

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 1955¹ 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 crystallization⁹ or polymer nucleation¹⁰ 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.

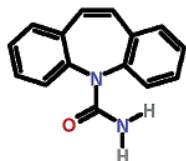
The pharmaceutically active molecule carbamazepine (CBZ) [5*H*-dibenz(b,f) azepine-5-carboxamide] was of interest to us because of its limited bioavailability¹¹ and its eight reported polymorphs^{12,13} and pseudopolymorphs.¹³ It is an important drug for the treatment of epilepsy and trigeminal neuralgia, and pure CBZ crystallizes as one of four polymorphs: tri-

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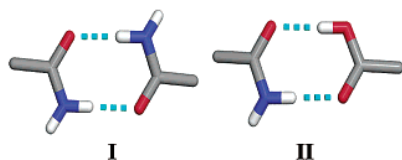
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clinic (form I); trigonal (form II); and monoclinic (forms III and IV). Its relevance, limited solubility, and the fact that it exists in multiple crystalline forms therefore makes CBZ an ideal candidate for a crystal engineering case study.



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 homosynthon¹⁵ 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 2₁-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.

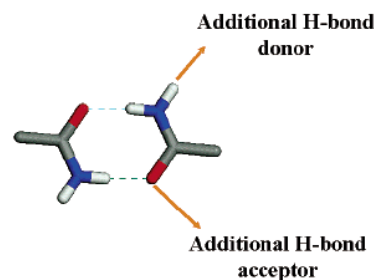


A survey of the Cambridge Structural Database (CSD)¹⁷ and a review of the literature indicated that only five of the eight forms of CBZ isolated thus far have been reported with full structural data (polymorphs II^{13b} and III,^{13c} a hydrate^{14a} with an *R* factor of ~10%, and two multiple-component phases¹⁴), 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 NH₂ group in CBZ is replaced with a CH₃ group; therefore, the supramolecular syn-

thon 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 cocrystal 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 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 pseudopolymorphs.²¹

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 ₂ O ₂	C ₁₇ H ₁₈ N ₂ O ₂ S ₁	C ₁₈ H ₁₄ N ₂ O ₂	C ₁₉ H ₁₅ N ₂ O ₂	C ₂₂ H ₁₇ N ₃ O ₄ S ₁	C ₂₁ H ₁₈ N ₄ O ₂	C ₁₇ H ₁₆ N ₂ O ₃	C ₁₆ H ₁₄ N ₂ O ₃	C ₁₉ H ₂₀ N ₂ O ₃	C ₂₄ H ₁₈ N ₂ O ₇	C _{23.5} H ₂₀ N ₃ O ₈	C ₄₄ H ₄₀ N ₄ O ₁₀	C ₁₆ H ₁₅ N ₃ O ₂
stochiometry	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	90	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)	98.132(3)	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	834.91(19)	4099.3(11)	4361.2(2)	3767.1(1)	1397.1(5)
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	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
density (g cm ⁻³)													
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	100	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 CuK α (λ = 1.540562, 30 kV, 15 mA). The powder data were collected over an angular range of 3–40° 2 θ in continuous scan mode using a step size of 0.02° 2 θ and a scan speed of 2.0°/min, and melting points were determined on a Mel-temp.

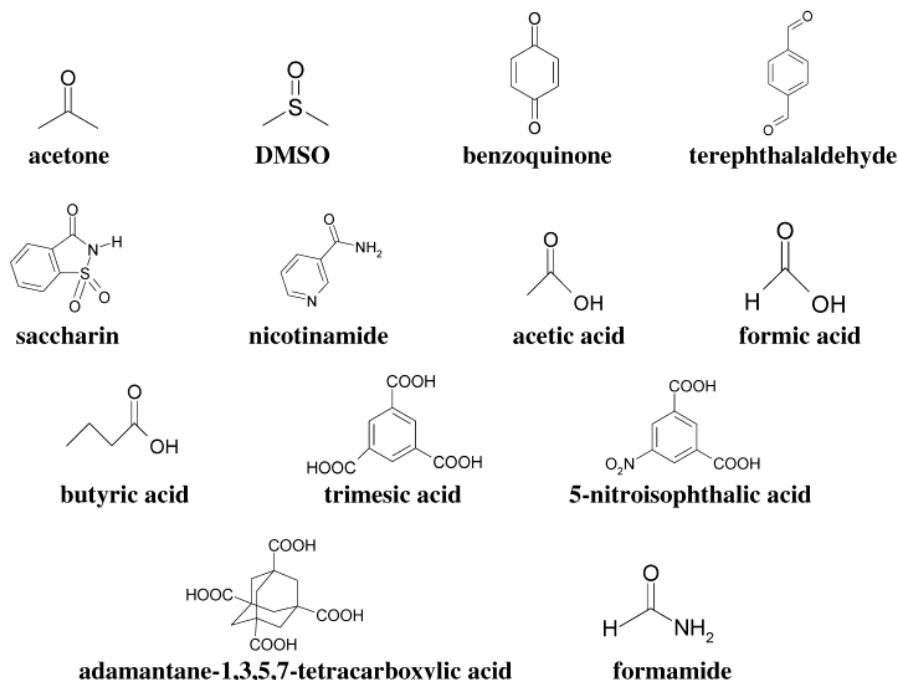
X-ray Crystallography. All single-crystal X-ray data were collected on a Bruker SMART-APEX CCD diffractometer. Lattice parameters were determined from least-squares analysis, and the reflection data were integrated using the program SAINT. Structures were solved by direct methods and refined by full 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 $\cdots$ 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 2₁-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

