

# Commensurate and Incommensurate Hydrogen Bonds. An Exercise in Crystal Engineering

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Received July 17, 2001

**Abstract:** Ureas characteristically form one-dimensional hydrogen-bonded  $\alpha$ -networks with a repeat distance of about 4.60 Å. Oxamides form similar  $\alpha$ -networks with a longer 5.05 Å repeat distance. The urea of glycine and the oxamide of glycine were each cocrystallized with a series of four bipyridines, including two urea derivatives and two oxamide derivatives. This series of eight cocrystals was studied by X-ray diffraction in order to see what would happen when molecules that would normally form  $\alpha$ -networks with incommensurate distances were forced into the same crystal. The two all-urea crystals and the two all-oxamide crystals contained the expected  $\alpha$ -networks with repeat distances in accordance with normal urea or oxamide values. Four of the crystals were mixed, containing both oxamide and urea molecules. Three consisted of two-dimensional  $\beta$ -networks with alternating parallel urea and oxamide subnetworks. The repeat distances averaged 4.87 Å, a value close to the value expected for oxamides, but shorter than any previously observed examples. In the fourth mixed crystal, the urea  $\alpha$ -network formed with a normal urea repeat distance, but the oxamide network did not form, the oxamide adopting an unusual molecular conformation that maximizes intramolecular hydrogen bonds instead.

Crystal engineering<sup>1–3</sup> is an important problem that requires a detailed knowledge of intermolecular interactions. One would like to be able to choose appropriate molecules or sets of molecules and predict with confidence the manner in which they will crystallize. This is a difficult problem of great complexity, and indeed in many cases there may be no simple thermodynamic basis for a successful prediction. Crystallization is a kinetic process, and polymorphism often appears when it is most inconvenient. As chemists we persevere with a certain confidence that by a clever design we will achieve the structural result we seek. Success is achieved either by wisely setting limited structural goals in the first place or by making judicious use of ex post facto crystal design.

Despite these difficulties, one can still imagine a scenario where one could reliably predict the total structure of a crystal purely on the basis of knowledge of molecular properties. Total structure prediction would require specification of molecular geometry and orientation, unit cell dimensions, and the space group. Our simplified approach to this problem has been to identify molecular functionalities that will predictably and persistently lead to crystals containing defined network structures.<sup>4</sup> Each of our chosen functionalities has a size and shape that leads to characteristic repeat distances within its networks. These molecular networks are substructures of the final crystal.

The networks have repeat distances commensurate with the unit cell of the crystal; their group symmetries are a subgroup of the space group of the final crystals. The distance parameters can be predicted; a consideration of molecular symmetry combined with the symmetry of each anticipated intermolecular bond can lead one to the correct network symmetry. By combining good chemical insight with solid crystallographic principles, one can design or engineer crystalline solids that contain networks with desired structural features.

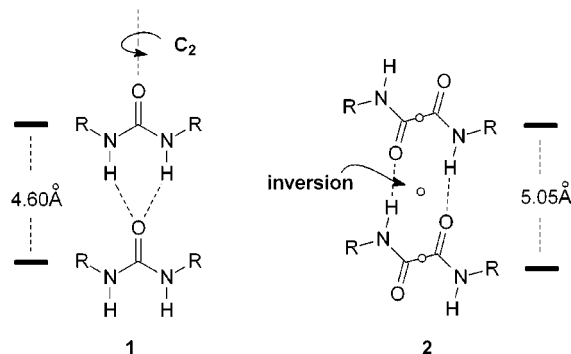
Crystal engineering is simply another form of synthesis: supramolecular synthesis, the preparation of crystals with defined properties. Like any new synthetic technique, one must develop the method and determine its scope and its limitations. One needs to test procedures and evaluate functional group compatibilities. In this paper we present such a study, an exercise that tests our understanding of the ways that molecules self-assemble into crystalline networks of defined geometry and symmetry. We explore the boundaries of our understanding by forming cocrystals of molecules from two separate families, the ureas and oxamides, each capable independently of forming defined one-dimensional hydrogen-bonded  $\alpha$ -networks with predictable and persistent symmetries and intermolecular repeat distances. The wrinkle is the fact that the two functionalities independently yield persistent intermolecular distances that are incommensurate. We ask the following questions: Will the characteristic molecular symmetry of each functionality persist in the crystalline state? If so, how will the incommensurate distances be reconciled?

