Molecular Symmetry and the Design of Molecular Solids: The Oxalamide Functionality as a Persistent Hydrogen Bonding Unit

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Abstract: A symmetry analysis based upon the structure of simple molecules and their anticipated intermolecular interactions can lead to successful predictions of molecular packing and crystal symmetry. As a demonstration of these ideas an in-depth study of the oxalamide functionality as a persistent hydrogen bonding unit is presented. The synthesis and structural characterization of a series oxalamide dicarboxylic acids is presented and the structures compared with the analogous urea compounds. Both the urea and oxalamide dicarboxylic acids form designed two-dimensional hydrogen-bonded β-networks with a significant degree of reliability. The urea designs are quite reliable when there is a molecular 2-fold axis, but competing hydrogen bond patterns are found when less symmetrical molecules are studied. The oxalamide design based on inversion centers is also quite reliable, with the designed layer structure found in most cases.

Introduction

The physical and chemical properties[1] of a molecular solid depend upon the nature of the constituent molecules as well as the relative orientations and spacing of the molecules within the solid. The preparation of a new solid, with specific properties, is an example of supramolecular synthesis.[2,3] As in the case of molecular synthesis, a successful supramolecular synthesis requires first a good design.

A successful design of a molecular crystal depends upon the identification and synthesis of molecular functionalities that will predictably and persistently lead to specific favorable intermolecular interactions. By combining such chemical insight with symmetry considerations, one may design and prepare molecules that will self-assemble into crystalline solids that contain desired structural features. However, this process of supramolecular synthesis is extremely difficult due to a multitude of inherent problems.

Intermolecular interactions are weak and relatively nondirectional as compared to intramolecular bonds. This makes the identification of predictable and persistent interactions difficult, since alternate unanticipated structures may be more stable or kinetically favored. Many designs that appear reasonable in theory are never realized fact, because of an inadequate accounting of the packing and symmetry requirements of a crystalline solid. Despite these problems, much progress has been made and many groups have completed successful supramolecular syntheses.

In our own work[3] we have identified two-dimensional layered solids as significant targets for supramolecular synthesis. Our approach to a two-dimensionl layered solid has been to design a two dimensional network of mutually hydrogen bonded molecules. This approach has required the identification of persistent and complementary hydrogen bond intereactions, but, in addition, we have focused upon the problem of including within our designs the necessary translational symmetry operators needed for a two-dimensional network.

A series of urea dicarboxylic acid derivatives have been designed, prepared, and structurally characterized.[3] The urea functionality was found to be a reasonably reliable and persistent unit that will self-assemble into a one-dimensional α-network[4] held together via hydrogen bonds. With two side chains that terminate in carboxylic acid or amide functionalities, urea dicarboxylic acid derivatives form additional hydrogen bonds in a second dimension, linking the one-dimensional α-networks into two-dimensional β-networks.[4] Simple symmetrical urea dicarboxylic acid derivatives were found to form structures consistent with this design, but various unsymmetrical racemates formed structures that lacked the necessary translational symmetry and failed to form the anticipated β-network. However, when a single enantiomer of an unsymmetrical chiral ureylene was studied, the β-network formed in accordance with the design.[3b] A discussion of the importance of chirality as a means to control the translational symmetry needed for layer structures was an important part of an earlier publication.

An examination of the racemate structures suggests that a factor for the failure of the molecules to form the designed β-networks was the tendency of these molecules to form discrete centrosymmetric dimer structures in a manner inconsistent with the layer design (Figure 1a). Centrosymmetric dimer formation by asymmetric molecules does not generate the translational

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(1) There are many examples of physical properties that depend upon molecular orientation and spacing as well as crystallographic symmetry. Optical properties depend critically upon the relative orientation of molecular dipoles in a crystal. Electronic properties depend upon molecular contacts and spacing. Topochemical reactions depend upon molecular spacing and relative orientations.

(2) Many groups are working on this problem. For a recent review see: Lehn, J.-M. *Supramolecular Chemistry. Concepts and Perspectives*; VCH Verlagsgesellschaft: Weinheim, 1995.

(3) (a) Zhao, X.; Chang, Y.-L.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 6627−6634. (b) Chang, Y.-L.; West, M. A.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 5991−6000. (c) Toledo, L. M.; Lauher, J. W.; Fowler, F. W. *Chem. Mater.* **1994**, *6*, 1222−1226. (d) Kane, J. J.; Liao, R. F.; Lauher, J. W.; Fowler , F. W. *J. Am. Chem. Soc.* **1995**, *117*, 12003−12004

(4) Supramolecular assemblies can be divided into four groups dependent upon the degree of translation symmetry.[3b] Discrete assemblies lack translation symmetry and are characterized by their point group symmetry. An α-network has one degree of translational symmetry and is characterized by its rod group symmetry. A β-network has two degrees of translational symmetry and is characterized by its layer group symmetry. A γ-network has three degrees of translational symmetry and is characterized by its space group symmetry. Lauher, J. W.; Chang, Y.-L.; Fowler, F. W. *Mol. Cryst. Liq. Cryst.* **1992**, *211*, 99−109.

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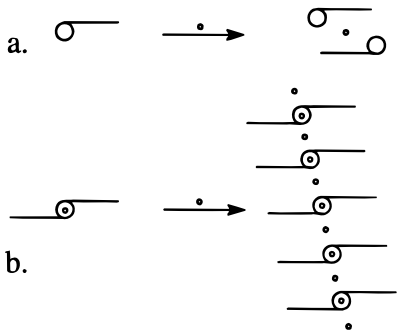


Figure 1. (a) If an external center of symmetry is added to a chiral molecule, then a centrosymmetric dimer with C_i point group symmetry is produced. (b) If an external center of symmetry is added to a centrosymmetric molecule, then the combination of the two centers produces a translational symmetry operator and the resulting assembly is an infinite one dimensional α-network with $P\bar{1}$ rod group symmetry.

symmetry operations needed for layer production. The tendency of racemates to form discrete centrosymmetric dimer structures is well discussed in the crystallographic literature.[5] The strategy of using a single enantiomer is one approach to solving this problem.

Another approach to the problem of discrete centrosymmetric dimer production is to avoid the question of chirality all together by choosing achiral molecules that will reliably maintain their symmetry element and their achirality in a crystalline lattice. The best approach is to choose molecules that possess and maintain in the crystal a center of symmetry. If a molecule, which is itself centric, forms a centrosymmetric dimer with another molecule then the combination of two different centers of symmetry, one internal to the molecule and the second external to the molecule, will necessarily generate a translational symmetry operator (Figure 1b). Chemically this will correspond to the supramolecular assembly of a one-dimensional α-network.