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 $\cdots$ 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 $\cdots$

O=S hydrogen bond with weak metrics ($d = 2.47$ Å, $D = 3.007(2)$ Å, $\theta = 113^\circ$). The inversion related saccharin molecules form auxiliary C—H $\cdots$ O hydrogen bonds ($d = 2.21$ Å, $D = 3.196(2)$ Å, $\theta = 150^\circ$), 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

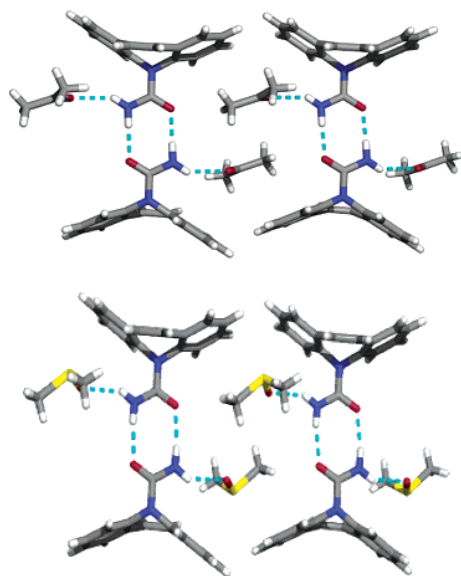


Figure 1. Illustration of the interactions between CBZ dimers and acetone (**1a**) or DMSO (**1b**). The cocrystal formers in these isostructural compounds are held by the anti N—H $\cdots$ O hydrogen bond of the CBZ dimers and thereby generate a void space between the CBZ dimers that is not present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

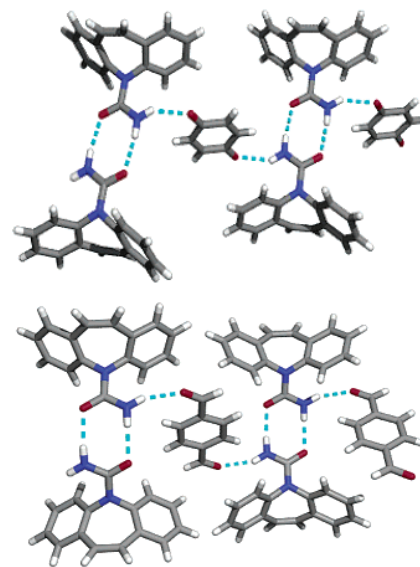


Figure 2. Interaction of CBZ dimers with cocrystal formers in structures **1c** and **1d**. The cocrystal formers are held by the anti N—H $\cdots$ O hydrogen bond of the CBZ dimers and not only generate a void space between the CBZ dimers but also sustain a 1-D hydrogen-bonded network.

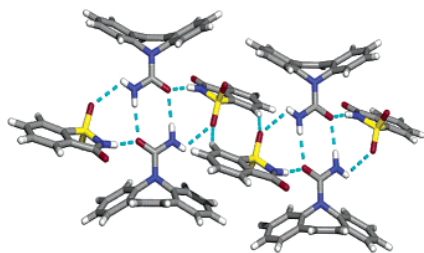


Figure 3. Illustration of the interaction between CBZ dimers and saccharin (**1e**). The cocrystal former in this structure is held by $\text{C}=\text{O}\cdots\text{H}-\text{N}$ hydrogen bonds with the CBZ dimers and is elongated into a 1-D network by $\text{C}-\text{H}\cdots\text{O}$ interactions between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

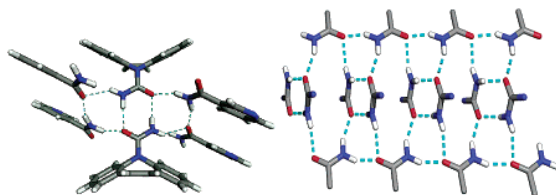


Figure 4. Cocrystal former, nicotinamide, links the CBZ homosynthon by forming a hydrogen-bonded strip in **1e**. For clarity, unwanted atoms are removed, and the hydrogen-bonded strip is shown in the adjacent figure.

