nitropyridine: intermolecular forces and polymorphism" *J. Mater. Chem.*, 1998, pp. 1385-1389, Vol. 8, No. 6.	
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	R110	AHN, S. *et al.* "Polymorphs of a 1:1 cocrystal with tunnel and layer structures: *p,p'*-biphenol/dimethyl sulfoxide" *Crystal Growth & Design*, 2001, pp. 107-111, Vol. 1, No. 2.	

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Sheet 17 of 33

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Filing Date	March 3, 2003
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Group Art Unit	1617
Examiner Name	Leonard Williams
Attorney Docket Number	USF-106XC1

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	R111	AKAZOME, M. *et al.* "Enantioselective inclusion of methyl phenyl sulfoxides and benzyl methyl sulfoxides by (*R*)-phenylglycyl-(*R*)-phenylglycine and the crystal structures of the inclusion cavities" *J. Org. Chem.*, 2000, pp. 68-76, Vol. 65.	
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	R135	BURGI, H. *et al.* "Crystallisation of supramolecular materials" *Current Opinion in Solid State & Materials Science*, 1998, pp. 425-430, Vol. 3.	
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Sheet 20 of 33

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

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	R146	CHINNAKALI, K. *et al.* "2-aminopyrimidine and *p*-phenylene-diacetic acid (1:1) co-crystal" *Acta Cryst.*, 1999, pp. 399-401, Vol. C55.	
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Sheet 21 of 33

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Filing Date	March 3, 2003
First Named Inventor	Michael J. Zaworotko
Group Art Unit	1617
Examiner Name	Leonard Williams
Attorney Docket Number	USF-106XC1

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Filing Date	March 3, 2003
First Named Inventor	Michael J. Zaworotko
Group Art Unit	1617
Examiner Name	Leonard Williams
Attorney Docket Number	USF-106XC1

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First Named Inventor	Michael J. Zaworotko
Group Art Unit	1617
Examiner Name	Leonard Williams
Attorney Docket Number	USF-106XC1

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Sheet 25 of 33

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

NON PATENT LITERATURE DOCUMENTS

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	R200	ISHIDA, T. *et al.* "Structural study of histamine H_2-receptor antagonists. Five 3-[2-(diamino-methyleneamino)-4-thiazolymethylthio] propionamidine and –amide derivatives" *Acta Cryst.*, 1989, pp. 505-512, Vol. B45.	
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First Named Inventor	Michael J. Zaworotko
Group Art Unit	1617
Examiner Name	Leonard Williams
Attorney Docket Number	USF-106XC1

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	R211	KRISHNAMOHAN SHARMA, C. V. *et al.* "X-ray crystal structure of $C_6H_3(CO_2H)_3$-1,3,5•1.5(4,4'-bipy): a 'super trimesic acid' chicken-wire grid" *Chem. Commun.*, 1996, pp. 2655-2656.	
	R212	KURODA, R. *et al.* "Generation of a co-crystal phase with coloristic properties *via* solid state grinding procedures" *Chem. Commun.*, 2002, pp. 2848-2849.	
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Sheet 27 of 33

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First Named Inventor	Michael J. Zaworotko
Group Art Unit	1617
Examiner Name	Leonard Williams
Attorney Docket Number	USF-106XC1

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	R222	ROBBINS, A. H. *et al.* "The crystal structure of the 1:2 adduct of potassium triiodide and 5,5-diethylbarbituric acid (barbital)" *American Crystallographic Association- Series 2, Papers and Abstracts*, 1973, p. 87.	
	R223	BEERGES, P. *et al.* "Phenothiazine tetracyanoethylene" *Private Communication*, 1994.	
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	R229	QUEHENBERGER, H. "Concerning organic molecular compounds and their polymorphism" *Monatshefte für Chemie*, 1949, pp. 595-606, Vol. 80, No. 5.	X
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Sheet 28 of 33

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Filing Date	March 3, 2003
First Named Inventor	Michael J. Zaworotko
Group Art Unit	1617
Examiner Name	Leonard Williams
Attorney Docket Number	USF-106XC1

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	R233	TOMURA, M. *et al.* "One-dimensional zigzag chain structures with intermolecular C-H••• π and C-H•••O interactions consisted of phthalic acid and pyridine derivatives" *Chemistry Letters*, 2001, pp. 532-533.	
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	R241	HELFRICH, B. *et al.* "Polymorphism as an indication of structural versatility (Abstract)" 223rd ACS National Meeting in Orlando, FL., April 7-11, 2002, published by the American Chemical Society, Washington, D.C.	
	R242	WEBER, E. *et al.* "Synthesis of new Schiff bases: reaction of monofluorobenzaldehydes with 3-aminosulfolane hydrochloride (Abstract)" 216th ACS National Meeting in Boston, MA., August 23-27, 1998, published by the American Chemical Society, Washington, D.C.	

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	R243	SCARBROUGH, F. *et al.* "Crystal structure of a complex between lumiflavin and 2,6-diamino-9-ethylpurine: a flavin adenine dinucleotide model exhibiting charge-transfer interactions" *Proc. Natl. Acad. Sci. USA*, November 1976, pp. 3807-3811, Vol. 73, No. 11.	
	R244	MUNN, R. *et al.* "A Model for resonance-assisted hydrogen bonding in crystals and its graph set analysis" *J. Phys. Chem. A*, 2001, pp. 6938-6942, Vol. 105.	
	R245	LYNCH, D. et al. "1:1 Molecular complexes of 4-amino-N-(4,6-dimethylpyrimidin-2-yl) benzene-sulfonamide (sulfamethazine) with indole-2-carboxylic acid and 2,4-dinitrobenzoic acid" Aust. J. Chem., 2000, pp. 383-387, Vol. 53.	
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	R251	VISHWESHWAR, P. *et al.* "Molecular complexes of homologous alkanedicarboxylic acids with isonicotinamide: X-ray crystal structures, hydrogen bond synthons, and melting point alternation" *Crystal Growth & Design,* 2003, pp. 783-790, Vol. 3, No. 5.	
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	R254	HU, Z. *et al.* "Separation of 4-aminobenzoic acid by cocrystallization: Crystal structure of the complex of 4-aminobenzoic acid with (2*R*,3*R*)-tartaric acid" *Journal of Chemical Crystallography*, December 2002, pp. 525-529, Vol. 32, No. 12.	
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	R257	CRIHFIELD, A. *et al.* "Crystal engineering through halogen bonding. 2. Complexes of diacetylene-linked heterocycles with organic iodides" *Crystal Growth & Design*, 2003, pp. 313-320, Vol. 3, No. 3.	
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	R262	CACCIAPUOTI, A. *et al.* "In vitro and in vivo activities of SCH 56592 (Posaconazole), a new triazole antifungal agent, against *Aspergillus* and *Candida*" *Antimicrobial Agents and Chemotherapy*, August 2000, pp. 2017-2022, Vol. 44, No. 8.	
	R263	CALLAHAN, J.C. *et al.* "Equilibrium moisture content of pharmaceutical excipients" *Drug Development and Industrial Pharmacy*, 1982, pp. 355-369, Vol. 8, No. 3.	
	R264	DANNAOUI, E. *et al.* "Acquired itraconazole resistance in *Aspergillus fumigatus*" *Journal of Antimicrobial Chemotherapy*, 2001, pp. 333-340, Vol. 47.	

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Sheet 31 of 33

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

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. [1]	Include name of the author (in CAPITAL LETTERS), title of the article, (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T [2]
	R265	DENNING, D. W. *et al.* "In vitro activity of Saperconazole (R66 905) compared with Amphotericin B and Itraconazole against *Aspergillus* species" *Eur. J. Clin. Microbial. Infect. Dis.*, 1990, pp. 693-697, Vol. 9.	
	R267	DRESSMAN, J. B. *et al.* "Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms" *Pharmaceutical Research*, 1998, pp. 11-22, Vol. 15, No. 1.	
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	R270	HEERES, J. *et al.* "Antimycotic azoles. 7. Synthesis and antifungal properties of a series of novel triazol-3-ones" *J. Med. Chem.*, 1984, pp. 894-900, Vol. 27.	
	R271	HONIG, P. K. *et al.* "Itraconazole affects single-dose Terfenadine pharmacokinetics and cardiac repolarization pharmacodynamics" *J. Clin. Pharmacol.*, 1993, pp. 1201-1206, Vol. 33.	
	R272	IMAI, T. *et al.* "Successful treatment of cerebral Aspergillosis with a high oral dose of Itraconazole after excisional surgery" *Internal Medicine*, October 1999, pp. 829-832, Vol. 38, No. 10.	
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	R274	LAVRIJSEN, A. P. M. *et al.* "Hepatic injury associated with itraconazole" *The Lancet*, July 25, 1992, pp. 251-252, Vol. 340.	
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Sheet 32 of 33

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

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	R277	ODDS, F. C. "Antifungal activity of saperconazole (R 66 905) *in vitro*" *Journal of Antimicrobial Chemotherapy*, 1989, pp. 533-537, Vol. 24.	
	R278	REMENAR, J. F. *et al.* "Crystal engineering of novel cocrystals of a triazole drug with 1,4-dicarboxylic acids" *J. Am. Chem. Soc.*, 2003, pp. 8456-8457, Vol. 125.	
	R279	SAKSENA, A. K. *et al.* "Advances in the chemistry of novel broad-spectrum orally active azole antifungals: recent studies leading to the discovery of SCH 56592" in Advances in the Chemistry of Novel Broad-Spectrum Orally Active Azole Antifungals (Royal Soc. Chem., Cambridge), 1997, pp. 180-199.	
	R280	SAKSENA, A. K. *et al.* "Concise asymmetric routes to 2,2,4-trisubstituted tetrahydrofurans via chiral titanium imide enolates: key intermediates towards synthesis of highly active azole antifungals SCH 51048 and SCH 56592" *Tetrahedron Letters*, 1996, pp. 5657-5660, Vol. 37, No. 32.	
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	R284	WEST, A. R., "Solid Solutions" In: Solid State Chemistry and its Applications, 1988, p. 358, p. 365, Wiley, NY.	
	R285	ARONHIME, J. *et al.* "Crystalline forms of pharmaceuticals and characterization thereof", Oral Presentation, March 8, 2005, USPTO, Alexandria, VA.	
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Sheet 33 of 33

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	R288	Physician's Desk Reference, 56th Ed., pp. 1800-1804, 2002.	
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	R297		
	R298		

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Supramolecular chemistry of boronic acids. Salmon, Janie; Levin, Brock; Aakeroy, Christer; Desper, John. Chemistry, Kansas State University, Manhattan, KS, USA. Abstracts, 38th Midwest Regional Meeting of the American Chemical Society, Columbia, MO, United States, November 5-7 (2003), 346. Publisher: American Chemical Society, Washington, D. C CODEN: 69ETUW Conference; Meeting Abstract written in English. AN 2004:140176 CAPLUS (Copyright 2004 ACS on SciFinder (R))

Abstract

From m.p. to color, the phys. properties of a solid are detd. by the compd.,s structure. These properties can be exploited to det. how different functional groups interact with one another. Arylboronic acids, such as the 3-tolylboronic acid, contain both hydrogen bond donors and acceptors, but-unlike carboxylic acids or amides-the hydrogen bond preferences of the boronic acid group remain unexplored. Substitution of various functional groups allows for slight changes in the hydrogen bonding ability of the mol. The synthesis of arylboronic acids is relatively straightforward. From simple starting materials, it is possible to create more complex functionalities. Characterization, however, gives rise to some problems, as arylboronic acid dehydrates to boroxine. Through the anal. of boronic acids, there lies the possibility of sophisticated supramol. chem.

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Supramolecular design of inorganic/organic networks using flexible ligands with self-complementary hydrogen bonds. Urbina, Joaquin F.; Aakeroy, Christer B.; Desper, John. Chemistry, Kansas State University, Manhattan, KS, USA. Abstracts, 38th Midwest Regional Meeting of the American Chemical Society, Columbia, MO, United States, November 5-7 (2003), 146. Publisher: American Chemical Society, Washington, D. C CODEN: 69ETUW Conference; Meeting Abstract written in English. AN 2004:134897 CAPLUS (Copyright 2004 ACS on SciFinder (R))

Abstract

Ligands contg. a coordination site and a hydrogen-bond moiety e.g. nicotinamide have afforded various inorg./org. motifs. This deliberate supramol. design has consequently been extended to incorporate longer and more flexible ligand spacers such as (benzimidazol-1-yl)methylbenzamide derivs. These ligands interconnect through self-complementary amide-amide hydrogen bonds as well as through N-H N interactions. Inorg./org. frameworks based on these ligands and metal ions with different coordination modes, for instance, Cu(I) and Ag(I), will be explored. In particular, the influence of the connectivity of the ligands on the resulting networks both by coordination to the metal ion, and via hydrogen bonds, will be investigated.

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The not-so-trivial synthesis and characterization of heterocyclic boronic acids. Levin, Brock; Aakeroy; Valdes-Martinez, Jesus; Desper, John. Chemistry, Kansas State University, Manhattan, KS, USA. Abstracts, 38th Midwest Regional Meeting of the American Chemical Society, Columbia, MO, United States, November 5-7 (2003), 66. Publisher: American Chemical Society, Washington, D. C CODEN: 69ETUW Conference; Meeting Abstract written in English. AN 2004:130476 CAPLUS (Copyright 2004 ACS on SciFinder (R))

Abstract

While there is a diverse catalog of substituted Ph boronic acids, there are relatively few well-documented heterocyclic boronic acids. The synthesis is often more complex and thorough characterization frequently proves more difficult than expected. We will present the syntheses of such mols. as well as their characterization. Addnl., the vast possibilities of these mols.' use in supramol. chem. will begin to be addressed through competitive cocrystn. reactions.

Solid state, crystal engineering and hydrogen bonds. Aakeroy, C. B.; Beatty, A. M. Kansas State University, Manhattan, KS, USA. Editor(s): McCleverty, Jon A.; Meyer, Thomas J. Comprehensive Coordination Chemistry II (2004), 1 679-688. Publisher: Elsevier Ltd., Oxford, UK. CODEN: 69EYWF Conference written in English. AN 2004:22586 CAPLUS (Copyright 2004 ACS on SciFinder (R))

Modular supramolecular synthesis based on a dominance hierarchy of intermolecular interactions.
Aakeroy, Christer B.; Helfrich, Brian A.; Beatty, Alicia M. Department of Chemistry, Kansas State University, Manhattan, KS, USA. Abstracts of Papers, 223rd ACS National Meeting, Orlando, FL, United States, April 7-11, 2002 (2002), IEC-144. Publisher: American Chemical Society, Washington, D. C CODEN: 69CKQP Conference; Meeting Abstract written in English. AN 2002:189417 CAPLUS (Copyright 2004 ACS on SciFinder (R))

Abstract

Chem. synthesis, the making and breaking of covalent bonds, is a fundamental scientific discipline with consequences for all aspects of human existence. A vast no. of reactions have been devised allowing more and more complicated mols. to be made using extraordinary multi-step synthetic processes. In contrast, crystal engineering, a new but rapidly expanding area of science concerned with the construction and properties of assemblies and extended networks of mols., has yet to reach anywhere near the same sophistication. In order to bring crystal engineering to a higher level of refinement and versatility it is necessary to identify reliable supramol. reactions and synthetic strategies that will allow us to build multi-component heteromeric structures, e.g. binary and ternary supermols. [1]. In this contribution we demonstrate how a variety of non-covalent interactions e.g. hydrogen-bonds, pi---pi, I---I, and I---N-R interactions can be manipulated simultaneously for the design and supramol. synthesis of several binary and ternary co-crystals with well-defined connectivity. [1] C.B. Aakeroy, A.M. Beatty, B.A Helfrich, Angew. Chem. Int. Ed. 2001, 40, 3240-3242.

Polymorphism as an indication of structural versatility. Helfrich, Brian A.; Aakeroy, Christer B.; Beatty, Alicia M.; Desper, John. Department of Chemistry, Kansas State University, Manhattan, KS, USA. Abstracts of Papers, 223rd ACS National Meeting, Orlando, FL, United States, April 7-11, 2002 (2002), IEC-112. Publisher: American Chemical Society, Washington, D. C CODEN: 69CKQP Conference; Meeting Abstract written in English. AN 2002:189385 CAPLUS (Copyright 2004 ACS on SciFinder (R))

Abstract

Predicting the solid-state architecture of a compd. has been a fascination of scientists even before the inception of X-ray crystallog. Discovering that certain compds. can yield polymorphs can be an exciting prospect or a horrible nightmare, depending upon your point of view. Good, bad, or indifferent, the crystal structures pose a challenge in understanding why a mol. would adopt more than one architecture. Over the past few years our research group has found - or more frequently stumbled across - polymorphs of simple org. compds. Furthermore, we have obsd. that mols. that have the ability to form polymorphs, also have a tendency to work well in the formation of org. co-crystals. Our hypothesis: mols. that can form strong intermol. interactions (e.g. hydrogen bonds), but are somewhat ambivalent as to how this occurs, are versatile co-crystg. agents. Successful co-crystg. agents are commonly used to facilitate sepn. and purifn. of org. compds. They also help us understand the preferences by which mols. interact. Common org. substituents such as acids, alcs., amides, nitros, and pyridines form strong hydrogen bonds, and are found frequently in architectures that are polymorphic. Yet, not all mols. that contain such groups yield polymorphs. It is of interest, then, to ascertain what types of mols. are likely to form polymorphs and, potentially, good co-crystg. agents.

Synthesis of new schiff bases: Reaction of monofluorobenzaldehydes with 3-aminosulfolane hydrochloride. Weber, Eileen; Dunn, Howard E.; Beatty, Alicia; Aakeroy, Christer. Department Chemistry, University Southern Indiana, Evansville, IN, USA. Book of Abstracts, 216th ACS National Meeting, Boston, August 23-27 (1998), CHED-246. Publisher: American Chemical Society, Washington, D. C CODEN: 66KYA2 Conference; Meeting Abstract written in English. AN 1998:525280 CAPLUS (Copyright 2004 ACS on SciFinder (R))

Abstract

Three new monofluorinated Schiff bases, I, II, and III, were synthesized as part of a group research project to create potential plant growth stimulants. These new compds. were characterized using 1H-NMR, 13C-NMR, FT-IR, and X-ray crystallog. Yields of I, II, and III, were 53%, 66%, and 23%, resp.

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Structure confirmation by single crystal X-ray diffraction of a series of new schiff bases and theoretical computations on 3-(N-2-α,α,α-trifluorotoluylidene amino)tetrahydrothiophene-1,1-dioxide. Smith, Dianne M.; Seyler, Jeffery W.; Dunn, Howard E.; Beatty, Alicia; Aakeroy, Christer. Department Chemistry, University Southern Indiana, Evansville, IN, USA. Book of Abstracts, 216th ACS National Meeting, Boston, August 23-27 (1998), CHED-250. Publisher: American Chemical Society, Washington, D. C CODEN: 66KYA2 Conference; Meeting Abstract written in English. AN 1998:525284 CAPLUS (Copyright 2004 ACS on SciFinder (R))

Abstract

We previously reported on the prepn. of 3-(N-2-α,α,α-trifluorotoluylideneamino)tetrahydrothiophene-1,1-dioxide, 3-(N-3-α,α,α-trifluorotoluylideneamino)tetrahydrothiophene-1,1-dioxide, and 3-(N-4-α,α,α-trifluorotoluylideneamino)tetrahydrothiophene-1,1-dioxide as part of an ongoing research project to synthesize potential plant growth stimulants. This presentation includes the use of single crystal X-ray diffraction to confirm the structures deduced from the 1H-NMR, 13C-NMR, APT, GC-MS, and FT-IR spectra. An interesting 19F-13C coupling pattern was obsd. for the 2-trifluoromethyl Schiff base, which was not consistent with a computed 13C spectrum. Semi-empirical calcns. were used in an attempt to explain the obsd. coupling.

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Aust. J. Chem. **2001**, *54*, 409–421

Crystal Engineering of Hydrogen-Bonded Assemblies—A Progress Report

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Manuscript received: 1 October 2001.
Final version: 15 November 2001.

Introduction

How do we build a crystal? The field of crystal engineering, a sub-discipline of supramolecular chemistry, concerns the construction of crystalline materials from molecules or ions using non-covalent interactions.[1] An important goal in this area is to synthesize *functional* materials with specific and tunable properties.[2] For example, we may want to design materials that can perform chemical separations, or that have non-linear optical,[3] magnetic,[4] or catalytic properties.[5] In order to obtain non-linear optical materials, molecules or ions must be organized in a non-centrosymmetric arrangement. For magnetic materials they must be positioned so that communication between spins is facilitated. For chemical separations the material must be able to house trapped molecules or ions. In other words, if we wish to build functional materials, we must be able to control *how* the building materials—molecules or ions—can be assembled into architectures with desirable structure.

Crystal engineering is still at the stage where much experimentation is concerned with *how* to control assembly.[6,7] However, the realization that molecular-recognition events are extraordinarily specific and selective has had a profound impact on our ability to assemble molecular solids and inorganic–organic hybrid materials. Thus, predicting and controlling the competition between intermolecular forces such as weak and strong hydrogen bonds, halogen–halogen interactions, $\pi\cdots\pi$ contacts, van der Waals forces, etc., are part of every crystal engineering effort. The challenge comes down to the following: how do we unravel the bundle of often inter-related interactions and identify strong, directional, reliable non-covalent interactions? How do we develop a reliable synthetic protocol for supramolecular synthesis?

Despite the inherent difficulties with using weak forces as primary synthetic tools, considerable progress has been made, and the preponderance of strategies for supramolecular synthesis prompted Desiraju[8] to introduce the term 'supramolecular synthon'. Synthons describe the precise recognition events that take place when molecules assemble into supermolecules (cf. Schemes 1 and 2) and provide an important illustration of the conceptual similarities between retrosynthetic organic synthesis and supramolecular assembly.[9]

Identifying supramolecular synthons is clearly as important to crystal engineering as is an understanding of reaction mechanisms and reagents to conventional covalent synthesis. It is essential to find the limits and conditions under which intermolecular recognition can be used to reliably assemble structures and materials with specific topologies. Such insight is most effectively obtained through systematic structural studies. Recent developments in crystallography/diffraction hardware and software have provided unprecedented access to structural information, both in terms of sheer numbers of new crystal structures and the type (size/quality) of samples that can be examined.

This review outlines some advances that have been made specifically in the use of strong hydrogen-bond interactions in directed assembly of organic molecular solids and inorganic–organic hybrid materials with desirable and well-defined supramolecular connectivity.[10] The field is currently experiencing enormous growth and a vast number of research groups have made invaluable contributions to crystal engineering. Unfortunately, the scope of this review only allows us to mention but a fraction of the many efforts that have been put forth in recent years. The main focus will be on extended networks and infinite architectures; directed assembly of discrete entities has been reviewed extensively.[11]

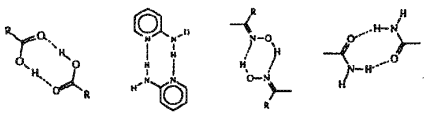
Hydrogen-Bond Types

The strength and directionality of the hydrogen bond, as compared with other intermolecular forces, account for its significance and has made it the most important interaction in molecular recognition; it is arguably the 'master key'[12] to successful and effective supramolecular synthesis.[13] Many design strategies for supramolecular synthesis have relied on the complementarity of hydrogen-bond interactions. The complementarity can involve both geometric factors and a suitable balance between the number of hydrogen-bond donors and hydrogen-bond acceptors. Self-complementary (or homomeric) interactions (Scheme 1) have been studied

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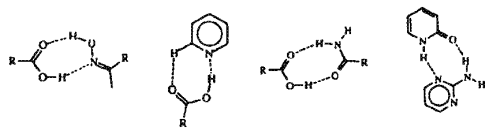
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extensively and they include the well-known carboxylic acid dimer, although other homomeric synthons have also been employed in crystal engineering.



Scheme 1. Examples of self-complementary (homomeric) hydrogen-bond interactions.

Not only do these complementary supramolecular synthons bring molecules and ions together, they also constrain the relative orientation of those components in much the same way as carbon–carbon double bonds impart specific stereochemistry to individual molecules. More recently, many heteromeric (but still complementary) hydrogen-bond interactions (Scheme 2) have been employed in supramolecular synthesis.



Scheme 2. Examples of complementary (heteromeric) hydrogen-bond interactions.

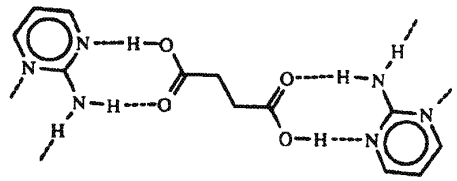
An increased degree of complementarity (triple,[14] quadruple,[15] or quintuple[16]) dramatically increases selectivity (cf. base-pairing in DNA), but may also lead to considerable covalent synthetic challenges; clearly a balance has to be struck in order to develop cost-effective and versatile supramolecular synthesis.

Developing Hydrogen-Bond Design Strategies

The reliability of and competition between synthons are most effectively determined through systematic database studies, not through detailed analyses of individual structures.[17,18] Etter and coworkers[19,20] were pioneers in this area, and after extensive studies of preferential hydrogen-bond patterns in organic crystals they presented the following empirical 'rules' as a guide to the deliberate design of hydrogen-bonded solids;

(i) All good proton donors and acceptors are involved in hydrogen bonding.[21]
(ii) Six-membered ring intramolecular hydrogen bonds form in preference to intermolecular hydrogen bonds.
(iii) The best proton donor and acceptor remaining after intramolecular hydrogen bond formation will form intermolecular hydrogen bonds.

These 'rules' are based upon observed correlations between hydrogen-bond patterns and functional groups, and generally, as a proton increases in acidity its donor properties will improve. The second rule derives from competition studies showing that intramolecular hydrogen bonds are more difficult to break than comparable intermolecular bonds formed from similar donors. The third rule can be illustrated by examining the structure of 2-aminopyrimidine/carboxylic acid cocrystals (Scheme 3), where the best donors (acidic proton) are paired with the best acceptors (ring nitrogen atom).[22]



Scheme 3. The primary hydrogen bonds in cocrystals of 2-aminopyrimidine and dicarboxylic acids.

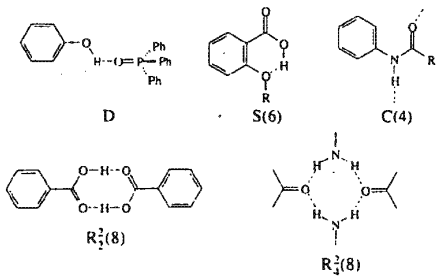
Describing Hydrogen-Bonded Motifs: Graph Sets

An important contribution by Etter, Bernstein and coworkers has been the introduction of a language based upon graph-theory for describing and analysing hydrogen-bond networks in three-dimensional (3-D) solids.[23] The process of assigning a graph set (Scheme 4) begins by identifying the number of different types of hydrogen bonds present in the structure, and then by defining the bonds by the nature of its donors and acceptors.

$$G_d^a(n)$$

Scheme 4. A generic graph-set descriptor.

A set of molecules connected via hydrogen bonds in a repeat unit, a motif, is characterized by one of four designators, C (chain), R (ring), D (dimer), or S (self, for intramolecular hydrogen bond). The numbers of donors and acceptors used in each motif are assigned as subscripts and superscripts respectively, and the total number of atoms in the repeat unit is denoted in brackets (Scheme 5). A benefit of using graph sets is that it brings the focus onto the hydrogen-bonded *pattern*, and not simply on the geometrical constraints of non-covalent interactions.



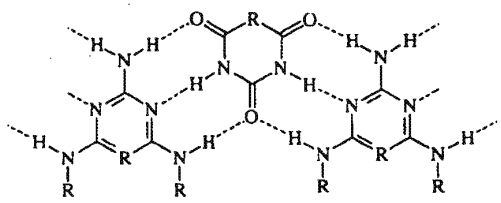
Scheme 5. Graph-set assignments for some hydrogen-bond motifs.

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Supramolecular Synthesis of Organic Solids: Some Practical Examples

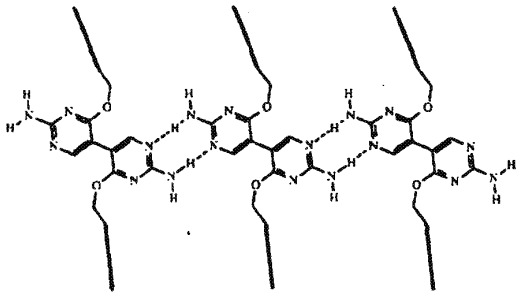
Tapes, Ribbons, Rosettes, and Other Extended Assembles

In the early nineties, several elegant studies on hydrogen-bond directed assembly of derivatives of triaminotriazine (and related heterocycles) and barbituric acid were carried out in the laboratories of Whitesides[24] and Lehn.[25] Both groups approached supramolecular design with the notion in mind that more hydrogen bonds would provide more stable assemblies. In addition, complementarity was seen as a key to predictability. The combination of barbituric acid/melamine derivatives provides all the necessary ingredients for the construction of a variety of tapes and other networks (Scheme 6).



Scheme 6. A typical hydrogen-bonded tape in an aminotriazine-barbituric acid network.

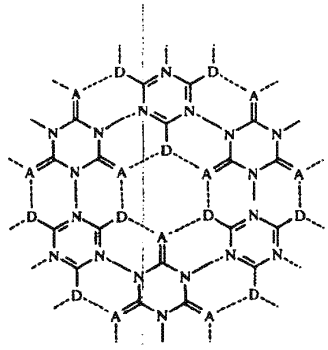
These results constitute a benchmark in terms of planning and execution, and they have generated genuine insight into issues like assembly stability (recent efforts have obtained molecular weights of hydrogen-bonded aggregates using electrospray ionization mass spectrometry[26]), as well as a large number of follow-up studies based upon similar components.[27] Recent work by Lehn has involved the assembly of alkoxy-functionalized ribbons and sheets constructed from self-complementary 2,2′-diamino-5,5′-bipyrimidine building blocks (Scheme 7).[28] This approach provides a way for modular attachment of functional groups in such a way that physical properties (e.g. liquid crystallinity) can be tuned in a specific manner.



Scheme 7. One-dimensional (1-D) ribbon that can be generated by complementary amino···pyrimidine hydrogen bonds.