In contrast to the urea functionality which is inherently acentric and polar, the oxalamide functionality is inherently centric. In crystals, symmetrical substituted ureas tend to possess C_2 molecular point group symmetry and form polar α-networks with P_2 rod symmetry, Figure 2. We anticipated that centric oxalamide derivatives would maintain C_i symmetry in a crystal and would form α-networks of $P\bar{1}$ rod symmetry. The necessary external center of symmetry would correspond to the self-complementary oxalamide hydrogen bonds between neighboring molecules in the α-networks, Figure 3.

In this paper we present an in-depth study of the oxalamide functionality as a persistent hydrogen bonding unit. Oxalamides have a chemical similarity to ureas and a similar propensity to form hydrogen bonds. We report the synthesis and structural characterization of oxalamide dicarboxylic acids and compare them with the analogous urea compounds. For purpose of comparison, the synthesis and structural analysis of additional urea dicarboxylic acid derivatives are also reported. Comparisons will also be made with other known oxalamides, particularly the work of Karle and Ranganathan,[6] who have studied a series of retro-bispeptides based upon the oxalamide functionality.

Results

Symmetrical ureas (**1u**−**6u**) and oxalamides (**1o**−**6o**) were prepared and crystals suitable for X-ray diffraction were grown

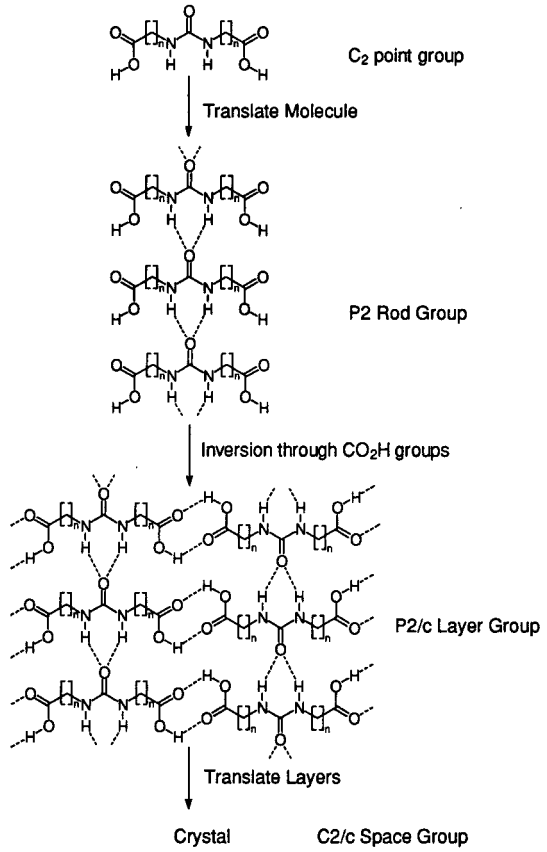
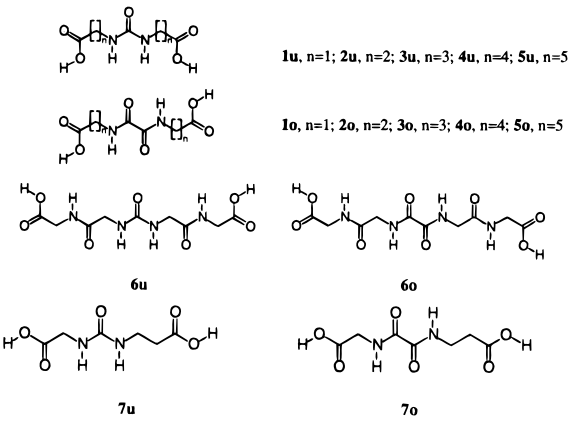


Figure 2. This diagram shows the self-assembly of a symmetric dicarboxylic acid substituted urea molecule. As each intermolecular interaction is considered, the corresponding symmetry operators can be combined to yield the corresponding symmetry group. Single molecules have *C*2 point group symmetry. Simple translation yields a linear α-network of *P*2 rod symmetry via urea hydrogen bonds. Neighboring α-networks self assemble into a *β*-network with *P*2/*c* symmetry by forming cyclic carboxylic acid dimers about centers of symmetry. Finally neighboring layers pack in an offset matter using a centering translation to give a crystal with *C*2/*c* space group symmetry.

from aqueous solutions. In previously reported work, we prepared and structurally characterized the lower members of the urea series, compounds **1u**−**3u,** the glycylglycine compound, **6u,** as well a representative unsymmetrical urea, **7u**.[3a] The syntheses and structure determinations of the urea compounds **4u** and **5u** as well as oxalamide compounds **1o** and **3o**−**7o** have now been completed. The crystal strucutrure of **2o** has been determined previously.[7]



(5) Brock, C. P.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 9811−9820.

(6) 6(a) Karle, I. L.; Ranganathan, D.; Sha, K.; Vaish, N. K. *Int. J. Peptide Protein Res.* **1994**, *43*, 160−165. (b) Karle, I. L.; Ranganathan, D. *Int. J. Peptide Protein Res.* **1995**, *46*, 18−23. (c) Karle, I. L.; Ranganathan, D. *Biopolymers* **1995**, *36*, 323−331.

(7) Shkol'nikova L. M.; Gasparyan A. V.; Poznyak A. L.; Bel'skii V. K.; Dyatlova N. M. *Koord. Khim.* **1990**, *16*, 50−54.

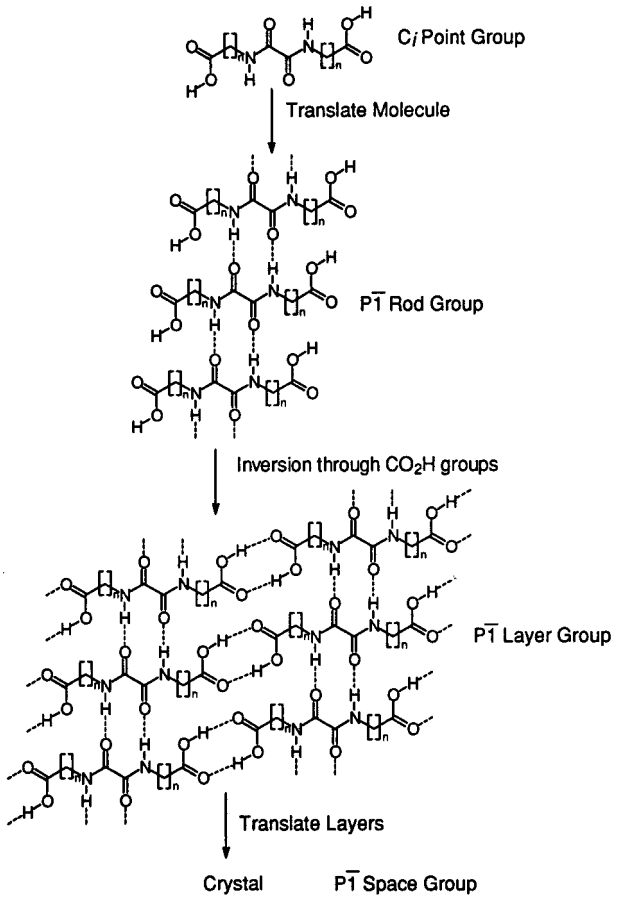


Figure 3. This diagram shows the self-assembly of a symmetric dicarboxylic acid substituted oxalamide molecule. As each intermolecular interaction is considered, the corresponding symmetry operators can be combined to yield the corresponding symmetry group. Single molecules have C_i point group symmetry. Simple translation yields a linear α-network of $P\bar{1}$ rod symmetry via oxalamide hydrogen bonds. Neighboring α-networks self-assemble into a β-network with $P\bar{1}$ symmetry by forming cyclic carboxylic acid dimers about centers of symmetry. Finally neighboring layers pack via simple translation to give a crystal with $P\bar{1}$ space group symmetry.