**Ureas.** Ureas are superb hydrogen-bonding molecules.<sup>5</sup> Indeed urea itself is widely used as a protein denaturant. Symmetrical disubstituted ureas, **1**, will form  $\alpha$ -networks with each urea molecule donating two hydrogen bonds, chelating the

(1) Schmidt, G. M. *J. Pure Appl. Chem.* **1971**, *27*, 647–678.  
(2) Desiraju, G. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2311–2327.  
(3) Moulton, B.; Zaworotko, M. J. *Chem. Rev.* **2001**, *101*, 1629–1658.  
(4) Supramolecular assemblies can be classified into four groups depending upon the degree of translational symmetry. Discrete assemblies lacking translational symmetry are characterized by their point group symmetry. An  $\alpha$ -network has one degree of translational symmetry and is characterized by its rod group symmetry. A  $\beta$ -network has two degrees of translational symmetry and is characterized by its layer group symmetry. A  $\gamma$ -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. Liquid Cryst.* **1992**, *211*, 99–109.

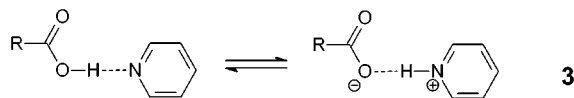
(5) Zhao, X. Q.; Chang, Y. L.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 6627–6634.

carbonyl oxygen of the next molecule in the network. In crystals, ureas commonly have  $C_2$  point group symmetry; the mirror planes are almost always lost. The resulting  $\alpha$ -networks tend to have  $P2$  rod group symmetry with a characteristic intermolecular spacing of 4.60 Å.



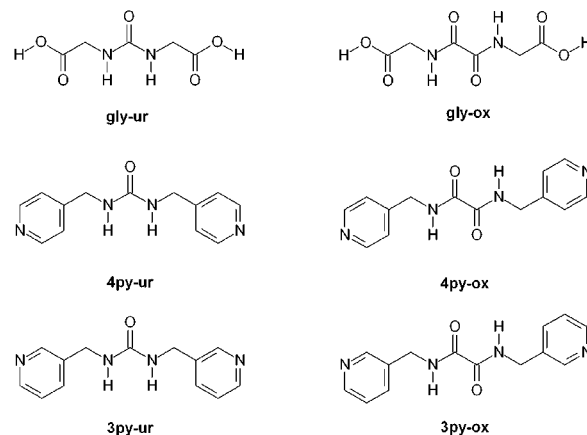
**Oxamides.** The oxamides are diamides of oxalic acid and are also superb hydrogen-bonding molecules.<sup>6</sup> Symmetrical disubstituted oxamides form  $\alpha$ -networks, **2**, with each molecule donating and receiving two hydrogen bonds. In a crystal each molecule, with  $C_i$  point group symmetry, commonly retains its inversion center, and the intermolecular bonds between neighboring molecules of the  $\alpha$ -networks also form about inversion centers. The resulting networks have  $P\bar{1}$  rod group symmetry and characteristic intermolecular spacing of 5.05 Å.

**Cocrystal Approach.** The efficiency and power of crystal engineering is enhanced if one uses more than one molecule. The cocrystallization of two separate molecules greatly increases the number of readily obtainable crystalline entities. It allows a convergent synthetic approach and lends itself to a combinatorial strategy. The design of a cocrystal is a natural part of supramolecular chemistry, it overlaps with host–guest chemistry, and it is an excellent example of applied molecular recognition. To reliably cocrystallize two different molecules, one needs a strong and dependable intermolecular interaction. One of the most dependable intermolecular bonds is the hydrogen bond that forms between a carboxylic acid and a base such as pyridine, **3**. In some cases the proton may transfer, but then one is left with a similar hydrogen bond (perhaps even stronger) between a carboxylate anion and a pyridinium cation.



In earlier work we prepared a series of six carboxylic acid and pyridine derivatives of both ureas and oxamides.<sup>5–10</sup> These molecules were used as host molecules to control the spacing of various guest molecules. For example, two dicarboxylic acids, the urea of glycine, **gly-ur**, and the oxamide of glycine, **gly-ox**, were used to align pyridine-substituted diacetylenes in accordance with the requirements needed for a topochemical polymerization. Conversely, the pyridine-substituted ureas and

oxamides were used as hosts to control the spacing of various dicarboxylic acids guests as well as various metal ions. In each set of host–guest complexes, the host molecule imposes a characteristic spacing upon the crystallographic unit cell, and consequently the same spacing is imposed upon the guest. In a similar manner the characteristic  $\alpha$ -network symmetries are generally carried over into the crystal lattice.