A variety of other hydrogen-bond interactions and supramolecular synthons have been used in the crystal engineering of infinite architectures, e.g. anilic acid···pyridine,[29] C≡C–H···N,[30] self-complementary sulfamide,[31] oxalamide,[32] 2-benzimidazolones,[33] C–H···N (in pyridine *N*-oxide),[34] pyrimidones,[35] and cyclic dipeptides.[36] A combination of interactions can also be employed, as demonstrated in some crystal structures of substituted alkoxy-1,4-benzoquinones.[37] Neighboring molecules are connected by C–H···O=C interactions and aligned through hydrophobic ordering of alkoxy chains into two-dimensional (2-D) layers. Even the copious fullerene literature has been supplemented with molecular recognition based results; fullerene dimers have been assembled by quadruple complementary AADD (A = acceptor; D = donor) hydrogen-bond interactions ($K_a \geq 1.0 \times 10^6\ M^{-1}$).[38]

Following the lead from Whitesides and Lehn, Rao and coworkers were able to synthesize organic channel structures by combining melamine with cyanuric and trithiocyanuric acids, respectively, using hydrothermal conditions[39] (Scheme 8).



Scheme 8. A hexagonal rosette formed by complementary interactions between trithiocyanuric acid and triaminotriazine resulting in channels with a cavity diameter of approximately 4 Å.

The fact that synthons repeatedly give rise to extended assemblies of predictable connectivity demonstrates that supramolecular synthesis has a solid foundation based upon robust and transferable design principles. The simultaneous control over hydrogen-bond based synthons and weaker intermolecular interactions should allow for even more complex supramolecular synthesis.

Charge-Assisted Hydrogen Bonds: Increasing the Strength of Synthons

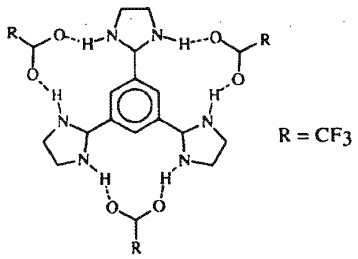
A deliberate strategy for strengthening non-covalent forces involves the use of charge-assisted interactions between complementary moieties on adjacent ions; as the hydrogen bond is essentially electrostatic in nature, an increase in charge on either, or both, participants, can increase the coulombic stabilization.

Hosseini and coworkers employed a combination of directional hydrogen bonds and electrostatic interactions

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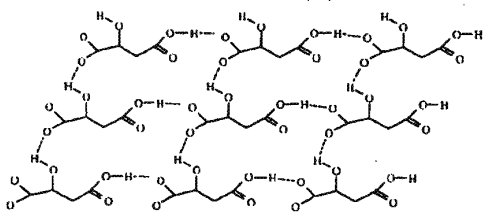
between complementary units (dicarboxylic acids and cyclic bisamidine).[40] By varying the ratio of acid to base, the outcome is either a 1-D or 2-D network. It has been shown[6,41] that partially or fully deprotonated trimesic acid generates hydrogen-bonded lamellar structures with ammonium moieties substituted with alkyl or aryl groups. The substituents furnish some degree of predictability (through interdigitation interactions) of the assembly of adjacent polar layers.[42] Mascal employed the triple complementarity of pyrimidine-2,4,6-triamines and 1,3,5-triazine-2,4,6-triones to create infinite ribbons that were subsequently brought together into sheets by charge-assisted (ammonium···carboxylate) hydrogen-bond interactions.[43]

Another example of supramolecular synthesis using charge-assisted N–H···O hydrogen-bonds was furnished by Kraft—a tetrameric structure built around a tris(imidazoline) base and four carboxylate anions that remains stable in non-polar solvents (Scheme 9).[44]



Scheme 9. Six charge-assisted N–H···O interactions operate in concert to form a tetrameric structure.

Charge-assisted interactions have also been instrumental for building low-dimensional ionic networks using both chiral (e.g. hydrogen-L-malate ions)[45] (Scheme 10) and achiral building blocks (e.g oxamate ions).[46]



Scheme 10. Charge-assisted O–H···O interactions between hydrogen-L-malate anions result in an infinite 2-D motif.

These networks, typically infinite 1-D ribbons or 2-D layers, tend to maintain their connectivity and topology even in the presence of a wide variety of counter ions, indicating a desirable robustness and reliability. The increased strength of charge-assisted hydrogen bonds may make them particularly suitable as structure-directing tools.

Ternary Supermolecules: a Step Towards Supramolecular 'Total Synthesis'

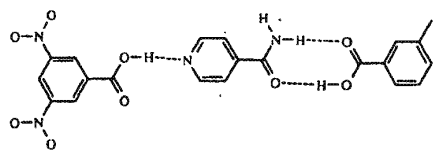
In order to bring crystal engineering to a higher level of refinement it is necessary to devise supramolecular strategies that will allow us to build multi-component heteromeric structures, e.g. binary and ternary supermolecules.[47] The fact that solid-state assembly is a complex process governed by a subtle balance between intermolecular forces certainly helps to explain the fact that multi-step *inter*molecular synthesis is not commonplace. However, a recent report[48] outlines a strategy for the assembly of 1 : 1 : 1 ternary cocrystal containing supermolecules with *well defined and predictable connectivity*.[49]

This approach is based upon two simple principles:

(i) Hydrogen-bonds often form in a hierarchical fashion (best-donor to best-acceptor, second best-donor to second best-acceptor, etc.).[19]

(ii) A small number of specific intermolecular interactions can provide a large part of the stabilization energy of molecular crystals.[50]

The centrepiece in this supramolecular system is isonicotinamide, which is a good example of a suitable building block for ternary cocrystals: it has two distinctly different, yet relatively strong, hydrogen-bond moieties and it shows good 'structural flexibility' (it can form well-defined crystals with different components). By offering two different carboxylic acids to the isonicotinamide molecule, it was expected that the stronger acid would interact preferentially with the best acceptor (the pyridine nitrogen atom) and the weaker acid to form a heteromeric motif with the remaining amide. This design strategy was put to the test by allowing equimolar amounts of a weaker acid, a stronger acid, and isonicotinamide to react in an aqueous solution. The resulting structures, exemplified by 3,5-dinitrobenzoic acid/isonicotinamide/3-methylbenzoic acid, are 1 : 1 : 1 ternary cocrystals containing the desired three-component supermolecule with the expected connectivity. The stronger acid (pK_a 2.8)[51] interacts with the pyridine nitrogen atom, and the weaker acid (pK_a 4.3)[51] competes successfully for the amide moiety and forms a heteromeric hydrogen-bonded motif (Scheme 11).



Scheme 11. The ternary supermolecule in 3,5-dinitrobenzoic acid/isonicotinamide/3-methylbenzoic acid with the 'best' hydrogen bond between stronger acid···pyridine and the 'second-best' hydrogen bond between weaker acid···amide.

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This work shows that three-component supermolecules can be constructed through the use of known intermolecular synthetic operations. Although these forces are weaker than covalent interactions, it is clearly possible to assemble more than two different building blocks in a preconceived manner. There is every reason to believe that more complex supermolecules can be readily synthesized through an improved awareness of the balance and competition between intermolecular interactions.

Incorporating Function into Engineered Organic Structures

The future viability and success of crystal engineering will undoubtedly be determined by its ability to produce new functional materials, but despite the fact that supramolecular synthesis is a young discipline, several important efforts illustrate that genuine progress is being made in a variety of materials-related disciplines.

Host–Guest Chemistry

Since Nature seeks to fill space whenever possible, questions have been asked about the feasibility of using hydrogen bonds in the construction of porous organic molecular solids. A common theme was that hydrogen bonds would never be sufficiently strong to support a host structure that contained an appreciable amount of open or available space. However, a landmark study by Wuest (over 120 citations since its publication in 1997) demonstrated that a collection of hydrogen bonds operating in concert could impart remarkable structural integrity to an organic material.[52] Their work provided considerable inspiration and momentum and, undoubtedly, allayed many fears about the prospects for crystal engineering as a realistic route towards porous molecular solids. Wuest et al., constructed a 3-D, highly porous structure from a tetrahedral building block with four diaminotriazine substituents that was able to interact with neighboring molecules by 16 self-complementary N–H···N hydrogen bonds (a synthon involving aminotriazine moieties). The resulting non-interpenetrating network contained infinite channels that were more than 11.0 Å wide (Fig. 1).

This host structure allowed for incorporation of a variety of guest molecules, e.g. water, dioxane, and acetonitrile, and, notably, remained intact upon exchange of the guests; the guest molecules together occupied as much as 40% of the total volume of the crystal. More remarkably, it was discovered that, after removal of up to 60% of the guest molecules, the crystals remained optically transparent and continued to diffract. This indicates that a suitable hydrogen-bonded host structure can display considerable structural integrity and, as such, can represent a viable alternative to some porous inorganic solids.

Host–Guest Chemistry: Extended Structures

The construction of supramolecular host-frameworks capable of reversible incorporation of guest molecules, preferably with a degree of selectivity, has been an important crystal engineering goal; the most thoroughly studied

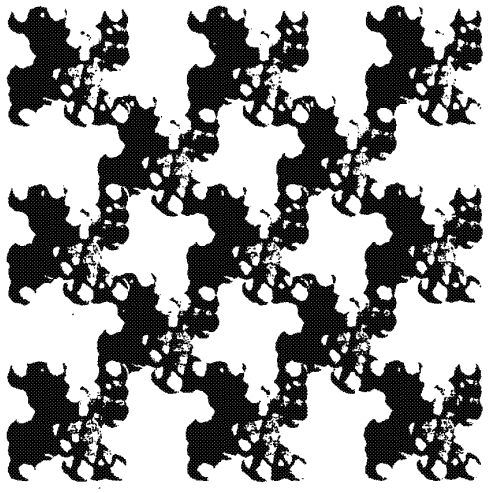
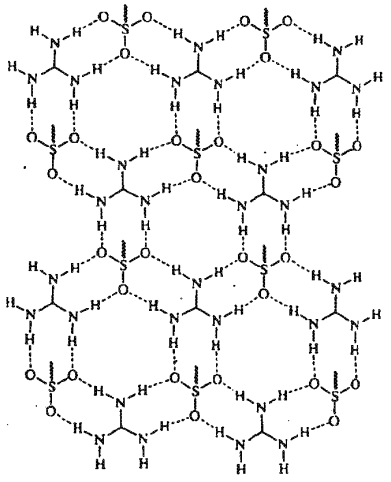


Fig. 1. Open channels in a porous molecular solid (the host occupies less than 60% of the total volume; guests removed for clarity).

framework is arguably the guanidinium/organic sulfonate two-component system developed by Etter, Ward and coworkers.[53] The supramolecular assembly of this extended host is based upon the C_3 symmetry and the complementarity of the hydrogen-bond sites on guanidinium cations and substituted sulfonate anions, leading to robust infinite hydrogen-bonded sheets (Scheme 12).

The precise topology of these structures (interlayer separation etc.), can be modified through appropriate



Scheme 12. Face-on view of the reliable hydrogen-bonded sheet in the guanidinium/sulfonate system.

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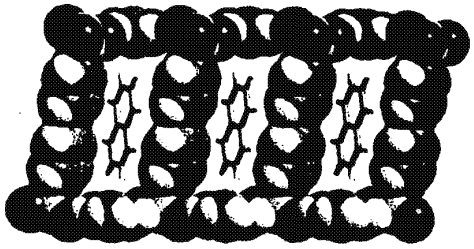


Fig. 2. Side-on view of the hydrogen-bonded host framework guanidinium/sulfonate system. Horizontal layers are bridged by vertical disulfonate ions; naphthalene guests in cavities.

substitution of the anion,[54] thus it is possible to employ these host structures (Fig. 2) for separation of isomeric mixtures of xylenes by selective inclusion.

The degree of selectivity is strongly dependent upon the host structure, but these lamellar materials certainly demonstrate that effective separation by crystallization is feasible.[55] The size and character of the cavities between layers can be tuned, and the lamellar character is persistent despite considerable variations in the nature of the sulfonate component. This reliability is probably related to the fact that the sheets are held together by rather 'soft' hydrogen-bond interactions; thus, the host can accommodate a variety of guests without disruptions to the 2-D sheets. The guanidinium/sulfonate system has provided inspiration to many other groups and, as an example, Mak[56] was able to construct 'fused rosettes' by combining the guanidinium cation with hydrogen carbonate dimers. Each supramolecular rosette displays a quasihexagonal assembly, with two cations and four anions linked by two homomeric and four heteromeric complementary synthons.

Another approach to the design of extended networks capable of host–guest chemistry couples well-established inclusion behaviour of discrete entities like calixarenes with the structure-directing ability of hydrogen bonds. Atwood and coworkers[57] were able to control the alignment of calixarenes in the solid state through O–H···N interactions; each calixarene is functionalized with eight hydroxyl groups on the upper rim. The bridge between adjacent calixarenes is furnished by 4,4′-bipyridine, a bifunctional linear hydrogen-bond acceptor; the two components assemble into a 1-D wave-like hydrogen-bonded architecture thereby aligning the calixarene cavities. Alternatively, macrocycles can be used as building blocks of extended assemblies, as illustrated by the construction of columnar nanotubes through self-complementary N···O interactions between neighbouring bisurea macrocycles.[58]

Crystal engineering of a wide range of low-dimensional architectures and networks with tuneable dimensions is clearly feasible, and the structural adaptability of many extended host-structures held together with hydrogen bonds make them versatile candidates for chemical separations. The path from 'esoteric' basic research on complementary hydrogen bonds to functional materials is seemingly shorter than what might have been expected.

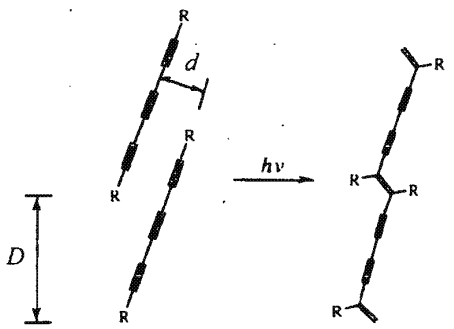
Host–Guest Chemistry: Discrete Structures

Although not normally included in discussions about crystal engineering (typically geared towards extended or infinite assemblies), it is worth mentioning a few successful supramolecular designs of discrete organic host-structures for encapsulation of guest molecules. As an example, sixteen hydrogen bonds operate in concert to construct a cavitand comprising two tetracarboxylic acids and four molecules of 2-aminopyrimidine molecules, which encapsulate two molecules of nitrobenzene in the solid state.[59] A slightly larger cavity was obtained by linking two bowl-shaped *C*-methylcalix[4]resorcinarenes with four molecules of 4,4′-bipyridine; two molecules of nitrobenzene were held within the interior of this capsule.[60] Similar bowl-shaped assemblies have also been used to capture several ferrocene derivatives in the solid state.[61] The host affects the conformation of the guest, which opens possibilities for entrapment and suitable organization of reactive guests in order to enable new stereoselective solid-state reactions.

Solid-State Photochemistry

Many early concepts regarding 'crystal engineering' were developed by Schmidt[62] and coworkers[63] based upon systematic studies on solid-state photodimerizations; it is encouraging to find that recent progress in supramolecular assembly has enabled many new such reactions by guiding adjacent molecules into the required orientation.[64] The 1,6-polymerization of a triacetylene was an elusive goal until Lauher and Fowler devised a supramolecular solution.[65] A topochemical reaction of this type will only proceed if the individual components can be organized such that adjacent triacetylene moieties are aligned, and the translational distance of monomeric units matches the geometric parameters of the resulting polymer (Scheme 13).

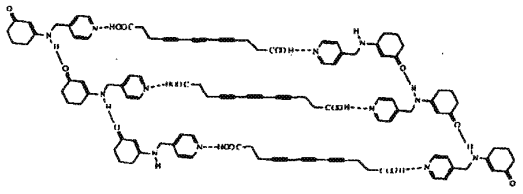
Through systematic structural studies, Fowler and Lauher were able to identify suitable building blocks



Scheme 13. Polymerization can be expected if d = 3.5 Å, D = 7.4 Å.

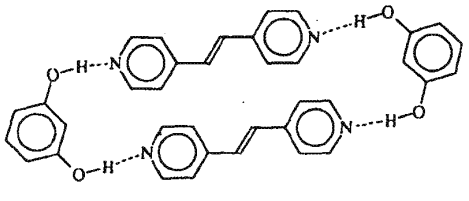
(aminoquinones) that would assemble, through N–H···O hydrogen bonds, at the required translation distance of about 7.4 Å. However, solubility problems with such compounds led instead to an examination of vinylogous amides, which, in principle, also could display the desired translation distance. A suitable molecule combining a triacetylene moiety with a vinylogous amide could undoubtedly have been made through rather complex covalent synthesis. Instead, the authors decided on a supramolecular approach involving the reliable carboxylic acid···pyridine synthon as a way of pre-organizing an appropriate spacer (a vinylogous amide that also provides the desired translation distance) and a triacetylene diacid.

After cocrystallization of the two components, the subsequent X-ray analysis revealed that the molecules had, indeed, been organized in accordance with the initial design strategy (Scheme 14). The topochemical reaction could now be carried out, and the desired polymer was obtained in about 70% yield upon exposure to ^{60}Co-γ radiation. In many ways this research puts the spotlight on the components that are essential to practical crystal engineering: a solid understanding of intermolecular interactions, coupled with an appreciation of the precise structural conditions that must be met in order to achieve a well defined objective.



Scheme 14. Successful alignment of triacetylene moieties.

Other topochemical reactions have also been carried out through supramolecular routes. MacGillivray and coworkers[66] were able to align two molecules of *trans*-1,2-bis(4-pyridyl)ethylene in the appropriate manner (intermolecular separation less than 4.2 Å; parallel double bonds) through cocrystallization with two molecules of 1,3-dihydroxybenzene (Scheme 15). Subsequent irradiation resulted in the desired cyclophane.

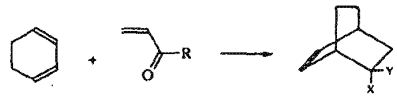


Scheme 15. O–H···N interactions position molecules in the orientation required for photodimerization.

These topochemical reactions provide beautiful illustrations of the fact that supramolecular synthesis has become a practical alternative to covalent synthesis and, in some cases, provides a quicker and more efficient route to advanced materials.

Catalysis

Solid-state reactions are important due to the possibilities for stereoselectivity, but there have been few examples of catalytically active organic solids. However, Aoyama and coworkers have demonstrated that certain bis resorcinol derivatives can form porous materials that feature intracavity Diels–Alder reactions (acrolein–cyclohexadiene) involving a catalytic cycle (Scheme 16).[67]



Scheme 16. Schematic Diels–Alder reaction between 1,3-cyclohexa-1,3-diene and acrolein (*endo*; X = COR, Y = H; *exo*: X = H, Y = COR).

The suggested mechanism involves intracavity incorporation of the reactants within the host, organization of the reactants, and subsequent desorption of the product. Evidence for intracavity reactions comes from solid–gas experiments and from changes in stereoisomerism of the products. The stereomeric ratios for the intracavity reaction depends on the bulkiness of R, whereas similar reactions run in the absence of host are practically independent of substituents.

These results demonstrate that microporous organic molecular solids can mimic the catalytic behavior of zeolites and provide further indication that engineered solids held together by weaker forces have considerable potential as new advanced materials.

Inorganic Crystal Engineering

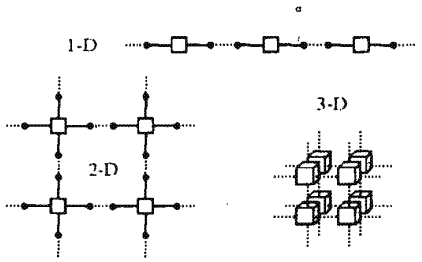
Brief History

Transition-metals can provide access to properties that are not readily accessible through crystal engineering of organic molecular solids, and many magnetic, electronic, and catalytic materials are formed by virtue of the presence of transition-metal ions.

The systematic investigation of supramolecular synthesis of coordination complexes began with coordination polymers,[68] infinite polymeric assemblies formed by connecting metal ions through coordinate–covalent bonds with multidentate bridging ligands such as the ubiquitous 4,4′-bipyridine. The resulting networks extend in directions dictated by the coordination geometry of the metal centre. Thus, to form 1-D (e.g. chains), 2-D (e.g. square or hexagonal grids), or 3-D (e.g. diamondoid or cubic lattices) structures (Scheme 17) one must choose the appropriate combination of metal centre and bridging ligand. For

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example, silver(I) ions are ideal for generating 1-D architectures, as they frequently adopt a linear coordination geometry. One drawback to coordination-polymer chemistry is that it employs a synthetic method that depends on polymerization events, which may lead to materials with poor solubility and unpredictable structures. Hence, assemblies of coordination complexes that have ligand-based hydrogen-bond functionalities as 'supramolecular glue', in which subunits can be formed independently and then later connected to themselves or other (complementary) subunits, are a useful addition to the field of crystal engineering.



Scheme 17. Possible architectures of hydrogen-bonded coordination complexes.

Mingos and coworkers[69] established the 'proof of principle' regarding the efficacy of hydrogen bonding for the directed assembly of coordination complexes. They synthesized metal-ion complexes containing hydrogen-bond functionalities on one or more ligands and were successful in cocrystallizing such ions with organic molecules that contained complementary hydrogen-bond functionalities. The resulting structures contained coordination complexes that were organized through directional hydrogen bonds into discrete dimers and infinite architectures.[70] This subset of crystal engineering is quite young, and today hydrogen-bonded coordination networks are still confused with coordination polymers.[71]

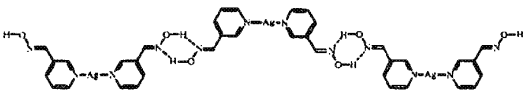
The problem remains, how reliable are hydrogen bonds in linking metal complexes into infinite assemblies? This issue is complicated by the fact that the very atoms that provide strong hydrogen-bonding sites are typically good sources of ligands for the metal ions as well. In fact, amide nitrogen and hydroxyl oxygen atoms (hydrogen-bond donors) coordinate to some metal ions, and good hydrogen-bond acceptors such as pyridine, pyrimidine, pyrazole and imidazole nitrogen atoms, as well as carboxylate and carboxamide oxygen atoms, may also act as ligands. Thus several groups have attempted to answer the question: to what extent are the lessons learned from organic crystal engineering applicable to transition-metal systems? This question has been addressed for organometallic supramolecular chemistry in other reviews,[72] but here we concentrate on answering the question for coordination complexes. Our focus then is to report on extended architectures that have been assembled by employing strategies that utilize hydrogen-bond interactions between ligand-based substituents. This is distinctly different from structures of coordination complexes that happen to contain hydrogen bonds involving e.g. solvent molecules or coordinated aquo and ammonia ligands (the latter two are not often considered to be sources of predictable hydrogen bonds). The results are grouped roughly by architectural type/dimensionality: 1-D, 2-D, or 3-D.

Directed Assembly of 1-D Architectures

Extended linear assemblies can be achieved by linear coordination geometries or by other coordination geometries (square planar, octahedral) with two linearly arranged hydrogen-bonding substituents.

Silver(I) Complexes

Much of the work done with Ag^I inorganic–organic hybrid materials was begun in our lab in order to test simple, well-known synthons such as the carboxylic acid, carboxamide, and oxime dimers (Scheme 1). We chose ligands with these hydrogen-bonding moieties that would coordinate to Ag^I by a pyridine nitrogen atom. Indeed, Ag^I pyridine–oximes[73] and isonicotinamide[74] have been shown to produce linear assemblies—the ligands form a linear coordination geometry with Ag^I, and this geometry is propagated into chains through self-complementary oxime–oxime and amide–amide interactions, respectively, (Scheme 18). Alternatively, 1-D ladders (from a combination of catemer and head-to-head amide–amide interactions) were obtained as a result of a *cis* relationship between amide functionalities in linear Ag^I-nicotinamide complexes.[75]



Scheme 18. Linear assembly of Ag^I (3-aldoximepyridine)$_2$ cations.

In a related system, nicotinic acid and its derivatives proved to be much more inconsistent as supramolecular building blocks.[76] In some cases, charge-assisted acid···carboxylate hydrogen bonds were formed, but the structures were dominated by coordinate-covalent Ag–O interactions, resulting in unpredictable coordination polymer assemblies.

1-D Assemblies with Other Transition-Metal Complexes

The oxime functionality was also used in assembly of Fe^{II} complexes.[77] FeL_4I_2 (L = 4-aldoximephenyl isocyanide) forms linear assemblies through four O–H···N interactions, despite the presence of four hydrogen-bonding ligands. Likewise, *trans*-PdL_2I_2 also forms a chain-like motif through self-complementary $R_2^2(6)$, O–H···N interactions. Both *cis*-[78] and *trans*-[79] platinum-phosphine complexes of nicotinamide and isonicotinamide contain hydrogen-bonded chains.

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Carboxylic acids can be useful hydrogen-bond linkers of Pt^{II} and Pd^{II} complexes—nicotinic acid, isonicotinic acid, and phenylquinoline complexes of $PtCl_2$ generate infinite chains.[80] (In related structures, dimethyl sulfoxide and dimethylformamide molecules break up the acid···acid hydrogen bonds, proving the unsurprising fact that solvent molecules can and do interrupt ligand–ligand hydrogen-bonding.)

Self-complementary melamine···melamine hydrogen bonds have been used in the 1-D assembly of a dimeric Cu^{II} complex that also involves an unusual example of metal–melamine coordination.[81]

More sophisticated ligands were used by Lehn and coworkers,[82] studying '[2×2] grid-type' tetranuclear metal complexes with either aminopyrazine or aminopyrimidine substituents attached to oligopyridine-derived ligands. Infinite 1-D hydrogen-bonded networks of the square grids are generated through self-complementary hydrogen bonds.

Macrocycles

Transition metal–macrocycle complexes have also been assembled through hydrogen-bonding substituents on the macrocycle and axial hydrogen bonded ligands (Fig. 3),[83] or solely through axial hydrogen-bonding ligands.[84]

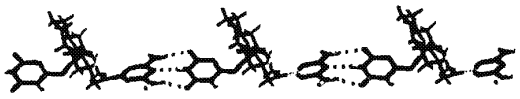


Fig. 3. Linear assembly of a macrocyclic complexes (note the complementary triple hydrogen-bond motif, ADA–DAD, see Scheme 6).

Another interesting macrocyclic assembly strategy has been employed by Min and Suh,[85] who synthesized a Ni^{II}-hexaazamacrocycle with pendant pyridine groups. An axial ligand with a carboxylic acid substituent forms a classic acid···pyridine hydrogen bond, connecting the complexes into linear assemblies.

Directed Assembly of 2-D Architectures

Lamellar assemblies tend to be organized through the use of square planar metal ions such as Pt^{II} or Pd^{II} or with hydrogen-bonding ligands in the basal planes of octahedral metal complexes. However, 2-D motifs can also be formed by catemeric amide–amide interactions in linear Ag^{I}-nicotinamide salts when 'spherical' counterions ($[BF_4]^-$ and $[PF_6]^-$) are used.[74,75]

Platinum(II) Complexes

Four-coordinate Pt^{II}-nicotinamide and isonicotinamide complexes were investigated by Brammer and coworkers;[86] while some hydrated structures did not exhibit self-complementary amide–amide motifs, the amide moieties in a nicotinamide complex did generate a linear assembly, and an isonicotinamide complex displayed a square grid-like structure. A similar grid-like assembly was observed in the structure of $[Pt(isoNA)_4][Cl]_2 \cdot 4$-isonicotinamide.[87] In this compound, adjacent Pt^{II} complexes are connected through hydrogen bonds, thus creating channels that contain non-coordinated isonicotinamide molecules (four per metal complex), resulting in a hydrogen-bonded 'host–guest' structure.

An isonicotinic acid complex of Pt^{II} also forms a channelled structure, this time through interpenetration of (4,4) nets.[68] $Pt(isonicotinate)_2(isonicotinic\ acid)_2$ is a neutral complex, due to the deprotonation of two of the acid ligands. Two unique hydrogen-bonded nets are formed through charge-assisted carboxylic acid···carboxylate hydrogen-bonding interactions between neighboring metal ions (Fig. 4). These square grids extend infinitely in two dimensions, leaving large square cavities that are filled by interpenetration of the nets—inclined inter penetration of the nets in three mutually perpendicular planes is the (quite rare) outcome of the assembly. The remaining cavities (5 Å in diameter) are occupied by water molecules. An advantage of using neutral complexes in the construction of porous materials is that no counter ions are present, allowing more accessible space for guest molecules.[87]

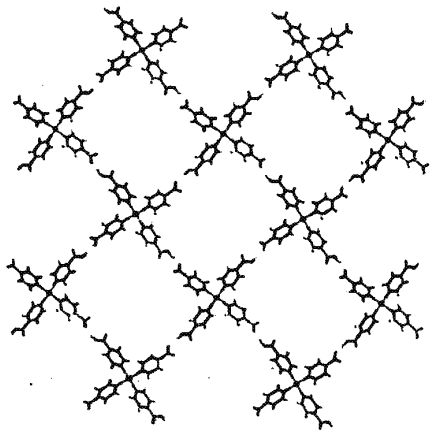


Fig. 4. Hydrogen-bonded (4,4) grid of Pt^{II} complexes (carboxylic acid···carboxylate links between square-planar complexes).

Nickel(II) Complexes

Simple pyridine-based ligands have also been used in the assembly of Ni^{II}-containing 2-D coordination networks. The oxime functionality has been used successfully in forming a Ni^{II} structure[87] in which O–H···O hydrogen bonds connect Ni^{II}-(4-pyridinealdoxime)$_4$ ions into grid-like sheets, resulting in hourglass-shaped holes. The sheets overlap such that the holes are essentially cut in half, but the resulting

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channels extend through the structure and contain free 4-pyridinealdoxime molecules (two per metal complex).

In a different Ni^{II} system, *hexagonal* nets form by using a trigonal arrangement of bidentate ligands. The ligand, 2,2′-biimidazolate forms self-complementary N–H···N intermolecular hydrogen bonds which result in either 1-D zigzag chains or 2-D 'honeycomb' sheets, depending on the counter ion.[88]

2-D Assemblies with Other Transition-Metal Complexes

In a recent paper by Lehn and coworkers,[89] 2,2′-bipyridine-based, propeller-like Fe^{II} complexes are linked through N–H···O hydrogen bonds to form 2-D sheets (sheets of alternating chirality are stacked parallel) with solvent-filled 1 nm cavities (crystallinity is maintained up to 564K). In another study, Lehn and coworkers synthesized terpyridine-derived ligands with moieties capable of self-complementary N–H···N hydrogen bonds;[90] Cu^{II} and Zn^{II} complexes formed either 1-D or 2-D assemblies, depending on the counter ion.