Symmetrical Urea Dicarboxylic Acids. Symmetrical disubstituted ureas usually crystallize with retention of the molecular 2-fold axis, thus in the crystal, they possess C_2 point group symmetry. This is illustrated by the structures of ureas **4u** and **5u** shown in Figure 4. Each of these molecules forms a layer structure in accordance with the scheme outlined in Figure 2. The presence of the urea functionality leads to a characteristic spacing along the 2-fold axis of each layer (4.69 Å in **4u**, 4.65 Å in **5u**). The nearly planar layers of the two structures are quite similar to the layer structure found earlier for compound **3u**.[3a] Compound **1u** crystallizes in the same *C*2/*c* space group and has the same intermolecular interactions and the same supramolecular structure, but because of a different molecular conformation, it forms distinctly pleated layers. The pleating of the layers in **1u** is likely due to steric interactions between the amide and carboxylic acid functional groups that force the molecular structure into a gauche conformation incompatible with a more planar layer structure. The nearly planar layer structure found for the higher members of the series, **3u**−**5u**, would maximize the van der Waals interactions between the layers. The remaining member of the series, **2u**, is unusual. Although it has a similar supramolecular structure and also crystallizes in the space group *C*2/*c*, it has three independent molecules in the unit cell. Thus, the first two members of the **1u**−**5u** series have somewhat unusual structures, while the three

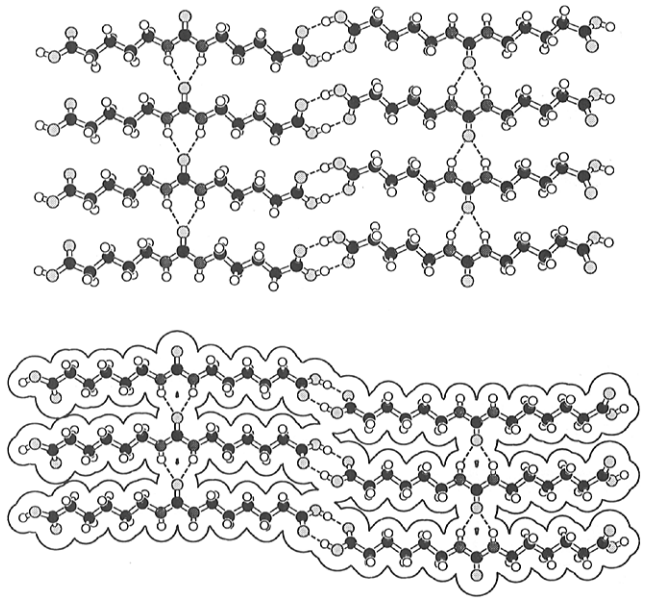


Figure 4. The β-network structures formed by compounds **4u** (at the top) and **5u** (at the bottom). The urea functionality of each molecule lies on a crystallographic 2-fold axis. The carboxylic acid functionalities dimerize about inversion centers.

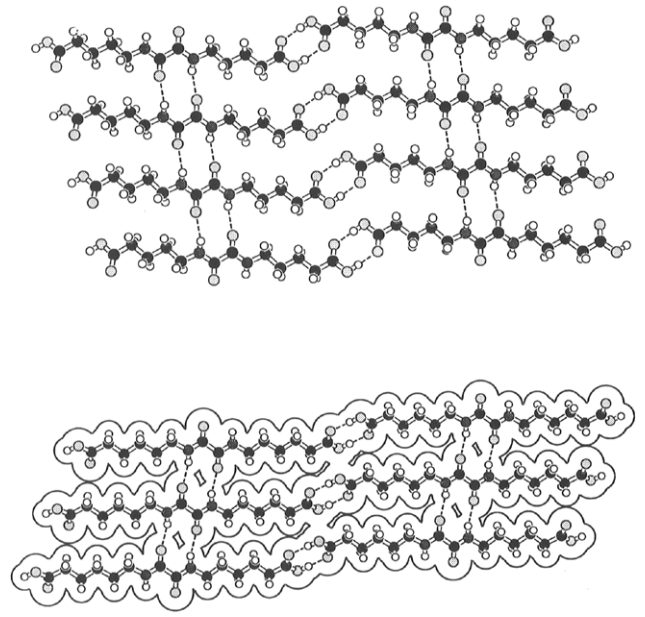


Figure 5. The β-network structures formed by compounds **4o** (at the top) and **5o** (at the bottom). The oxalamide functionality of each molecule lies on a inversion center. The carboxylic acid functionalities dimerize about inversion centers.

higher members form a isostructural series. Since there is no obvious problem with the molecular packing in these structures, it is reasonable to predict that symmetrical ureylene dicarboxylates with even longer side chains would have similar structures.

Symmetrical Oxalamide Dicarboxylic Acids. The structures of the five compounds **1o**−**5o** also form an isostructural series with one exception, compound **3o**. The symmetrical oxalamides are centrosymmetric molecules. In an isostructural series they crystallize in the space group $P\bar{1}$ and retain their center of symmetry as they crystallize forming layers in accordance with the scheme illustrated in Figure 3. The nearly planar layer structures of the two higher members of the series **4o** and **5o** are shown in Figure 5. The first member of the series, compound **1o**, forms a similar layer, but like the first member of the urea series, compound **1u** discussed above, compound

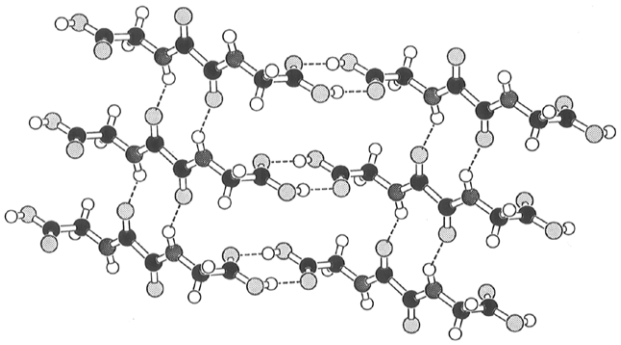


Figure 6. The β-network formed by compound **1o**, polymorph **A**. Compare this β-network to the designed β-network shown in Figure 3.