These six molecules were designed as host molecules. Since two of them are dicarboxylic acids and four of them are bipyridines, we realized that by taking matched pairs of these molecules we could potentially grow eight different mixed acid–base cocrystals. In this paper we describe the results of our attempts to prepare and study this proposed series of eight new compounds. The urea of glycine **gly-ur** was expected to easily form cocrystals with the two bipyridyl ureas, **3py-ur** and **4py-ur**; we expected the molecules to form commensurate hydrogen bonds. However, it was not so clear what would happen when the urea **gly-ur** was allowed to cocrystallize with the two bipyridyl oxamides, **3py-ox** and **4py-ox**. In this case the two expected  $\alpha$ -networks would have incommensurate repeat distances. Perhaps cocrystallization would not take place at all, or perhaps alternate hydrogen-bonded structures might form. Similarly the oxamide of glycine, **gly-ox**, was used to form cocrystals with the same four bipyridines. Again we expected the like-to-like all-oxamide cocrystals to form readily, but we did not know what to expect for the like-to-unlike oxamide–urea mixed crystals.

## Results and Discussion

**Commensurate Urea–Urea Cocrystals.** The urea of glycine, **gly-ur**, readily forms cocrystals with both **3py-ur** and **4py-ur**. Since the molecules are all ureas, we expected  $\beta$ -networks with commensurate hydrogen bonding between neighboring urea  $\alpha$ -networks, but there are various possible  $\beta$ -network structures that can be constructed from a pair of complementary urea molecules. Making the assumption that the urea  $C_2$  axis is retained, one can construct four likely structures as shown in Figure 1. There are two main variations that generate the four structures. The urea molecules will either segregate into separate like-to-like  $\alpha$ -networks as in Figure 1a or b, or they will form one like-to-unlike  $\alpha$ -network, as in Figure 1c or d. The disadvantage of segregated  $\alpha$ -networks is that the two  $\alpha$ -networks must be exactly commensurate when they come together to form the  $\beta$ -network. However, since all ureas tend to have a similar repeat distance, 4.60 Å, this may not be a problem. The second variation is the relative orientation of successive  $\alpha$ -networks. In Figure 1a and c, neighboring  $\alpha$ -networks run in

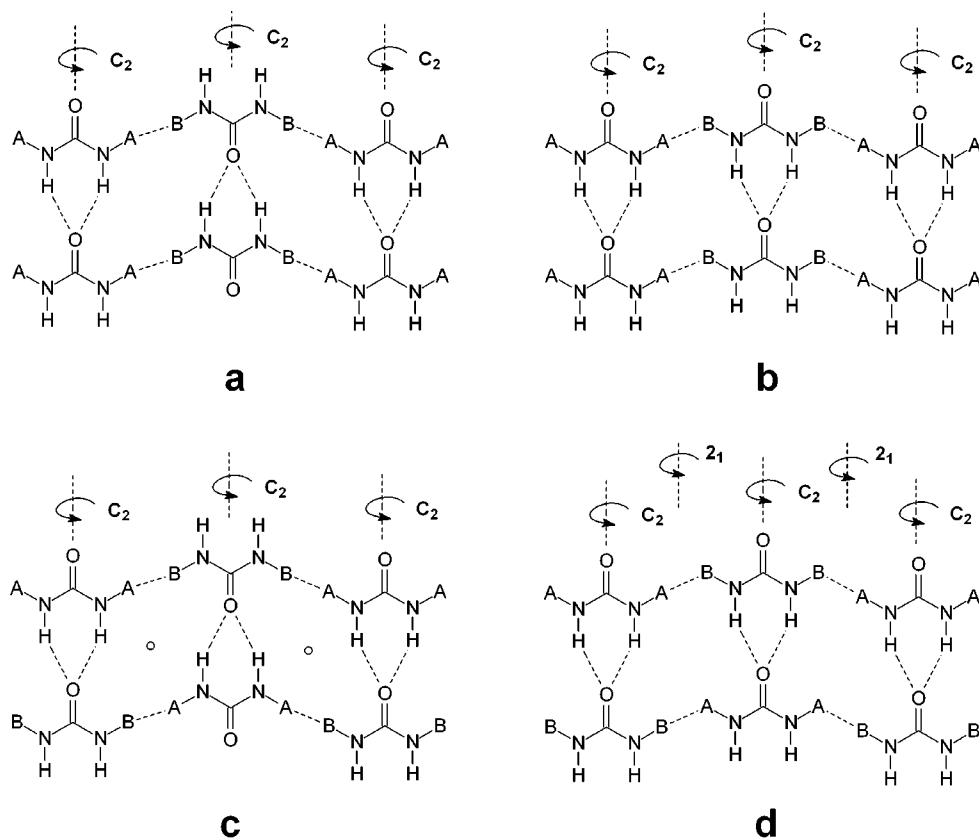
(6) Coe, S.; Kane, J. J.; Nguyen, T. L.; Toledo, L. M.; Winger, E.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 86–93.