packing with unsatisfied amide $\text{N}-\text{H}$ moieties? Comparison of the supramolecular complexes **1a–1e** with the pure forms suggests that approach of two molecules of CBZ via the anti $\text{N}-\text{H}\cdots\text{O}=\text{C}$ is sterically disfavored because of the shape of the CBZ dimers. However, the supramolecular complexes satisfy these $\text{N}-\text{H}$ 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 $\text{N}-\text{H}$ 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 heterosynths, the strongest hydrogen-bond donor (acid $\text{O}-\text{H}$) should hydrogen bond with the best acceptor atom (amide $\text{C}=\text{O}$).²⁴ This leaves the slightly weaker donor (amide $\text{N}-\text{H}$) to hydrogen bond to the weaker acceptor group (acid $\text{C}=\text{O}$). It should be noted that this heterosynthon minimizes intermolecular lone-pair repulsions that would occur between the acid $\text{O}-\text{H}$ and carbonyl moieties in hydrogen-bonded chains constructed from the homosynthon and $\text{N}-\text{H}\cdots\text{O}$ hydrogen bonds.^{18,23}

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

Table 2. Geometric Parameters of Intermolecular Interactions^a

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

^a The syn and anti $\text{N}-\text{H}$ 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)	1l	258–260°
CBZ.formamide (1:1)	1m	142–144°

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

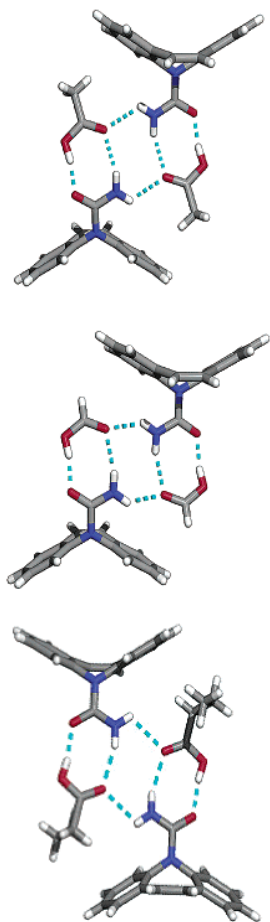


Figure 5. Heterosynthon **II** formed with cocrystal formers, acetic acid (**1g**), formic acid (**1h**), and butyric acid (**1i**). The anti-N-H group of CBZ is utilized to form the inversion related N-H...O hydrogen bond with carboxylic acid C=O of the cocrystal former, thereby generating a four-component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

$\theta = 163^\circ$) that are glide related. The CBZ azepine rings orient 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, $\theta = 122^\circ$; **1h**: $d = 2.06$ Å, $D = 2.894(2)$ Å, $\theta = 139^\circ$; **1i**: $d = 2.44$ Å, $D = 2.929(2)$ Å, $\theta = 109^\circ$).

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 homosynths and acid-amide heterosynths. Two carboxylic acid groups of the trimesic acid are free to form homosynths, and

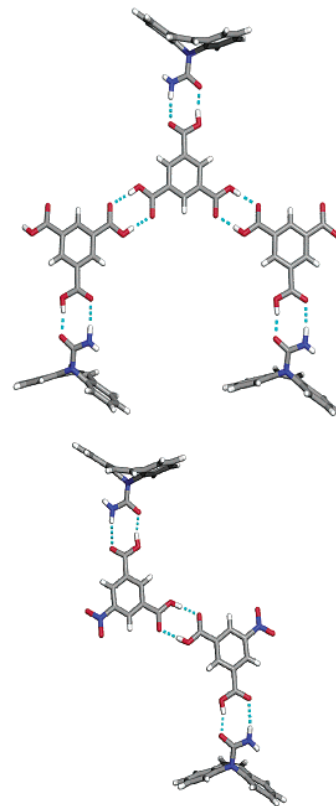


Figure 6. Illustration of portions of the structures observed in compounds **1j** and **1k**. One carboxylic acid group in the cocrystal former is utilized to form a heterosynthon, and the other carboxylic acid groups form homosynths that propagate a 1-D hydrogen-bonded pattern in **1j** and a 0-D discrete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

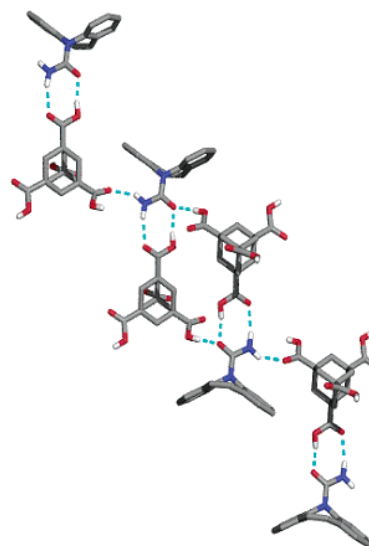


Figure 7. All the hydrogen-bonding sites of the cocrystal former are utilized in **1l**. Notice the heterosynthon **II** and absence of any carboxylic acid dimer homosynths.