The versatility of inorganic supramolecular synthesis is nicely illustrated by a modified hexamolybdate cluster: six equivalents of 4-hydroxybenzamide were reacted with hexamolybdate to form clusters with octahedrally arranged amide groups. Hydrogen bonds between four of the amide groups lead to 2-D assemblies that are separated by counter ions.[91]

Metal Porphyrins

The directed assembly of porphyrin derivatives is of particular interest because or the possibilities of harnessing their photoelectronic properties. Goldberg and coworkers have synthesized a number of substituted porphyrin complexes with the aim of creating extended assemblies.[92] Flat, grid-like 2-D networks were formed through amide···amide[93] and acid···acid hydrogen-bond interactions (Fig. 5).[94,95] Similarly, Aoyama and coworkers used 3,5-dihydroxyphenyl substituents to connect Zn^{II} porphyrin units into 2-D assemblies.[96]

In contrast to the coplanar hydrogen-bonded assemblies above, Suslick and coworkers prepared hydrogen-bonded *stacks* of porphyrin rings using four 3,5-dihydroxyphenyl substituents on a Zn^{II} porphyrin complex.[97] Thus, the distance between the chromophores can be controlled in two directions by modifying the length and nature of the substituents.

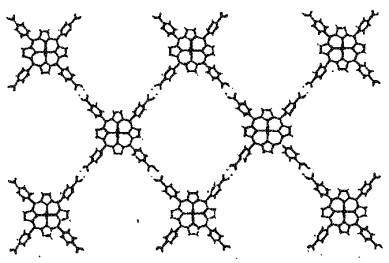


Fig. 5. Metal-porphyrins assembled using carboxylic acid dimers.

Directed Assembly of 3-D Architectures

While it would seem that 3-D networks could result from using, say, six pyridine-based ligands on an octahedral metal center, steric constraints usually prevent that kind of complex from forming. Further, metal ions coordinated to three bis-chelating ligands tend to produce propeller-like complexes that assemble in two dimensions (e.g. hexagonal sheets). Thus, 3-D assemblies, constructed from ligand-based hydrogen bonds only, are quite rare.

Probably the earliest report of a 3-D hydrogen-bonded array of coordination complexes was by Munakata and co workers.[98] They synthesized a tetrahedral Cu^{I} complex of 6-methyl-2-oxopyridin-3-carbonitrile, where the metal ion is coordinated to the cyano group, and pyridone–pyridone interactions generate a 3-D diamond-like hydrogen-bonded network (Fig. 6). However, in one case the combination of the same ligand and Cu^{I} led to a linear assembly of dimers (an acetone molecule bridges the metal centers); thus, a hydrogen-bonded chain (1-D) is formed.[99] Another example of a 3-D network was observed when trigonal Ag^{I} isonicotinamide complexes generated a $ThSi_2$-like interpenetrating structure by catemeric amide–amide interactions.[100]

Combination of Coordination Polymers and Hydrogen Bonds

The idea of combining coordination polymers and ligand-based hydrogen bonds has been recently introduced. There are some advantages to this approach because it allows a combination of strength, imparted by a coordination network, and flexibility, allowed by the softer hydrogen-bond interactions. Furthermore, by using coordination polymers

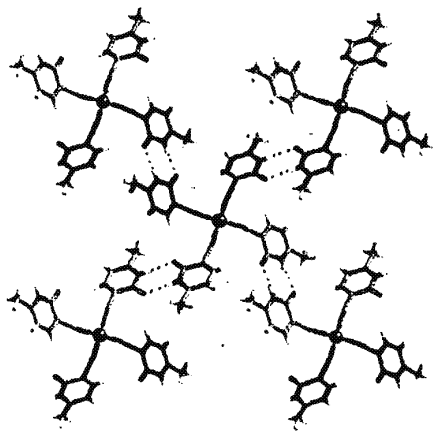


Fig. 6. Sub-unit of a diamondoid network based on tetrahedral Cu^{I} complexes and held together by self-complementary 2-pyridone hydrogen bonds.

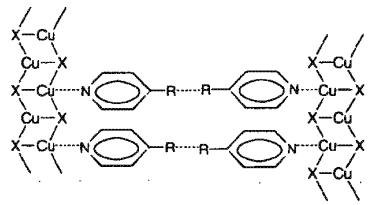
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instead of discrete complexes as building blocks, the resulting structures have fewer degrees of freedom, which facilitates structural prediction and control. This type of strategy has not yet been employed in a systematic manner.

Early examples of combination networks were provided by Fowler, Lauher and coworkers, following their syntheses of pyridyl-derivatized ureas and oxalamides. Tetrahedrally coordinated Ag^{I} ions were connected into 2-D coordination polymers by bridging bipyridine-like ligands. Complementary N–H···O hydrogen bonds between ligands completed the assembly process, leading to an overall 3-D network.[101]

A different strategy involves the use of an additional ligand to link, through hydrogen bonds, to the ligand that produces the coordination polymer. In a series of complexes from Burrows and coworkers,[102] Zn^{II} is coordinated to bridging carboxylate ligands, forming coordination polymer chains. The metal is also coordinated to a thiourea ligand, where the ligand amine groups connect through hydrogen bonds to the carboxylate oxygen atoms on a neighboring chain.

Leaving less to chance, additional ligands with the potential for self-complementary hydrogen bonds (hydrogen bonds that are *independent* of the ligands required to assemble the coordination polymer) can be used. Cu^{I} halides can form linear coordination polymers by bridging halide interactions, and simple pyridine-based ligands with carboxylic acid, carboxamide and oxime substituents have been used to create 2-D assemblies through the resulting self-complementary hydrogen bonds (Scheme 19).[103]



Scheme 19. 2-D network based upon a combination of linear Cu^{I} coordination polymers and self-complementary R···R hydrogen-bond interactions.

This approach was also used by Chen and coworkers, who synthesized 1-D and 2-D coordination polymers with thiocyanate ligands bound to cadmium(II); self-complementary hydrogen bonds between additional nicotinic acid, nicotinamide, and isonicotinamide ligands lead to 2-D and 3-D networks.[104] A linear coordination polymer formed from Cu^{II} with bridging dicyanamide, assembles by complementary 2-aminopyrimidine hydrogen bonds.[105] Even more interesting are Co^{II} and Ni^{II} complexes of dicyanamide, which create infinite tubes through coordinate covalent bonds. 2-Aminopyrimidine ligands located on the periphery form hydrogen bonds that connect the tubes into a 3-D assembly.[106]

Examples of transition-metal complexes assembled through hydrogen bonds also at times illustrate the potential problems that can be found in forming hydrogen-bonded assemblies. Solvent molecules, counter ions, and coordinate–covalent bond formation (e.g. Ag–O) can interrupt the intended ligand···ligand hydrogen bonding. However, despite these occasional complications, hydrogen bonds have proved remarkably reliable in forming coordination complex assemblies. For example, though some of these structures have not been reported, we have thirty structures of silver(I) with nicotinamide, substituted nicotinamide, or isonicotinamide. 93% are linear complexes, 7% are trigonal. 54% exhibit 1-D amide···amide hydrogen bonding motifs. 32% exhibit 2-D amide···amide hydrogen bonding motifs, and 14% give no extended architectures by amide···amide hydrogen bonds.[75,100,107] Thus, the *type* of hydrogen bond motif can be modified by changing the counter ion and/or the placement of the hydrogen bond functionality, but the hydrogen-bonding interactions persist and are a major steering force in the assembly of these coordination complexes.

Codicil

Crystal engineering has undoubtedly made considerable progress during the last five years, and recent developments clearly indicate that many more functional materials and desirable structures will appear. However, it is also worth pointing out that there are several pitfalls on the way to success in this young field, and the key component here is *strategy*. Although serendipity will continue to play a role, it is essential that we have clear synthetic plans and targets before embarking upon our next supramolecular venture. Much too often an isolated crystal structure that contains some hydrogen-bond interactions, an 'unprecedented' connectivity, or a 'novel and intriguing' network structure, is presented in the literature. There is a risk that crystal engineering will become nothing more than a hollow reason for presenting numerous small-molecule crystal structures, therefore some degree of self-restraint and realism are important prerequisites for every enthusiastic crystal engineer. In this context, Dunitz has produced a gem of a paper that should be on the reading list for crystal engineering novices and grizzled aficionados alike.[108]

We have tried, in this review, to describe the tools and tactics employed by laboratories around the world as they try to engineer crystals with predictable structures and properties. The recent syntheses of functional materials that are capable of chemical separations and topochemical reactivity remind us that progress leads to produce. Moreover, lessons learned in organic crystal engineering are being successfully applied in the synthesis of predictable networks of coordination complexes, and will continue to have an impact on the design and synthesis of advanced materials.

Gavezzotti's[109] question continues to haunt crystal engineers: 'Are crystal structures predictable?' But with results from continued investigations into the effect and limits of intermolecular interactions such as the hydrogen bond guiding us, we can surely say that, in many cases, crystal structures are more predictable now than they used to be.

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Acknowledgments

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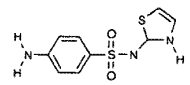
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The sulfadrug sulfathiazole forms an extensive family of solvates and adducts, the crystal structures of which show a large variety of hydrogen-bonded frameworks.

In a recent communication, Nangia and Desiraju[1] analysed the relative solvate-forming propensities of fifty common solvates, and highlighted the need for systematic studies of the formation and structure of solvates. We have been engaged in such a study, largely based on one compound, the sulfadrug sulfathiazole, I,



I

with remarkable solvate forming abilities, which developed out of a detailed reinvestigation of the polymorphism of this compound[2]. We present here a preliminary report of our findings.

The sulfadrugs show extensive polymorphism.[2,3] They also crystallise erratically from solution, despite the contrary impression that might be gained from the literature. In the search for reliable crystallisation procedures for sulfathiazole polymorphs, several less common solvents were tried and in quite a number of cases solvates were obtained. This was surprising, since the only well-defined solvate encountered in over 40 papers[4] during 60 years of investigation was that from dioxane.[5] Shirotani *et al.*[6] have described 3 further solvates of sulfathiazole, but their work seems to have been subsequently overlooked. In the belief that a detailed preparative and structural study of solvate formation may give an insight into the crystallisation behaviour of the parent materials, we have explored this topic further. The first solvate we produced was that from cyclohexanone. Reasoning from the analogy between the structures of dioxane and cyclohexanone, we tried numerous other 6- and 5-membered saturated heterocyclic and carbocyclic rings possessing at least one polar group, the function of the latter being presumed to involve hydrogen bonding with one of the 5 acceptors and 3 donors in the sulfathiazole molecule. Single crystal X-ray determinations however showed a remarkable variety of structures with varying propensity for hydrogen bonding between the sulfathiazole and the solvent guest. The study was extended to a wider range of solvents with different molecular shapes and sizes, different polarities and different functional groups, and also to the preparation of mixed crystals with partners that are solids at ambient temperature. The solvates are easily made by crystallisation from the appropriate solvent, sometimes with the help of chloroform as a crystallisation aid. Sulfathiazole has a solubility at elevated temperatures of around 10% in typical solvate-forming solvents. It is very soluble (30–60%) in more polar solvents such as dimethylformamide or tetramethylurea but generally fails to form solvents from such solutions. It has a limited solubility in solvents of low polarity and usually only sulfathiazole polymorphs crystallise from these solutions. Surprisingly, we found that molecules with long aliphatic hydrocarbon chains can form solvates provided a solvatophilic group such as lactone or lactam is present. The two-component solid–solid adduct crystals can be made by fusion or sometimes by crystallisation of the components using an inert solvent. The presence of a third component is detrimental on thermodynamic grounds,[7] but in practice, as noted above for chloroform, may be favourable for kinetic reasons.

More than 100 solvates plus many related 2-component systems containing sulfathiazole have now been made, including inter-sulfa-drug combinations such as sulfapyridine with sulfathiazole.‡ All have been characterised by near- and mid-infrared spectroscopy, powder XRD and hot-stage microscopy, and studied, in some cases also by DSC/TGA, solid state NMR, Raman spectroscopy and microscopy. The crystal structures of more than 60 solvates and adducts have so far been determined; others are in progress. The existence of such a large collection of data allows a unique opportunity for the comparative investigation of the structural and spectral characteristics and of the factors determining solvate formation. Detailed consideration of this is beyond the scope of a Communication, and is the central theme of a series of full papers, now in preparation. However, the results obtained can be usefully summarised as follows.

No solvent containing an aromatic carbocyclic group has given a solvate. Virtually every saturated carbocycle or heterocycle of appropriate polarity, and of ring size 3 to 8 produces a solvate. Only the behaviour of aliphatic solvates is difficult to predict, although polarity can be distinguished as a key factor. A wide range of groups including cyano, ester, ether, keto, sulfonyl, and amido groups are capable of providing the necessary polar characteristics. A hydroxy group generally seems to be detrimental to solvate formation, although a very unstable solvate has been made from *n*-propanol. The identification of the latter solvate together with that of acetonitrile raises the question as to whether many of the outcomes of sulfathiazole polymorph preparation procedures are mediated by the intervention of unstable solvates. Competitive experiments, in which sulfathiazole is crystallised from mixed solvates, have shown a stability sequence of lactams > lactones > cyclic carbonates > cyclic ketones, which parallels the order of solvent polarity. The relative stabilities of adducts with different sized rings have not been determinable so far because the crystalline product from these competition reactions has often not been one of the expected products. Some of these may be polymorphs of solvates, since DSC shows that some of the solvates are di- or tri-morphic. (Fig. 1.) The infrared spectra of the solvates are almost always close to that of the highest melting polymorph 1 (mp 203 °C), (the structure of which contains two crystallographically independent molecules, and which we regard as a sulfathiazole solvate of sulfathiazole), and unlike those of the three mutually similar low-melting polymorphs, even though the solvates always desolvate to the lower melting polymorphs, especially polymorph IV.§ This may be explained by the fact that in the structures so far determined the

† Electronic supplementary information (ESI) available: solvates and adducts of sulfathiazole. See http://www.rsc.org/suppdata/cc/b0/b009540k/

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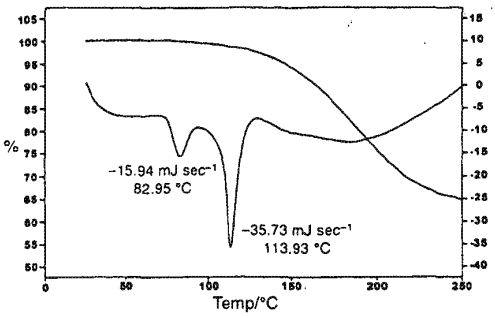


Fig. 1 DSC and TGA traces of the sulfathiazole-ε-caprolactone adduct. The endotherms without mass loss indicate phase transitions to new polymorphs, confirmed by hot-stage microscopy.

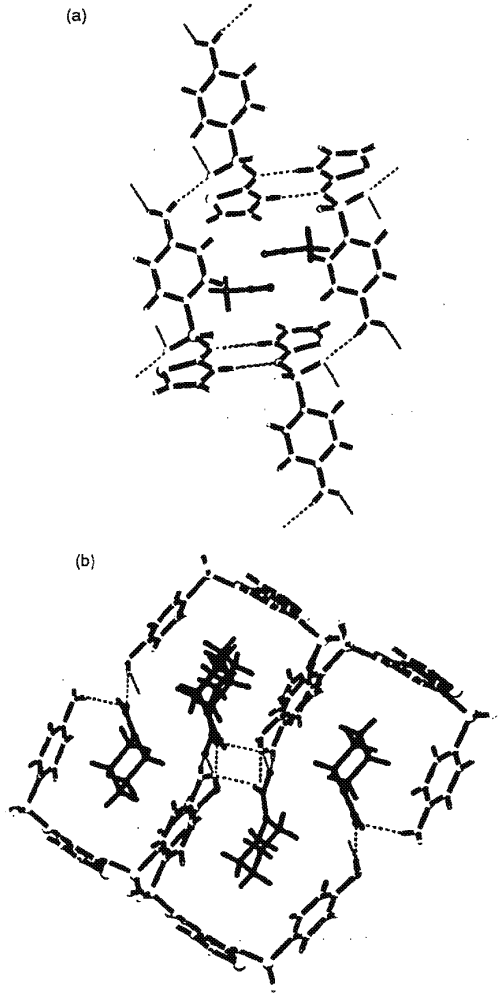


Fig. 2 (a) Detail from the crystal structure of the 1 : 1 adduct sulfathiazole–acetonitrile—a clathrate. (b) Detail from the crystal structure of the 1:1 adduct sulfathiazole–*N*-formylpiperidine—a co-crystal.

close amido–imido dimer present in sulfathiazole polymorph I but not in any of the others, features extensively in the solvate structures. The similarity of IR spectra for systems that are found to have quite different crystal structures is explained in terms of the presence of similar H-bonding associations but different supramolecular assemblies.

Terminology for the description of solid state molecular structures is unsatisfactory, even for single component systems.[8,9] Consideration of the multitude of structures displayed by the solvates listed in Nangia and Desiraju's paper raises the question as to whether nomenclature is even less adequate for the greater complexity resulting from two-component systems.

On the basis of the structure determinations so far completed in our study, we identify two types of structure which might provide a more generally useful classification—a) *clathrates*, or, more generally *inclusion phases*, in which the main function of the guest molecule is cavity filling, with or without additional weak H-bonding, in a host molecule assembly having a channel, layer or 3D framework structure, and b) *co-crystals* in which the partner molecule forms an essential part of the hydrogen bonded framework. In each class we have also found salts where proton transfer has occurred from the sulfathiazole molecule to a basic function on the guest. An example of each of the two main structure types is shown in Figs. 2a and 2b.¶

Multiple solvates have been reported for a variety of compounds, but these invariably show a large degree of isostructurality.[10] By contrast, our study has shown that sulfathiazole would appear to show more solid state structural versatility than any other organic molecule. We are investigating why this might be the case and whether other compounds form huge numbers of overlooked solvates or whether sulfathiazole is unique. To this end, the solvate forming propensities of other sulfadrugs are being examined. Preliminary experiments indicate that sulfapyridine forms many solvates, but not so extensively as sulfathiazole, and often with different solvates. The host–solvent relationship appears to be a very specific one even for such closely related hosts as the sulfadrugs, as might be expected from the huge variety of structures displayed by the sulfadrug polymorphs.

Notes and references

‡ A list of the solvates and adducts prepared so far, is given in the Supplementary Material.

§ The numbering scheme used here for the five fully characterised polymorphs is that described in D. C. Apperley, R. A. Fletton, R. K. Harris, R. W. Lancaster, S. Tavener and T. L. Threlfall, *J. Pharm. Sci.*, 1999, **88**, 1275.

¶ *Crystal data:* compound **1**, sulfathiazole–acetonitrile, $[C_9H_9N_3O_2S_2][C_2H_3N]$ M_r = 296.37, monoclinic, a = 10.741(2), b = 7.592(2), c = 16.748(3) Å, β = 103.99(3)°, U = 1325.2(5) Å^3, space group $P2_1/c$, Z = 4, T = 150 K. Reflections measured 5364 (θ_{max} = 25.35°, 82.6% complete), observed [$I > 2\sigma(I)$] 1997, R_{int} = 0.15. R = 0.059, ωR_2 = 0.111, 211 parameters. Compound **2**, sulfathiazole–*N*-formylpiperidine, $[C_9H_9N_3O_2S_2][C_6H_{11}NO]$ M_r = 368.47, triclinic, a = 10.539(2), b = 12.189(2), c = 13.981(3), α = 95.29(30), β = 107.38(3), γ = 90.63(3)°, U = 1705.3(6) Å^3, space group $P\bar{1}$, Z = 2, T = 150 K. Reflections measured 10626, θ_{max} 24.97°, 91.7% complete), observed 2877, Rint = 0.044. R = 0.0450, ωR_2 = 0.0955, 557 parameters. CCDC 154065 and 154066. See http://www.rsc.org/suppdata/cc/b0/b009540k/ for crystallographic data in .cif or other electronic format.

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Molecular Cocrystals of Carboxylic Acids. IX* Carboxylic Acid Interactions with Organic Heterocyclic Bases. The Crystal Structures of the Adducts of (2,4-Dichlorophenoxy)acetic Acid with 3-Hydroxypyridine, 2,4,6-Trinitrobenzoic Acid with 2-Aminopyrimidine, and 4-Nitrobenzoic Acid with 3-Amino-1,2,4-triazole

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Abstract

The cocrystal adducts of a number of carboxylic acids with organic heterocyclic bases have been prepared, and their structures and intermolecular interactions interpreted through X-ray diffraction and infrared spectroscopic techniques. The crystal structures of three of these compounds, the 1:1 adducts [{(2,4-dichlorophenoxy)acetic acid}(3-hydroxypyridine)] (1), [(2,4,6-trinitrobenzoic acid)(2-aminopyrimidine)] (2), and [(4-nitrobenzoic acid)(3-amino-1,2,4-triazole)] (3), have been determined by single-crystal X-ray diffraction and refined to residuals R 0·026, 0·033 and 0·040 for 1814, 1531 and 727 observed reflections, respectively.

Introduction

The basis of the behaviour of amino acids as free metabolic intermediates and as components of proteins stems from the fact that amino acids exist mostly as dipolar ions (zwitterions). These active sites are available not only for direct chemical attack but also lend themselves to hydrogen-bonding interactions. This paper presents a series of model compounds that demonstrate such directed hydrogen bonding. Both the acids (donors) and bases (acceptors) chosen have previously proved useful in adduct formation. (2,4-Dichlorophenoxy)acetic acid (2,4-d) is a commercial member of the biologically active series of phenoxyalkanoic acids which are presently under investigation as donors in adduct formation.[1–3] The nitro-substituted

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benzoic acids, 4-nitrobenzoic acid (4-nba), 3,5-dinitrobenzoic acid (dnba) and 2,4,6-trinitrobenzoic acid (tnba), are strong donors and as such have proved useful in adduct formation[4–7]. Of the four bases used, only one is biologically active, 3-amino-1*H*-1,2,4-triazole (3-at, 1*H*-1,2,4-triazol-3-amine) and is a commercial herbicide.[8] The other three heterocyclic bases, 3-hydroxypyridine (3-hp, pyridin-3-ol), 2-aminopyrimidine (2-ap, pyrimidine-2-amine), and 1,10-phenanthroline (phen), provide various sites for hydrogen-bond interaction. Each of these bases has proved useful as an acceptor in adduct formation.[5,7,9]

In the present study, three crystal structures have been determined: the 1:1 adducts of (2,4-dichlorophenoxy)acetic acid with 3-hydroxypyridine [(2,4-d)(3-hp)] (1), 2,4,6-trinitrobenzoic acid with 2-aminopyrimidine [(tnba)(2-ap)] (2), and 4-nitrobenzoic acid with 3-amino-1,2,4-triazole [(4-nba)(3-at)] (3). Results are also presented for a number of other complex adducts: 3,5-dinitrobenzoic acid with 1,10-phenanthroline [$(dnba)_2(phen)$] (4), 3,5-dinitrobenzoic acid with 3-hydroxypyridine [(dnba)(3-hp)] (5), 2,4,6-trinitrobenzoic acid with 1,10-phenanthroline [(tnba)(phen)] (6), and phenoxyacetic acid (pa) (2,4-dichloro-5-fluorophenoxy)acetic acid (dfpa) and (2,4,5-trichlorophenoxy)acetic acid (2,4,5-t) with 3-hydroxypyridine (7a–c). Powder diffraction and infrared spectroscopic data have also been used in the interpretation of the hydrogen-bonding interactions.

Preparation of Adducts

[(2,4-d)(3-hp)] (1).—Equimolar amounts of (2,4-dichlorophenoxy)acetic acid (2,4,-d) and 3-hydroxypyridine (3-hp) were dissolved in hot 50% aqueous ethanol. Evaporation to dryness at room temperature yielded colourless needles (m.p. 147–149°).

[(tnba)(2-ap)] (2).—Equimolar amounts of 2,4,6-trinitrobenzoic acid (tnba) and 2-aminopyrimidine (2-ap) was dissolved in boiling 50% aqueous ethanol. Evaporation to dryness at room temperature yielded light brown plates (m.p. 119–121°).

(4-nba)(3-at) (3).—Equimolar amounts of 4-nitrobenzoic acid (4-nba) and 3-amino-1,2-4-triazole (3-at) were refluxed in toluene (*c.* 150°) for 20 min. After evaporation to dryness the resultant red powder was recrystallized from 50% aqueous ethanol to yield large, square, red blocks (m.p. 188·5–190°).

[$(dnba)_2(phen)$] (4).—3,5-Dinitrobenzoic acid (dnba) and 1,10-phenanthroline (phen) in 2:1 molar amounts were refluxed in ethanol (*c.* 100°) for 20 min. Evaporation to dryness at room temperature yielded yellow prisms (m.p. 168–169·5°), subsequently found to be the 2:1 adduct. No 1:1 complex was successfully prepared.

[(dnba)(3-hp)] (5).—Equimolar amounts of 3,5-dinitrobenzoic acid (dnba) and 3-hydroxypyridine (3-hp) were refluxed in 50% ethanol/toluene (*c.* 150°) for 20 min. Evaporation to dryness at room temperature yielded pale brown *needles* (m.p. 168–170°) [Found for (5): C, 46·6; H, 2·9; N, 13·4. $C_7H_4N_2O_6.C_5H_5NO$ requires C, 46·9; H, 2·9; N, 13·7%].

[(tnba)(phen)] (6).—Equimolar amounts of 2,4,6-trinitrobenzoic acid (tnba) and 1,10-phenanthroline were dissolved in boiling water. The solution was allowed to evaporate to

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dryness at room temperature, giving pale brown needle *crystals* (m.p. 184–186°) [Found for (6): C, 52·4; H, 2·8; N, 16·5. $C_7H_3N_3O_8.C_{12}H_8N_2$ requires C, 52·2; H, 2·5; N, 16·0%].

Cocrystals (7a–c) of pa, dfpa and 2,4,5-t with 3-hp.—Equimolar amounts of three phenoxyalkanoic acids, phenoxyacetic acid (pa), (2,4-dichloro-5-fluorophenoxy)acetic acid (dfpa), and (2,4,5-trichlorophenoxy)acetic acid (2,4,5-t), were each separately heated in 50% aqueous ethanol with 3-hp. Evaporation to dryness at room temperature gave the crystalline *products* (7a), (7b) and (7c), (m.p. 70–73, 138–139, 143–144·5°, respectively) [Found for (7a): C, 62·8; H, 5·3; N, 6·7. $C_8H_8O_3.C_5H_4NO$ requires C, 63·4; H, 5·3; N, 5·7%. Found for (7b): C, 46·6; H, 3·0; N, 4·1. $C_8H_5Cl_2FO_3.C_5H_5NO$ requires C, 46·8; H, 3·0; N, 4·2%. Found for (7c): C, 44·4; H, 2·8; N, 3·9. $C_8H_6Cl_3O_3.C_5H_5NO$ requires C, 44·6; H, 2·9; N, 4·0%]. These were unsuitable for single-crystal X-ray diffraction work but cocrystals were identified in each case by using X-ray powder diffraction techniques. Powder diffractometry was completed with an Enraf–Nonius Guinier camera (Cu Kα X-radiation).

Infrared spectra were recorded for all samples as KBr disks on a Perkin–Elmer 1600 Fourier-transform infrared spectrophotometer.

Crystallography

Crystal Data

(1) $[(C_8H_5Cl_2O_3)^-.(C_5H_6NO)^+]$, mol. wt 316·1, triclinic, space group $P\bar{1}$, a 4·284(3), b 10·065(5), c 15·65(1) Å, α 80·24(5), β 88·13(4), γ 89·01(4)°, V 664·6(8) Å^3, $F(000)$ 324, $D_c(Z=2)$ 1·579 g cm^{-3}, μ (Mo Kα) 5·03 cm^{-1}, temperature 297 K.

(2) $[(C_7H_2N_3O_8)^-.(C_4H_6N_3)^+]$, mol. wt 352·2, triclinic, space group $P\bar{1}$, a 8·029(7), b 8·622(6), c 12·18(1) Å, α 91·42(5), β 104·30(5), γ 60·07(9)°, V 703(1) Å^3, $F(000)$ 360, $D_c(Z=2)$ 1·664 g cm^{-3}, μ (Mo Kα) 1·56 cm^{-1}, temperature 297 K.

(3) $[(C_7H_4NO_4)^-.(C_2H_5N_4)^+]$, mol. wt 252·2, monoclinic, space group $P2_1/c$, a 8·491(4), b 10·999(4), c 11·794(5) Å, β 90·11(2)°, V 1101·5(8) Å^3, $F(000)$ 520, $D_c(Z=4)$ 1·521 g cm^{-3}, μ (Mo Kα) 1·32 cm^{-1}, temperature 297 K.

(4) $[(C_7H_4N_2O_6)_2.(C_{12}H_8N_2)]$, mol. wt 604·4, orthorhombic, space group $P2_12_12_1$, a 5·734(1), b 10·021(2), c 45·655(7) Å, V 2623·4(8) Å^3, $F(000)$ 1240, $D_c(Z=4)$ 1·530 g cm^{-3}, μ (Mo Kα) 1·34 cm^{-1}, temperature 297 K.

(5) Precession photographs for [(dnba)(3-hp)] indicated crystal twinning. The space group was determined as $P2_1/c$, with approximate cell dimensions a 24·86, b 8·86, c 11·84 Å, β 94·5°, V 2600 Å^3, $D_c(Z=8)$ 1·57 g cm^{-3}, D_m 1·55 g cm^{-3} ($CHCl_3/CHBr_3$).

(6) Weissenberg photographs for [(tnba)(phen)] indicated crystal twinning in a monoclinic C cell, with an approximate cell volume, V 1920 Å^3, $D_c(Z=4)$ 1·51 g cm^{-3} (assuming a 1 : 1 molecular ratio), D_m 1·50 g cm^{-3} ($CHCl_3$).