(7) Kane, J. J.; Liao, R. F.; Lauher, J. W.; Fowler, F. W. *J. Am. Chem. Soc.* **1995**, *117*, 12003–12004.

(8) Fowler, F. W.; Lauher, J. W. *J. Phys. Org. Chem.* **2000**, *13*, 850–857.

(9) Schauer, C. L.; Matwey, E.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 10245–10246.

(10) Schauer, C. L.; Matwey, E.; Fowler, F. W.; Lauher, J. W. *Mater. Res. Bull., Suppl. S* **1998**, 213–233.



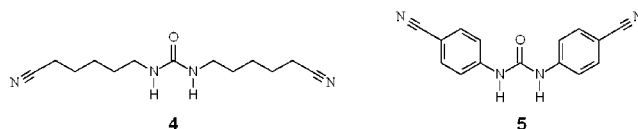
**Figure 1.** Four likely  $\beta$ -network structures for pairs of complementary urea molecules. In a and b the molecules form a striped pattern with segregated  $\alpha$ -networks. The a and b  $\beta$ -networks differ by the orientation of the urea functionality in successive columns. The layer group symmetry of both  $\beta$ -networks is predicted to be  $P2$ . In  $\beta$ -networks c and d the molecules form a checkerboard pattern with one alternating  $\alpha$ -network. In c there is an inversion center between neighboring  $\alpha$ -networks, and the layer symmetry is predicted to be  $P2/c$ . In d all ureas point in the same direction, and the layer symmetry is  $C_2$ . Other variations are possible, but these four structures seem the most likely.

opposite antiparallel directions, one up and one down. In Figure 1b and d, neighboring  $\alpha$ -networks run in the same direction: all urea dipoles within a given  $\beta$ -network point in the same direction.

The crystal structures of **gly-ur** with **3py-ur** and **4py-ur** are shown in Figure 2. Both structures show a striped  $\beta$ -network pattern with segregated  $\alpha$ -networks, but the orientation of the urea groups is different in the two structures. In the **gly-ur/3py-ur** structure, Figure 2a, the two unique urea molecules point in the same direction as shown in Figure 1b. The **gly-ur/4py-ur** structure adopts the alternate structure, with the ureas pointing in opposite directions as shown in Figure 1a. This difference is a consequence of the different orientation of the methylpyridine substituents. In the **3py-ur** structure the methylpyridine groups are turned downward away from the urea carbonyl oxygen, while in the **4py-ur** structure the methyl pyridine groups are turned in the opposite direction toward the urea carbonyl oxygen. The repeat distances of 4.62 and 4.58 Å for the two structures are consistent with expectations for an all-urea network.

There are two related structures in the literature. Hollingsworth et al.<sup>11</sup> reported the cocrystals of urea itself with two urea nitriles, **4** and **5**. The urea cocrystal with **4** formed a  $\beta$ -network with segregated  $\alpha$ -networks (4.588 Å repeat) running in the same direction as shown in Figure 1b and analogous to the **gly-ur/3py-ur** structure, Figure 2a. The 4-cyanophenyl urea derivative, **5**, has a very rigid structure with little conformational freedom. Its cocrystal with urea has the checkerboard pattern

of Figure 1c. The repeat distance of 9.240 Å represents two urea molecules and averages 4.620 Å.