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

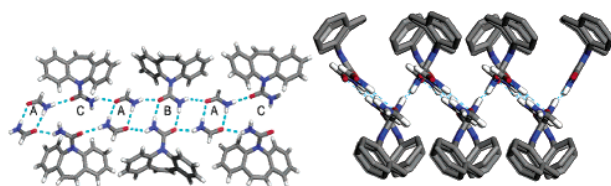


Figure 8. All the hydrogen-bonding sites of the CBZ molecule are utilized with the formamide cocrystal former in the supramolecular complex **1m**. Notice the homosynthon **I** formed by formamide molecules. The adjacent illustration represents the cross-section view of the hydrogen-bonded 2-D structure.

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.

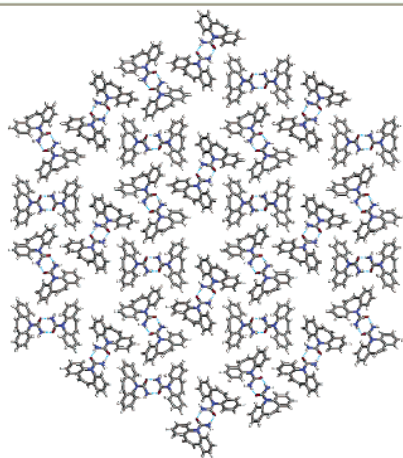
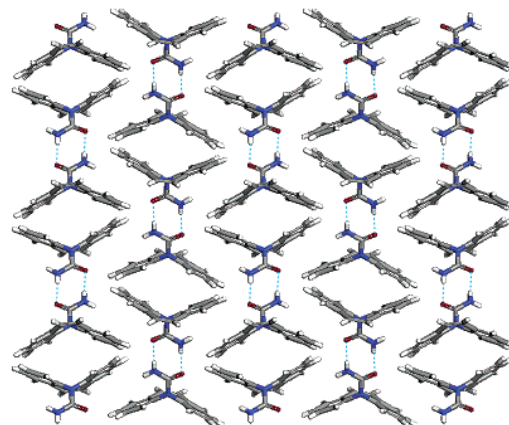
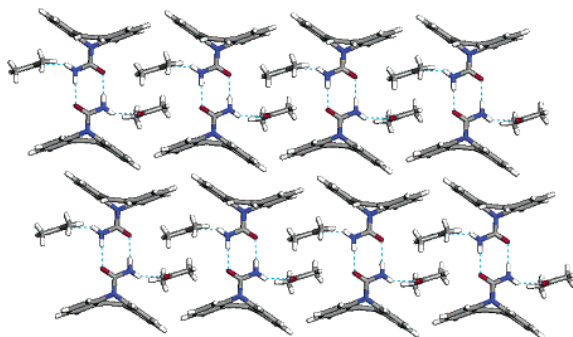
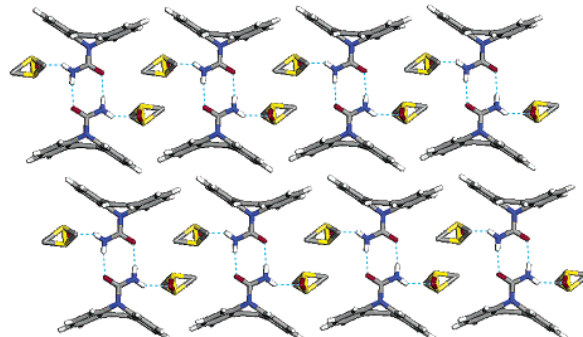
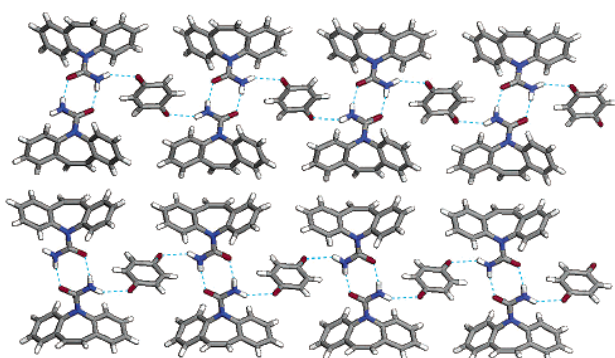
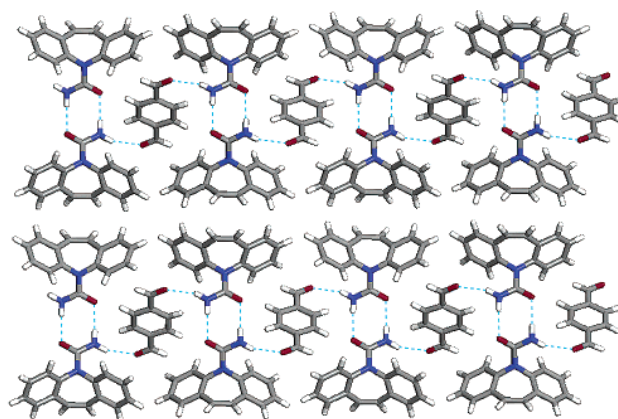
As revealed by Figure 9, there is a considerable degree of superstructural diversity in the crystal packing observed within compounds **1a–m**. Indeed, they also differ from the crystal packing exhibited by forms II and III of CBZ itself. An analysis of **1a–m** reveals that it is possible for the CBZ 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