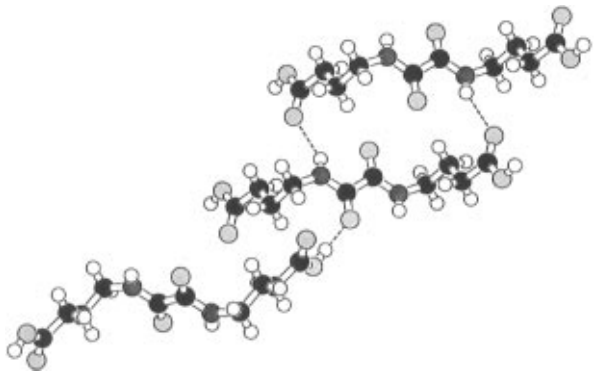


Figure 7. Compound **3o** does not form the designed β-network. Instead of the expected like to like, acid to acid, amide to amide hydrogen bonds there is a like to unlike pattern that results in a large 20-member ring held together by amide hydrogen to acid carbonyl hydrogen bonds.

1o forms a pleated layer structure due to its molecular conformation, Figure 6.

Compound **3o** is an exception. Instead of forming the designed layer structure as outlined in Figure 3, it forms a complex three-dimensional structure in which the anticipated like to like, acid to acid, amide to amide hydrogen bonds are replaced by like to unlike, acid to amide, and amide to acid hydrogen bonds. The molecules are centrosymmetric, but their characteristic hydrogen bond motif now includes a large 20-membered ring held together by amide hydrogen to acid carbonyl hydrogen bonds, Figure 7. These large rings are linked together via acid hydrogen to amide carbonyl hydrogen bonds.

The Oxalamide of Glycylglycine. The urea of glycylglycine, **6u**, was found to form a two-dimensional β-network in complete accordance with the scheme outlined in Figure 2.[3a] The amide functionality of each side arm turned sideways and formed additional amide−amide hydrogen bonds between neighboring β-networks and united the entire structure into a complex γ-network. The oxalamide of glycylglycine, **6o**, forms an analogous arrangement, Figure 8, consistent with the scheme outlined in Figure 3. Again the amide groups turns sideways and form additional amide−amide hydrogen bonds to translation related amide groups in the next layers of the structure.

An Unsymmetrical Oxalamide. Oxalamides, **1o**−**6o**, all have symmetrical substituents and crystallize with a molecular inversion center. Oxalamide, **7o**, is unsymmetrical with one acetic acid substitutent and one propionic acid substituent, and thus cannot have an inversion center. However, the molecule still forms a layered β-network structure, Figure 9, one with less symmetry than the layer shown in Figure 3. The oxalamide α-network lacks an inversion center and has only $P1$ symmetry. The inversion center at the carboxylic acid functionality still exists giving an overall layer symmetry of $P\bar{1}$, but with fewer

Figure 8. The β-network structure formed by compound **6o** which has glycylglycine derived side chains. The structure is similar to those shown in Figures 5 and 6, but an extra set of amide hydrogen bonds forms between the layers. These extra hydrogen bonds are not shown in the figure but the protruding amide hydrogen and oxygen atoms can be seen.

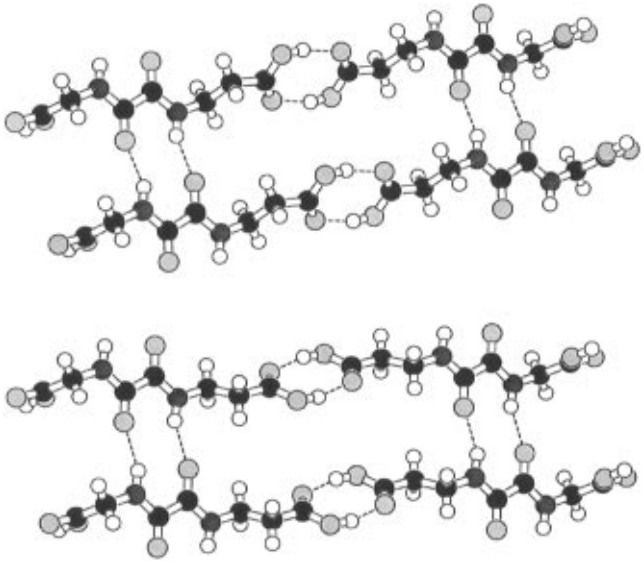


Figure 9. The two independent β-networks formed by the two independent molecules of compound **7o**. The main differences between the two layers are the dihedral angles within the propionic acid side chains. These two layer alternate in the crystal.

inversion centers per molecule. There are actually two independent molecules in the asymmetric unit of the crystal, with each of the two molecules forming an independent β-network of $P\bar{1}$ layer symmetry. The only significant difference between the two molecules is the orientation of the propionic acid side chain, Figure 9. It should be noted that unsymmetrical urea, **7u**, did not form a layered β-network, it formed a complex three-dimensional γ-network with the expected complementarity of the hydrogen bond network completely broken.[8]

The Unexpected Polymorph. One fascinating aspect of molecular crystallography is the unexpected appearance of a second polymorph of a well-studied compound. Chronologically the first compound studied among those reported here was the simplest member of the oxalamide series, compound **1o**. The molecule was chosen for study to test the design scheme shown in Figure 3. The fact that the observed structure was in accordance with the design led us to prepare and determine structures of the remaining members of the oxalamide series. Subsequently in connection with another project, a second polymorph of **1o** was observed. It was found that while crystallization from acidic aqueous solution gives the original polymorph, **A**, crystallization from neutral or basic solutions

(8) In **7u** the hydrogen of the carboxylic acid forms a hydrogen bond to the oxygen atom of the urea carbonyl, while the hydrogen atoms of the urea form hydrogen bonds to the acid carbonyl. See ref 3b.

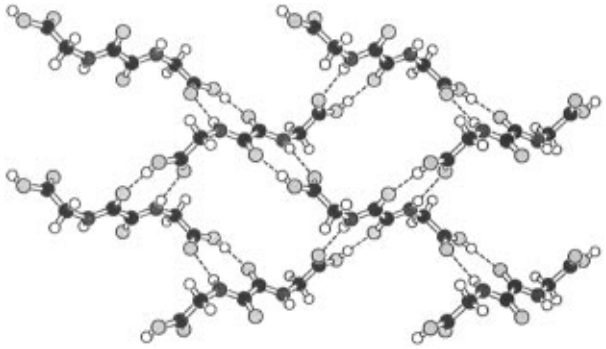


Figure 10. The β-network of polymorph **B** of compound **1o**. This layer structure is formed by acid to amide hydrogen bonds.