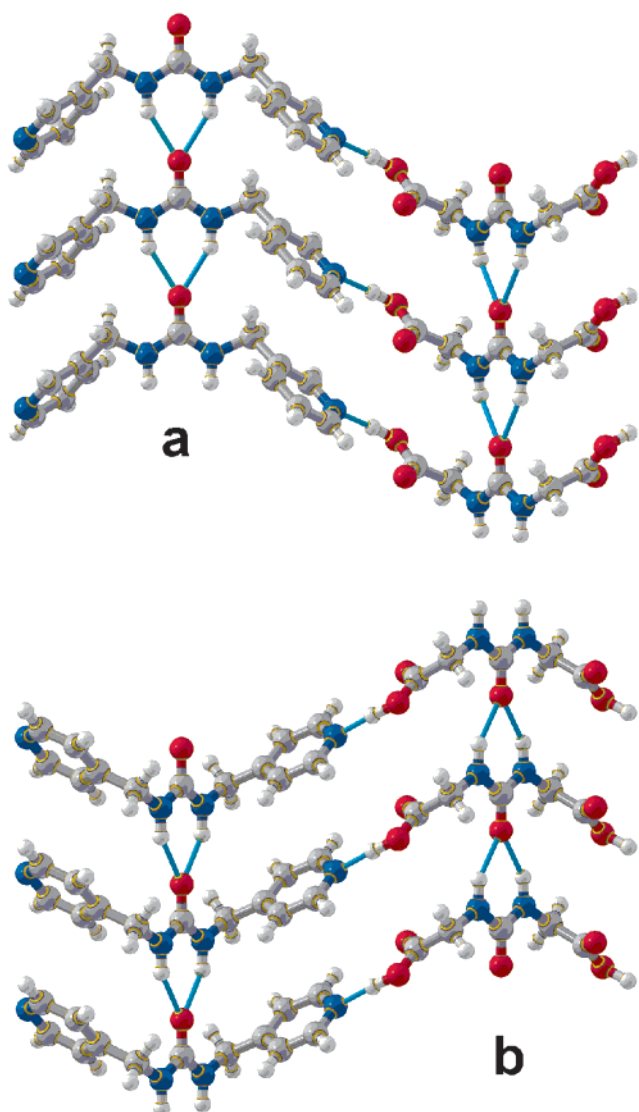


**Commensurate Oxamide–Oxamide Cocrystals.** The oxamide of glycine, **gly-ox**, readily forms cocrystals with both **3py-ox** and **4py-ox**. Since an oxamide does not have a natural polar axis like a urea, there are only two good candidate structures, not four as in the urea case. There is a striped pattern with segregated like-to-like  $\alpha$ -networks, Figure 3a, and the checkerboard pattern with like-to-unlike  $\alpha$ -networks, Figure 3b.

The two crystal structures are shown in Figure 4. The two  $\beta$ -network structures are different, each representing one of the two candidate structures shown in Figure 3. The **gly-ox/3py-ox** structure has segregated like-to-like  $\alpha$ -networks with a repeat distance of 5.03 Å, while the **gly-ox/4py-ox** structure forms with a checkerboard pattern with like-to-unlike  $\alpha$ -networks. The  $\alpha$ -networks are aligned with the 10.18 Å  $c$  axis of the unit cell. This distance represents the two unlike oxamide molecules and must be divided by 2 to give the oxamide repeat distance of 5.09 Å.

**Incommensurate Urea–Oxamide Cocrystals.** It appears that complementary urea–urea or oxamide–oxamide cocrystals can be formed reliably. Each cocrystal adopts the intermolecular repeat distance characteristic of the group functionality, 4.60

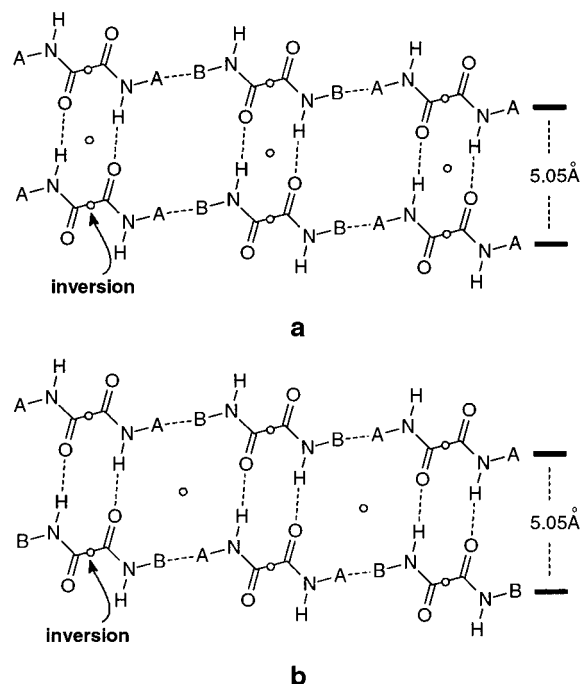
(11) Hollingsworth, B. D.; Brown, M. E.; Santasievo, B. D.; Huffman, J. C.; Gross, C. R. *Chem. Mater.* **1994**, *6*, 1227–1244.