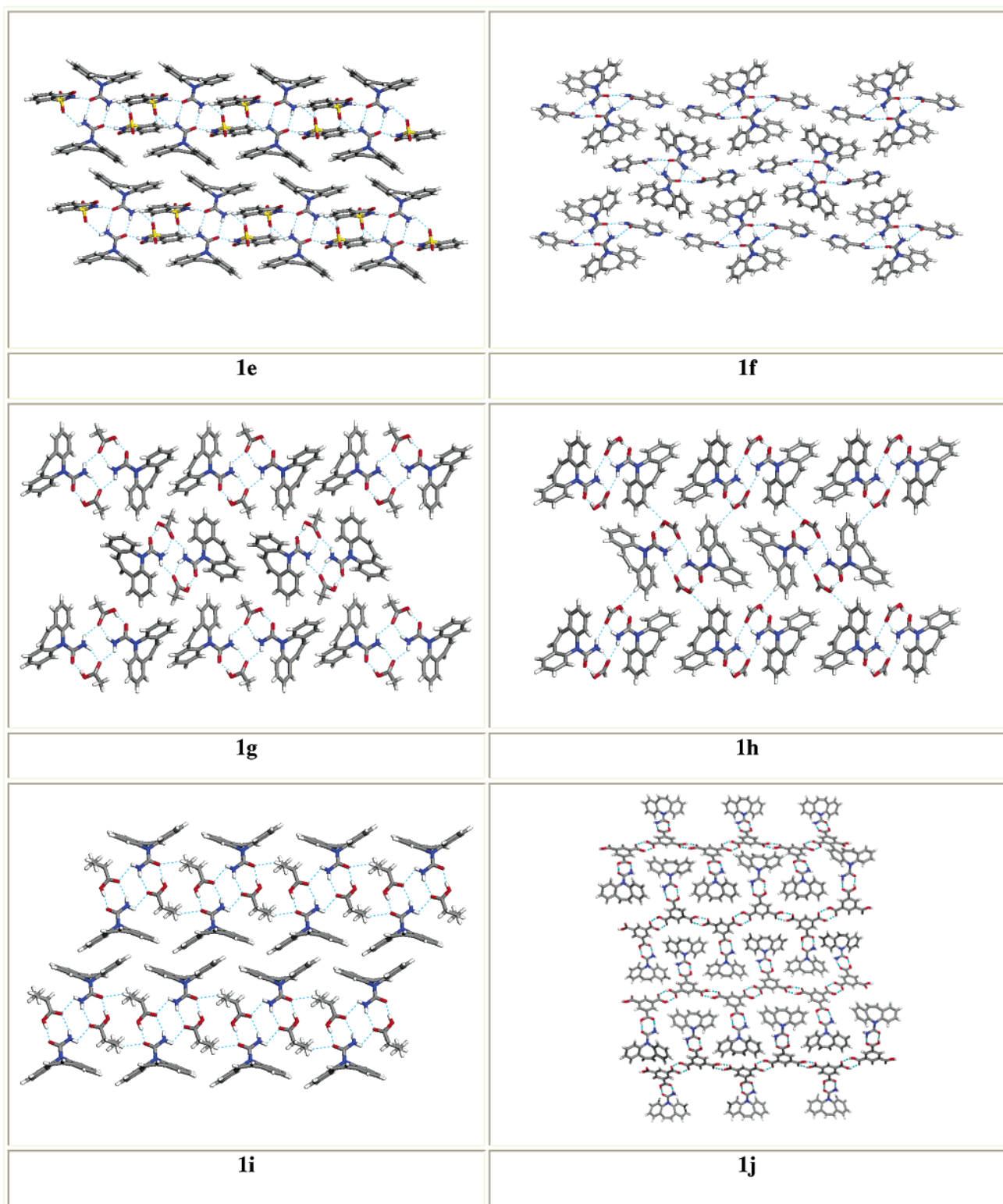
of supramolecular complex **1f** that does not follow the conventional amide hydrogen-bonded pattern.