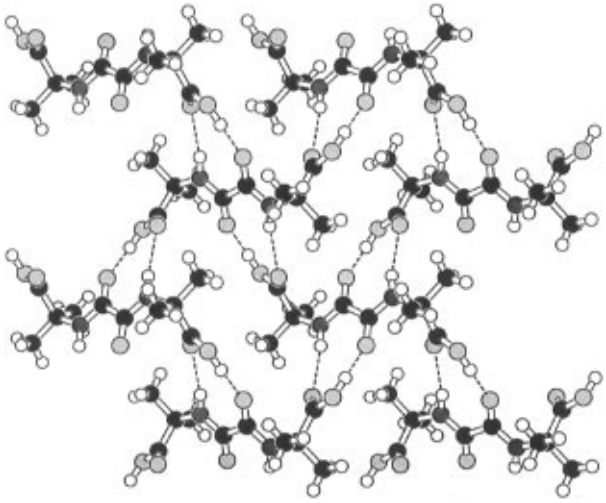


Figure 11. The β-network of compound **8**. This layer structure is isostructural to that of polymorph **B** of compound **1o**, Figure 10. This figure was generated from the original literature coordinates.[6c]

gives instead a second polymorph, **B**. Polymorph **B** has a completely unanticipated structure, Figure 10. The hydrogen bond pattern in **B** consists of like to unlike, acid to amide, and amide to acid hydrogen bonds instead of the like to like pattern of polymorph **A**. The molecules of **B** have assembled into a β-network, but it is quite different that the β-network of **A**. The layer symmetry of B is $P2_1/a$ with neighboring centrosymmetric molecules related by a screw axis and a glide plane. Interestingly, the β-network of **B** does not contain independent α-networks. The β-network of **A** contained two independent α-networks, one based upon the oxalamide hydrogen bonds, the second roughly perpendicular to the first based upon the carboxylic acid hydrogen bonds.

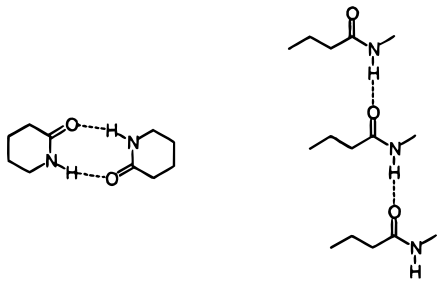
Discussion

A successful design of a molecular solid depends upon the identification and synthesis of molecular functionalities that will predictably and persistently lead to specific favorable intermolecular interactions.[9] Hydrogen bonds are ideal since they are generally the strongest available intermolecular interactions in an organic crystal and, with good design, they can be as highly specific as Watson−Crick hydrogen bonds. With this principle in mind we have been seeking to develop a library of functionalities that will allow one to design and synthesize supramolecular assemblies with desired properties and structure.

The first criterion in choosing a hydrogen bonding functionality is a chemical one. The number of hydrogen donor positions should match the number of acceptors and the strength of the designed interaction should be greater than alternate arrangements. The second criterion is a crystallographic one. Molecules pack in a crystal only as allowed by the rules of crystallographic symmetry.

An individual molecule in a crystal will have many different intermolecular contacts. Commonly, there will be about twelve nearest neighbors corresponding to a close-packed environment of spheres. Each pair of adjacent molecules will be related to each other by a symmetry operator. Usually about half of these nearest-neighbor contacts will correspond to unique symmetry operations. In most cases only about three of these distinct symmetry operators are needed to generate the symmetry of the crystal. The remaining symmetry operators can be derived from these generating operators.

Various hydrogen bonding functionalities will be compatible with certain symmetry operators and incompatible with others. Indeed some functional groups strongly favor certain operators. Consider the two secondary amides shown below, one a cyclic molecule with a *syn* hydrogen and the second an acyclic molecule with a *anti* hydrogen. With a *syn* hydrogen centrosymmetric dimer formation about an inversion center will be favored. But with an *anti* hydrogen an inversion center is an incompatible operator and a one-dimensional α-network will be favored using a translational symmetry operator. The urea and oxalamide functionalities are each unique amide forms that have their own symmetry characteristics as we will discuss below.



To design a supramolecular structure one must predict the intermolecular interactions that will take place between the molecules. If the symmetry operators corresponding to these interactions can be anticipated as well, then these operators can be combined following the rules of group theory to generate the symmetry group of the anticipated supramolecular structure. Knowing the most probable symmetry groups of the supramolecular structure can lead to a correct prediction of the space group of the crystal.

Ureas. The urea functionality has two hydrogen donor nitrogen atoms and only one carbonyl acceptor, but the one carbonyl commonly accepts both hydrogen bonds, one at each lone pair position. Symmetrical ureas have a 2-fold axis through the carbonyl and importantly can retain this 2-fold when they form a one-dimensional hydrogen bonded α-network via simple crystallographic translation, Figure 2. Using group theory one would say that when a translation axis is added to the C_2 point group (the urea monomer), the $P2$ rod group (the urea α-network) is generated. The carboxylic acid residues on the ends of the side chains characteristically dimerize about crystallographic inversion centers giving a two-dimensional β-network. Adding an external inversion center to the $P2$ rod group generates the $P2/c$ layer group. The β-network layers stack on top of each other to form the crystal; with no further hydrogen bonds available presumably the layers are held together by mainly van der Waals interactions. One could imagine two simple ways for this stacking to occur. If the layers were

(9) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120−126.

directly on top of each other using a simple translation operator, then the space group of the final molecular assembly and the crystal would be $P2/c$. However, it seems more likely that the layers would be offset such that the molecules of one layer fall over the groves between the molecules of the layer below. This would generate a centering operation and the final space group would be $C2/c$.

Five of the six ureas **1u**−**6u** do indeed crystallize in the space group $C2/c$ in exact agreement with the above analysis. The urea functionalities lie on a 2-fold axis of the $C2/c$ space group, and the carboxylic acid groups dimerize about inversion centers. The exception, **2u**, has three independent molecules in the unit cell, but the molecular packing is very similar and still in the $C2/c$ space group.

Compound **7u** has differing side arms and lacks the 2-fold axis of molecules **1u**−**6u**. It thus cannot follow the $C2/c$ scheme, but could instead form a β-network with lower symmetry. Computer modeling suggested a β-network of $P1$ layer symmetry formed only by the simple translation operator. However, the actual structure showed a complete breakdown of the design and a complex three-dimensional γ-network of hydrogen bonds.[8] Several other ureas lacking the 2-fold axis were also studied in our earlier work.[3b] These molecules were chiral, but racemic, and they uniformly failed to form a layer structure. Instead they tended to form centrosymmetric dimers about crystallographic inversion centers via unpredicted hydrogen bond patterns. However, when a single enantiomer was used, the inversion center was symmetry forbidden and a simple translation based β-network was formed as designed.

Thus, with ureas we can conclude that the 2-fold axis is an important part of the layer design. *All the symmetrical urea molecules with a 2-fold axis formed β-networks in accordance with the design*. Ureas with differing side chains, lacking the 2-fold axis, tend to form alternate hydrogen bond patterns about centers of inversion unless forbidden by symmetry.