**Figure 2.** Crystal structures of **gly-ur** with **3py-ur** (a) and of **gly-ur** with **4py-ur** (b). The  $\beta$ -network of a has repeat distance of 4.62 Å and a  $P2$  group layer symmetry matching the structure shown in Figure 1b. The  $\beta$ -network of b has repeat distance of 4.58 Å and a  $P2$  layer group symmetry matching the structure shown in Figure 1a.

Å for the ureas or 5.05 Å for the oxamides. What happens if the two functionalities are brought into the same crystal by cocrystallization? Perhaps the cocrystals will not form at all, but if they do form, one possible structure is a complex network with the urea  $\alpha$ -networks running in one direction and the oxamide  $\alpha$ -networks in a second nonparallel direction. Combined with the strong carboxylic acid–pyridine hydrogen bond, this arrangement would produce a complex three-dimensional  $\gamma$ -network. A second possibility is a two-dimensional  $\beta$ -network analogous to the ones we have seen before, but with some intermediate value for the repeat distance. Interestingly, there is only one reasonable candidate  $\beta$ -network. If a urea  $\alpha$ -network with  $P2$  rod group symmetry is combined with an oxamide  $\alpha$ -network with  $P1$  rod group symmetry, the resulting  $\beta$ -network has  $P2/c$  layer group symmetry, Figure 5.

With the six molecules we are considering, one can make four different 1:1 mixed urea–oxamide cocrystals. The first two, **gly-ur/3py-ox** and **gly-ur/4py-ox**, are shown in Figure 6. The **gly-ur/3py-ox** structure contains a  $\beta$ -network in accordance with the  $P2/c$  candidate structure shown in Figure 5. The **gly-ur/4py-ox** layer structure has only  $Pc$  symmetry; however, a close



**Figure 3.** Two likely  $\beta$ -network structures for pairs of complementary oxamide molecules. In a, the molecules form a striped pattern with segregated  $\alpha$ -networks. In b, the molecules form one alternating  $\alpha$ -network, and the molecules form a checkerboard pattern. In both structures the layer group symmetry is  $P\bar{1}$ .

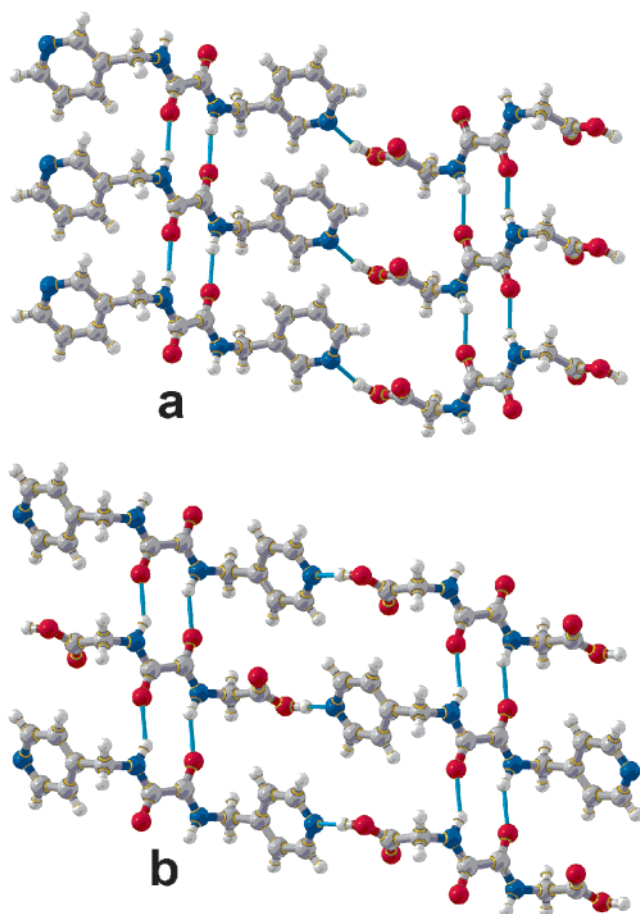
examination of the structure shows that structure has a strong pseudosymmetry of  $P2/c$ . The deviation from  $P2/c$  is due to a twisting of the oxamide pyridine rings that destroys the oxamide inversion center. The repeat distances of 4.87 and 4.88 Å for the two cocrystals are very similar. The urea hydrogen bonds have been stretched; the oxamides are compressed. The oxamide repeat distance is shorter than any similar listed in the Cambridge Structural Data Base. Prior to this study, the shortest reported oxamide repeat distance was a value of 4.99 Å reported for the oxamide of pentafluoroaniline.<sup>12</sup> Stretched urea distances are unusual but are not new because steric hindrance can cause the repeat to stretch. For example, the repeat distance found for the urea derivative of the ethyl ester of phenylalanine is 4.90 Å.<sup>13</sup>