Data Collection, Structure Solution and Refinement

X-Ray diffraction data were collected from crystals of dimensions 0·25 by 0·10 by 0·50 mm (1), 0·24 by 0·05 by 0·36 mm (2), 0·28 by 0·20 by 0·40 mm (3), and 0·20 by 0·14 by 0·42 mm (4) on an Enraf–Nonius CAD-4 diffractometer by using crystal monochromatized Mo Kα X-radiation (λ 0·71073 Å). Negligible change in the intensities of three standards monitored throughout the data collection period for each adduct indicated no crystal decomposition. Of 2325 (1), 2175 (2), 1773 (3) and 2685 (4) unique reflections collected up to $2\theta_{max}$ 50°, 1814 (1), 1531 (2), 727 (3) and 1546 (4) with $I > 2{\cdot}5\sigma(I)$ were considered observed and were used in the structure analysis. Data were corrected for Lorentz and polarization effects with empirical absorption correction being applied to complexes (1) and (2). The structures of complexes (1)–(4) were solved by direct methods (SHELXS-86[10]). Blocked-matrix least-squares refinement (SHELX-76[11]) with anisotropic thermal parameters for all non-hydrogen atoms [for

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Table 1. Atomic coordinates and equivalent isotropic thermal parameters
$U_{eq} = \frac{1}{3}(U_{11}+U_{22}+U_{33})$

Compound	Atom	*X/a*	*Y/b*	*Z/c*	$10^3 U_{eq}$ (Å)
(1)	N(1A)	0·5195(3)	0·8752(2)	1·1530(1)	55(5)
	C(2A)	0·3939(4)	0·8470(2)	1·0813(1)	42(5)
	C(3A)	0·4529(4)	0·7240(2)	1·0555(1)	40(6)
	O(3A)	0·3301(3)	0·6912(1)	0·9848(1)	41(6)
	C(4A)	0·6451(5)	0·6323(2)	1·1059(1)	48(6)
	C(5A)	0·7709(5)	0·6645(2)	1·1792(1)	51(7)
	C(6A)	0·7048(5)	0·7876(2)	1·2021(1)	50(7)
	C(1B)	0·0881(4)	0·2960(2)	0·3295(1)	53(2)
	C(2B)	0·1792(4)	0·3613(2)	0·3963(1)	60(2)
	Cl(2B)	0·4044(1)	0·5045(1)	0·3708(1)	41(4)
	C(3B)	0·0861(4)	0·3174(2)	0·4813(1)	48(4)
	C(4B)	−0·1068(4)	0·2071(2)	0·4998(1)	48(4)
	Cl(4B)	−0·2296(1)	0·1494(1)	0·6069(1)	35(5)
	C(5B)	−0·2053(5)	0·1427(2)	0·4349(1)	41(6)
	C(6B)	−0·1081(4)	0·1874(2)	0·3501(1)	39(5)
	O(7B)	0·2010(3)	0·3469(1)	0·2484(1)	36(5)
	C(8B)	0·0576(5)	0·3040(2)	0·1767(1)	41(6)
	C(9B)	0·1668(4)	0·1682(2)	0·1566(1)	42(6)
	O(10B)	0·0435(3)	0·1322(1)	0·0927(1)	47(6)
	O(11B)	0·3691(3)	0·1024(1)	0·2023(1)	42(6)
(2)	N(1A)	0·4138(3)	0·5405(3)	0·6498(2)	38(1)
	C(2A)	0·2533(4)	0·5284(3)	0·5912(2)	37(1)
	N(21A)	0·0729(3)	0·6586(3)	0·5906(2)	48(1)
	N(3A)	0·2773(3)	0·3882(3)	0·5321(2)	42(2)
	C(4A)	0·4627(4)	0·2597(4)	0·5383(2)	43(1)
	C(5A)	0·6313(4)	0·2615(4)	0·6002(2)	42(1)
	C(6A)	0·6006(4)	0·4088(3)	0·6548(2)	40(1)
	C(1B)	0·2344(3)	0·9882(3)	0·8986(2)	27(1)
	C(11B)	0·2211(3)	0·9027(3)	0·7884(2)	37(1)
	O(11B)	0·3774(3)	0·8254(3)	0·7573(2)	54(1)
	O(12B)	0·0582(3)	0·9169(3)	0·7421(2)	48(1)
	C(2B)	0·2302(3)	1·1520(3)	0·9049(2)	30(1)
	N(2B)	0·2201(3)	1·2439(3)	0·8009(2)	39(1)
	O(21B)	0·1145(3)	1·2411(3)	0·7106(2)	64(2)
	O(22B)	0·3157(3)	1·3201(3)	0·8123(2)	59(1)
	C(3B)	0·2330(3)	1·2359(3)	1·0024(2)	35(1)
	C(4B)	0·2385(3)	1·1521(3)	1·0990(2)	33(1)
	N(4B)	0·2280(3)	1·2427(3)	1·2031(2)	44(1)
	O(41B)	0·1569(3)	1·4053(3)	1·1927(2)	60(1)
	O(42B)	0·2880(3)	1·1494(3)	1·2937(2)	61(1)
	C(5B)	0·2478(3)	0·9894(3)	1·1014(2)	34(1)
	C(6B)	0·2475(3)	0·9098(3)	1·0017(2)	32(1)
	N(6B)	0·2609(3)	0·7338(3)	1·0075(2)	41(1)
	O(61B)	0·2255(3)	0·6883(3)	1·0881(2)	67(2)
	O(62B)	0·3045(5)	0·6423(3)	0·9316(2)	96(3)
(3)	N(1A)	−0·1807(6)	0·0808(3)	1·0069(4)	63(3)
	N(2A)	−0·0921(5)	0·1673(3)	0·9501(3)	47(2)
	C(3A)	−0·0774(5)	0·1425(3)	0·8406(3)	41(3)
	N(31A)	−0·0041(6)	0·2075(3)	0·7649(4)	53(3)
	N(4A)	−0·1592(5)	0·0389(3)	0·8238(3)	48(2)
	C(5A)	−0·2175(8)	0·0052(4)	0·9270(5)	65(3)
	C(1B)	0·2561(6)	0·5177(3)	1·0309(3)	38(3)
	C(11B)	0·1546(6)	0·4208(3)	0·9759(4)	36(3)
	O(21B)	0·0741(4)	0·3546(2)	1·0406(2)	48(2)
	O(22B)	0·1571(4)	0·4105(2)	0·8703(3)	44(2)
	C(3B)	0·3685(7)	0·6064(4)	1·1997(4)	46(3)
	C(4B)	0·4545(6)	0·6806(3)	1·1316(4)	41(3)
	N(4B)	0·5691(6)	0·7643(3)	1·1850(4)	56(3)
	O(41B)	0·6234(5)	0·8458(3)	1·1273(3)	82(3)
	O(42B)	0·6095(5)	0·7438(3)	1·2830(3)	69(2)
	C(2B)	0·2644(6)	0·5239(4)	1·1495(4)	45(3)
	C(5B)	0·4442(7)	0·6810(4)	1·0148(5)	47(3)
	C(6B)	0·3425(7)	0·5960(3)	0·9653(4)	44(3)

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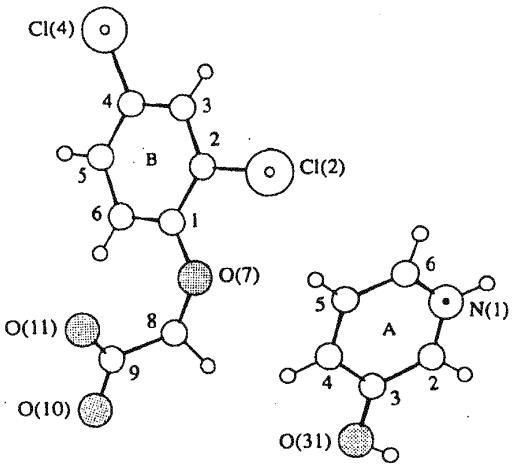


Fig. 1. Molecular conformation and atom naming scheme for the individual molecules in (1). Unless otherwise indicated, atoms are carbons. Hydrogens take the number of the parent atom.

Table 2. Bond distances (Å)

Compound	Atoms	Distance	Atoms	Distance
(1)	C(2A)–N(1A)	1·334(2)	C(6A)–N(1A)	1·335(2)
	C(3A)–C(2A)	1·383(2)	O(3A)–C(3A)	1·332(2)
	C(4A)–C(3A)	1·385(3)	C(5A)–C(4A)	1·372(3)
	C(6A)–C(5A)	1·370(3)	C(2B)–C(1B)	1·394(2)
	C(6B)–C(1B)	1·379(2)	O(7B)–C(1B)	1·362(2)
	Cl(2B)–C(2B)	1·731(2)	C(3B)–C(2B)	1·377(2)
	C(4B)–C(3B)	1·381(3)	Cl(4B)–C(4B)	1·744(2)
	C(5B)–C(4B)	1·375(2)	C(6B)–C(5B)	1·380(3)
	C(8B)–O(7B)	1·428(2)	C(9B)–C(8B)	1·517(2)
	O(10B)–C(9B)	1·255(2)	O(11B)–C(9B)	1·250(2)
(2)	C(2A)–N(1A)	1·362(1)	C(6A)–N(1A)	1·342(2)
	N(21A)–C(2A)	1·315(2)	N(3A)–C(2A)	1·346(1)
	C(4A)–N(3A)	1·323(2)	C(5A)–C(4A)	1·386(2)
	C(6A)–C(5A)	1·357(2)	C(11B)–C(1B)	1·522(2)
	C(2B)–C(1B)	1·396(2)	C(6B)–C(1B)	1·396(1)
	O(11B)–C(11B)	1·245(1)	O(12B)–C(11B)	1·234(1)
	N(2B)–C(2B)	1·475(1)	C(3B)–C(2B)	1·377(2)
	O(21B)–N(2B)	1·220(1)	O(22B)–N(2B)	1·219(1)
	C(4B)–C(3B)	1·376(2)	N(4B)–C(4B)	1·470(1)
	C(5B)–C(4B)	1·368(2)	O(41B)–N(4B)	1·217(1)
	O(42B)–N(4B)	1·221(1)	C(6B)–C(5B)	1·380(2)
	N(6B)–C(6B)	1·469(1)	O(61B)–N(6B)	1·210(1)
	O(62B)–N(6B)	1·203(1)		
(3)	N(2A)–N(1A)	1·386(5)	C(5A)–N(1A)	1·295(6)
	C(3A)–N(2A)	1·325(5)	N(31A)–C(3A)	1·303(6)
	N(4A)–C(3A)	1·348(5)	C(5A)–N(4A)	1·365(7)
	C(11B)–C(1B)	1·516(6)	C(2B)–C(1B)	1·400(6)
	C(6B)–C(1B)	1·372(6)	O(21B)–C(11B)	1·257(5)
	O(22B)–C(11B)	1·250(5)	C(4B)–C(3B)	1·358(7)
	C(2B)–C(3B)	1·397(7)	N(4B)–C(4B)	1·479(6)
	C(5B)–C(4B)	1·379(7)	O(41B)–N(4B)	1·216(6)
	O(42B)–N(4B)	1·225(6)	C(6B)–C(5B)	1·399(7)

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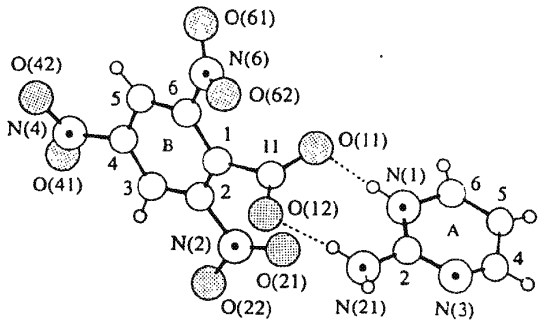


Fig. 2. Molecular conformation and atom naming scheme for (2).

Table 3. Bond angles (degrees)

Compound	Atoms	Angle	Atoms	Angle
(1)	C(6A)–N(1A)–C(2A)	122·1(2)	C(3A)–C(2A)–N(1A)	120·3(2)
	O(3A)–C(3A)–C(2A)	122·3(2)	C(4A)–C(3A)–C(2A)	118·1(2)
	C(4A)–C(3A)–O(3A)	119·5(2)	C(5A)–C(4A)–C(3A)	120·1(2)
	C(6A)–C(5A)–C(4A)	119·5(2)	C(5A)–C(6A)–N(1A)	119·8(2)
	C(6B)–C(1B)–C(2B)	118·2(2)	O(7B)–C(1B)–C(2B)	116·3(1)
	O(7B)–C(1B)–C(6B)	125·5(1)	Cl(2B)–C(2B)–C(1B)	118·9(1)
	C(3B)–C(2B)–C(1B)	121·7(2)	C(3B)–C(2B)–Cl(2B)	119·4(1)
	C(4B)–C(3B)–C(2B)	118·5(2)	Cl(4B)–C(4B)–C(3B)	119·6(1)
	C(5B)–C(4B)–C(3B)	129·9(2)	C(5B)–C(4B)–Cl(4B)	119·5(1)
	C(6B)–C(5B)–C(4B)	119·9(2)	C(5B)–C(6B)–C(1B)	120·8(2)
	C(8B)–O(7B)–C(1B)	117·5(1)	C(9B)–C(8B)–O(7B)	115·7(1)
	O(10B)–C(9B)–C(8B)	115·3(2)	O(11B)–C(9B)–C(8B)	119·4(1)
	O(11B)–C(9B)–O(10B)	125·2(2)		
(2)	C(6A)–N(1A)–C(2A)	121·0(1)	N(21A)–C(2A)–N(1A)	119·1(1)
	N(3A)–C(2A)–N(1A)	120·9(1)	N(3A)–C(2A)–N(21A)	120·1(1)
	C(4A)–N(3A)–C(2A)	117·1(1)	C(5A)–C(4A)–N(3A)	124·4(1)
	C(6A)–C(5A)–C(4A)	116·6(1)	C(5A)–C(6A)–N(1A)	119·9(1)
	C(2B)–C(1B)–C(11B)	123·2(1)	C(6B)–C(1B)–C(11B)	122·2(1)
	C(6B)–C(1B)–C(2B)	114·6(1)	O(11B)–C(11B)–C(1B)	115·5(1)
	O(12B)–C(11B)–C(1B)	116·1(1)	O(12B)–C(11B)–O(11B)	128·4(1)
	N(2B)–C(2B)–C(1B)	118·7(1)	C(3B)–C(2B)–C(1B)	124·3(1)
	C(3B)–C(2B)–N(2B)	117·0(1)	O(21B)–N(2B)–C(2B)	117·9(1)
	O(22B)–N(2B)–C(2B)	117·2(1)	O(22B)–N(2B)–O(21B)	124·9(1)
	C(4B)–C(3B)–C(2B)	117·1(1)	N(4B)–C(4B)–C(3B)	119·0(1)
	C(5B)–C(4B)–C(3B)	122·5(1)	C(5B)–C(4B)–N(4B)	118·4(1)
	O(41B)–N(4B)–C(4B)	117·8(1)	O(42B)–N(4B)–C(4B)	117·4(1)
	O(42B)–N(4B)–O(41B)	124·7(1)	C(6B)–C(5B)–C(4B)	117·9(1)
	C(5B)–C(6B) C(1B)	123·5(1)	N(6B)–C(6B)–C(1B)	119·9(1)
	N(6B)–C(6B)–C(5B)	116·6(1)	O(61B)–N(6B)–C(6B)	118·4(1)
	O(62B)–N(6B)–C(6B)	118·6(1)	O(62B)–N(6B)–O(61B)	123·1(1)
(3)	C(5A)–N(1A)–N(2A)	102·7(4)	C(3A)–N(2A)–N(1A)	112·4(3)
	N(31A)–C(3A)–N(2A)	126·9(4)	N(4A)–C(3A)–N(2A)	105·5(3)
	N(4A)–C(3A)–N(31A)	127·6(4)	C(5A)–N(4A)–C(3A)	106·7(4)
	N(4A)–C(5A) N(1A)	112·6(4)	C(2B) C(1B)–C(11B)	119·2(4)
	C(6B)–C(1B)–C(11B)	120·3(4)	C(6B)–C(1B)–C(2B)	120·4(4)
	O(21B)–C(11B)–C(1B)	117·2(4)	O(22B) C(11B)–C(1B)	118·6(4)
	O(22B)–C(11B) O(21B)	124·2(4)	C(2B) C(3B)–C(4B)	118·7(4)
	N(4B)–C(4B)–C(3B)	118·5(4)	C(5B) C(4B)–C(3B)	123·9(4)
	C(5B)–C(4B)–N(4B)	117·6(4)	O(41B)–N(4B)–C(4B)	118·1(4)
	O(42B)–N(4B)–C(4B)	118·0(4)	O(42B)–N(4B)–O(41B)	123·9(4)
	C(3B)–C(2B)–C(1B)	119·0(4)	C(6B)–C(5B)–C(4B)	116·9(4)
	C(5B)–C(6B)–C(1B)	121·0(5)		

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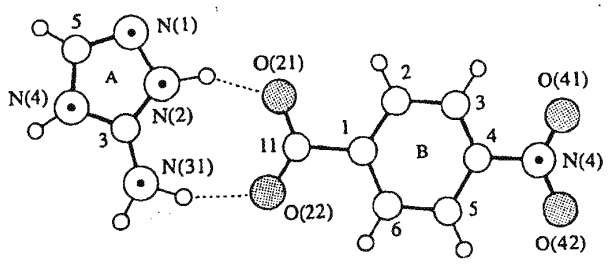


Fig. 3. Molecular conformation and atom naming scheme for (3).

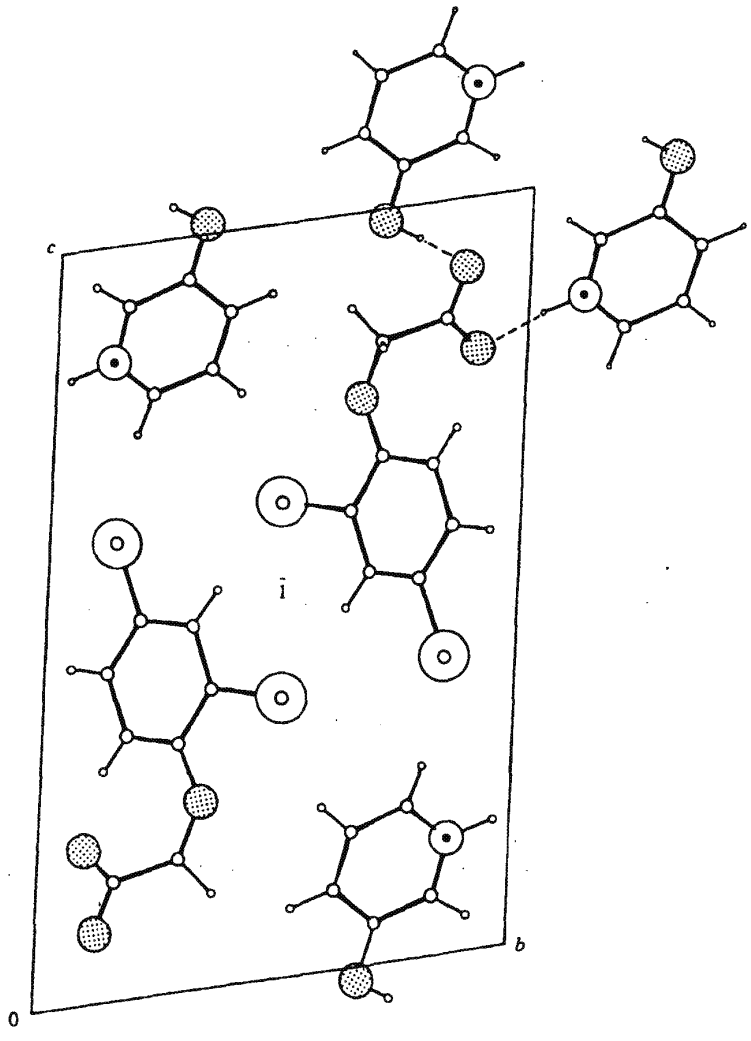


Fig. 4. Packing of (1) in the unit cell viewed down *a*.

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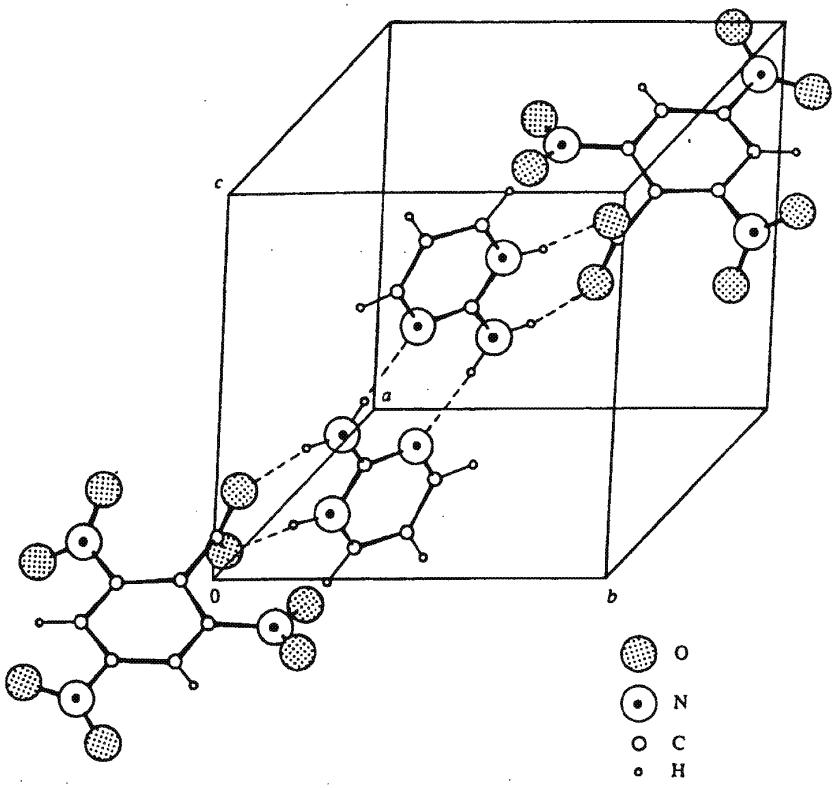


Fig. 5. Perspective view of the packing of (2) in the unit cell.

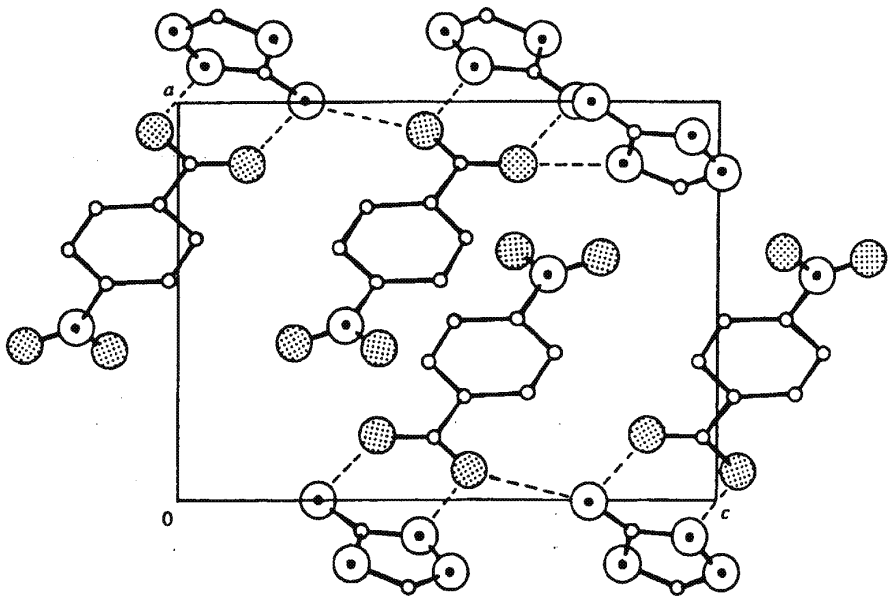


Fig. 6. Packing of (3) in the unit cell viewed down *b*.

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complexes (1)–(3)] gave residuals* R 0·026 (1), 0·033 (2), 0·040 (3) and R_w 0·030 (1), 0·044 (2), 0·044 (3). The values of B in the weighting scheme $w = (\sigma^2 F_o + B F_o^2)^{-1}$ were $4{\cdot}8\times10^{-4}$ (1), $2{\cdot}3\times10^{-2}$ (2) and $1{\cdot}7\times10^{-3}$ (3). Hydrogens were located by difference methods and both positional and thermal parameters were refined. A solution for the structure of (4) was obtained but could not be refined to less than R 0·33. The failure to obtain convergence was considered to be a consequence of poor resolution between mid to high angle reflections because of the 45 Å axis and the use of Mo Kα radiation. No results are presented for this compound beyond a qualitative interpretation of the cocrystal stoichiometry and the intermolecular associations.

Results

Final atomic coordinates for adducts (1)–(3) are given in Table 1 while bond distances and angles are listed in Tables 2 and 3. Lists of anisotropic thermal parameters, observed and calculated structure factors, hydrogen atom coordinates, torsion angles, and infrared spectra for all compounds have been deposited as an Accessory Publication.† The atom numbering schemes for the two associated molecule types in complexes (1)–(3) are shown in Figs 1–3.

Discussion

[(2,4-d)(3-hp)] (1)

The 1:1 complex of (2,4-dichlorophenoxy)acetic acid with 3-hydroxypyridine [(2,4-d)(3-hp)] (1) conforms to the packing mode already described in the adduct of 2,4,6-trinitrobenzoic acid (tnba) and 3-hp.[5] The carboxylic acid proton is located on the pyridine nitrogen (Fig. 1), giving a single NH···O hydrogen bond [N(1A)···O(11B), 2·60 Å: x, y, $1-z$] [graph set D[12]]. Unlike that in the [(tnba)(3-hp)] complex, the hydroxy group interacts with the other carboxylic oxygen [O(3A)···O(10B), 2·55 Å: $-x$, $1-y$, $1-z$: graph set D]. These two interactions

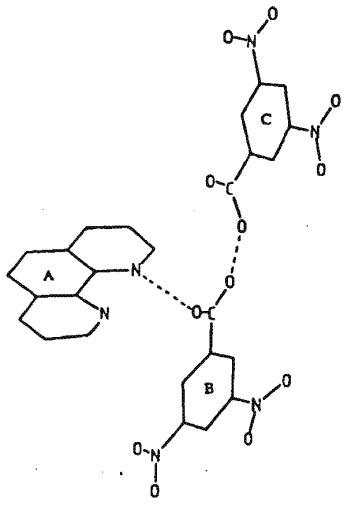


Fig. 7. Diagrammatic representation of the molecular configuration for (4). Hydrogen bonds are indicated as dashed lines.

* $R = \sum ||F_o| - |F_c|| / \sum |F_o|$ and $R_w = (\sum w||F_o| - |F_c||^2 / \sum w|F_o|)^{1/2}$.

† Copies are available from the Australian Journal of Chemistry, P.O. Box 89, East Melbourne, Vic. 3002.

[12] Etter, M. C., *Acc. Chem. Res.*, 1990, **23**, 120.

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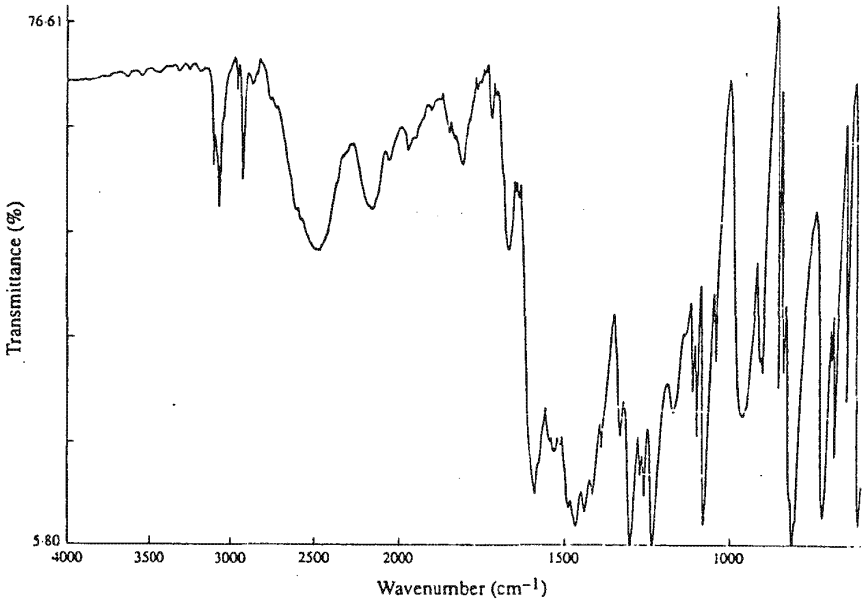


Fig. 8. The infrared spectrum of [(2,4-d)(3-hp)] (1).

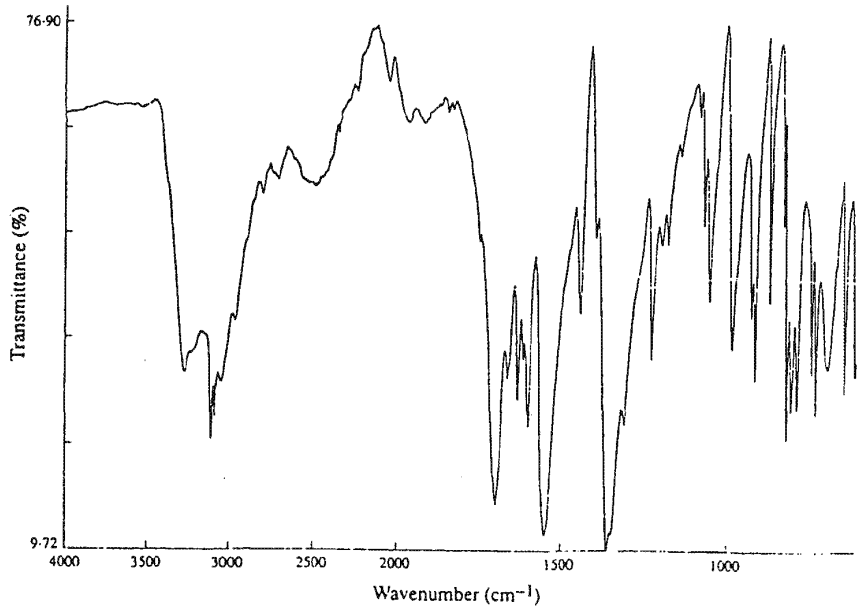


Fig. 9. The infrared spectrum of [(tnba)(2-ap)] (2).

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form a hydrogen-bonded spiral down the *a* axis [graph set C(9)] (Fig. 4). Typically the 2,4-d molecule in (1) is non-planar [torsion angles: C(2)–C(1)–O(7)–C(8), −165·7°; C(1)–O(7)–C(8)–C(9), −81·2°; O(7)–C(8)–C(9)–O(11), +0·3°] which is observed not only in the parent acid[13] [torsion angles: −179·1, −80·4 and +173·1°, respectively] but also in a 1:1 adduct of 2,4-d with triphenylphosphine oxide[2] [(2,4-d)(tppo)] [torsion angles: −176·6, +85·4, +176·3°, and −175·4, +77·2, −175·4°, respectively, for the two independent molecules].