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 cocrystal²⁶ and an amide-secondary amide cocrystal²⁷ 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 pyridine-carboxylic 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-

**Form II****Form III****1a****1b****1c****1d**



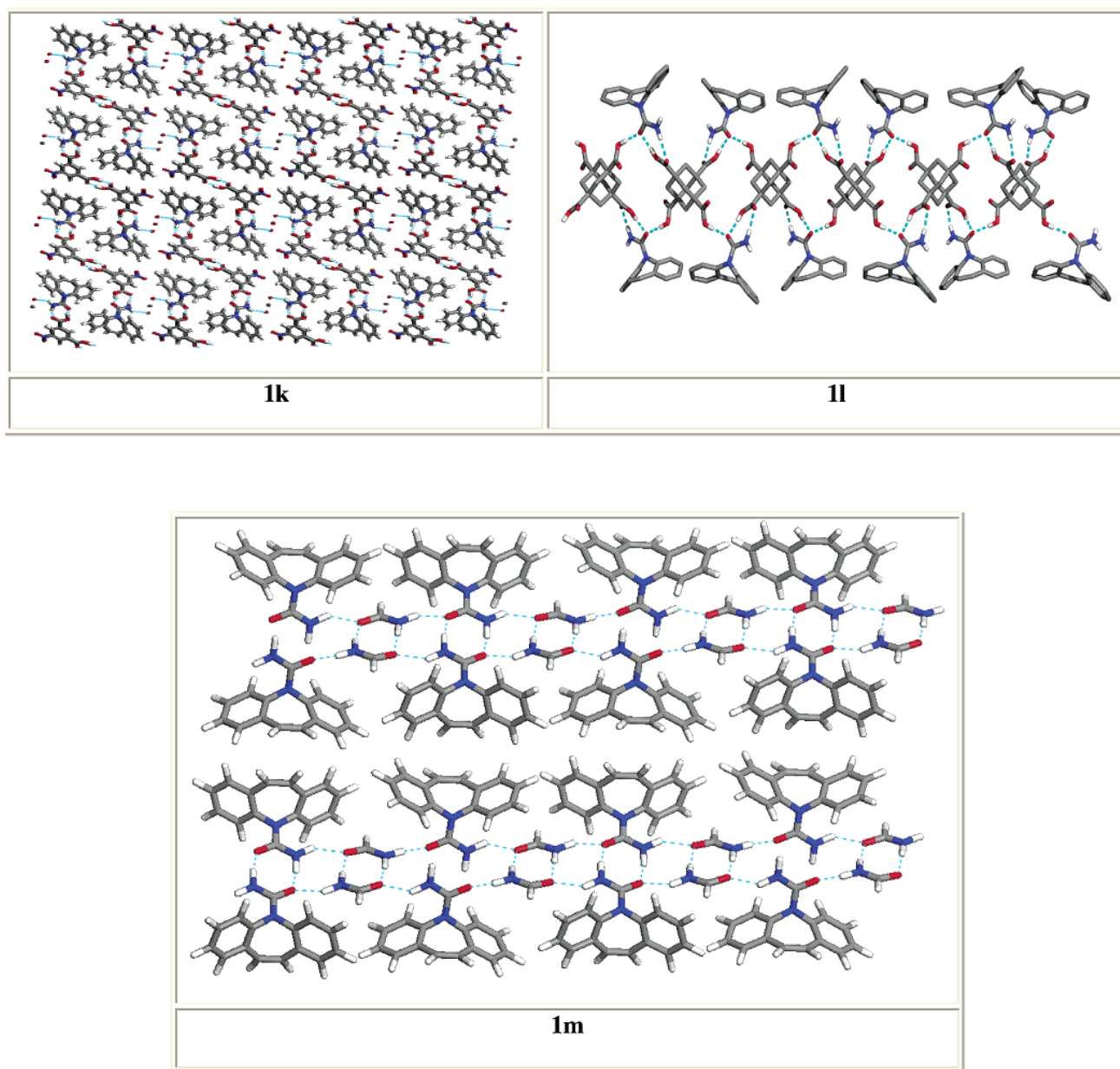


Figure 9. Crystal packing of pure CBZ (forms II and III) and supramolecular complexes **1a–1m**.

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

trate upon other supramolecular synthons, the use of GRAS²⁸ 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>.

References

- (1) Pepinsky, R. *Phys. Rev.* **1955**, *100*, 971.
- (2) Schmidt, G. M. J. *Pure Appl. Chem.* **1971**, *27*, 647.
- (3) (a) Hamilton, T. D.; Papaefstathiou, G. S.; MacGillivray, L. R. *J. Am. Chem. Soc.* **2002**, *124*, 11606. (b) MacGillivray, L. R.; Papaefstathiou, G. S.; Reid, J. L.; Ripmeester, J. A. *Cryst. Growth Des.* **2001**, *1*, 373. (c) Papaefstathiou, G. S.; MacGillivray, L. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2070. (d) Metzger, J. O. *Angew. Chem., Int. Ed.* **1998**, *37*, 2975. (e) Joy, A.; Ramamurthy, V. *Chem.—Eur. J.* **2000**, *6*, 1287.
- (4) (a) Desiraju, G. R. *Crystal Engineering—The Design of Organic Solids*; Elsevier: Amsterdam, 1989. (b) Lehn, J. M. *Supramolecular Chemistry: Concepts and Perspectives*; VCH: Weinheim, Germany, 1995. (c) Philp, D.; Stoddart,

