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

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

Introduction

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

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

Crystal Design Strategies

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

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

(1) This paper is dedicated to the memory of an inspirational colleague, Professor Margaret C. Etter.

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(3) (a)Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1304. (b) Vögtle, F. *Supramolecular Chemistry*; John Wiley & Sons Ltd: Chichester, U.K. 1991.

(4) Desiraju, G. R. *Crystal Engineering: The Design of Organic Solids*; Elsevier: New York, 1989.

(5) For example see selected volumes in the series: *Physics and Chemistry of Materials with Low-Dimensional Structures*; D. Reidel: Dordrecht, The Netherlands, 1977.

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(9) (a) Frankenbach, G. M.; Etter, M. C. *Chem. Mater.* **1992**, *4*, 272. (b) Etter, M. C.; Reutzel, S. M. *J. Am. Chem. Soc.* **1991**, *113*, 2586. (c) Etter, M. C.; Adsmond, D. A. *J. Chem. Soc., Chem. Commun.* **1990**, 589. (d) Etter, M. C.; Urbaficzyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. V. *J. Am. Chem. Soc.* **1990**, *112*, 8415. (e) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120. (f) Etter, M. C.; Frankenbach, G. M.; Adsmond, D. A. *Mol. Cryst. Liq. Cryst.* **1990**, *187*, 25. (g) Etter, M. C.; Frankenbach, G. M. *Chem. Mater.* **1989**, *1*, 10. (h) Etter, M. C.; Frankenbach, G. M.; Bernstein, J. *Tetrahedron Lett.* **1989**, *30*, 3617.

(10) For some recent approaches on the use of hydrogen bonds to assemble molecules in the solid state see: (a) Vaida, M.; Shimon, L. J. W.; Van Mil, J.; Ernst-Babrera, K.; Addadi, L.; Leiserowitz, L.; Lahav, M. *J. Am. Chem. Soc.* **1989**, *111*, 1029. (b) Zerowski, J. A.; Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1992**, *114*, 5473. (c) Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 712. (d) Zerowski, J. A.; Seto, C. T.; Wierda, D. A.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 9025. (e) Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 6409. (f) Garcia-Tellado, F.; Geib, S. J.; Goswami, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1991**, *113*, 9265. (g) Lehn, J.-M.; Mascal, M.; DeCian, A.; Fischer, J. *J. Chem. Soc., Perkin Trans. 2* **1992**, 461. (h) Lehn, J.-M.; Mascal, M.; DeCian, A.; Fischer, J. *J. Chem. Soc., Chem. Commun.* **1990**, 479. (i) Fouquey, C.; Lehn, J.-M.; Levelut, A.-M. *Adv. Mater.* **1990**, *2*, 25. (j) Simard, M.; Su, D.; Wuest, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 4696. (k) Ducharme, Y.; Wuest, J. D. *J. Org. Chem.* **1988**, *53*, 5789. (l) Gallant, M.; Biet, M. T. P.; Wuest, J. D. *J. Org. Chem.* **1991**, *56*, 2284.

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Table I. Four Fundamental Supramolecular Structures

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

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

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

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

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

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

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

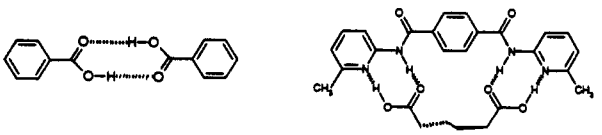


Figure 1. Examples of *discrete assemblies*. On the left is an example of a carboxylic acid dimer.[8,9a] Such dimers usually form about inversion centers, meaning that the complex is a *symmetric discrete assembly* with point group symmetry C_i. On the right is a host–guest complex.[10f] Such complexes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