[(tnba)(2-ap)] (2)

The associative mode found in the 1:1 adduct of 2,4,6-trinitrobenzoic acid with 2-aminopyrimidine [(tnba)(2-ap)] (Fig. 2) is similar to that found in the adduct of succinic acid (sa) and 2-ap.[14] This comprises an eight-membered heteromolecular ring [graph set $R_2^2(8)$]. The only difference in (2) is that the carboxylic acid protonates the adjacent hetero nitrogen of the pyrimidine ring. This also occurs with the oxalic acid/2-ap cocrystal.[15] Hydrogen-bonding interactions [N(1A)···O(11B), 2·67 Å; N(21A)···O(12B), 2·83 Å] are comparable to those in (sa)(2-ap) (2·67, 2·98, and 2·69, 2·96 Å, respectively), while the pyrimidinium dimer distance [N(21A)···N(3A), $-x$, $1-y$, $1-z$] is 3·05 Å (Fig. 5). The increased size and rigidity of tnba may be responsible for the slightly increased distances, compared with succinic acid.

[(nba)(3-at)] (3)

The 1:1 4-nitrobenzoic acid, 3-aminotriazole complex [(4-nba)(3-at)] (3) consists of an eight-membered hetero molecular ring (Fig. 3) [graph set $R_2^2(8)$] similar to [(tnba)(2-ap)] (2) and the adduct of 3,5-dinitrobenzoic acid (dnba) and 3-at.[7] This includes the carboxylic proton located on the adjacent hetero nitrogen N(4). Unlike the (dnba)(3-at) adduct,[7] complex (3) is dimerized through the carboxylic acid group of 4-nba (molecule B) and both the hetero nitrogen, N(2), and amine nitrogen of 3-at (molecule A) [N(2A)···O(21B), 2·71 Å; N(31A)···O(22B), 2·91 Å]. Another interaction is found between N(31A) and O(21B) (2·67 Å: x, $\frac{1}{2}-y$, $\frac{3}{2}-z$) which completes a hydrogen-bonded zig-zag polymer down the *c* cell direction [graph set C(6)], while N(4A)···O(22B) (2·68 Å: $-x$, $\frac{1}{2}+y$, $\frac{3}{2}-z$) extends a spiral chain in the *b* cell direction [graph set C(6)] (Fig. 6).

[(dnba)$_2$(phen)] (4)

Although the structure of the 2:1 adduct of 3,5-dinitrobenzoic acid with 1,10-phenanthroline [(dnba)$_2$(phen)] was not successfully refined, a reasonable qualitative interpretation of the molecular associations involved may be made. This structure comprises two almost perpendicular dnba molecules linked by a single hydrogen bond (*c.* 2·5 Å). Another association is found between a dnba acid group and a phenanthroline nitrogen (*c.* 2·7 Å) (Fig. 7). Although hydrogens were not located, it might be expected that an acid proton from the adjacent

[13] Smith, G., Kennard, C. H. L., and White, A. H., *J. Chem. Soc., Perkin Trans. 2*, 1976, 791.
[14] Etter, M. C., Adsmond, D. A., Britton, D., *Acta Crystallogr., Sect. C*, 1990, **46**, 933.
[15] Etter, M. C., personal communication.

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dnba (B) molecule would be located on the phen nitrogen. The basis of this assumption is that phen is commonly protonated,[16] enhancing adduct formation, and that the two dnba molecules would normally be dimerized if both acids were protonated.

[(dnba)(3-hp)] (5)

It is expected that the 1 : 1 3,5-dinitrobenzoic acid adduct with 3-hydroxypyridine would involve molecular associations similar to that in the (tnba)(3-hp) adduct. The difference is that the acid group of dnba is coplanar with the ring while on tnba it is non-planar.

[(tnba)(phen)] (6)

There is no other example with which to compare the adduct of 2,4,6-trinitrobenzoic acid with 1,10-phenanthroline (6) but it is expected (from the infrared spectrum) that the carboxylic acid group on tnba has protonated one of the phenanthroline nitrogens. This would result in only one (NH···O) hydrogen bond.

Different chloro-substituted phenoxyacetic acids were chosen because they might be expected to have a similar packing mode to (1). However, none of a series of adducts of these acids with 3-hydroxypyridine has yielded crystals suitable for single-crystal X-ray analysis.

Infrared Spectroscopy

One common aspect of each of these complexes is the zwitterionic form, i.e. N^+H and CO_2^-. These groups are usually present in the α-amino acids, hence their infrared characteristics are well documented. However, the structures in this paper exhibit interzwitterionic molecules, particularly the dimers, which are not found in homo moleculer structures. Protonated tertiary amines absorb in the 2000–2500 cm^{-1} region with medium to broad bands, due to overtones and combinations.[17] Carboxylate ions have strong antisymmetric and symmetric stretching frequencies between 1610–1550 and 1420–1300 cm^{-1}, respectively. More-distinct carbonyl stretching occurs at higher frequencies ($\geq$1700 cm^{-1}). Complexes (1), (5) and (7), as well as [(tnba)(3-hp)], which have a characteristic single directed hydrogen bond, each display similar infrared spectral features (see Fig. 8). A number of medium broad peaks between 2500 and 1800 cm^{-1} are observed, indicating N^+–H stretching. No significant carbonyl peak ($\geq$1700 cm^{-1}) is present in any of the spectra. The carboxylate peaks range from 1560 to 1590 cm^{-1}, and from 1330 to 1350 cm^{-1}. Each spectrum also has a medium to weak peak between 1610 and 1670 cm^{-1} due to the amine salt. Complexes (2) and (3) also have all of these peaks as well as a strong peak at 1694 cm^{-1}. This peak is characteristic of the complexes which have hydrogen-bonded cyclic interactions between carboxylate groups (Fig. 9).

The spectra of complexes (4) and (6) show carboxylate group frequencies (1550 and 1350 cm^{-1}) but do not convincingly show amine salt peaks in the

[16] Shklover, V. E., Struchkov, Yu T., Gubarova, L. I., and Voronkov, M. G., *Zh. Struckt. Kim.*, 1987, **28**, 118.

[17] Williams, D. H., and Fleming, I., 'Spectroscopic Methods in Organic Chemistry' 2nd Edn, pp. 35–73 (McGraw Hill: London 1973).

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2000–2500 cm^{-1} region. Complex (4) has a carbonyl peak (1700 cm^{-1}) due to the second dnba molecule, while (6) has no strong peak in this region. This would indicate that the acid group in (6) is deprotonated. Both spectra show other peaks that would indicate the presence of an amine salt [1620 (4) and 1650 cm^{-1} (6)].

Acknowledgments

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Supramolecular Synthons in Crystal Engineering—A New Organic Synthesis

Gautam R. Desiraju*

Dedicated to Professor David Y. Curtin and Professor Iain C. Paul

A crystal of an organic compound is the ultimate supermolecule, and its assembly, governed by chemical and geometrical factors, from individual molecules is the perfect example of solid-state molecular recognition. Implicit in the supramolecular description of a crystal structure is the fact that molecules in a crystal are held together by noncovalent interactions. The need for rational approaches towards solid-state structures of fundamental and practical importance has led to the emergence of crystal engineering, which seeks to understand intermolecular interactions and recognition phenomena in the context of crystal packing. The aim of crystal engineering is to establish reliable connections between molecular and supramolecular structure on the basis of intermolecular interactions. Ideally one would like to identify substructural units in a target supermolecule that can be assembled from logically chosen precursor molecules. Indeed, crystal engineering *is* a new organic synthesis, and the aim of this article is to show that rather than being only nominally relevant to organic chemistry, this subject is well within the mainstream, being surprisingly similar to traditional organic synthesis in concept. The details vary because one is dealing here with intermolecular interactions rather than with covalent bonds; so this article is divided into two parts. The first is concerned with strategy, highlighting the conceptual relationship between crystal engineering and organic synthesis and introduces the term *supramolecular synthon*. The second part emphasizes methodology, that is, the chemical and geometrical properties of specific intermolecular interactions.

Keywords: crystal engineering · hydrogen bonding · molecular recognition · organic synthesis · supramolecular chemistry

Par ma foi! il y a plus de quarante ans que je dis de la prose sans que j'en susse rien.[**]
Molière

1. Introduction

Chemistry constantly seeks analogies and connections and supramolecular chemistry has grown into a distinct field around Lehn's analogy that "supermolecules are to molecules and the intermolecular bond what molecules are to atoms and the covalent bond".[1] This analogy represents a departure from classical chemical thought in that it discards the notion that the molecular structure of an organic substance embodies all of its chemical and physical properties.[2–4] Supermolecules are not just collections of molecules; their structure and characteristic properties are distinct from the aggregate properties of the constituent molecular species.[5] Of course, the hydrogen bond has always been recognized by organic chemists as being significant, especially in biomolecular structures,[6] and it is known that the strongest intermolecular interactions are stronger than the weakest of covalent bonds.[7] However, in general it has been felt that the aims of supramolecular chemistry fall somewhat outside the mainstream of organic chemistry.[8]

Structural chemists and crystallographers have, however, been quick to realise that a crystal of an organic compound is the perfect supermolecule,[9, 10] according to Dunitz "a supermolecule par excellence", an assembly of literally millions of molecules self-crafted by mutual recognition at an "amazing level of precision".[11] If molecules are built by connecting atoms with covalent bonds, solid-state supermolecules (crystals) are built by connecting molecules with intermolecular interactions. So, the supramolecular equivalents of structural isomers are crystalline polymorphs, and the solid-state topochemical photodimerization of cinnamic acids a very good example that relates polymorphism (in the reactant) with structural isomerism (in the product).[12] Continuing the analogy further, a molecular isomerization may be compared with a phase transition and stereoisomers with enantiomorphous crystals. Again, disorder in a topochemically reactive crystal finds a molecular parallel in alternative reaction pathways.[13] Homology is not a

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[**] With regard to organic synthesis, the practitioner of crystal engineering today seems to be in the position of M. Jourdain in "Le Bourgeois Gentilhomme" when he exclaims, "I've been talking prose for the last forty years and have never known it!"

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property restricted to molecules alone, and crystalline homologous series have been identified in which patterns of intermolecular interactions (rather than patterns of covalent bonds) are systematically graded; typical examples are benzene, naphthalene and anthracene, or alternatively, benzene, biphenyl, terphenyl.[14]

Given this background, it is instructive to consider the subject of crystal engineering, which has been defined as "the understanding of intermolecular interactions in the context of crystal packing and in the utilisation of such understanding in the design of new solids with desired physical and chemical properties".[15] Crystal engineering is concerned with the systematic architecture of crystal structures.[16] This architecture is governed by the rules of supramolecular valence, that is, by the chemistry and geometry of the intermolecular interactions, which are, in effect, the supramolecular cement.[17] Therefore, if crystals are the supramolecular equivalents of molecules, crystal engineering is the supramolecular equivalent of organic synthesis.

2. General Principles and Strategies

> *... structural units within molecules which can be formed and/or assembled by known or conceivable synthetic operations.*[*]
>
> Corey's definition of a synthon

Targets in organic synthesis are defined in terms of the connectivity of covalent bonds (that is, a molecular structural formula). At a supramolecular level, it should be recognized that targets in crystal engineering are defined in terms of interaction connectivity, that is, in geometrical and topological terms. One aims, for example, at particular patterns such as ribbons, sheets, layers, channels, tubes, and cavities, which may be appropriately functionalized to yield materials that act as templates for subsequent chemical transformations (catalysts, nanostructures, organic zeolites). Alternatively, the desired geometrical pattern may itself be of inherent significance, because it defines a useful physical property (electronic or proton conductivity, ferromagnetism, nonlinear optics).

[*] This and succeeding quotations are taken from Refs. [18, 19].

All crystal structures of organic compounds may be formally depicted as networks with the molecules being the nodes and the intermolecular interactions representing node connections.[5] Therefore, the predictable self-organization of molecules into one-, two-, or three-dimensional networks is of the utmost importance in crystal engineering. For such rational design, hydrogen bonding of the conventional OH ··· O and NH ··· O variety has been the most commonly used supramolecular cement, yet weaker forces such as CH ··· O, CH ··· N, I ··· I, O ··· I, N ··· Cl, or even C ··· H and C ··· C can be used. All these interactions, be they strong or not so strong, are directional—anyway directional enough in combination that the orientation of molecules in the solid can be predicted with a reasonable degree of accuracy. These interactions can be combined by a designed placement of functional groups in the molecular skeleton to generate *supramolecular synthons*, examples of which are shown in Scheme 1.

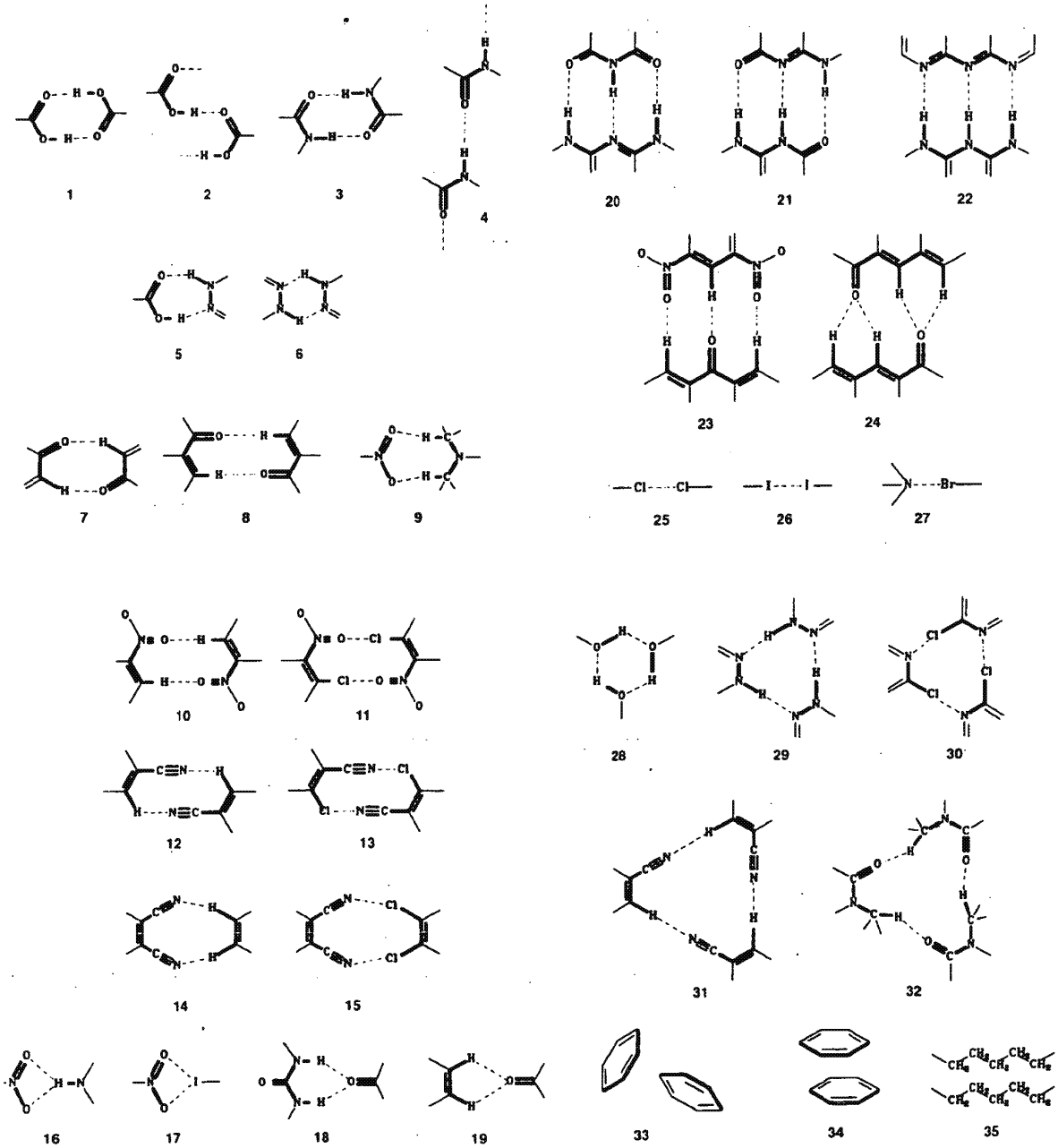
The term "synthon" was introduced by Corey in 1967 in an article entitled "General Methods for the Construction of Complex Molecules".[18] This article was of extraordinary importance in shaping the course of organic synthesis. Corey's definition of a synthon is stated above, and the term was traditionally used to represent key structural features in a target molecule in organic synthesis. In later years the term fell into disuse as explained by Corey himself in 1988[19] and Seebach in 1990,[20] because it degenerated into a descriptor of synthetic intermediates. However, since crystal engineering and an appreciation of the properties of intermolecular interactions are probably today at that stage of sophistication that organic synthesis and an appreciation of the properties of covalent bonds were in the fifties and sixties, and also because the term synthon is so useful in the context of retrosynthetic analysis,[20] the supramolecular counterpart of which is crystallographic database analysis, the term "synthon" has been retained here and used in the manner originally intended. In keeping with modern organic synthetic parlance the term "retron" might have been more appropriate[21] but this is a subjective matter. Corey's definition of a synthon is so general and flexible that more than twenty-five years later it can be used with almost the same connotations but in a supramolecular sense. Thus *supramolecular synthons are structural units within supermolecules which can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interactions*, and crystal engineering is the new

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organic synthesis. To summarize, supramolecular synthons are spatial arrangements of intermolecular interactions and play the same focusing role in supramolecular synthesis that conventional synthons do in molecular synthesis. In effect, the goal of crystal engineering is to recognize and design synthons that are robust enough to be exchanged from one network structure to another, which ensures generality and predictability. Such structural predictability leads, in turn, to the anticipation of one-, two-, and three-dimensional patterns formed with intermolecular interactions. There is a particular relevance of the solid state to this kind of supramolecular chemistry, because many of the weaker interactions are probably deformed if not destroyed in solution. However, the persistent recurrence of patterns mediated by weak forces in crystals indicates that such interactions might still be important in solution for transient processes such as those associated with biomolecular structure and conformation.



Scheme 1. Representative supramolecular synthons.

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2.1. Solid-State Architecture with Supramolecular Synthons

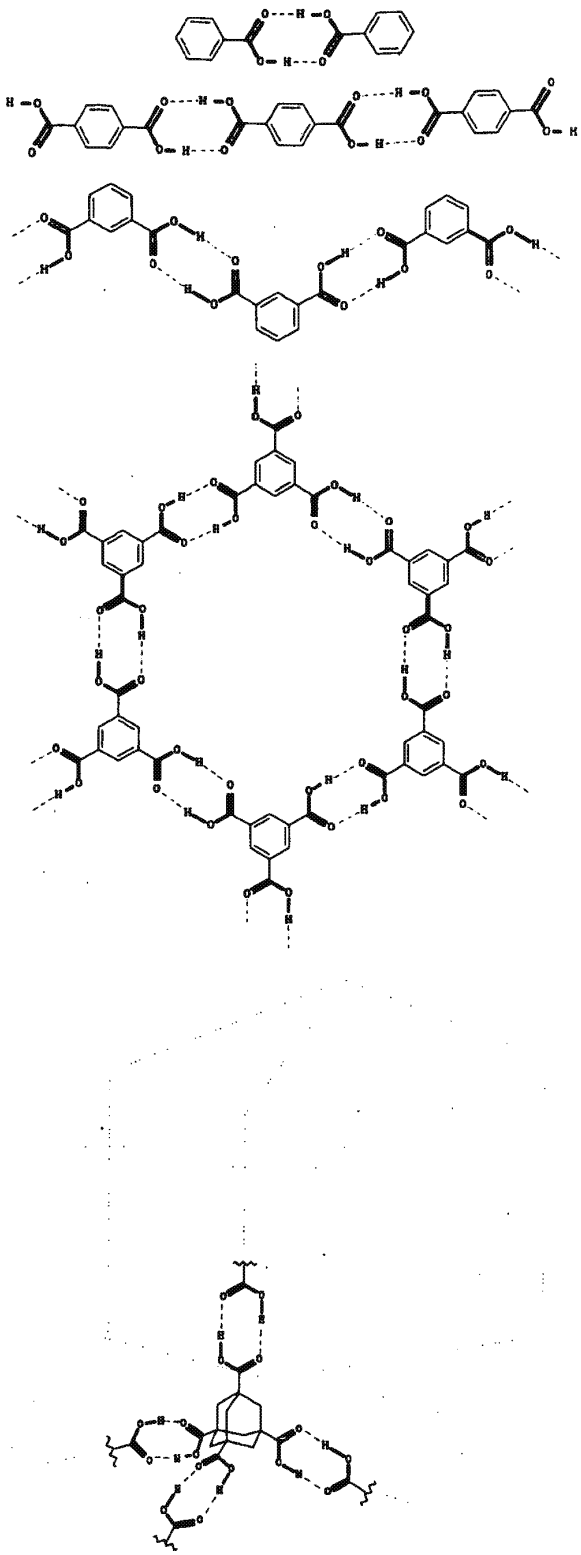
...recognition of some synthons (usually the larger or major synthons) normally is more useful in analysis than that of others.

Scheme 1 shows a variety of supramolecular synthons **1**–**35**, culled from the recent literature. A supramolecular synthon is an identifiable design element and should be, strictly speaking, distinguished from an intermolecular interaction. It must be emphasized that synthons are *derived* from designed combinations of interactions and are *not identical* to the interactions. For example, the carboxyl dimer synthon **1** is assembled with two centrosymmetrically related C=O···HO hydrogen bonds. In still other synthons, for example **33**–**35**, the involvement of the interactions is implicit. Though subtle, this distinction between an interaction and a synthon is real, because supramolecular synthons incorporate *both* chemical and geometrical recognition features of molecular fragments, in other words both explicit and implicit involvement of intermolecular interactions. On occasion, however, when chemistry and geometry are inextricably linked, a single interaction may be regarded as a synthon, for instance Cl···Cl, **25** or N···Br, **27**.

The supramolecular synthon concept is conveniently illustrated in the crystal structures of some aromatic carboxylic acids. Scheme 2 shows how the structures of benzoic, terephthalic, isophthalic, trimesic, and adamantane-1,3,5,7-tetracarboxylic acids (**36**) are built with phenyl rings and dimer synthons **1** in a logical progression. The benzoic acid dimer is zero-dimensional, the linear or crinkled ribbons in the dibasic acid structures are one-dimensional patterns, while the sheet structure in trimesic acid is two-dimensional.[22] The three-dimensional extension of these structures is the diamondoid structure of acid **36**, where synthons **1** are disposed tetrahedrally about the adamantyl nucleus to yield a network that is topologically similar to diamond, in which **1** replaces C–C bonds, and the adamantyl nucleus becomes a super-C atom.[23]

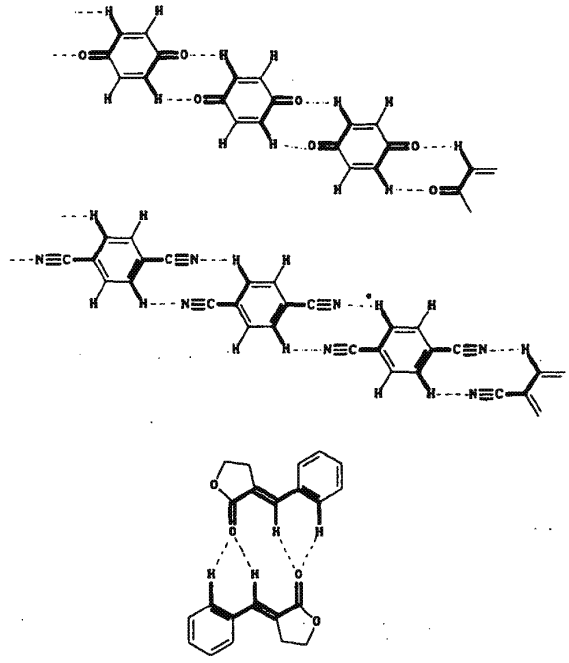
Weaker hydrogen bonding of the CH···X variety may now be considered. Although these bonds have energies only in the 2–20 kJ mol^{-1} range, their effects on crystal structure and packing are just about as predictable as the effects of conventional hydrogen bonding.[24] Scheme 1 includes several CH···X-mediated synthons, and Scheme 3 shows some typical crystal structures based on these synthons. In crystalline 1,4-benzoquinone, the symmetrical disposition of functional groups results in a linear ribbon pattern linked by synthon **7**. This pattern is carried over largely unscathed into the crystal structure of 2-methoxy-1,4-benzoquinone, while the CH···N≡C analogue **12** is observed in 1,4-dicyanobenzene.[25] Another common CH···O synthon **24** is seen in the crystal structure of α-benzylidene-γ-butyrolactone.[26]

A comparison of the crystal structures of solid chlorine and the monoclinic form of 1,4-dichlorobenzene (Fig. 1) is revealing and shows how the supramolecular synthon concept may be extended to lesser known intermolecular interactions.[15] The contacts between the halogen atoms define the Cl···Cl synthon **25** and are virtually identical in the two structures. The aromatic rings in 1,4-dichlorobenzene fulfill a spacer function.



Scheme 2. Construction of aromatic carboxylic acid crystal structures with synthon **1**.

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Scheme 3. Construction of crystal packing patterns with CH···X synthons **7**, **12**, and **24**.

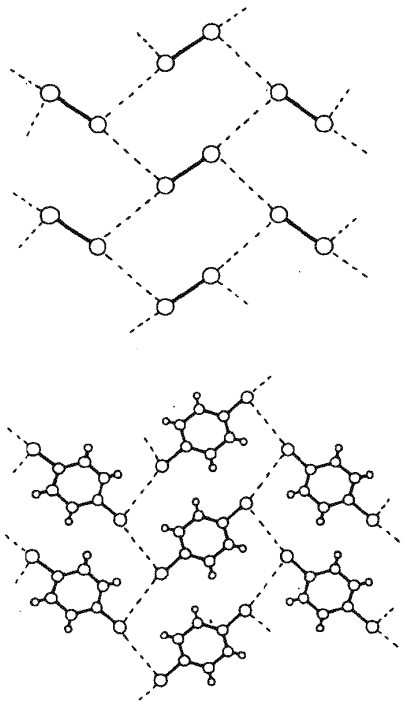


Fig. 1. Similarity between the crystal structures of chlorine (top) and 1,4-dichlorobenzene (bottom). Note the identical disposition of the Cl···Cl synthons **25** in the two cases.

The above examples cannot be exhaustive, but they illustrate the importance of being able to identify structurally significant synthons in a supermolecule. Such identification helps in the analysis of more complex crystal packings and the design of new target structures. These examples also highlight two other important features that should be noted in systematic crystal engineering. These are the following:

1) Consideration of a crystal structure in terms of supramolecular synthons can effect a simplification, which facilitates comparison with other seemingly different crystal structures. Accordingly, different molecular functionalities can result in similar crystal structures provided synthons in the various crystal structures possess shape or topological similarity.

2) The interference between the significant supramolecular synthons should be a minimum. Alternatively, the nature of such interference should be understood so that it may be exploited in the engineering strategy. These features will now be discussed in greater detail.

2.2. Simplification of Crystal Structures

...even in the earliest stages of the process of simplification of a synthetic problem, the chemist must make use of a particular form of analysis which depends on the interplay between structural features that exist in the target molecule...

Kitaigorodskii's close-packing principle implies that molecules undergo a shape simplification as they progress towards dimers, higher aggregates, and ultimately crystals.[27] Shape is a very powerful agent of molecular recognition that in crystals generally proceeds in a way such that supramolecular fragments of a crystal structure have simpler shapes than the constituent molecular species. Accordingly their packing patterns may be easier to predict (see Section 2.8). Molecules in organic crystals are surrounded typically by twelve to fourteen near-neighbors to define quasi-spherical clusters.[28] Similar shape-simplifying effects are seen in Rebek's "tennis ball" dimer,[29] and the tertiary structural features in globular proteins are responsible for converting an exceedingly complicated molecular structure into a nearly spherical unit.[30]

These geometrical consequences of shape recognition can be employed in crystal engineering. A comparison of the crystal structures of benzoic acid and *p*-terphenyl (Fig. 2) is pertinent. Because of the parallel hydrogen bonds in synthon **1**, the shape and size of the benzoic acid dimer mimics that of *p*-terphenyl. The two crystal structures are not identical but reasonably similar with the same space group $P2_1/n$, comparable cell dimensions and volumes, and most importantly, the benzoic acid dimers are packed together using the same herringbone C···H interactions that exist in *p*-terphenyl.[31] To be sure, there are differences in the two structures but these can be understood and rationalized. For example, *p*-terphenyl molecules are tilted along their molecular lengths to optimize herringbone interactions and form slabs that are themselves aligned parallel to optimize other herringbone interactions. In benzoic acid, the dimers are stacked rather than tilted to form slabs, which are then inclined in a herringbone fashion. Stacking rather than

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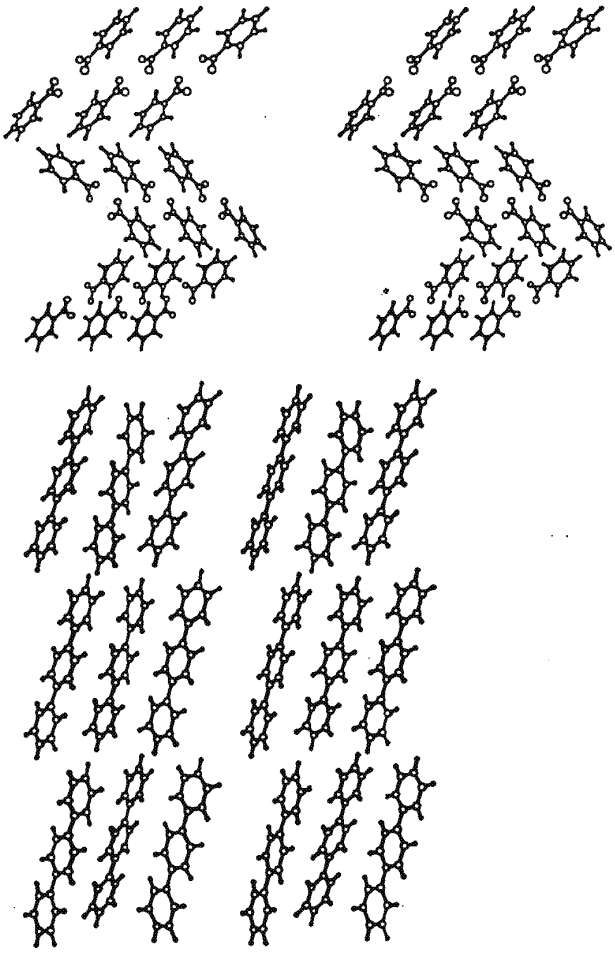
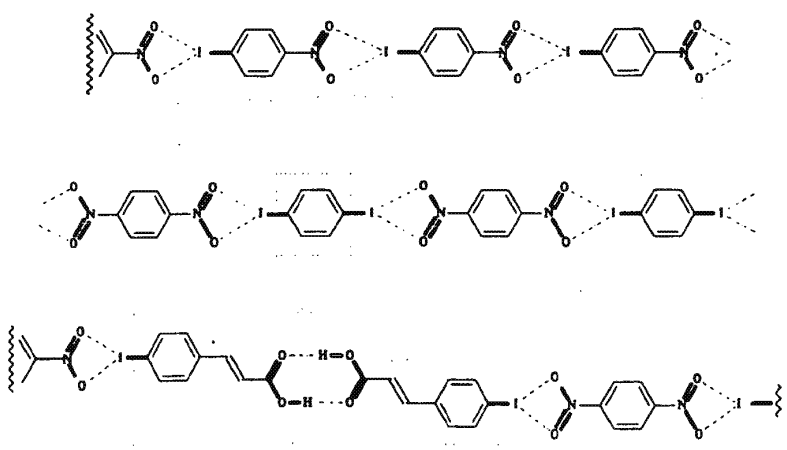


Fig. 2. Stereoviews of the crystal structures of benzoic acid (top) and *p*-terphenyl (bottom), each showing three slab sections. Notice that the benzoic acid dimer mimics the shape of the terphenyl molecule and also the similar herringbone dovetailing between slabs in the two structures.

tilting occurs within the benzoic acid slabs because of the tendency of a phenyl ring to be overlaid on a carboxyl dimer ring.[32] However, the main message is clear—the carboxyl dimer synthon **I** can be used as a surrogate for a 1,4-disubstituted phenyl ring, and it is pertinent to compare this dissection of the benzoic acid dimer supramolecular skeleton with that of the squalene molecular skeleton by Corey.[18]

This strategy can now be used in the design of crystal structures. We found that halogen atoms, especially iodine, tend to form short polarization-induced contacts with nitro groups (synthon **17**) where the oxygen atoms of the nitro group grip the iodine atom in a two-pronged fashion.[33] This synthon was initially introduced in the crystal structure of 4-iodonitrobenzene, where it alternates with the phenyl rings to give a ribbon as expected (Scheme 4).[34] In fact, this molecule has few other crystallization options. The strategy was then extended to the crystal structure of the 1:1 complex of 1,4-dinitrobenzene and 1,4-diiodobenzene where again **17** alternates, but in opposite senses with phenyl rings.[35] At this stage the hydrocarbon spacer between the **17** synthons was extended by crystallizing a 2:1 complex of 4-iodocinnamic acid with 1,4-dinitrobenzene.[34] The carboxyl synthon **1** elongates the (now supramolecular) diiodo moiety, which is then able to link with the nitro moiety through synthon **17**. These results are surprising—acids are known to complex with bases or with other acids but not with neutral compounds; however, in this case the acid dimer behaves effectively like a neutral diiodohydrocarbon because the hydrogen bonding requirements of the monomers are completely satisfied by dimer formation.