Oxalamides. With the oxalamide functionality the inversion center is part of the design. The oxalamide functionality is centrosymmetric and with symmetrical side arms the molecular symmetry will be C_i. Most importantly the oxalamide−oxalamide hydrogen bond also forms about an inversion center. Adding an external inversion center to a molecule that already has one generates a translation axis, Figure 3, and an α-network. Adding a second external inversion center corresponding to the carboxylic acid dimerization produces a β-network. The two independent α-networks have $P\bar{1}$ rod group symmetry, the layer has $P\bar{1}$ layer group symmetry, and the crystal has $P\bar{1}$ space group symmetry. Since the inversion center seemed to be so favorable in the urea compounds, even to the extent of destroying the expected hydrogen bond complementary, one might expect that the oxalamide hydrogen bonds based upon the inversion center would be highly persistent.

Of the six symmetrical oxalamides studied, **1o**−**6o**, five of them form $P\bar{1}$ structures in accordance with the design in Figure 3. The exception, **3o**, has a breakdown in the hydrogen bond complementary and forms a large centrosymmetric ring with hydrogen bonds occurring between the oxalamide and the carboxylic acid functionalities. The occurrence of this like to unlike hydrogen bond is not in accordance with the design, but perhaps not totally surprising either. Others[10] have examined the question of like to like versus like to unlike hydrogen bonds in acid−amide molecules. They have concluded that the strongest hydrogen bond should occur between the most acidic hydrogen, the one on the carboxylic acid, and the most basic carbonyl, the one on the amide. Obviously this cannot be an absolute rule since all compounds that follow the design in Figure 3 violate the rule, but it does point out the nature of one competing force.

The one example of an unsymmetrical oxalamide, **7o**, forms a β-network with simple translation along the oxalamide α-network and inversion centers along the carboxylic acid α-network. In this case the oxalamide design is more successful than the urea design, since the urea **7u** did not form a layered structure.

The Second Polymorph. A crystal of a second polymorph **B** of **1o** was prepared and its structure determined. Like compound **3o**, polymorph **B** contains a network of acid to amide, like to unlike hydrogen bonds, Figure 10. The oxalamide functionality retains its inversion center and forms two planar nine-member hydrogen-bonded rings. The molecules form a two-dimensional β-network of $P2_1/a$ layer symmetry. The structure is generated by the addition of an external 2_1 screw axis to single molecules of C_i point group symmetry.[11] The structure appears to be compact and has a higher calculated density than the original structure.

These two polymorphs can be prepared selectively and reproducibly. Polymorph **A**, the original structure with like to like hydrogen bonds, Figure 6, precipitates from acidic solutions. Polymorph **B**, the second polymorph with like to unlike hydrogen bonds, precipitates from pure water or basic solutions.

The existence of the **1o** polymorphs illustrates both a difficulty and the power of crystal engineering. We are dealing with simple functional groups. They can in general be expected to form certain hydrogen bond patterns. However, there will always be competing structures that are only slightly different in energy. Since crystallization is governed by kinetics as well as thermodynamics, predictions of crystal structures will always be difficult. The existence of polymorphism both compounds and illustrates the problem. The preparation of the second polymorph of compound **1o** was not anticipated. It has a structure that differs from the design of Figure 3. On the other hand when we look at compound **3o**, the lone exception in the oxalamide series, we can conjecture that one might also be able to prepare a second polymorph of that compound, a polymorph that would have a layered structure in accordance with the design of Figure 3. Unfortunately, there is no universal scheme for preparing polymorphs.[12]

Other Oxalamide Structures. An examination of the Cambridge Structural Data Base[13] and the recent literature reveals nine additional examples of well-characterized, metal free, acyclic oxalimides. The three examples with simple symmetrical substituents, *N*,*N*′-dimethyloxalamide,[14] *N*,*N*′ -bis-(pentafluorophenyl)oxalamide,[15] and *N*,*N*′-bis(3-nitratopropyl)-oxalamide,[16] all crystallize to form the characteristic primary $P\bar{1}$ α-network discussed above and shown in Figure 3. This

(10) Berkovitch-Yellin, Z.; Leiserowitz, L. *J. Am. Chem. Soc.* **1983**, *105*, 765−767. Leiserowitz, L.; Nader, F. *Acta Crystallogr., Sect. B* **1977**, *33*, 2719−2723. Leiserowitz, L. *Acta Crystallogr., Sect. B* **1976**, *32*, 775−802.

(11) It is interesting to note that in polymorph **A** of **1o** the β-network can be considered to be an assembly of independent α-networks, the α-networks in turn being assemblies of discrete molecules. However, in polymorph **B** of **1o** the β-network is assembled directly from discrete molecules, and there are no symmetry independent α-networks.

(12) We have tried the obvious experiment of growing crystals of **3o** from solutions with various pH values, but we have seen no evidence of polymorphism.

(13) Allen, F. H.; Taylor, R.; Kennard, O. *Acc. Chem. Res.* **1983**, *16*, 146−153.

(14) Klaska, K. H.; Jarchow, O.; Scham, W.; Widjaja, H.; Voss, J.; Schmalle, H. W. *J. Chem. Res.* **1980**, *104*, 1643−1700.

(15) Yamaguchi, K.; Matsumura, G.; Haga, N.; Shudo, K. *Acta Crystallogr., Sec. C* **1992**, *48*, 558−559.

(16) Bhattacharjee, S. K.; Ammon, H. L. *Acta Crystallogr., Sec. B* **1982**, *38*, 2503−2505.