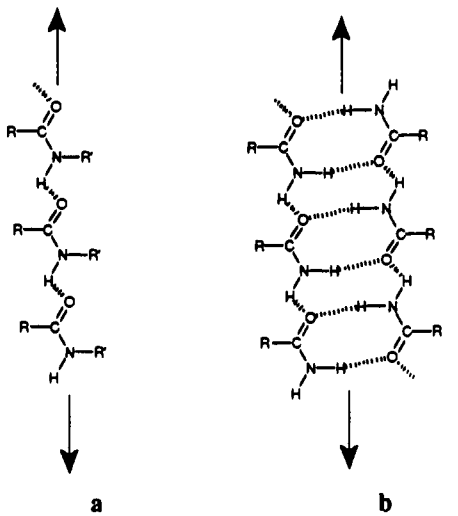


Figure 2. Examples of α-networks. The drawing on the left shows an α-network of a secondary amide.[15b] Such networks are commonly found with one of three different rod group symmetries, $P1$, $P2_1$, or Pa, depending upon the identity of the symmetry element (translation, screw axis, or glide plane)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

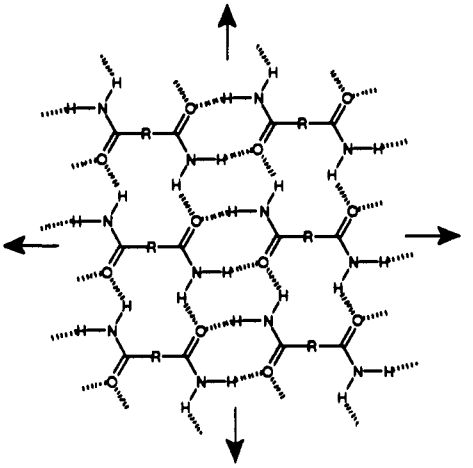


Figure 3. Common hydrogen bonding pattern for primary diamides.[15a] An example of a β-network.

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

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

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

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

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

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

(16) (a)Leiserowitz, L.; Hagler, A. T. *Proc. R. Soc. London* **1983**, *A*, 133. (b) Weinstein, S.; Leiserowitz, L. *Acta Crystallogr.* **1980**, *B36*, 1406.

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

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

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

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

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

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

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

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

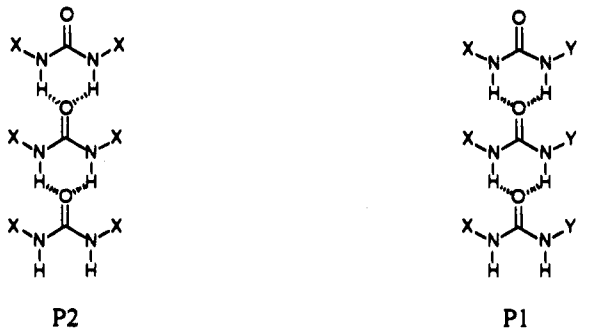


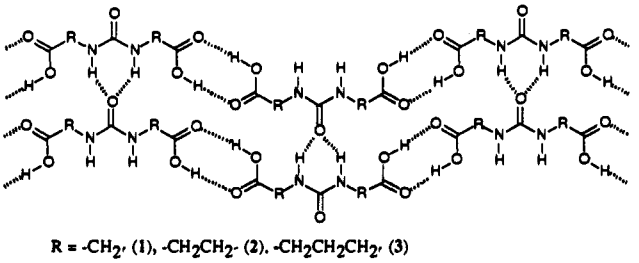
Figure 4. *N,N'*-Disubstituted ureas form α-networks by forming pairs of complementary hydrogen bonds. In our work, we have observed that symmetrical ureas usually retain their two-fold axis within the solid state and form α-networks of *P*2 symmetry. If the substituents differ, then there usually is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

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

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

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

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



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

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

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

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

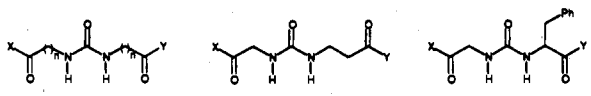
(24) Close packing has long been recognized as a primary determinent of molecular crystal structures. Kitaigorodskii, A. I. *Organic Chemical Crystallography*; Consultants Bureau: New York, 1961.