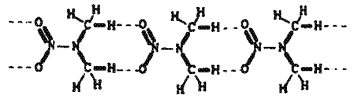
A very similar exercise may be carried out with CH···O hydrogen bonds. Nitro and dimethylamino groups form a CH···O-mediated synthon **9**, and the crystal structure of *N*,*N*-dimethylnitramine is unique in that it consists exclusively of infinite ribbons of this synthon (Scheme 5).[36] The crystal structure of the 1:1 complex of 4-nitrobenzoic acid and 4-(*N*,*N*-dimethylamino)benzoic acid may now be anticipated as a ribbon consisting of synthon **9** alternating with an extended terphenyl surrogate formed by a linking of acid molecules with synthon **1**.[37] To summarize, the crystal packing properties of an aromatic carboxylic acid dimer are distinct from those of the monomer and are more reminiscent of an aromatic hydrocarbon.

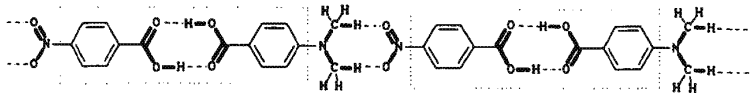


Scheme 4. Use of the iodo···nitro synthon **17** in crystal engineering. Note how the 1,4-disubstituted phenyl ring and the extended carboxylic dimer are similarly employed.

Inherent in structural simplification is a reduction of a crystal structure to its interaction network information. The crystal structure of tetraacid **36** has been described in Section 2.1 in terms of a diamond network with synthons **1** tetrahedrally disposed about the adamantyl skeleton.[23] It is therefore possible to substitute other synthons for **1** on adamantyl or other tetrahedral templates and generate similar diamondoid structures (Fig. 3). Typical examples of such alternative synthons are metal···NC,[38] I···I **26**,[39,40] O–H···N,[41] and the *cis*-amide dimer synthon **3**.[42] We have

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Scheme 5. Use of the dimethylamino ··· nitro synthon 9. The strategy for the design of these structures is similar to that employed for the design of the structures in Scheme 4.

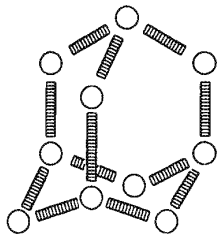


Fig. 3. Archetypical diamondoid network structure. ○ represents a tetrahedral molecular template (for example, adamantyl) and ▥ an appropriate supramolecular synthon.

used the same strategy with the much weaker N···Br synthon **27**;[43] the crystal structure of the 1:1 complex of hexamethylenetetramine (**42**) and CBr_4 contains a tetrahedral arrangement of synthon **27** resulting in a super-ZnS type structure (Fig. 4). That the N···Br and similar interactions are polarization-induced is well-known from the work of Hassel,[44] but their use in crystal engineering strategies is relatively new.[45]

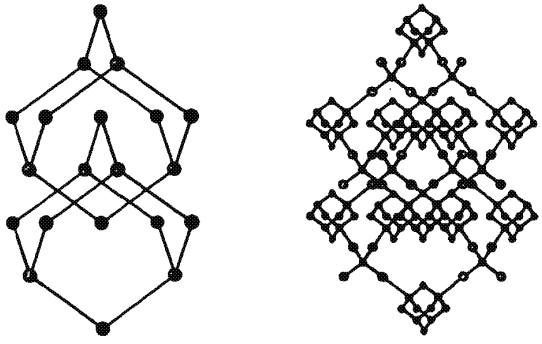


Fig. 4. Schematic (left) and complete (right) representations of the diamondoid network structure of the 1:1 complex hexamethylenetetramine (**42**, blue) and CBr_4 (red). Both intra- and intermolecular bonds are shown as solid lines. The N···Br synthon **27** connects molecules. Notice the catenation of networks and the similarity to Fig. 3.

A recurring theme in crystal engineering is that quite different covalent bond frameworks and chemical functionalities in the monomer building blocks can still result in similar supramolecular (crystal) structures. It has long been known that molecules with similar sizes, shapes, and functionalities have similar crystal structures; this principle of structural mimicry explains, for instance, phenomena such as solid-solution formation.[46] However, a more powerful generalization in the crystal engineering context is that *supramolecular fragments with similar sizes, shapes, and topologies have similar crystal structures*. Such a generalization is more useful, because it recognizes the interchangeability of supramolecular synthons within a particular family of crystal structures.

2.3. Synthon Interference and Structural Robustness

Proximity of reactive functional groups is of major importance in synthesis.

The examples discussed above might imply that supramolecular synthons are completely modular, capable of being introduced, removed, or replaced at will to generate new crystal structures. This would be an ideal, indeed a Utopian situation. However, chemistry is not geometry, and the major challenge in the practice of crystal engineering is that a crystal structure is a compromise, at times quite uneasy, between interactions of varying strengths, directionalities, and distance-dependence properties (see Section 2.9). Indeed, interference between synthons is *the* critical problem in crystal engineering, and structural robustness or the ability to use the same supramolecular synthon in a variety of situations is the key to a successful practice of the subject. A thorough understanding of the several ways in which intermolecular interactions interfere with one another is essential for a predictive control over crystal packing. Interactions in an organic crystal are numerous and weak. At a basic level, one attempts to insulate various types of interactions from one another so that their individual (geometrical) features are manifested more effectively. At a higher level, one can exploit the interfering effects of one interaction type on another to realize a supramolecular target structure very much as a synthetic chemist would use a neighboring or proximal group effect.

A discussion of structural robustness begins again with the carboxyl dimer synthon **1**. Generally, aliphatic and aromatic carboxylic acids RCO_2H adopt this dimer pattern in crystals, because its stability and packing efficiency are largely unaffected by the nature of the R group.[32] The robustness of **1** is revealed by considering the packing preferences of the patterns in Scheme 2. In benzoic, isophthalic, and terephthalic acids, the dimers and ribbons can close-pack without complications. In trimesic acid, however, the "holes" in the hexagonal hydrogen-bonded patterns pose a packing problem, which is solved by inclusion of a second molecular species (a guest).[22] This problem of voids is seemingly worse in acid **36**, but Nature solves it in a fascinating way by the catenation of as many as five distinct diamondoid networks.[23] Significantly, the close-packing problems caused by awkwardly shaped networks do not perturb the **1** synthons. However, even such a seemingly robust supramolecular synthon has limits on its use, and we have, in recent years, described four anomalous situations (Fig. 5) in which the centrosymmetric dimer synthon **1**, though expected, is not observed: 1) 4-Chloro- and 4-bromophenylpropiolic acids adopt a variation of the carboxyl catemer synthon **2** (actually 50:50 *syn*:*anti* O=C–OH conformations), while the corresponding cinnamic and benzoic acids adopt synthon **1**. This occurs because the phenylpropiolic acids cannot form CH···O hydrogen bonds.[47] 2) 3,5-Dinitrocinnamic acid forms a carboxylic dimer, but this pattern has two-fold rather than inversion symmetry. This occurs because of the dominance of CH···O bonding.[48] 3) In the 1:1 complex between

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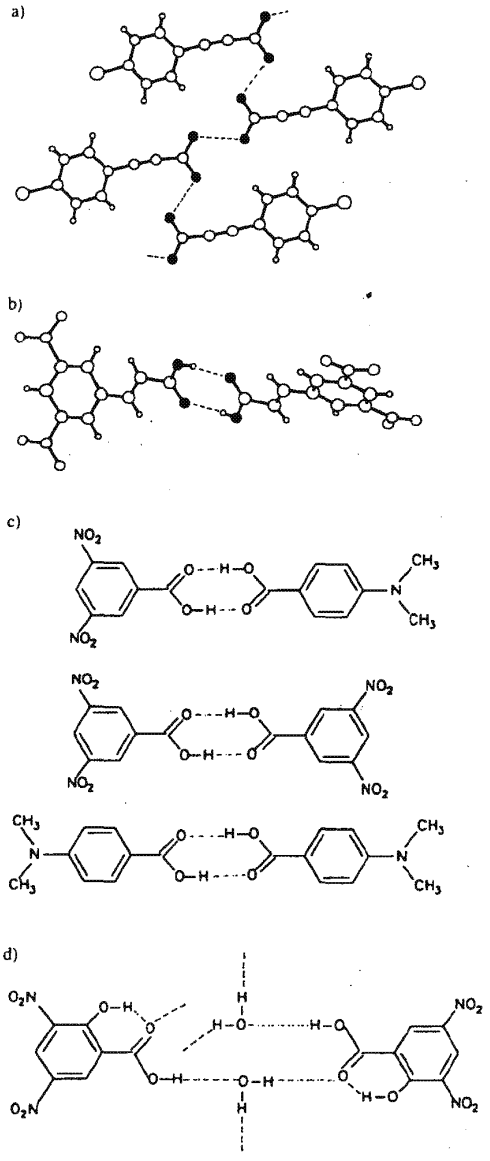


Fig. 5. Anomalously hydrogen-bonded carboxylic acid structures: a) modified catemer synthon **2** in 4-chlorophenylpropiolic acid; b) dimer located on a twofold axis in 3,5-dinitrocinnamic acid; c) observed homodimers (bottom) and unobserved, though expected, heterodimer (top) in the 1:1 complex 3,5-dinitrobenzoic acid and 4-(*N*,*N*-dimethylamino)benzoic acid; d) 3,5-dinitrosalicylic acid monohydrate with interrupting water molecules. In all cases, OH ··· O hydrogen bonds are shown as dashed lines.

3,5-dinitrobenzoic acid and 4-(*N*,*N*-dimethyl)aminobenzoic acid, homodimers are formed between like acids rather than the expected heterodimers between unlike acid monomers. This occurs because of the importance of $\pi \cdots \pi$ interactions.[49] 4) Unlike other salicylic acids, which adopt the dimer pattern, 3,5-dinitrosalicylic acid crystallizes as a hydrate in which hydrogen-bonded water molecules interrupt the dimer network.[50]

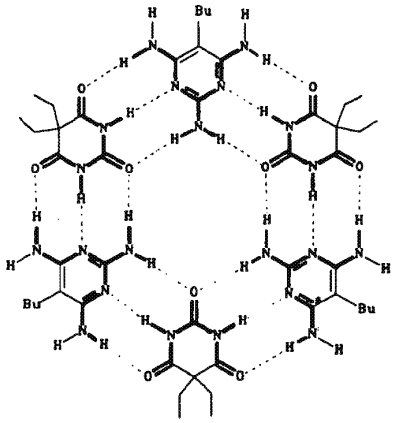
Multipoint recognition of functional groups is expected to improve synthon robustness as in the triply hydrogen-bonded synthon **20**, which has been used by Lehn, Whitesides, Kunitake, Ringsdorf, and others.[51] The relationship of **20** to recognition patterns between nucleotide bases in DNA is unmistakable. The existence of three hydrogen bonds in **20** (rather than two bonds in, say, synthon **1**) means that it can be used to construct more intricate supramolecular structures. For example, **20** is a constituent of the rosette structures **37**–**39** in Scheme 6. Such rosettes themselves occur within the proposed infinite network structure of the 1:1 complex of cyanuric acid and melamine.[52] Rosettes **37**–**39** are supermolecules of intermediate hierarchy (see Section 4) in that they consist of a finite number of molecules and have become attractive goals in what is perhaps one of the first examples of a target-oriented supramolecular synthesis. While synthon **20** is quite robust, it can align with itself through further hydrogen bonding in at least three distinct ways to yield, in Whitesides's terminology, a linear tape, a crinkled tape, and the desired rosette.[53] Two possible approaches to the rosette have been described. Lehn et al. found that the molecular complex of 5,5-diethylbarbituric acid and 5-*n*-butylpyrimidine-2,4,6-triamine contains a linear tape pattern rather than **37**. Cocrystallization of unsymmetrical precursors was expected to yield rosette **38**, but the compounds crystallized separately instead.[54] Whitesides and co-workers, on the other hand, employed bulky *tert*-butyl substituents on the amine component. The buttressing effects of these groups disfavor linear and crinkled patterns for steric reasons, leading successfully to rosette **39**.[55] Further attempts to synthesize similar rosette structures based on hydrogen bonding[56] and other types of interactions are anticipated, but already a certain sophistication in the manipulation of supramolecular synthons is apparent, and the resemblance to logic-directed organic synthesis is clearly discernible.[57] As our knowledge about intermolecular forces increases, there can be no doubt that complex supramolecular structures will be synthesized with increasing reliability and regularity.

2.4. Subjectivity in Synthon Choice

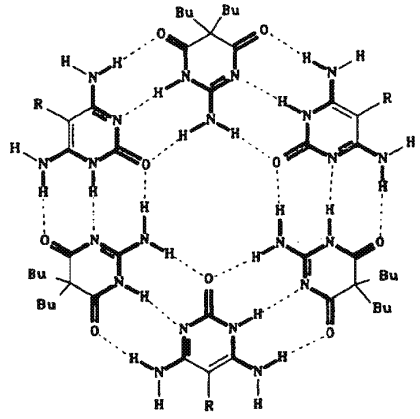
The recognition of synthons within molecules is purely a utilitarian device; the derivation of all possible synthons in a molecule may never be required.

The dissection of a crystal structure and the identification of particular supramolecular synthons within it is entirely subjective. A variety of patterns may be derived from any given structure and none of these are fundamentally more significant than the others. Rather, all of them assist in what is hopefully a better comprehension of the crystal structure and better methods for the systematic design of related structures. The same intermolecular interaction may be a constituent of several overlapping supramolecular synthons. Assessments of the "significance" of a particular supramolecular synthon are related to the question of structure simplification and could be quite arbitrary. For instance, in the iodo–nitro structures discussed in Section 2.2, it is arguable whether synthon **1** or **17** is the more significant.

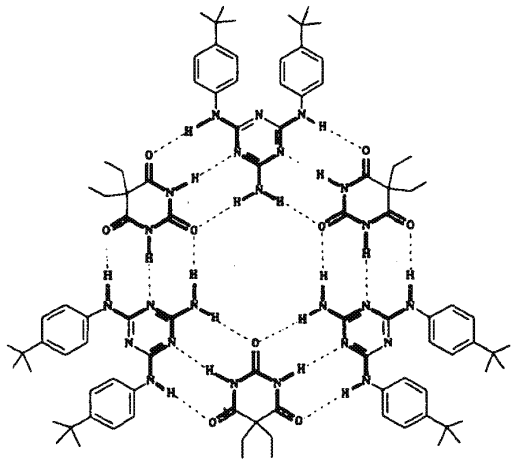
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37



38 (R = C_8H_{17})



39

Scheme 6. Target rosette structures: 37, 38 (not observed); 39 (observed). The synthons are highlighted. Notice the slightly different synthon structure in 38.

It is particularly appropriate here to discuss the aryl···aryl synthons 33 and 34, which are based, respectively, on herringbone and stacking modes of association of aromatic rings,[58] and the hydrophobic synthon 35. The geometries of 33 and 34 are well-defined and occur in thousands of structures. If one were to assign significance to supramolecular synthons on the basis of specific interaction strengths, these synthons might not rank very high. However, it is known that they play an important role in determining stable crystal packing arrangements characterized by sparing solubility and high crystallinity.[59] Figure 6 shows the crystal structures of benzene and 2-amino-

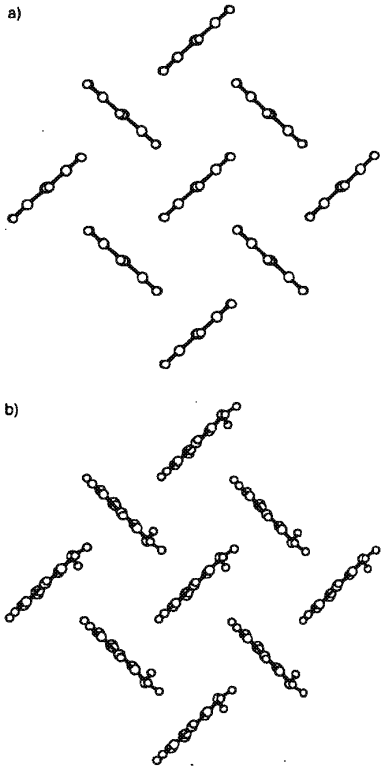


Fig. 6. Comparison of the crystal structures of benzene (top) and 2-aminophenol (bottom). Note the almost identical arrangement of phenyl rings (synthon 33) in the two structures.

phenol. The latter structure contains alternating polar and apolar bilayers. The structure of the apolar layer is almost identical to the benzene structure with aromatic rings mutually perpendicular. The identification of synthon 33 in both these structures confirms their close relationship.[60] The nature of aryl···aryl stacking interactions, as manifested in synthon 34, has also been the subject of intensive studies, and their utilization in crystal engineering depends on the well-known proclivity of planar π donors and acceptors to form overlapped layered structures.[61] Hydrophobic effects are revealed by the appearance of synthons such as 35 and have been exploited in the design of monolayer structures.

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2.5. Conventional and Exotic Interactions

. . . it may be desirable to attempt a synthesis by the use of new reactions if a great simplification can result or if there is simply no alternative.

Reactions are used in organic synthesis to make covalent bonds, and if structural transformations are to be reliable and efficient, such reactions should evidently be of known mechanism and scope. In the supramolecular context, one would like to use interactions of known directionalities, which can be combined to give structurally robust synthons. Not surprisingly, many current studies in crystal engineering are centered around conventional hydrogen bonding of the OH···O or the NH···O type. But just as organic synthesis progressed by the study of new and (at the time) exotic reaction types, crystal engineering is also amenable to the use of lesser known or weaker and possibly less directional interactions. Gratifyingly, it appears that these weaker interactions are just as effective, especially if they are used in multipoint recognition.

A recent example of the use of CH···O interactions in supramolecular design is provided by the complexation of 1,3,5-trinitrobenzene with dibenzylidene ketones.[62] The target synthon **23** is obtained by replacing the conventional hydrogen bonds in **20** with CH···O hydrogen bonds. The precursor molecular components suggest themselves naturally, and **23** is obtained in the crystal structures of the molecular complexes formed by either 1,3,5-trinitrobenzene or picryl chloride with either dibenzylideneacetone or 2,5-dibenzylidenecyclopentanone (Fig. 7). Reference has already been made to diamondoid structures assembled with I···I synthons (**26**) and N···Br synthons (**27**, Section 2.2, Fig. 4).[39, 40, 43] The scope of ionic interactions in crystal engineering studies is only just beginning to be realized. The structures of organic malates and tartrates, for example, contain strongly hydrogen-bonded networks that are robust in two dimensions, permitting other structural variations in the third dimension.[63]

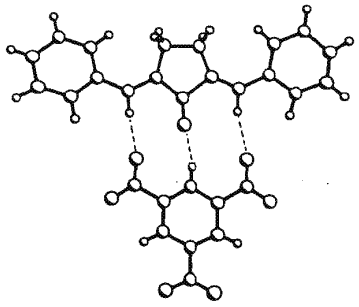


Fig. 7. CH···O-mediated recognition (synthon **23**) in the 1:2 molecular complex formed between 2,5-dibenzylidenecyclopentanone and 1,3,5-trinitrobenzene. Only one of the two symmetry-independent trinitrobenzene molecules is shown.

Conventional hydrogen bonding continues to be used in new and ingenious ways.[64] Two recent reports are based on the complementarity of the hydrogen-bonding capabilities of the OH and NH_2 groups. Ermer and Eling have pointed out that while an OH group has one hydrogen bond donor and two acceptors, an NH_2 group has two donors and one acceptor.[65] Accordingly, compounds or complexes that contain equal stoichiometric amounts of these groups are likely to have highly organized hydrogen-bonded networks with a tetrahedral environment about the O and N atoms. Ermer and Eling have utilized this fact in the design of several diphenol–diamine complexes. Hanessian et al. have discussed the crystal structure of the 1:1 complex between *trans*-1,2-cyclohexanediol and *trans*-1,2-diaminocyclohexane while recognizing again that half of the heteroatoms are fully tetracoordinated.[66]

In general, one may expect to witness several new and exciting developments in the systematic engineering of crystal structures based on interactions with boron, sulfur, and halogen atoms,[67, 68] on hydrogen bonding of the CH···X[24] and XH···π[69] type (in which X can also perhaps be C), and metal–atom interactions, the latter being, of course, exclusive to organometallic clusters and complexes.[70] These constitute the supramolecular reaction methodologies of the future.

2.6. Knowledge of Other Crystal Structures

Knowledge or enlightened speculation as to the way in which a molecule to be synthesized has previously been brought into existence can be extremely helpful in simplifying a synthetic problem.

As far back as 1961 Hassel commented on the hexagonal, layered network of weak N···Cl interactions (synthon **30**) in the crystal structure of cyanuric chloride,[71] which had been previously reported by Hoppe, Lenné, and Morandi in 1957.[72] More recently we noted that synthons such as **12** are common in cyanoaromatic compounds.[73] These ideas and the knowledge of the linearity of CH···N hydrogen bonds led to the identification of 1,3,5-tricyanobenzene as a potential candidate for the formation of similar hexagonal networks. Cocrystallization with hexamethylbenzene proved serendipitous, for the 1:1 complex of these two compounds contains the desired hexagonal network (synthon **31**; Fig. 8).[74] A comparison of **30** and **31** shows that they are interchangeable with a substitution of the N···Cl interaction by the CH···N interaction.

A knowledge of the 1,3,5-tricyanobenzene–hexamethylbenzene crystal structure leads to the possibility of obtaining similar hexagonal networks with related molecules. Trimethylisocyanurate (**40**) was identified, because it contains only CH···O donor and acceptor groups in its symmetrical framework, and the crystal structure of its 1:1 complex with 1,3,5-trinitrobenzene con-

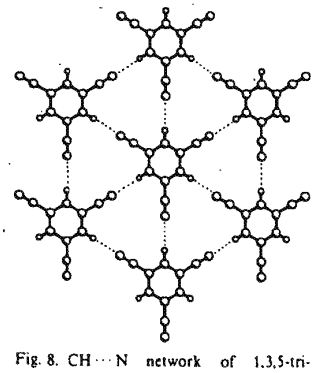


Fig. 8. CH···N network of 1,3,5-tricyanobenzene molecules (synthon **31**) in the crystal structure of the 1:1 complex formed by this substance with hexamethylbenzene. The interleaving hexamethylbenzene network is not shown.

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sists of discrete molecular layers.[75] The layers of **40** are networked into a hexagonal pattern (synthon **32**), while the trinitrobenzene molecules are close-packed in two dimensions to yield another hexagonal pattern (Fig. 9).[76] Most interestingly,

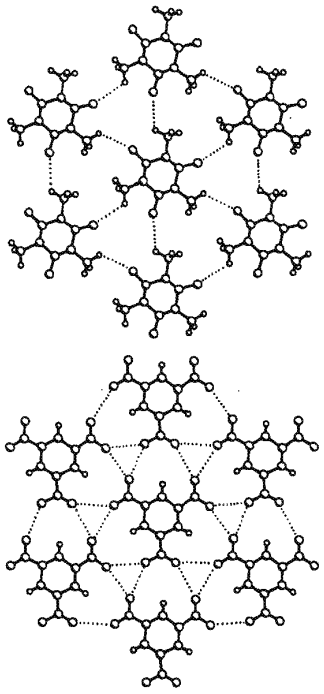
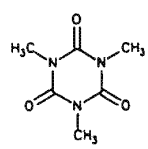


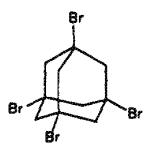
Fig. 9. Hexagonal CH···O network of trimethylisocyanurate (**40**, synthon **32**) (top) and O···O-mediated network of 1,3,5-trinitrobenzene (bottom) in the layered structure of the 1:1 complex formed by these substances.

and unlike the 1,3,5-tricyanobenzene–hexamethylbenzene complex, which is monoclinic, this complex crystallizes in the hexagonal space group $P\bar{6}$; in other words the molecular symmetries have been fully retained in the crystal, a rare and exceptional event (see also Section 2.8). Why this happens is not clear—perhaps it has to do with a certain amount of structural insulation of the layers of **40** and trinitrobenzene, thereby reducing three-dimensional interference.

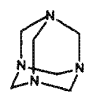
We have observed recently that tetrabromoadamantane (**41**) and hexamethylenetetramine (**42**) form a 1:2 complex in which the molecules of **41** and half those of **42** form a CH···N-mediated diamondoid network related topologically to that in tetraacid **36** (Fig. 10).[77] Instead of catenation as in acid **36**,[23] the other half of the molecules of **42** are clathrated within the



40



41



42

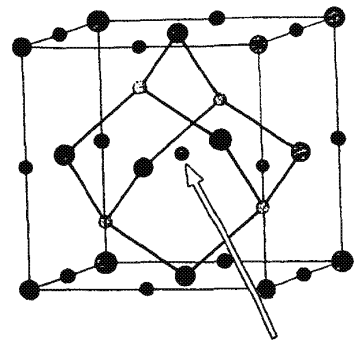


Fig. 10. Organic alloys; a molecule of hexamethylenetetramine (**42**, blue) may be replaced (arrow) by a CBr_4 molecule, leaving the diamondoid CH···N network of **42** (green) and 1,3,5,7-tetrabromoadamantane (**41**, pink) intact.

diamondoid cavities and are disordered. We therefore felt that these clathrated molecules of **42** could be replaced by another molecule of similar shape and size. Accordingly we cocrystallized a 1:1:1 complex of **41**, **42**, and CBr_4. The structure of this ternary complex was exactly as expected. The diamondoid network is retained and the CBr_4 molecules enter the cavities formerly occupied by the disordered molecules of **42**. Interestingly, the CBr_4 molecules are ordered, because they participate in auxiliary Br···Br interactions with the molecules of **41**.

2.7. Supramolecular Retrosynthesis—The Cambridge Structural Database

This is the oldest and most traditional of all synthetic strategies ...

Retrosynthetic analysis in organic synthesis associates synthons, the substructural units in the target structure, with precursor structures in a sequential pathway. This process eventually leads to an identification of one or more potential starting materials.[19, 21] In crystal engineering, target structures are geometrically and topologically defined, and so the equivalent thought process should associate these target networks with precursor molecules that when crystallized will yield appropriate supramolecular synthons that are compatible with the target network structure. Retrosynthetic analysis is at the heart of organic synthesis, because it uses what is known (target structure) to heuristically derive what is unknown (precursor structure). Supramolecular retrosynthesis is of equal importance in crystal engineering and for the same reason. It uses a particular target network and works backwards to identify molecules that by using their intermolecular interactions will crystallize in the target structure.

Traditional retrosynthetic analysis is based on the bedrock of knowledge of the various reactions (covalent bond-making processes) available to the synthetic chemist. This knowledge has been built up through the endeavors of generations of organic chemists.[20] The practice of supramolecular retrosynthesis must analogously depend on an intimate knowledge of the myriad ways in which intermolecular interactions are manifested in crystals. This knowledge has come to us through the endeavors

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of generations of crystallographers who have bequeathed to us around 125000 accurate crystal structures of organic and organometallic small-molecules. To a large extent, the assimilation and digestion of the organic synthetic repertoire is still a manual, individual effort.[78] However, because of the peculiarly geometrical nature of intermolecular forces, supramolecular synthetic methodology is suited to computer storage and retrieval techniques, and the essential tool for retrosynthetic analysis in crystal engineering already exists in the form of the Cambridge Structural Database (CSD).[79]

The CSD is now more than ever suited to the purpose of supramolecular retrosynthesis, because it may be searched for patterns of intermolecular forces. Till very recently, the search protocols in the CSD were molecular in their bias; only questions based on covalent bond connectivity could be posed. In studies of interaction geometry, the hits that were thus obtained through molecular-type searches were manipulated with geometrical calculation programs. Today it is possible to code the supramolecular synthon structure directly (as shown in Scheme 1) *inclusive of geometrical attributes* in the search question and obtain all crystal structures that contain the chosen synthon. As a typical example, in attempting to extract all structures that contain dimer synthon **1**, one might typically, in former times, have retrieved all carboxylic acid structures using in the search question a molecular fragment such as CO_2H. This search would have yielded not only compounds that contain the desired **1**, but also acids that adopt the alternative catemer **2**. Yet, structurally related synthons like **3** would not have been obtained. In contrast, the distinctly supramolecular bias of the latest versions of the CSD surely takes into account its ever-increasing relevance in systematic crystal engineering.