In Figure 7 the remaining two structures, **gly-ox/3py-ur** and **gly-ox/4py-ur**, are shown. The **gly-ox/3py-ur** cocrystal is also based on a  $P2/c$   $\beta$ -network, with a similar 4.84 Å repeat distance. The last structure, that of **gly-ox/4py-ur**, is a surprise. The structure consists of a  $\beta$ -network, but the layer group symmetry is completely unexpected: it is  $P\bar{1}$ . This is a result of the **4py-ur** molecules being disordered about crystallographic inversion centers. The usual  $C_2$  symmetry axis is gone. The **4py-ur** molecules have one pyridine substituent oriented upward as in the **gly-ur/3py-ur** structure and the other downward as in the **gly-ur/4py-ur** structure, Figure 2. The central disordered urea functionalities are pointing half in each direction. Instead of the expected intermediate distance found in the other three structures, the repeat distance in **gly-ox/4py-ur** is 4.64 Å, the usual value for a simple urea structure.

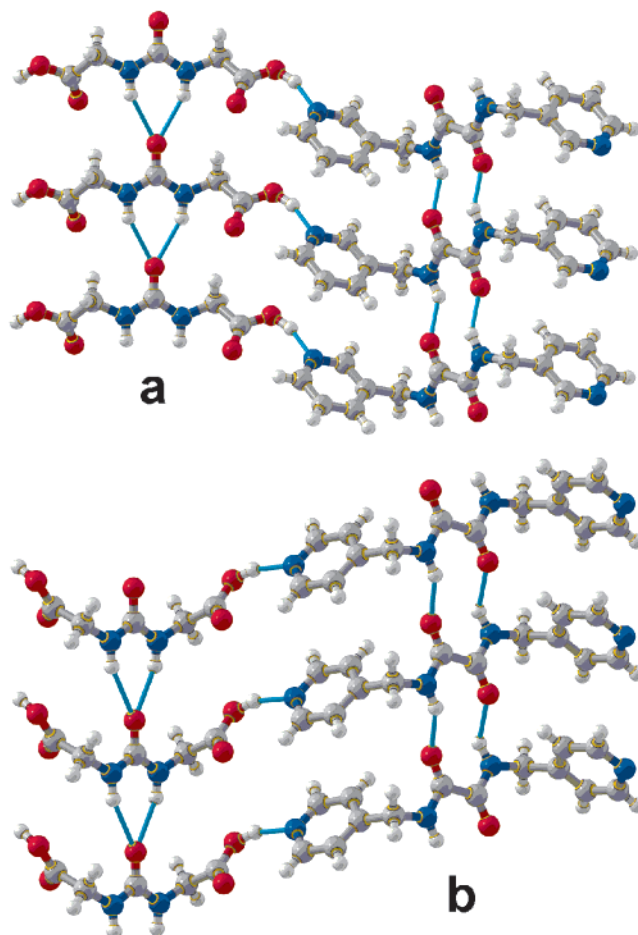
So how does the oxamide  $\alpha$ -network accommodate this short urea distance? Remarkably, the oxamide molecules adapt by not forming an  $\alpha$ -network at all. The closest contacts between

(12) Yamaguchi, K.; Matsumara, N.; Haga, N.; Shudo, K. *Acta Crystallogr., Sect. C* **1992**, *48*, 558–559.