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

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

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

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



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

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

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

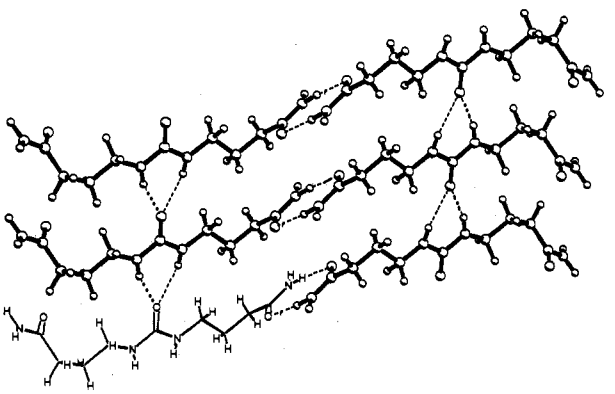


Figure 5. β-Network of the diamide **4**. There is a two-fold axis passing through the urea carbonyl groups and an inversion center at the center of the cyclic amide hydrogen bonds. The α-network defined by the urea hydrogen bonds has *P*2 rod symmetry; the layer symmetry of the β-network is *P*2/*c*.

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

Results

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

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

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

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

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

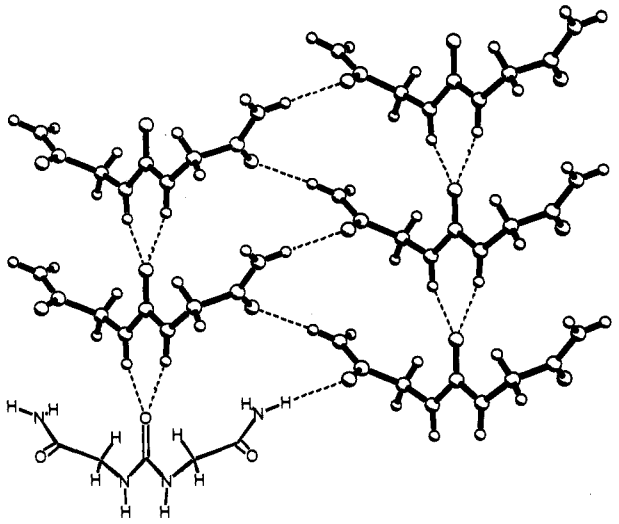


Figure 6. β-Network of the diamide **5**. The urea carbonyl groups lie on a two-fold axis and form an α-network of $P2$ rod symmetry. The amide hydrogen bonds form a helix about a two-fold screw axis. The layer symmetry of the β-network is $C2$.

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

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

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

When the crystal structures of compounds **6** and **7** were determined, the results were somewhat surprising (Figure 7). The best interpretation of the X-ray data indicates that in *both* cases the molecules are completely disordered about a pseudo-two-fold axis passing through the urea carbonyl group. Indeed, the crystal structure of the monoamide **6** is isomorphous with the structure of **1**. This apparent crystallographic disorder prevents us from unambiguously determining the amide and acid hydrogen bond patterns. The observed disorder was not anticipated in either case. Its presence illustrates one problem that can interfere with any design effort. This pseudosymmetry also illustrates the similarity of the amide and acid functionalities in terms of size and shape as well as intermolecular bonding capabilities.