The CSD is extremely useful in the study of intermolecular forces weaker than conventional hydrogen bonding. For any given interaction there is an ideal intermolecular orientation. However, this ideal geometry is deformed to a greater or lesser extent in crystals, because the crystal geometry is the result of interaction interference (see Section 2.3). Therefore a statistical analysis of crystal structures is mandatory when studying weak interactions. These statistical techniques minimize the crystallographic noise, that is, the effects of the various deformations, which are inevitable when the interactions are weak. The greater the sampling of crystal structures, the weaker the interaction that may be analyzed. It is reasonable to expect that the present size of the CSD is sufficient to permit an analysis of most types of intermolecular interactions that have been used in crystal engineering or are likely to be used in the foreseeable future.

2.8. Supramolecular Symmetry

. . .any synthetic scheme which does not take full cognizance of stereochemical possibilities or problems will have a correspondingly low expectation of success.

Stereochemistry is an expression of molecular topology, and its supramolecular equivalent is expressed in terms of the spatial and geometrical relationships between supramolecular fragments in the crystal. For instance, how does one obtain particular dispositions and arrangements *between* ribbons, layers and networks within a crystal structure? This is a matter of considerable importance in crystal engineering, because it results in the manifestation or disappearance of physical effects such as Second Harmonic Generation (SHG) or chemical effects such as host–guest complexation. For instance, crystallization in an enantiomorphous space group of an SHG-active material may be likened to a supramolecular asymmetric synthesis. Such considerations are closely linked to questions concerning symmetry. In general, three sorts of symmetry need to be considered: molecular symmetry, the symmetry of supramolecular fragments (tapes, helices, knots, sheets, channels, voids), and crystal symmetry. The first and the third kinds of symmetry are matters of fact, while the second is subject to individual interpretation.

The carry-over of molecular symmetry into the crystal is not a trivial matter, and in no aspect of crystal engineering is the practitioner of the subject quite so helpless today as in establishing connections between molecular and crystal symmetry. Indeed, Kitaigorodskii's laws of close-packing almost dictate that molecular symmetry is a very poor guide to the molecular site-symmetry in the crystal. The inversion center is the only molecular symmetry element that is routinely carried over into the crystal, because it is the only crystal symmetry element that does not entail loss of packing efficiency by its presence.[27, 80] In practice this means that higher symmetry molecules almost always do not adopt higher crystal symmetries. However, the shape factor is also important and when the molecular shape exceeds a certain awkwardness, which is still not really quantifiable, close-packing is problematic leading to the formation of open networks in which the full molecular symmetry is retained, and a second molecular species is included as a guest to improve packing efficiency. For example, 1,3,5-triphenylbenzene forms 1:3 host–guest complexes with benzene, whereas mesitylene, 1,3,5-trichlorobenzene, and 1,3,5-trinitrobenzene form single-component crystals.[10] The presence of high molecular symmetry coupled with a symmetrical interaction pattern is a more powerful combination for the engineering of host networks. In such cases, there is a pronounced conflict between close-packing and directional factors. Such a situation often arises when groups capable of hydrogen bonding are symmetrically disposed in a symmetrical molecular framework. The rigid scaffolding of hydrogen bonds is also compelled to be symmetrical, because the directionality of the hydrogen bonds cannot be compromised. Gross violations of the close-packing principle may sometimes result leading to guest-molecule inclusion (hydroquinone-C_{60}), catenation of networks (acid **36**), or simultaneous inclusion and catenation (hydroquinone with small guests, trimesic acid).

Consideration of spatial relationships between supramolecular fragments in a crystal reveal the following alternatives: 1) Translation versus inversion stacking of two-dimensional fragments such as ribbons and sheets.[81] 2) Packing of fragments of similar and opposite chiralities, for example helices.[82] 3) Alternative topologies of catenation of two- and three-dimensional networks.[83] 4) Segregated versus mixed stacks of planar donor and acceptor molecules in organic metal structures.[84] Many of these possibilities are influenced by extremely weak interactions and are not only poorly understood at present, but also not very amenable to computational techniques. Since the final outcome of crystallization is often governed by a combination of kinetic

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and thermodynamic factors, stereoselective supramolecular synthesis remains a difficult though achievable goal for the future.

2.9. Polymorphism

...the possibility of competing reaction paths should be minimized...

No discussion of crystal engineering can sidestep the problem of polymorphism. This phenomenon is as mysterious and vexing as when a wrong isomer is obtained in a reaction sequence in spite of the best planning and effort. As in traditional synthesis, our inability to grapple with such a problem stems from an incomplete or incorrect knowledge of the factors that affect structure. On occasion it also appears to arise because of outright bad luck, a commodity that is probably as prevalent in crystal engineering as in organic synthesis.

Much has been said about the frequency of occurrence of polymorphism among small-molecule substances, on whether the proportion of polymorphic structures in the CSD is representative of the global proportion of polymorphs in all possible crystal structures (if such details could be ascertained reliably), or even if the number of polymorphs of a given substance increases with the amount of time and effort spent on studying the compound.[85] Many of these questions are rhetorical and quasi-philosophical and are not very helpful in solving the practical problems of crystal engineering. However, a few generalizations may be made: 1) The frequency of occurrence of polymorphic modifications is not uniform in all categories of substances. The phenomenon is probably more common among molecules that have flexible conformations or many different groups capable of hydrogen bonding. By the same token, rigid, flat molecules such as condensed aromatic hydrocarbons are unlikely to have many polymorphic modifications under normal conditions of temperature and pressure. Again, the likelihood of polymorphism may be greatest in an intermediate molecular weight range, approximately C_{10} to C_{20}. 2) Ingenious methods of crystal engineering that create several sites for (three-dimensional) multipoint recognition of molecules will probably decrease the likelihood of polymorphism. In such cases, the general strategy would be to ensure that there is a unique pattern of supramolecular synthons. 3) For the particular application under consideration, it may not really matter whether polymorphs exist, because the critical, property-defining supramolecular fragment (that is, the particular synthon) may be found intact in all the polymorphs. 4) Polymorphism is strongly solvent-dependent in some cases, and computer simulation of crystal structures with and without adhering solvent molecules may provide guidelines for the crystallization of a particular polymorph.

The study of polymorphism in organic crystals is still in a process of evolution, and much more data will be required before firm and general conclusions can be drawn. Recent computational approaches based on molecular dynamics calculations seem to show considerable promise. The Monte-Carlo-based Polymorph Predictor technique has been implemented in the Cerius^2 package from BIOSYM/Molecular Simulations to obtain ab initio predictions of a number of polymorphs.[85] Yet, crystallization almost certainly does not depend exclusively on energetics and may proceed through discrete stages with the result that multimolecular clusters are trapped in higher energy minima in the final crystal structure. A better understanding of polymorphism will depend on a better understanding of the crystallization process itself, and this in turn will rely on advances in spectroscopy (detection of crystal nuclei), physical chemistry (thermodynamics, chaos theory), and biophysics (protein folding). These are difficult issues, and only better experimental and theoretical insights will lead to any measure of control over the problem of polymorphism.

3. Methodology—Intermolecular Interactions

A number of intermolecular interactions, the nuts and bolts of crystal engineering, have been discussed implicitly in the preceding sections, and several detailed and definitive experimental CSD-based and theoretical studies of these interactions have been the subject of recent publications.[6–10, 13, 15, 24, 40, 58, 59, 67–70, 85, 86] The purpose of this section is therefore only to enumerate these forces and to very briefly highlight some of our own results especially those pertaining to the weaker interactions.

The most meaningful criteria for the classification of intermolecular forces from the crystal engineering standpoint are distance-dependence and directionality. Typically, the medium-range forces are isotropic in character and define molecular shape, size, and close-packing (implicit involvement of interactions). Generally, these forces are limited to C···H, C···C and H···H interactions. The long-range forces on the other hand are electrostatic and anisotropic and involve heteroatom interactions, that is, interactions among N, O, S, Cl, Br, I (rarely B, F, P, Se) or between any of these elements and C or H (explicit involvement of interactions). Ionic forces are extremely long-range in nature and are quite specific, directing supramolecular structure effectively.

3.1. Nondirectional Forces

Nondirectional forces (2–10 kJ mol^{-1}) traditionally, though not necessarily exclusively, include C···C, C···H and H···H interactions.[87] The relative importance of these interactions in any particular crystal depends on the C:H stoichiometry. Aromatic compounds (high C:H ratios) have a much stronger tendency to stack, since this would increase the number of C···C interactions. The coulombic character of the C···H interaction could account for its prevalence in a wide variety of aromatic and aliphatic compounds (Section 2.4). For planar aromatic compounds these interactions result in the characteristic T-shaped herringbone synthon **33**. Crystal structures are also known where an unusually acidic C–H group (alkyne) makes close contacts with conjugated π systems.[88] Whether these contacts are to be termed CH···π hydrogen bonds, like the recently studied OH···π hydrogen bonds (see Section 3.2.1), or whether they are merely extreme manifestations of the C···H herringbone interaction is an open question.

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3.2. Hydrogen Bonding

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. As a vast amount of work has been carried out on the various aspects of hydrogen bonding, it would be futile to attempt even a brief review of these efforts here. Hydrogen bonds of the type OH···O and NH···O may be termed "strong" or "conventional" (energies 20–40 kJ mol^{-1})[89] to distinguish them from the weaker CH···O$_2$ and OH···π interactions (energies 2–20 kJ mol^{-1}), which share many of their characteristics and which are discussed in greater detail in Section 3.2.1.

The distinctive geometrical attributes of a hydrogen bond D–H···A–X (D = donor, A = acceptor) are the D···A and H···A lengths, the hydrogen bond angle D-H-A or θ, the H-A-X angle or ϕ and the planarity of the DHAX system. All these features have been discussed extensively.[6, 15] Typical values for the H···A distance are 1.80 to 2.00 Å for NH···O bonds and 1.60 to 1.80 Å for OH···O bonds. More relaxed definitions of these distance criteria permit a consideration of the slightly longer three-centered and four-centered bonds, which seem to be very common in several hydrogen-bonded structures. Ranges for θ and ϕ occur around 150–160° and around 120–130°, respectively. This marked directionality of hydrogen bonds is well-established and is the basis for efficient and reliable supramolecular construction using supramolecular synthons that contain groups such as –OH, –CO$_2$H, –CONHR, and –CONH$_2$. Synthon **28**, for instance, occurs in several phenols and in the water trimer and is related to other synthons such as $(OH)_4$ and $(OH)_6$.[90] We have found recently that many hydrogen-bonded synthons containing carboxyl and hydroxyl groups in organic crystals are retained largely intact in organometallic crystals.[91]

3.2.1. CH···O and OH···π Hydrogen Bonds

This discussion is also valid for the related CH···N and NH···π[69, 92] interactions. Furthermore, while there is some question whether the CH···Cl interaction is a viable one, recent reports provide evidence for CH···F[94] and CH···Se[95] hydrogen bonds.

There is little doubt that CH···O hydrogen bonds are important, even if subtle, determinants of crystal packing, especially when strong OH···O and NH···O hydrogen bonds are absent.[24, 96] As has been discussed in Section 2.3, CH···O hydrogen bonds may distort the geometry and topology of even the strong hydrogen-bond network in specific instances. Anomalies and puzzles in the strong hydrogen-bond patterns of certain crystal structures are explained on the basis of the interplay of strong and weak hydrogen bonds. In general, the strength and effectiveness of a CH···O hydrogen bond depends on C–H carbon acidity[97] and on O-atom basicity,[98] which is enhanced by cooperative effects. We have shown for instance that CH···O distances in crystals correlate so well with solution C–H group pK_a values that it is even possible to define a crystallographic scale of carbon acidity.[99]

The criteria for the significance of a particular CH···O geometry have also been the subject of some discussion. Recent analysis has shown that the angular characteristics of many longer CH···O contacts (C···O 3.50–4.00 Å) and their effects on crystal structures resemble those of the shorter contacts (3.10–3.50 Å).[24] It should be emphasized that the CH···O bond is not really a van der Waals contact but is primarily electrostatic; as its strength therefore falls off much more slowly with distance, it is viable at distances equal to or longer than the van der Waals limit. Therefore, even long C···O separations (about 4.00 Å) have to be considered seriously, and these weak hydrogen bonds are expected to have orienting effects on molecules prior to nucleation and crystallization. This underlines the important role of these bonds in crystal engineering especially in orchestration.

While CH···O hydrogen bonds are widespread, the complementary OH···π interactions are rare, because C is not as electronegative as O and also because unsaturated carbon atoms are not often situated in sterically unhindered positions, unlike carbonyl and ethereal O atoms, which permit easy access for C–H groups to form CH···O bonds. In spite of these limitations, a sufficiently electron-rich C atom (alkyne, alkene, aromatic) has a propensity to form a hydrogen-bond-like interaction with O–H groups thus contributing to crystal stability.[100] We have studied these interactions systematically with the CSD: around 50 unambiguous cases of intermolecular OH···π and NH···π hydrogen bonding were found in the 1993 update.[69]

3.3. Halogen Atom Interactions

It has long been known that the halogens Cl, Br, and I form short nonbonded contacts in crystals.[15] Not only are these contacts (synthons **25**, **26**) clearly manifested in the crystal structures of the elements themselves; they are also of historical importance in crystal engineering, because they form the basis of the so-called "4 Å chloro rule" enunciated by Schmidt for planar dichloroaromatic compounds.[101] The nature of these interactions is still somewhat obscure. Nyburg and Wong-Ng,[102] and more recently, Price et al.,[86] have held that these short contacts are the result of elliptically shaped atoms (anisotropy), while others including ourselves have maintained that there are specific attractive forces between halogen atoms in crystals.[40, 103] Certainly atomic polarization is an important factor here, because there are clear distinctions between Cl···Cl, Br···Br and I···I interactions and between these symmetrical interactions on the one hand and unsymmetrical interactions such as I···Cl, Br···F and I···F on the other. Directional interactions formed by the halogens with O and N atoms are also polarization-induced and have been used by us and others in systematic crystal engineering (Section 2.1).[33–35, 45]

3.4. Other Interactions: Hardness and Softness

As in the case of halogens, polarization effects are important for sulfur, which is known to form short directional contacts of the type S···N, S···S, and S···Cl. These contacts have been thoroughly studied in the crystal chemistry of the TTF–TCNQ family of compounds.[104] Intermolecular interactions that are

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specific to organometallic compounds have only been the subject of very recent study.[105] Our systematic survey of Au···Au interactions has shown that they affect molecular conformation and crystal packing.[106] Hydrogen-bonding patterns in organometallic crystals are, in general, similar to those in simple organic compounds. However, the CO ligand is a base unique to organometallic compounds, and our results indicate that it is more important for CH···O bonding than for OH···O bonding.[91, 107] A possible explanation for such an observation considers the hardness and softness of intermolecular interactions. It appears that the hard and soft acid and base (HSAB) principle may be profitably extended to supramolecular chemistry. For instance, NH···O and OH···O could be considered hard hydrogen bonds, CH···O and CH···π soft hydrogen bonds, and NH···N have perhaps intermediate character.[107] Accordingly, it might be argued that the soft acceptor CO prefers to form a hydrogen bond with the soft donor C–H, or alternatively the hard donor O–H prefers to form bifurcated or solvated hydrogen bonds with hard acceptors rather than waste itself on the soft acceptor CO. Along these lines, the unexpected formation of the CH···Se may be understood in terms of the relative softness of both donor and acceptor species.[95] Again, Scheme 3 shows how the hard synthon **1** and the soft synthon **17** operate independently, but equally effectively, in the crystal.

4. Summary and Outlook

...although chemistry is a science of vast scope and countless specialties, it has no real boundaries...

In writing this article and drawing an analogy between crystal engineering and organic synthesis, I have tried to address two groups of chemists whose concerns and goals might at the outset appear to be somewhat unrelated. Yet, crystal engineering today seems to be poised at the point where organic synthesis was in the fifties and sixties. Empirical, largely intuitive strategies or manipulations within narrowly defined structural families dominate the scene even as one already discerns glimmers of a more logic-driven approach. All these developments have generated a substantial body of data on intermolecular interactions and crystal packing. It is from this corpus that more systematic strategies of crystal engineering will appear. I have attempted to show that the kernel of such strategies already exists in synthetic organic chemistry, and that with this foreknowledge, solid-state supramolecular chemists might well be able to create patterns of extraordinary finesse in crystals. On the other hand, it is hoped that synthetic organic chemists will recognize in crystal engineering a natural extension of so many principles in their canon and realize that with an appreciation of the properties of intermolecular interactions, they may be equally well-equipped to undertake research in this challenging discipline. In either case, crystal engineering, which has been recognized as the central issue in organic materials chemistry, is well set to become the breakthrough technology for industrial research and development.

The term "supermolecule" has been used synonymously with "crystal" in this article, and as mentioned at the very outset, a crystal is the *ultimate* example of a supermolecule in that it consists of an infinity of molecules divergently bound. Hierarchies of supramolecular species may accordingly be recognized, and the synthesis of lower hierarchy supermolecules consisting of two or more convergently bound molecular components has become an extremely attractive and competitive area of research combining molecular synthetic methodology with supramolecular ideas of molecular association.[108] However, such efforts must logically progress towards crystal engineering in the quest for complex three-dimensional networks based on complex polyfunctional molecules.

At one level it is remarkable that concepts and models which were developed in the sixties for organic synthesis can be so readily reapplied today, and in such minute and faithful detail, to a research area which was barely conceived at that time. This parallelism has continued to unfold itself for me even during the writing of this article—I have little doubt that other structural and synthetic chemists will be able to uncover more relationships between these two fascinating areas of chemistry. Yet, at another level such a striking resemblance only reaffirms the oneness or nonduality in the chemical thought process. Though I have quoted only a few sentences from Corey's 1967 article here,[18] almost the entire Part I can be reread and reassimilated in the context of crystal engineering and solid-state supramolecular chemistry, and perhaps even such an eventuality was foreseen, for it is stated while justifying the quest for a general strategy of synthesis that *"such an effort surely is more than an intriguing theoretical exercise; it is a prerequisite to a deeper comprehension of Synthesis and the methodologies which are fundamental to it, and it is likely to be the keystone in the rational development of Synthesis* ***to still higher forms.***"[*]

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[*] The emphasis is mine.

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band at 2200 cm.$^{-1}$ and a new band at 508 cm.$^{-1}$ assigned to Pd–Cl stretching, but not a Pd–Cl band at 360 cm.$^{-1}$. In 2% pyridine solution, the CN band was shifted to 2130 cm.$^{-1}$ and remarkably sharpened, indicating the co-ordination of nitrile to the metal. In addition, the complex (II) can also be obtained by the reaction of diazoacetonitrile with a palladium–cyclohexene complex of the type $[C_6H_{10}\cdot PdCl_2]_2$,[5] followed by ligand exchange with triphenylphosphine. We therefore suggest the above structure for (II), in which cyanomethylenes are inserted into palladium–chloride bonds.

Such surprisingly specific cyanomethylene insertions occurred with the analogous palladium chloride derivatives such as di-μ-chloro-di-π-allyldipalladium[6] and palladium dichloride irrespective of the presence of cyclohexene. On the other hand, ethyl diazoacetate reacted with cyclohexene to give norcarane derivatives without the formation of the insertion products.[7] This characteristic feature of the reactivity of cyanomethylene may be attributed to the effect of a cyano-group on the stabilization of the insertion products both by co-ordination to palladium and by the increased electronegativity of the α-carbon.

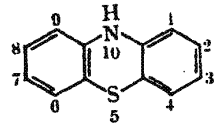
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The Configuration of Phenothiazine in Various Molecular Complexes

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ONLY a few cases are known of two forms of a molecular species, differing only in total charge, that have been stable enough for structure analysis, and the changes in which are found to be small.[1] Changes in geometry with charge may



(I)

be observed in phenothiazine (I), since the cation of 2,8-bis(dimethylamino)phenothiazine has been shown[2] to be planar, whereas neutral phenothiazine is assumed to be nonplanar.[3] Proof of nonplanarity of phenothiazine and correlation of the degree of nonplanarity with charge would also be useful in constructing and evaluating models of complex bonding[4] in phenothiazine-based drugs.

We have reported[5] that in phenothiazine–trinitrobenzene (1 : 1) the phenothiazine moiety, although disordered, is most stable in a folded configuration, with a dihedral angle of 168 ± 4°. The S–C and N–C distances were estimated to be 1·76—1·81 and 1·40—1·45 Å. We report the configuration of phenothiazine in the crystal structure of phenothiazine–3,5-dinitrobenzoic acid (1 : 1), in which there is no disorder.

Crystals of phenothiazine–3,5-dinitrobenzoic acid (1 : 1) were prepared by slow cooling and evaporation of a 30 : 70 acetone–benzene solution equimolar in phenothiazine and the acid chloride. The crystal structure is triclinic, symmetry $P\bar{1}$, $z = 2$, $a = 7{\cdot}54 \pm 0{\cdot}01$, $b = 10{\cdot}00 \pm 0{\cdot}01$, $c = 13{\cdot}92 \pm 0{\cdot}01$ Å, $\alpha = 101{\cdot}79 \pm 0{\cdot}05$, $\beta = 105{\cdot}79 \pm 0{\cdot}05$, $\gamma = 105{\cdot}21 \pm 0{\cdot}05°$. These values were determined by least-squares fitting of 2θ measurements using a Picker four-circle diffractometer, and Cu-K_α radiation. The same diffractometer was used with a molybdenum X-ray target to collect all independent intensity data having $2\theta < 45°$.

Reflections were processed[6] and the structure solved by use of Patterson and successive electron-density functions. The structure has been refined by least squares[7] to $R = 9{\cdot}9$.

The structure is similar to the classical charge-transfer case, in that phenothiazine and dinitrobenzoic acid molecules occur alternately in a stack parallel with a, with virtually identical interplanar spacing (*ca.* 3·33 Å). However, each molecule overlaps one of its neighbours more extensively than the other. Furthermore, the phenothiazine moiety is not planar but consists of two planar halves folded along the N–S axis, with a dihedral angle of 156 ± 2°. Contrary to the trinitrobenzene complex, there seems to be no packing

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influence to force this angle to differ from its intrinsic value, and it therefore seems that this degree of folding represents the configuration of free phenothiazine.

The interatomic distances also seem to indicate that there is little, if any, aromatic character to the central ring of phenothiazine. The C–N distance of 1·39 ± 0·02 Å is nearly the same as in pyrrole,[5] whereas the C–S distance is 1·76 ± 0·02 Å, virtually what is expected by correcting the C_{sp^3}–S distance[6] of 1·82 Å for the change (0·04 Å) expected on going from C_{sp^3} to C_{sp^2}. The C–S–C angle is 101 ± 1 and the C–N–C angle is 123 ± 1°; all other angles appear to be 120°. All C–C distances are equal to the benzene value.

If we assume the phenothiazine cation radical to be planar,[2,9] we can then conclude that the ground state in the present complex is essentially the no-bond structure (DA), in contrast with the situation in the complexes of phenothiazine with quinone and 2,3-dichloro-5,6-dicyanoquinone,[10] which appear to be essentially ionic (D^+A^-). Because of disorder, the position of the trinitrobenzene complex is unclear, but it is probably the no-bond type.

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Infrared Radiometry of Thermal Transients on Surfaces. An Approach to the Study of Thermal Effects caused by Gas–Solid Interactions

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THE kinetics and energetics of various gas–solid interactions have been much studied, but because a significant time may elapse between the "start" of a reaction and the first measurement, there is little direct information dealing with the initiation and early stages of most reactions. Such information would be useful, as rapid changes in temperature would certainly effect the kinetics,[1] or might affect the solid such as to exert some influence on the later stages of reaction. Extrapolation to initial conditions could thus be misleading. Measurements of temperature-transients during the early stages of gas–solid interactions are capable, in principle, of giving useful information about such processes. Some temperature effects caused by the rapid adsorption of water on bentonite have been reported[2] but the procedures were obscure and the treatment of data uncertain. We have now examined radiometrically the sorption of gases on supported metals and describe some preliminary results for the sorption of oxygen on nickel to illustrate the techniques involved.

Adsorbents containing 1, 5, and 10 atom-% Ni were prepared[3] by impregnating Cab-O-Sil silica, which was compressed into 1 in. diameter discs mounted on a movable quartz carriage in a high-vacuum cell fitted with a NaCl window. Samples were reduced at 400° with Pd-filtered H_2 for 12 hr., degassed at 10^{-6} torr, and then cooled to room temperature *in vacuo*. Oxygen was then introduced at a pre-determined pressure, and the radiation was monitored by a Kodak Ektron PbS

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through C(6)—(9) [Plane (2) in Table 9]; C(10) is then displaced by 0·161, and C(5) by —0·626 Å. These values compare well with those of 0·15 and —0·61 Å for the cyclohexene ring in the serratene derivative,[16] where the double bond is also under some torsional strain. As predicted [15] by the intra-annular angles at C(7) and C(8) in this ring are somewhat in excess of 120°.

The ring C adopts a ' twist-boat ' conformation [19] being forced out of the energetically preferred chair form by the presence of the 7,8-double-bond, and by the fusion of the cyclopentane ring D. The agreement between the observed and the calculated torsion angles is good (Table 8). The angle C(9)–C(8)–C(14) is contracted to 114·7° and the mean angle in the ring [including that at the C(sp^2) atom] is 111·7°, close to the predicted value.[15]

The cyclopentane ring D is in the half-chair conformation with C(13) and C(14) respectively 0·407 above and 0·379 Å below the plane through C(15)—(17). Hendrickson [20] has shown that there are a number of cyclopentane conformations of equal energy corresponding to values of ω_1 between 0 and 45°. His calculated conformation for ω_1 15° corresponds closely to the values found in this investigation. In agreement with the results cited by Geise *et al.*[18] the torsion angle in this ring about the C(13)–C(14) bond falls in the range 46—50° and the intra-annular angles at C(13) and C(14) approach 100° (101·6 and 101·1°). Hendrickson [20] predicts a mean valency angle of 104·2°; in the present structure it is 103·2°.

Ring E is planar (Table 9), so that the lactone grouping itself, C–(CO)–O–C, is also planar, as expected from the results of Mathieson and Taylor [21] who also predict that the bond length C(23)–O(2) should be *ca.* 0·1 Å longer than O(2)–C(27). Here the difference in length is 0·063 Å. The valency angles within the ring range from 104·5—109·6° and there is, therefore, some angular distortion at the C(sp^2) atoms C(24), C(25), C(27); the four extra-annular angles at C(25) and C(27) being expanded to a mean of 125·6°.

The molecular packing viewed down the *a* axis is illustrated in Figure 3. The plane of the steroid nucleus is roughly parallel to the crystallographic *bc* plane, while the lactone group is almost perpendicular to the nucleus. Intermolecular contacts correspond to van der Waals interactions, the shortest being C · · · C 3·52 and C · · · O 3·26 Å.

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Molecular Packing Modes. Part XI.[1] Crystal Structures of the 2:1 Complexes of Benzamide with Succinic Acid and Furamide with Oxalic Acid

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The benzamide–succinic acid adduct (I) crystallises in space group $P2_1/c$, with $Z = 2$ in a unit cell of dimensions: $a = 9·194$, $b = 5·116$, $c = 19·480$ Å, $\beta = 105·66°$. The structure was refined from three-dimensional film data to R 0·10 (1441 reflections). The furamide–oxalic acid adduct (II) crystallises in space group $P\bar{1}$, with $Z = 1$ in a unit cell of dimensions: $a = 7·459$, $b = 6·579$, $c = 8·064$ Å, $\alpha = 92·19$, $\beta = 95·60$, $\gamma = 120·29°$. The structure was refined from three-dimensional counter data to R 0·05 (1451 reflections).

Both (I) and (II) form 2:1 molecular-complex units in which the amide and carboxy-groups are linked by cyclic hydrogen-bonded (asymmetric) pairs [(I): O–H · · · O 2·60, N–H · · · O 2·98; (II): O–H · · · O 2·53, N–H · · · O 2·92 Å]. The units of (I) are interlinked, along the 5 Å axis, by amide–amide hydrogen bonds (N–H · · · O 3·02 Å). Those of (II) are joined, along the 6·6 Å axis, by bifurcated N–H · · · O bonds [N–H · · · O(hydroxy) 3·10, N–H · · · O(carbonyl) 2·94 Å] between the furamide and oxalic acid fragments.

THE X-ray structure analyses of the 2 : 1 addition compounds of benzamide with succinic acid (I) and of furamide with oxalic acid (II) were undertaken as part of a study on the molecular packing modes of functional groups. Primary amides and carboxylic acids form crystalline complexes with each other, the molecular association being due to the hydrogen bonding between the carboxy- and amide-groups. We have determined the crystal structures of (I) and (II) in order to reveal the geometry of molecular association.

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EXPERIMENTAL

Compound (I).—*Crystal data.* $2(C_7H_7NO),(C_4H_6O_4)$, $M = 360·4$. Monoclinic, $a = 9·194(1)$, $b = 5·116(1)$, $c = 19·480(2)$ Å, $\beta = 105·66(1)°$, $U = 882·1$ Å^3, $D_c = 1·36$,

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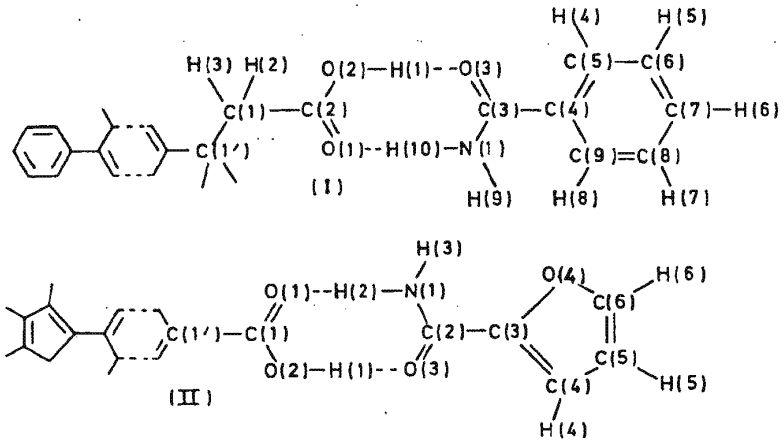
$Z = 2$, $D_m = 1{\cdot}36$, $F(000) = 380$. Space group $P2_1/c$. Cu-K_α radiation, $\lambda = 1{\cdot}5418$ Å; μ(Cu-K_α) = 8·7 cm^{-1}.