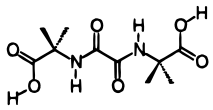
Table 1. Crystallographic Parameters

	1o (form A)	**1o** (form B)	**3o**	**4o**	**5o**	**6o**	**7o**	**4u**	**5u**
emperical formula	$C_6H_8N_2O_6$	$C_6H_8N_2O_6$	$C_{10}H_{16}N_2O_6$	$C_{12}H_{20}N_2O_6$	$C_{14}H_{24}N_2O_6$	$C_{10}H_{14}N_4O_8$	$C_7H_{10}N_2O_6$	$C_{11}H_{20}N_2O_5$	$C_{13}H_{14}N_2O_5$
formula wt	204.1	204.1	260.2	288.3	316.4	318.2	218.2	260.3	278.3
a (Å)	4.446(2)	5.037(2)	5.877(5)	5.1205(4)	5.183(2)	4.761(2)	5.069(3)	26.903(24)	13.206(2)
b (Å)	5.020(2)	7.911(3)	9.864(4)	5.3932(3)	6,701(3)	5.004(2)	8.026(3)	4.6919(6)	4.648(3)
c (Å)	10.853(6)	10.192(5)	10.556(6)	12.692(7)	12.354(3)	16.445(7)	24.194(9)	10.144(13)	25.084(2)
α	94.19(4)			97.567(8)	102.79(1)	96.69(3)	83.63(3)		
β	91.19(3)	100.28(3)	104.13(11)	92.090(10)	98.72(1)	90.94(3)	84.74 (3)	99.90(4)	103.73(1)
γ	115.72(3)			94.249(8)	102.43(1)	118.02(2)	83.88(3)		
volume (Å^3)	218.2(4)	399.6(3)	593.4(3)	346.2(1)	399.6(3)	342.4(5)	969.1(3)	1261.3(5)	1496(1)
space group	$P\bar{1}$(No. 2)	$P2_1/c$ (No. 14)	$P2_1/c$ (No. 14)	$P\bar{1}$(No. 2)	$P\bar{1}$(No. 2)	$P\bar{1}$(No. 2)	$P\bar{1}$(No. 2)	$C2/c$ (No. 15)	$C2/c$ (No. 15)
Z	1	2	2	1	1	1	4	4	4
d_{calc} (g/cm^3)	1.553	1.696	1.456	1.383	1.315	1.543	1.495	1.371	1.236
hydrogens	refined	refined	refined	refined	fixed calc	refined	fixed calc	fixed calc	fixed calc
observations collected (total)	915	1306	1242	1368	1735	1337	1612		
observations ($I > 3\sigma$)	813	891	1018	921	1139	984	808	634	665
variables	81	81	115	132	100	129	271	83	92
R	0.051	.065	0.034	0.055	0.064	0.054	0.066	0.045	0.071
R_w	0.074	.081	0.056	0.067	0.093	0.065	0.069	0.055	0.087

gives further support to the primary oxalamide α-network as a reliable design element. However, due to a variety of problems none of the remaining examples of oxalamides from the literature were found to form this simple α-network. The first of these exceptions is the sterically hindered *N,N′*-bis(2,2,2-trinitratoethyl)oxalamide[17] which forms only intramolecular hydrogen bonds. The next is an unsymmetrical oxalamide with a large benzodiazepin substituent.[18] It forms an alternate hydrogen bonded network involving the substituent.

The remaining four literature oxalamides were reported in a series of papers by Karle and Ranganathan.[6] They report the structures of three dimethyl esters of oxalamido retropeptides, MeO-Aib-COCO-Aib-OMe, MeO-Leu-COCO-Leu-OMe, and MeO-Ser-Leu-COCO-Leu-Ser-OMe. Each of these three structures form alternate networks that involve hydrogen bonds between an oxalamide unit and the hetero atoms of side arm substituents. The latter two compounds are of course chiral and are prevented by symmetry from forming a $P\bar{1}$ α-network.

The fourth compound from Karle and Ranganathan[6c] is the one most closely related to the present work. This is compound **8**, the oxalamide derived from the amino acid dimethylglycine.



8

Compound **8** is a direct analogue of compound **1o**, the oxalamide of glycine. Most interestingly the crystal structure of **8** is isostructural with that of polymorph **B** of **1o**. It crystallizes in the same $P2_1/c$ space group with somewhat similar cell constants.[19] The compound forms a *β*-network based upon acid to amide hydrogen bonds completely analogous to the one found in polymorph **B** of **1o**. The *β*-network of **8** is analogous to the *β*-network of polymorph **B** of **1o** and not to the designed *β*-network found in polymorph **A**. It is possible that the steric hindrance of the four methyl groups of **8** would perhaps preclude a *β*-network structure analogous to the one in polymorph **A**.

(17) Chen, R.; Rheingold, A. L.; Brill, T. B. *J. Crystallogr. Spectrosc.* **1991**, *21*, 173−177.

(18) Fryer, R. I.; Earley, J. V.; Blout, J. F. *J. Org. Chem.* **1977**, *42*, 2212−2219.

(19) Compound 8 was found (ref 6c) to crystallize in the space group $P21/c$ with $Z = 2$ and cell constants of $a = 6.342(2)$ Å, $b = 9.910(2)$ Å, $c = 10.020(2)$ Å, and $\beta = 91.65(2)°$. These values are somewhat similar to those found for 1o (polymorph B) as shown in Table 1.

Characteristic Spacing. An approach to supramolecular synthesis based upon a combination of chemical insight and symmetry considerations has a high probability of success. The urea functionality has a characteristic repeat spacing of about 4.65 Å along the urea α-network, Table 1. This means that the molecules in a *β*-network will be spaced at regular intervals equal to this approximate distance. For example, in Figure 4 the molecules **4u** and **5u** are spaced at 4.69 and 4.65 Å, respectively. The oxalamide functionality also has a characteristic spacing, about 5.1 Å, longer than the value found in the ureas. The longer distance is due to the fact that the C−O···H bond angle is nearly linear in the oxalamide case, but is bent in the urea case. These two different characteristic spacings are quite reliable and can serve as the basis for controlling topochemical reactions such as diacetylene polymerizations.[3d]

Conclusions. A symmetry analysis based upon the structure of simple molecules and their anticipated intermolecular interactions can lead to successful predictions of molecular packing and crystal symmetry. Both the urea and oxalamide dicarboxylic acids form designed *β*-networks with a significant degree of reliability. The urea designs are quite reliable when there is a molecular 2-fold axis, but competing hydrogen bond patterns are found when less symmetrical molecules are studied. The oxalamide design based on inversion centers is also quite reliable, with the designed layer structure found in most cases. In the exceptions the designed like to like patterns of acid−acid and amide−amide hydrogen bonds are replaced by like to unlike acid−amide and amide−acid hydrogen bonds. The urea and oxalamide functionalities are thus both good entries in our library of functionalities useful for designed supramolecular syntheses. They have different symmetry properties and give different characteristic spacings, 4.6 Å for the urea and 5.1 Å for the oxalamide functionality.

Experimental Section

X-ray Diffraction Studies. Crystals were obtained as described below, 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 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 Table 2, and the structures were solved and refined using the TEXSAN crystallographic program package of the Molecular Structure Corporation. The quality of the structures varied due to the quality of the available single crystals. In the best cases, hydrogen atoms were located in difference maps and refined. In the cases with

poorer data sets, the hydrogen atoms were placed in calculated positions and added as fixed contributions.

General Method A. The following procedure, adapted from the literature,[20] was used to prepare the ureylene dicarboxylic acids described in this paper. To a solution of 20 mmol of the amino acid in 4 mL of water was added 0.40 mL of 6.25 N NaOH. This solution was placed in an ice bath and 0.88 g (3.3 mmol) of triphosgene in 5 mL of toluene was added. The reaction mixture was stirred in an ice bath for 30 min and at room temperature for 2 h. The reaction mixture was cooled in an ice bath, 5 mL of water was added, and the pH was adjusted to approximately 2 with 6 N HCl. The urea precipitate was collected by filtration and washed with a small amount of cold water.