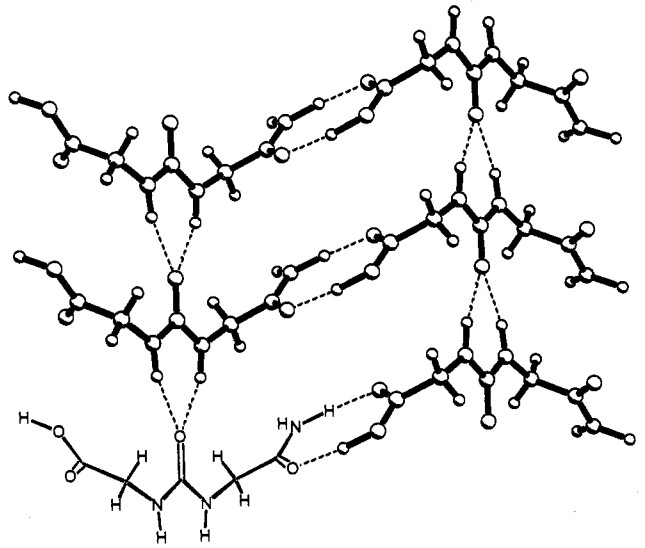


Figure 7. β-Network of the monoamide **6**. The compound has a disordered structure. There is a crystallographic two-fold axis passing through the urea carbonyl groups and an inversion center at the center of the cyclic acid–amide hydrogen bond. This disorder makes it impossible to distinguish the true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

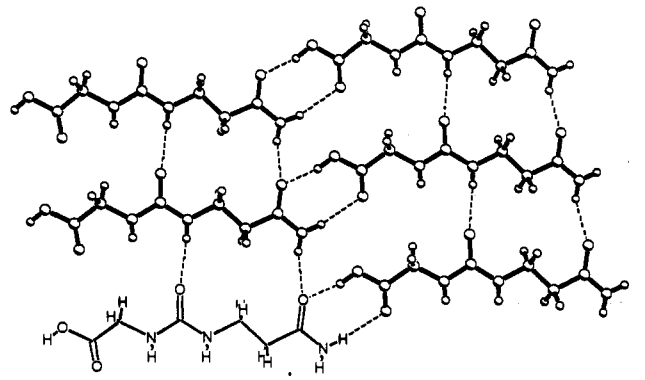


Figure 8. β-Network of the monoamide **8**. This β-network has $P1$ layer symmetry, with neighboring molecules related by simple translations only. The intermolecular urea to urea hydrogen bonds are unusual in this structure. Instead of the normal symmetrical structure there is only one urea hydrogen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

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

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

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

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

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

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

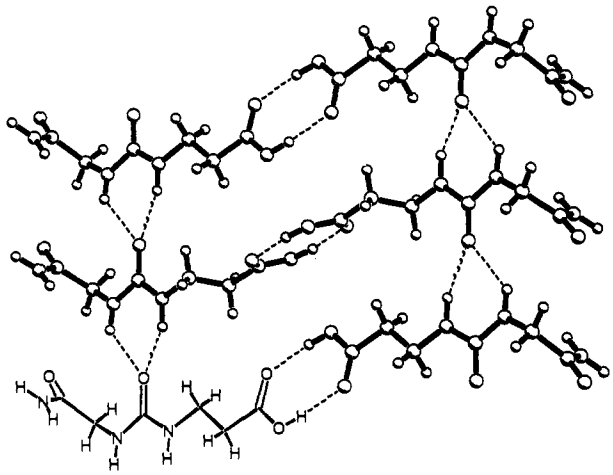


Figure 9. β-Network of the monoamide **9**. This structure contains two molecules in the asymmetric unit. The carboxylic acid ends of the two independent molecules have different conformations. The urea α-network of $P\bar{1}$ rod symmetry consists of alternate independent molecules. Neighboring α-networks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

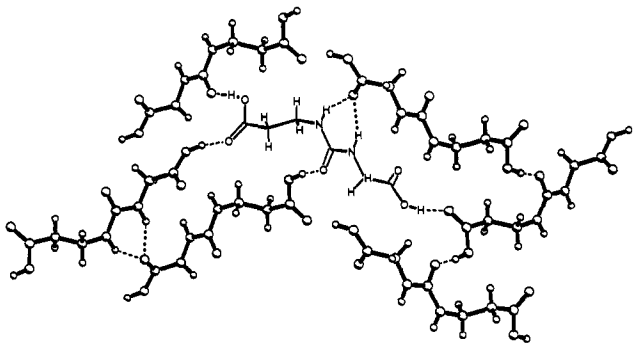


Figure 10. Crystal structure of the diacid **10**. In this structure the expected complementary hydrogen-bond patterns have been broken. The molecules form a γ-network of $P2_12_12_1$ space group symmetry. There is no β-network.