Monoclinic crystals of benzamide–succinic acid (I), m.p. 126—129 °C, were grown from a slowly cooled solution in nitromethane as needle-like plates elongated along [010], showing well-developed {001} and {100} forms. Cell constants were obtained from a least-squares analysis of high order ($\theta > 65°$) reflections measured on a General Electric goniostat with Cu-K_α radiation.

Intensities of the layers $h0$—$4l$, and the $0kl$ zone, were recorded by the equi-inclination Weissenberg technique with Cu-K_α radiation by the multiple-film method. Intensities were estimated visually, and processed for spot extension in nonzero levels,[2] and the Lorentz polarisation factor. The levels were brought to a common scale by the indices for all reflections were R 0·10 and R' [$= \Sigma w(k^2F_o^2 - F_c^2)^2/\Sigma wk^4F_o^4$] 0·05.

Compound (II).—*Crystal data.* $2(C_6H_5NO_2),(C_2H_2O_4)$. $M = 312{\cdot}2$. Triclinic, $a = 7{\cdot}459(1)$, $b = 6{\cdot}579(1)$, $c = 8{\cdot}064(1)$ Å, $\alpha = 92{\cdot}19(1)$, $\beta = 95{\cdot}60(1)$, $\gamma = 120{\cdot}29(1)°$, $U = 338{\cdot}3$ Å^3, $D_c = 1{\cdot}53$, $Z = 1$, $D_m = 1{\cdot}50$, $F(000) = 162$. Space group $P1$ or $P\bar{1}$ (the latter proved correct by the present analysis). Cu-K_α radiation: μ(Cu-K_α) = 11·5 cm^{-1}.

Triclinic crystals of the 2 : 1 complex of furamide with oxalic acid (II), m.p. 144 °C, were grown from a slowly cooled solution in nitromethane as laths, showing well-developed {001}, {1$\bar{1}$0}, {010}, and {1$\bar{1}\bar{1}$} forms. Cell constants were determined by a least-squares analysis of high-angle ($\theta > 60°$) reflections measured as before.



Labelling of atoms used in the structures analyses

procedure of Rollet and Sparks.[3] The applied weighting scheme $w(hkl)$ has been described elsewhere.[4] 1729 Independent reflections were measured of which 288 were unobserved.

There are two succinic acid molecules and four benzamide molecules in the unit cell so it was assumed that a centrosymmetric succinic acid was linked to two benzamide molecules *via* hydrogen bonds between the carboxy- and amide-groups as shown in (I). The structure was solved by means of SEARCH[5] with the molecular model (I). SEARCH yielded essentially one trial structure which proved to be correct when tested in a constrained-geometry least-squares programme on 41 low-order reflections. In the refinement only the scale factor and the three Eulerian orientation angles of the planar molecule model were adjusted. After six cycles of refinement R was 0·32.

Individual atomic parameters were then refined by a full-matrix least-squares programme of Busing, Martin, and Levy, the function minimised being $w(k^2F_o^2 - F_c^2)$,[2] with isotropic thermal parameters and fixed hydrogen parameters and finally with anisotropic temperature parameters for all but the hydrogen atoms which were refined isotropically. Refinement was terminated when the shifts were $<0{\cdot}02\sigma$ for all atoms including hydrogen. The final discrepancy

Three-dimensional intensity data of a crystal specimen *ca.* 0·4 × 0·2 × 0·5 mm were collected on a General Electric goniostat with Ni-filtered Cu-K_α radiation according to the stationary-crystal–stationary-counter technique, to a 2θ maximum of 160°. The $I(hkl)$ were corrected for absorption and reduced to $F(hkl)$ by a procedure described elsewhere.[6] 1611 Independent reflections were recorded, of which 60 were treated as unobserved. The weight $w(hkl)$ attached to $F_o(hkl)$ in our least-squares programme was taken equal to $1/\sigma^2(F_o^2)$.

The structure was solved from packing considerations. The molecular model was assumed to consist of an oxalic acid molecule hydrogen-bonded to two furamide molecules *via* the carboxy–amide pairing shown in (II). This molecular complex was assumed to lie in the (102) plane in view of the very high value of $F(102)$. The orientation of the complex unit (II) within this plane was fixed by assuming that these units were interlinked by N–H · · · O hydrogen bonds along the b axis. However, there remained one ambiguity, the direction (positive or negative) of b within the hydrogen-bonded network. Thus we tested both models in a constrained-geometry least-squares programme on 30 low-order reflections in which only the scale factor and the angular orientation parameters (three Eulerian

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angles) of the planar molecular model (II) were adjusted. After four cycles R was 0·4 and 0·7. The model with the lower R index, and which proved to be the correct structure, was chosen for further refinement.

Next, individual atomic parameters were refined, first with isotropic thermal parameters and fixed hydrogen parameters, and finally with anisotropic parameters for all but the hydrogen atoms which were refined isotropically. Refinement was terminated when the shifts were $< 0{\cdot}05\sigma$ for all atoms. The final agreement factors were R 0·05 and R' 0·02.

The scattering factor curves used for carbon, nitrogen, and oxygen were taken from ref. 7. Observed and calculated structure factors are listed in Supplementary Publication No. SUP 20567 (5 pp., 1 microfiche).†

RESULTS AND DISCUSSION

Tables 1 and 2 list the positional and thermal parameters with their estimated standard deviations of (I)

TABLE 1

Fractional atomic co-ordinates ($\times 10^4$ for C, N, and O; $\times 10^3$ for H) and standard deviations referred to a, b, c

(*a*) Compound (I)

Atom	*x*	*y*	*z*
O(1)	−2318(3)	−2016(6)	200(1)
O(2)	−2019(4)	1439(6)	906(1)
O(3)	−4627(3)	0503(5)	1136(1)
N(1)	−4808(4)	−3717(7)	808(1)
C(1)	−212(4)	818(8)	287(2)
C(2)	−1618(4)	−114(7)	449(1)
C(3)	−5225(3)	−1651(7)	1128(1)
C(4)	−6454(3)	−2010(6)	1490(1)
C(5)	−6513(4)	−259(8)	2036(2)
C(6)	−7608(5)	−536(10)	2391(2)
C(7)	−8675(5)	−2472(10)	2211(2)
C(8)	−8647(5)	−4161(8)	1665(2)
C(9)	−7535(4)	−3966(8)	1304(2)
H(1)	−297(8)	83(13)	90(3)
H(2)	−32(5)	267(10)	14(2)
H(3)	53(5)	76(8)	70(2)
H(4)	−581(5)	96(8)	214(2)
H(5)	−756(5)	70(9)	268(2)
H(6)	−947(6)	−252(11)	242(3)
H(7)	−944(6)	−552(10)	156(2)
H(8)	−745(5)	−537(10)	98(2)
H(9)	−527(6)	−508(11)	83(2)
H(10)	−385(7)	−328(11)	66(3)

(*b*) Compound (II)

O(1)	495(1)	2881(1)	88(1)
O(2)	2057(1)	1247(1)	−1208(1)
O(3)	4383(1)	5052(1)	−2440(1)
O(4)	6119(1)	11143(1)	−2509(1)
N(1)	3074(2)	7222(2)	−1416(1)
C(1)	696(2)	1230(2)	−287(1)
C(2)	4403(2)	6958(2)	−2241(1)
C(3)	5961(2)	9025(2)	−2955(1)
C(4)	7306(2)	9305(3)	−4060(2)
C(5)	8374(2)	11750(3)	−4280(2)
C(6)	7615(2)	12771(2)	−3334(2)
H(1)	288(3)	275(3)	−160(2)
H(2)	226(3)	602(4)	−88(2)
H(3)	300(3)	853(4)	−129(3)
H(4)	742(3)	811(4)	−450(3)
H(5)	940(3)	1248(3)	−500(2)
H(6)	794(4)	1437(5)	−309(3)

and (II). Deviations from some best planes through (I) are given in Table 3(*a*), and those from the best planes of the analogous groups in (II) are listed in Table 3(*b*). Short intermolecular contacts in both structures are listed in Table 4.

Molecular Shape.—The complex (I) is non-planar (see Table 3). The heavy-atom skeleton of the succinic acid fragment is almost planar, the carboxy-group being twisted out of the plane of the ethylene chain by 4·4° about the C(1)–C(2) bond. The benzamide fragment is non-planar; the angle between the planes of the phenyl ring and the amide group being 24·2°, as a result of torsion about the exocylic C–C bond. The carboxy–amide pair which links the acid and amide fragments, is not a co-planar system, the angle between the planes of the carboxy- and amide-groups being 19·7°, primarily a result of a twist about the C(1) · · · C(4) vector. The carboxy-group is twisted, with reference to the amide group, in the same direction as the phenyl ring, the angle between their planes being 9·3°.

The oxalic acid fragment, of (II), is planar to within 0·002 Å; the furamide molecule is non-planar, the

TABLE 2

Observed thermal parameters * ($\times 10^4$ for C, N, and O; $\times 10^3$ for H) and their standard deviations (Å²)

(*a*) Compound (I)

Atom	u_{11}	u_{22}	u_{33}	u_{12}	u_{23}	u_{13}
O(1)	590(28)	516(20)	653(18)	−268(16)	−219(16)	434(14)
O(2)	599(19)	492(21)	811(22)	−211(17)	−291(17)	474(17)
O(3)	523(16)	291(17)	816(21)	−99(14)	−114(14)	442(15)
N(1)	575(21)	304(21)	634(22)	−107(18)	−133(15)	433(18)
C(1)	389(18)	320(26)	410(18)	−114(18)	−054(16)	190(15)
C(2)	413(18)	244(20)	382(16)	−71(18)	−009(14)	147(14)
C(3)	332(15)	249(20)	390(16)	−21(16)	−005(13)	136(13)
C(4)	360(16)	216(19)	321(15)	17(15)	−001(13)	111(12)
C(5)	411(19)	364(23)	437(18)	−66(19)	−128(17)	187(15)
C(6)	595(26)	477(28)	440(19)	12(22)	−141(20)	260(18)
C(7)	597(27)	541(29)	493(22)	−23(23)	028(19)	344(19)
C(8)	570(20)	349(24)	635(24)	−127(21)	−074(19)	402(21)
C(9)	436(20)	340(22)	448(18)	−44(18)	−063(17)	256(16)

Atom	*U*	Atom	*U*
H(1)	57(20)	H(6)	45(16)
H(2)	25(12)	H(7)	34(13)
H(3)	15(11)	H(8)	25(12)
H(4)	16(11)	H(9)	37(17)
H(5)	17(11)	H(10)	51(17)

(*b*) Compound (II)

Atom	u_{11}	u_{22}	u_{33}	u_{12}	u_{23}	u_{13}
O(1)	546(6)	381(5)	739(9)	278(4)	154(4)	329(5)
O(2)	502(6)	389(5)	700(7)	272(4)	158(4)	290(5)
O(3)	622(7)	410(5)	819(8)	296(5)	177(5)	401(6)
O(4)	565(6)	379(5)	558(6)	233(4)	76(4)	188(4)
N(1)	519(7)	395(6)	649(8)	258(5)	114(5)	259(5)
C(1)	389(6)	360(6)	507(7)	217(5)	78(5)	111(5)
C(2)	423(6)	384(6)	479(6)	215(5)	58(5)	126(5)
C(3)	413(7)	373(6)	488(7)	199(5)	62(5)	84(5)
C(4)	531(8)	545(9)	656(9)	300(7)	155(7)	261(7)
C(5)	518(8)	597(9)	683(9)	249(7)	253(7)	254(7)
C(6)	590(9)	418(7)	662(9)	186(7)	149(6)	156(7)

Atom	*U*	Atom	*U*
H(1)	35(5)	H(4)	48(6)
H(2)	28(4)	H(5)	35(5)
H(3)	48(6)	H(6)	59(7)

* Debye–Waller factor is defined as $\exp[-2\pi^2\sum_i\sum_j a_i^* a_j^* h_i h_j u_{ij}]$ for the C, N, and O atoms, and $\exp[-8\pi^2 U \sin^2\theta/\lambda^2]$ for hydrogen.

† For details see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1970, Issue No. 20 (items less than 10 pp. are sent as full size copies).

[7] 'International Tables for *X*-Ray Crystallography,' vol. III, Kynoch Press, Birmingham, 1962, p. 202.

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TABLE 3

Equations of planes in the form $Ax + By + Cz + D = 0$ where x, y, z are fractional co-ordinates; distances (10^3 Å) of relevant atoms from the planes are given in square brackets

(*a*) Compound (I)

Plane (I): C(1), C(2), C(1'), C(2')
$-3{\cdot}3626x + 3{\cdot}0978y - 11{\cdot}3330z = 0$
[O(1) −72, O(2) 98, H(2) 774, H(3) −740]

Plane (II): C(1), C(2), O(1), O(2)
$-3{\cdot}2661x + 2{\cdot}8025y - 12{\cdot}3378z + 0{\cdot}0562 = 0$
[C(1) 1, C(2) −2, O(1) 1, O(2) 1, C(3) −93, N(1) −414, O(3) 306, H(1) 140]

Plane (III): C(3), C(4), N(1), O(3)
$-4{\cdot}3043x + 1{\cdot}2333y - 13{\cdot}4836z - 0{\cdot}5219 = 0$
[C(3) 2, C(4) −1, N(1) −1, O(3) −1, O(1) −42, O(2) −697, H(9) 0, H(10) −160]

Plane (IV): C(2), C(3), N(1), O(1)—(3)
$-3{\cdot}4397x + 2{\cdot}0619y - 13{\cdot}6976z + 0{\cdot}0665 = 0$
[C(2) −16, C(3) −23, N(1) −154, O(1) 173, O(2) −184, O(3) 204, C(1) −85, C(4) −170, H(1) 20, H(9) −310, H(10) −190]

Plane (V): C(4)—(9)
$-3{\cdot}9598x + 3{\cdot}1338y - 10{\cdot}1652z - 0{\cdot}4178 = 0$
[C(4) −7, C(5) 10, C(6) −5, C(7) −5, C(8) 9, C(9) −3, C(3) −13, N(1) −501, O(3) 417, H(4) 10, H(5) 80, H(6) 80, H(7) −10, H(8) −160]

(*b*) Compound (II)

Plane (I): C(1), O(1), O(2), C(1'), O(1'), O(2')
$4{\cdot}0633x - 0{\cdot}8839y + 6{\cdot}0075z = 0$
[C(1) 2, O(1) −1, O(2) 0, H(1) −30]

Plane (II): C(1'), N(1), C(1)—(3), O(1)—(3)
$3{\cdot}9820x - 0{\cdot}6084y + 5{\cdot}9635z - 0{\cdot}0093 = 0$
[C(1') −40, C(1) 22, C(2) −16, C(3) 53, O(1) 65, O(2) 13, O(3) −26, N(1) −70, H(1) 10, H(2) −10, H(3) −100]

Plane (III): C(3)—(6), O(4)
$4{\cdot}7707x - 1{\cdot}5606y + 5{\cdot}5031z + 0{\cdot}1965 = 0$
[C(2) −22, C(3) 5, C(4) −5, C(5) 2, C(6) 1, O(3) 157, O(4) −4, N(1) −244, H(4) −10, H(5) −20, H(6) 40]

furan ring being twisted out of the plane of the amide group by 17·4° about the exocyclic C–C bond. The hydrogen-bonded carboxy-amide pair is almost coplanar, the angle between the planes of the amide- and the carboxy-groups being 3°.

With regard to the conformation of the furamide molecule, the endocyclic C=C double-bond and the carbonyl C=O bond adopt the cisoid conformation about the exocyclic C–C bond, in contrast to the crystal molecular structures of furoic acid [8] and furan-$\alpha\alpha'$-dicarboxylic acid [9] in which the conformations are transoid. An *anti*-planar conformation of C=C–C=O in furamide would lead to a fairly short intramolecular H · · · H contact.

Bond Lengths and Angles.—The experimental bond lengths and angles of (I) are shown in Figure 1, the mean σ values being 0·005 Å and 0·3°. The corresponding values where one hydrogen atom is involved, are 0·04 Å and 3°.

Figure 2 shows the experimental bond lengths and angles in (II). The mean of the σ value of the bond lengths is 0·002 Å, and of angles 0·1°; the corresponding values where one hydrogen is involved, are 0·03 Å and 1°.

Molecular Packing.—Benzamide and succinic acid form a centrosymmetric 2 : 1 complex unit (I) *via* the hydrogen-bond pairing of their carboxy- and amide-groups (see Figure 3). These complex units are interlinked, along

TABLE 4

Short intermolecular contacts (Å) *

(*a*) Compound (I)

H(6) · · · H(7^{I})	2·64	O(1) · · · H(10^{VI})	1·98
O(1) · · · H(8^{II})	2·63	O(2) · · · O(3^{VI})	2·60
O(1) · · · H(9^{II})	2·96	O(3) · · · H(1^{VI})	1·71
N(1) · · · N(1^{II})	3·34	C(5) · · · H(8^{VII})	3·20
C(5) · · · H(4^{III})	3·01	O(3) · · · N(1^{VII})	3·02
C(9) · · · H(3^{IV})	3·04	O(2) · · · O(1^{VII})	3·60
O(1) · · · O(3^{V})	3·36	H(2) · · · H(2^{VIII})	2·56
O(1) · · · C(3^{V})	3·48	C(1) · · · H(7^{IX})	3·05
C(9) · · · H(2^{V})	3·05	O(2) · · · H(7^{IX})	2·83
O(1) · · · N(1^{VI})	2·98	H(3) · · · H(7^{IX})	2·53

* Roman numeral superscripts refer to the molecules in the following equivalent positions relative to the reference molecule at x, y, z:

(*a*) Benzamide—succinic acid

I $-2 + x, \frac{1}{2} + y, \frac{1}{2} - z$	VI x, y, z
II $-1 - x, -1 - y, -z$	VII $x, 1 + y, z$
III $-1 + x, -\frac{1}{2} + y, \frac{1}{2} - z$	VIII $-x, 1 - y, -z$
IV $-1 + x, y, z$	IX $1 + x, 1 + y, z$
V $-1 - x, -y, -z$	

(*b*) Compound (II)

O(1) · · · C(6^{I})	3·30	O(3) · · · H(6^{III})	3·00
O(1) · · · O(4^{I})	3·33	O(3) · · · H(4^{IV})	2·89
O(1) · · · N(1^{II})	2·92	C(3) · · · C(6^{V})	3·52
O(1) · · · H(2^{II})	2·05	H(4) · · · H(5^{VI})	2·64
O(2) · · · O(3^{II})	2·53	O(1) · · · O(1^{VII})	3·23
O(3) · · · H(1^{II})	1·59	O(1) · · · N(1^{VII})	2·94
O(2) · · · N(1^{III})	3·10	O(1) · · · H(3^{VIII})	2·60
O(2) · · · O(4^{III})	3·33	C(1) · · · C(3^{VIII})	3·50
O(2) · · · H(3^{III})	2·23	O(2) · · · C(2^{VIII})	3·36
O(3) · · · C(6^{III})	3·53	O(1) · · · H(6^{IX})	2·74
O(3) · · · O(4^{III})	3·41	N(1) · · · O(4^{IX})	3·20

Equivalent positions:

I $-1 + x, -1 + y, z$	VI $2 - x, 2 - y, -1 - z$
II x, y, z	VII $-x, 1 - y, -z$
III $x, -1 + y, z$	VIII $1 - x, 1 - y, -z$
IV $-x, -y, -1 - z$	IX $1 - x, 2 - y, -z$
V $1 - x, 2 - y, -1 - z$	

the 5 Å axis, by N–H · · · O bonds between the benzamide molecules (Figure 3). Interatomic distances and angles of the hydrogen-bonded network are also shown in Figure 3. The amide groups, joined by hydrogen bonds along the 5 Å axis, are not coplanar, rather their planes are offset by 1·2 Å. The separation between the phenyl rings, along this axis, is 3·1 Å as the ring is twisted 24° away from the plane of the amide group. Crystalline benzamide [10,11] shows very similar structural features as the benzamide component of (I), namely, the molecules are linked along a 5 Å axis by N–H · · · O bonds between amide groups the planes of which are offset by 1·2 Å, and the phenyl ring is twisted 26° out of the plane of the amide group. The twist angle of 26° in benzamide represents the balance between the probable loss of hydrogen-bond energy implied in the offset of 1·2 Å of the amide planes along the 5 Å axis, and the resistance to further torsion with possible loss of conjugation and

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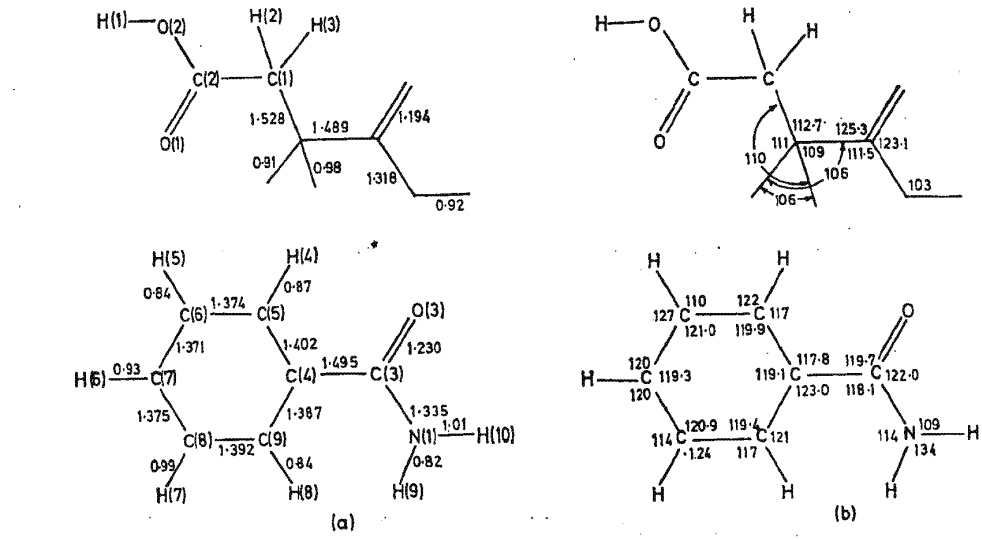


FIGURE 1 (a) Bond lengths (Å), and (b) bond angles (°) in (I)

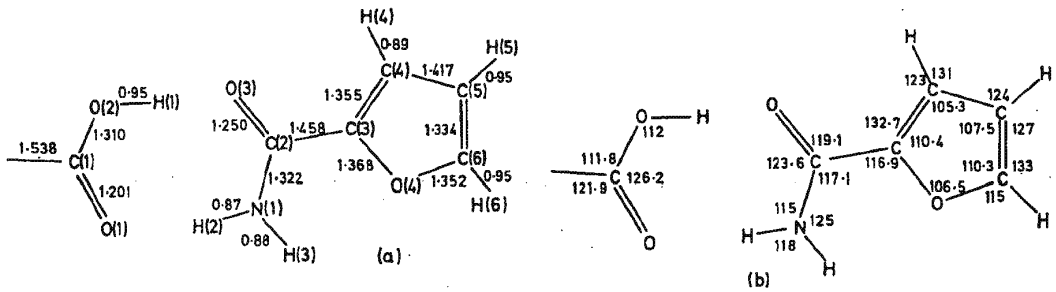


FIGURE 2 (a) Bond lengths (Å) and (b) bond angles (°) in (II)

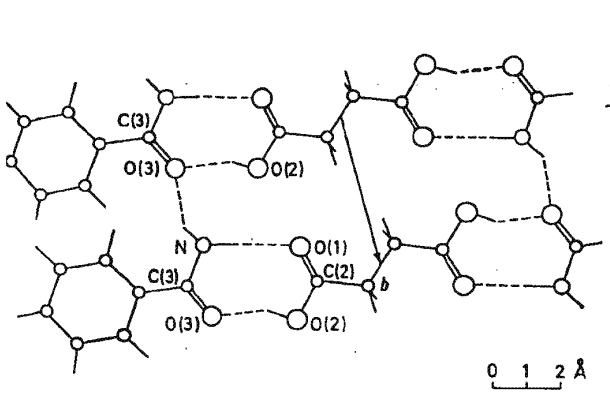


FIGURE 3 Packing arrangement of the hydrogen-bonded molecules seen normal to the planes of the succinic acid molecule in (I). Distances (Å) and angles of the hydrogen-bonded system are: O(2) · · · O(3) 2·60, N · · · O(1) 2·98, N · · · O(3) 3·02, O(1) · · · O(2) 3·60; C(3)–O(3) · · · O(2) 126·4°, C(2)–O(2) · · · O(3) 116·3°, C(3)–N · · · O(1) 107·6°, C(2)–O(1) · · · N 117·6°, C(3)–N · · · O(3) 133·0°, C(3)–O(3) · · · N 150·1°

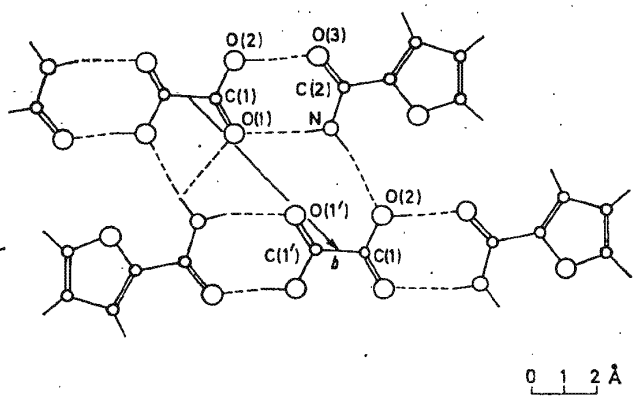


FIGURE 4 Packing arrangement of the hydrogen-bonded molecules seen normal to the plane of the oxalic acid molecule in (II). Distances (Å) and angles of the hydrogen-bonded system are: O(2) · · · O(3) 2·53, N · · · O(1) 2·92, N · · · O(1′) 2·94, N · · · O(2) 3·10; C(1)–O(2) · · · O(3) 117·5°, C(2)–O(3) · · · O(2) 126·1°, C(1)–O(1) · · · N 116·3°, C(2)–N · · · O(1) 109·1°, C(2)–N · · · O(2) 131·7°, C(2)–N · · · O(1′) 176·0°, C(1)–O(2) · · · N 123·0°, C(1′)–O(1′) · · · N 127·2°

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inefficient packing of molecules normal to the overall benzamide plane.[11]

The N–H · · · O geometry of (I) along the translation axis (Figure 3) is consistent with the observed pattern of N–H · · · O (carbonyl) hydrogen bonding[11] insofar as the N · · · H vector points toward the region where one would expect the electron lone-pair lobe of the carbonyl oxygen to lie. The carboxy-amide pair is distorted, the twist angle between the planes of the carboxy- and amide-groups being as large as 19·7°. The mean deviation of the oxygen and nitrogen atoms from the best plane through this system is 0·18 Å (Table 3). By way of comparison, the carboxy-amide pair of (II) is planar to within 0·07 Å (Table 3), with a twist angle of 3° between the planes of the carboxy- and amide-groups. In the crystal structure of fumaramic acid[12] ($HO_2C{\cdot}CH{:}CH{\cdot}CONH_2$), where the carboxy- and amide-groups are linked to each other to form the cyclic asymmetric pair as in (I) and (II), the dihedral angle between the two planes (carboxy and amide) is 0·5°, and the system is planar to within 0·07 Å.

The torsional distortion of the hydrogen-bonded pair of (I) is due to intermolecular forces. In order to determine their nature we construct the 'ideal' co-planar hydrogen-bonded pair, by bringing the plane of the succinic acid molecule into coincidence with that of the amide group, and consider the changes induced in the intermolecular contacts along the 5 Å axis. Although the offset between the planes of the neighbouring succinic acid molecules along the 5 Å axis is reduced from 3·0 Å (observed) to 1·2 Å in the hypothetical structure the ethylene chains would not be overcrowded in this model structure, for the intermolecular distance between the methylene hydrogens would be 2·9 Å. Moreover, in the crystal structure of adipamide,[13] the almost planar molecules are hydrogen-bonded (N–H · · · O) along a 5 Å axis with an offset between their carbon sheets of only 0·4 Å. Let us now consider the contact between the carboxy-groups along the 5 Å axis. The O(1) · · · O(2) separation, observed value 3·6 Å (see Figure 3 and Table 4) would be 3·0 Å, *i.e.* the observed interpair N–H · · · O distance, in the model arrangement.

Now an O · · · O contact of 3·1 ± 0·1 Å would not be unusual,[9,14] since the van der Waals radius of oxygen is reported[15] to be 1·4 Å. However, assuming that the van der Waals interaction between two oxygen atoms is dependent upon their direction of approach, and that the atoms O(1) and O(2) are respectively sp^2 and sp^3 hybridised, then the lone-pair lobes of O(1) and O(2), which would be partially directed towards each other in the hypothetical structure, are further removed from each other in the observed structure by virture of the 20° twist of the carboxy-group. We therefore tend to the view that the torsional distortion of the carboxy–amide pair is induced by intermolecular oxygen lone-pair–lone-pair repulsions.

In the crystal structure of (II) the oxalic acid is hydrogen-bonded to two furamide molecules *via* the carboxy–amide pairing (see Figure 4), a pattern identical to that in (I). These complex units (II) are interlinked, along the *b* axis, by N–H · · · O hydrogen bonds between furamide and oxalic acid fragments; in contradistinction to the packing motif in (I) in which the units are joined by amide–amide hydrogen bonds. The interatomic distances, and angles of the hydrogen-bonded network of (II) are shown in Figure 4. The N–H · · · O hydrogen bond interlinking the units of (II) appears to be bifurcated; the nitrogen atom straddles the oxygens of the oxalic acid with the N · · · H vector pointing along the bisectrix of the C–O(2)–H angle. The N · · · O(2) distance is 3·10 Å. The N–H proton also lies close to the available lone-pair lobe of the carbonyl oxygen O(1), the N · · · O(1) distance being 2·94 Å. Indeed, this hydrogen-bond network is similar to that of the (bifurcated) hydrogen-bonded system in azodicarboxamide.[11,16]

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