- J. F. *Angew. Chem., Int. Ed.* **1996**, 35, 1154. (d) Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*; John Wiley & Sons: New York, 2000. (e) Desiraju, G. R. in *Stimulating concepts in Chemistry*; Vögtle, F.; Stoddart, J. F.; Shibasaki, M., Eds.; Wiley-VCH, Weinheim, Germany, 2000, p 293. (f) Holman, K. T.; Pivovar, A. M.; Swift, J. A.; Ward, M. D. *Acc. Chem. Res.* **2001**, 34, 107. (g) Aakeröy, C. B.; Beatty, A. M.; Helfrich, B. A. *Angew. Chem., Int. Ed.* **2001**, 40, 3240.
- (5) (a) Aakeröy, C. B. *Acta Crystallogr.* **1997**, B53, 569. (b) Kuduva, S. S.; Craig, D. C.; Nangia A.; Desiraju, G. R. *J. Am. Chem. Soc.* **1999**, 121, 1936. (c) Zaworotko, M. J. *Chem. Commun.* **2001**, 1. (d) Nguyen, T. L.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **2001**, 123, 11057. (e) Moulton, B.; Zaworotko, M. J. *Chem. Rev.* **2001**, 101, 1629. (f) Aakeröy, C. B.; Beatty, A. M. *Aust. J. Chem.* **2001**, 54, 409. (g) Zaworotko, M. J. *Nature* **1999**, 402, 242. (h) Kahn, O. *Curr. Opin. Solid State Mater. Sci.* **1996**, 1, 547. (i) Fyfe, M. C. T.; Stoddart, J. F. *Acc. Chem. Res.* **1997**, 30, 393. (j) Kaes, C.; Katz, A.; Hosseini, M. W. *Chem. Rev.* **2000**, 100, 3553.
- (6) (a) Threlfall, T. L. *Analyst* **1995**, 120, 2435. (b) Desiraju, G. R. *Science* **1997**, 278, 404. (c) Henck, J.-O.; Bernstein, J.; Ellern, A.; Boese, R. *J. Am. Chem. Soc.* **2001**, 123, 1834.
- (7) Bernstein, J.; Davey, R. J.; Henck, J.-O. *Angew. Chem., Int. Ed. Engl.* **1999**, 38, 3440.
- (8) Seddon, K. R.; Zaworotko, M. J. *Crystal Engineering: The Design and Application of Functional Solids*, NATO-ASI Series, Vol. 539; Kluwer: Dordrecht, The Netherlands, 1999.
- (9) (a) Peterson, M. L.; Morissette, S. L.; McNulty, C.; Goldsweig, A.; Shaw, P.; LeQuesne, M.; Monagle, J.; Encina, N.; Marchionna, J.; Johnson, A.; Gonzalez-Zugasti, J.; Lemmo, A. V.; Ellis, S. J.; Cima, M. J.; Almarsson, Ö. *J. Am. Chem. Soc.* **2002**, 124, 10958. (b) Morissette, S. L.; Soukasene, S.; Levinson, D.; Cima, M. J.; Almarsson, Ö. *Proc. Natl. Acad. Sci. U.S.A.*, **2003**, 100, 2180.
- (10) Lang, M.; Grzesiak, A. L.; Matzger, A. J. *J. Am. Chem. Soc.* **2002**, 124, 14834.
- (11) Kobayashi, Y.; Ito, S.; Itai, S.; Yamamoto, K. *Int. J. Pharm.* **2000**, 193, 137.
- (12) (a) Himes, V. L.; Mighell, A. D.; De Camp, W. H. *Acta Crystallogr.* **1981**, B37, 2242. (b) Reboul, J. P.; Cristau, B.; Soyfer, J. C.; Astier, J. C. *Acta Crystallogr.* **1981**, B37, 2242. (c) Lowes, M. M. J.; Cairo, M. R.; Lotter, A. P.; Van der Watt, J. G. *J. Pharm. Sci.* **1987**, 76, 744. (d) Lisgarten, J. N.; Palmer, R. A.; Saldanha, J. W. *J. Crystallogr. Spectrosc. Res.* **1989**, 19, 641. (e) Rustichelli, C.; Gamberini, G.; Ferioli, V.; Gamberini, M. C.; Ficarra, R.; Tommasini, S. *J. Pharm. Biomed. Anal.* **2000**, 23, 41. (f) Ceolin, R.; Toscani, S.; Gardette, M. F.; Dzyabchenko, V. N.; Bachet, B. *J. Pharm. Sci.* **1997**, 86, 1062. (g) Lang, M.; Kampf, J.; Matzger, A. J. *J. Pharm. Sci.* **2002**, 91(4), 1186.
- (13) (a) Chang, C. H.; Yang, D. S. C.; Yoo, C. S.; Wang, B. L.; Pletcher, J. *Acta Crystallogr.* **1981**, A37, C71. (b) Reck, G.; Dietz, G. *Cryst. Res. Technol.* **1986**, 21, 1463.