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

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

Introduction of a Stereogenic Center. Molecular chirality plays a fundamental role in determining solid-state structure. All of the urea derivatives discussed above have been achiral. It was of interest to determine the response of the solid-state structure of this class of compounds to the introduction of a stereogenic center. The urea dicarboxylic acids and their derivatives are prepared from amino acids, and most of the available amino

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

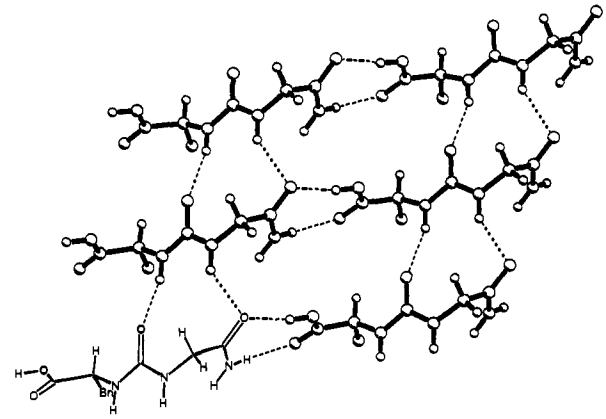


Figure 11. β-Network of the acid amide **14**. This β-network has $P\bar{1}$ layer symmetry, with neighboring molecules related by simple translations only. To simplify the figure, the benzyl groups have been omitted and are represented by a dummy atom labeled Bn. The distorted urea hydrogen-bond distance,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

acids are chiral. In our initial studies a relatively simple example was chosen: the urea formed from glycine and phenylalanine, a molecule possessing a single stereo center. The diacid **11** and the two isomeric monoamide derivatives **12** and **13** were prepared in racemic form, and their crystal structures were determined.

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

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

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

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

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

Polymorphism is a common phenomenon for some classes of

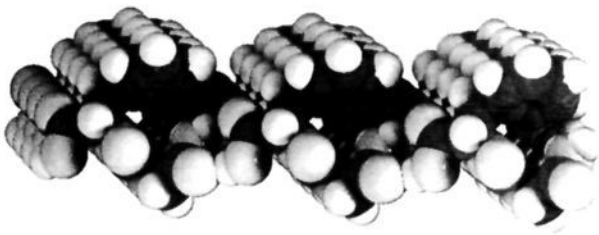


Figure 12. Edge view of the β-network of the acid amide **14**.

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

Discussion

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

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

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

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

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

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

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

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

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

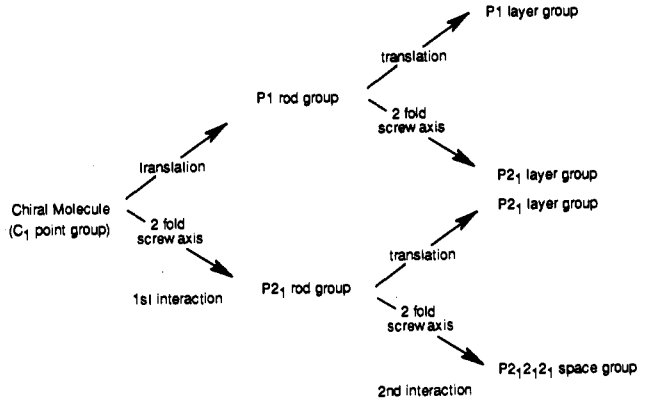
Chirality. There remains one powerful form of symmetry control that can be used in a design effort. One can turn to pure

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

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

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

Scheme I. Probable Self-Assembly Pathways for Chiral Molecules



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

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

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

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

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

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

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

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

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

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

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

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

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

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

Summary

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

Experimental Section

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

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

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

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

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

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

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

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

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Table III. Crystal Data

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

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

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

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

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

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

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

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

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