5,5′-Ureylenedipentanoic Acid (4u). Using general method A with 5-aminopentanoic acid, 5,5′-ureylenedivaleric acid was prepared in 20% yield: mp 188−189 °C (lit.[21] mp 189 °C). Recrystallization from hot water gave needles of good quality for X-ray crystallography.

6,6′-Ureylenedihexanoic Acid (5u). Using general method A with 6-aminohexanoic acid, 6,6′-ureylenedihexanoic acid was prepared in 56% yield: mp 162−163 °C (lit.[22] mp 162−163 °C). Recrystallization from hot water gave needles of adequate quality for X-ray crystallography.

General Method B. The following procedure, adapted from the literature,[23] was used to prepare the symmetrical oxalamides described in this paper. To a stirred solution of 3.73 mL (27.5 mmol) of ethyl oxalate in 50 mL of water at 40 °C was added 55 mmol of the amino acid. The reaction mixture was stirred for 2 h, allowed to cool to room temperature, and acidified to pH ≅ 2 with concentrated HCl. The precipitated product was collected by filtration and air dried. Crystals suitable for crystallographic analysis were obtained by recrystallization from water, unless otherwise specified.

***N*,*N*′-Oxalyldiglycine (1o, polymorphs A and B).** Using general method B with glycine gave *N*,*N*′-oxalyldiglycine in 17% yield as colorless plates from the original reaction mixture: mp (with decomposition, turning red) 250−255 °C (lit.[23] mp 250−255 °C). These needles were subjected to single crystal X-ray analysis and are given the designation polymorph **A**. Recrystallization of polymorph **A** (plates) from water gave crystals with a block-like habit. Single-crystal X-ray diffraction of these crystals showed that they were a second polymorph, polymorph **B**: mp (with decomposition) 245−250 °C. Subsequent experiments showed that samples of either form of **1o** recrystallized from solutions of pH 7 or higher (0.3 M NaOH or aqueous NH_3) consistently gave polymorph **B**, while recrystallization from acidic solutions (0.3 M HCl) gave polymorph **A**. IR (KBr): polymorph **A**, 3302 (N−H), (1712, 1660) (C═O), 1434, 1407, 1237, 858; polymorph **B**, 3264 (N−H), 1671 (C═O), 1406, 1191, 841.

4,4′-(Oxalyldiimino)dibutyric Acid (3o). Using general method B with 4-aminobutyric acid gave 4,4′-(oxalyldiimino)dibutyric acid as colorless needles in 20% yield: mp 214−217 °C (lit.[24] mp 210−215 °C).

5,5′-(Oxalyldiimino)dipentanoic Acid (4o). Using general method B with 5-aminopentanoic acid gave 5,5′-(oxalyldiimino)dipentanoic acid in 29% yield as colorless needles: mp 209−211 °C dec; ^{1}H NMR (DMSO-d_6) δ 12.01 (bs, 1H), 8.74 (t, J = 6.0 Hz, 1H), 3.12 (d, J = 5.7 Hz, 2H), 2.20 (2H), 1.45 (4H); IR (KBr) 3298 (N−H), 1699 (C═O), 1648 (C═O) cm^{-1}.

6,6′-(Oxalyldiimino)dihexanoic Acid (5o). Using general method B with 6-aminohexanoic acid gave 4,4′-(oxalyldiimino)dihexanoic acid as colorless needles in 30% yield: mp 178−180 °C dec; ^{1}H NMR (DMSO-d_6) δ 11.9 (bs, 1H), 8.71 (t, 1H), 3.09 (qt, J = 5.0 Hz, 2H), 2.18 (q, J = 7.2 Hz, 2H), 1.48 (m, 4H), 1.25 (tt, J = 8.0 Hz, 2H); IR (KBr) 3300 (N−H), 1703 (C═O), 1647 (C═O) cm^{-1}.

***N*, *N*′-Oxalyldiglycylglycine (6o).** Using general method B with glycylglycine gave *N*,*N*′-oxalyldiglycylglycine colorless needles in 32% yield: mp 262−267 °C dec; ^{1}H NMR (DMSO-d_6) δ 8.82 (t, J = 6.0 Hz, 1H), 8.28 (t, J = 5.5 Hz, 1H), 3.81 (d, J = 6.0 Hz, 2H), 3.76 (d, J = 5.6 Hz, 2 H); IR (KBr) 3289 (N−H), 1708 (C═O), 1649 (C═O) cm^{-1}.

Oxalyl-*N*-glycyl-*N*′-*β*-alanine (7o). To 80 mL of THF was added ethyl oxalylchloride (5.60 mL, 50 mmol) and glycine ethyl ester hydrochloride (6.98 g, 50 mmol). The solution was stirred and allowed to reflux for 90 min. The solvent was removed *in vacuo* to give the intermediate diester as an oil. A basic solution was prepared from 10 mL of water and 3.2 mL of 6.25 N NaOH. To this solution was added 4.06 g (20 mmol) of the above diester and 1.78 g (20 mmol) of β-alanine. The reaction mixture was stirred for 1.3 h. The intermediate monoester was directly hydrolyzed by addition of 2 mL of 6.25 N NaOH. The solution was acidified with an ion exchange resin in its acid form (Rexyn 101H, Fisher Scientific) until pH ≅ 4. Filtration of the resin followed by removal of the solvent gave 3.15 g (32%) of a colorless precipitate which was purified by recrystallization from methanol: mp 228−229 °C; ^{1}H NMR (DMSO-d_6) δ 8.92 (t, J = 6.0 Hz, 1H), 8.78 (t, J = 6.0 Hz, 1 H), 3.80 (d, J = 7.0 Hz, 2 H), 3.35 (q, J = 7.0 Hz, 2 H), 2.48 (t, J = 7.0 Hz, 2 H); IR (KBr) 3300 (N−H), 1711 (C═O), 1650 (C═O) cm^{-1}.

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Supporting Information Available: X-ray crystallographic data for the nine compounds listed in Table 1 including tables of atomic coordinates, temperature factors, bond distances and angles, intermolecular contacts, and hydrogen-bond parameters (26 pages). See any current masthead page for ordering and Internet access instructions.

JA961958Q

(20) Kondo, K.; Murata, K.; Miyoshi, N.; Murai, S.; Sonoda, N. *Synthesis* **1979**, 735−736.

(21) McKay, A. F.; Tarlton, E. J.; Petri, S. I.; Steyermark, P. R.; Mosley, M. A. *J. Am. Chem. Soc*. **1958**, *80*, 1510−1517.

(22) Giesemann, H.; Oertel M. *J. Prakt. Chem.* **1959**, *4(8)*, 292−297.

(23) Hearn, W. R.; Hendry, R. A. *J. Am. Chem. Soc*. **1957**, *79*, 5213−5217.

(24) Wieland; Hasse, Kurt, *Chem. Ber*. **1960**, 1686−1692.