- (14) (a) Leiserowitz, L.; Schmidt, G. M. J. *J. Chem. Soc. A* **1969**, 2372. (b) MacDonald, J. C.; Whitesides, G. M. *Chem. Rev.* **1994**, 94, 2383. (c) Bernstein, J.; Etter, M. C.; Leiserowitz, L. *Structure Correlation*; Burgi, H.-B., Dunitz, J. D., Eds.; VCH: Weinheim, Germany, 1994; Vol. 2, p 431. (d) Whitesides, G. M.; Simanek, E. E.; Mathias, J. P.; Seto, C. T.; Chin, D. N.; Mammen, M.; Gordon, D. M. *Acc. Chem. Res.* **1995**, 28, 37. (e) Melendez, R. E.; Hamilton, A. D. *Hydrogen-Bonded Ribbons, Tapes, and Sheets as Motifs for Crystal Engineering in Design of Organic Solids*; Weber, E., Ed.; Springer: Berlin, 1998, p 130. (f) Rebek, J., Jr. *Acc. Chem. Res.* **1999**, 32, 278. (g) MacDonald, J. C.; Palmore, G. T. R. *The Role of Amides in the Noncovalent Synthesis of Supramolecular Structures in Solution, at Interfaces and in Solids in The Amide Linkage: Selected Structural Aspects in Chemistry, Biochemistry, and Materials Science*; Greenberg, A.; Breneman, C. M.; Liebman, J. F. Eds.; John Wiley & Sons: New York, 2000, p 291.
- (15) Bailey Walsh, R. D.; Bradner, M. W.; Fleischman, S.; Morales, L. A.; Moulton, B.; Rodríguez-Hornedo, N.; Zaworotko, M. J. *Chem. Commun.* **2003**, 186.
- (16) Allen, F. H.; Motherwell, W. D. S.; Raithby, P. R.; Shields, G. P.; Taylor, R. *New J. Chem.* **1999**, 25.
- (17) Allen, F. H.; Kennard, O. *Chem. Des. Automation News* **1993**, 8, 31.
- (18) Harding, M. M. *Acta Crystallogr.* **1983**, C53, 397.
- (19) Nair, R.; Gonen, S.; Hoag, S. W. *Int. J. Pharm.* **2002**, 240, 11.
- (20) (a) Holy, P.; Zavada, J.; Cisarova, I.; Podlaha, J. *Tetrahedron: Asymmetry* **2001**, 21, 3035. (b) Leiserowitz, L.; Nader, F. *Acta Crystallogr.* **1977**, B33, 2719. (c) Chang, Y.-L.; West, M.-A.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **1993**, 115, 5991. (d) Wash, P. L.; Maverick, E.; Chiefari, J.; Lightner, D. A. *J. Am. Chem. Soc.* **1997**, 119, 3802. (e) Leiserowitz, L.; Hagler, A. T. *Proc. R. Soc. London* **1983**, A388, 133. (f) Ohba, S.; Hosomi, H.; Ito, Y. *J. Am. Chem. Soc.* **2001**, 123, 6349.
- (21) (a) Kumar, V. S. S.; Kuduva, S. S.; Desiraju, G. R. *J. Chem. Soc., Perkin Trans. 2*, **1999**, 1069. (b) Nangia, A.; Desiraju, G. R. *Chem. Commun.* **1999**, 605.
- (22) Sheldrick, G. M. *SHELXTL*, Release 5.03; Siemens Analytical X-ray Instruments, Inc.: Madison, WI, 1994.
- (23) (a) Jeffrey, G. A.; Saenger, W. *Hydrogen bonding in biological structures*; Springer-Verlag: Berlin, 1991. (b) Jeffrey, G. A. *An introduction to hydrogen bonding*; Oxford University Press: New York, 1997. (c) Desiraju, G. R.; Steiner, T. *The Weak hydrogen bond in structural chemistry and biology*; Oxford University Press: Oxford, 1999. (d) Desiraju, G. R. *Acc. Chem. Res.* **2002**, 35, 565.
- (24) Etter, M. C. *Acc. Chem. Res.* **1990**, 23, 120.
- (25) Crystallizing pure CBZ from formamide did not yield X-ray quality crystals.
- (26) Emsley, J.; Ma, L. Y. Y.; Hursthouse, M. B.; Karaulov, S. A.; Motevalli, M. *J. Chem. Soc., Perkin Trans. 2*, **1990**, 1077.
- (27) Etter, M. C.; Reutzel, S. M. *J. Am. Chem. Soc.* **1991**, 113, 2586.
- (28) FDA GRAS notices can be found at www.cfsan.fda.gov/~dms/eafus.html.
- (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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