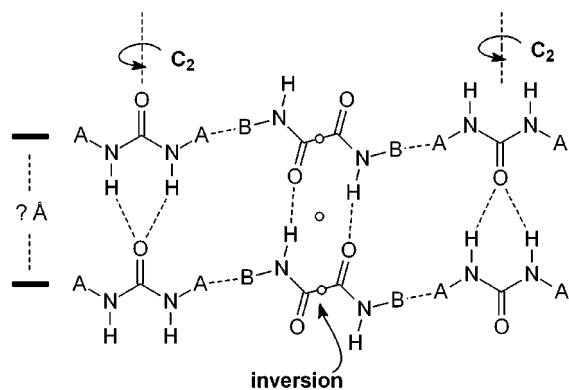
(13) Ala, P.; Asante-Appiah, E.; Chan, W. W.; Yang, D. S. C. *Acta Crystallogr., Sect. C* **1994**, *50*, 1830–1832.



**Figure 4.** Crystal structures of **gly-ox** with **3py-ox** (a) and of **gly-ox** with **4py-ox** (b). The  $\beta$ -network of a has repeat distance of 5.03 Å and a  $P\bar{1}$  layer group symmetry. With segregated  $\alpha$ -networks it matches the structure shown in Figure 3a. The  $\beta$ -network of b has an average repeat distance of 10.18 Å/2 (5.09 Å) and has a  $P\bar{1}$  layer group symmetry matching the checkerboard structure shown in Figure 3b.



**Figure 6.** Crystal structures of **gly-ur** with **3py-ox** (a) and of **gly-ur** with **4py-ox** (b). The **gly-ur/3py-ox**  $\beta$ -network has  $P2/c$  layer group symmetry and is in accordance with the anticipated structure shown in Figure 5. The **gly-ur/4py-ox**  $\beta$ -network has only  $Pc$  layer group symmetry but has a strong pseudosymmetry of  $P2/c$ . The repeat distances of 4.87 and 4.88 Å are intermediate between the expected value for a urea, 4.60 Å, and the expected value for an oxamide, 5.05 Å.

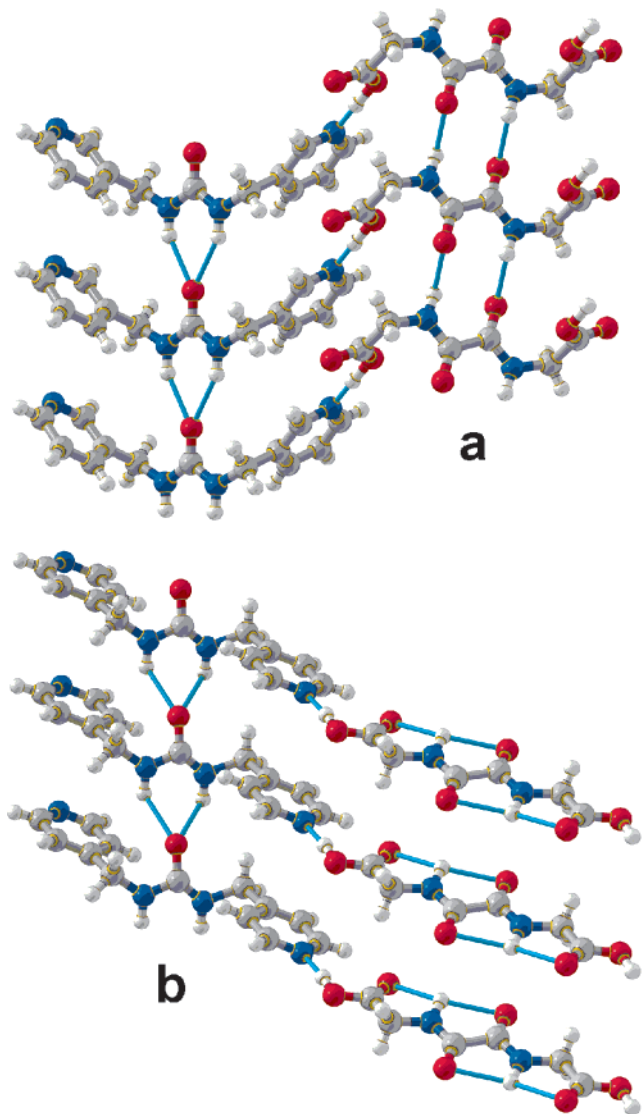


**Figure 5.** Likely  $\beta$ -network structure formed from a urea and a complementary oxamide molecule. The structure is predicted to have  $P2/c$  layer group symmetry. The repeat distance would presumably be intermediate between the normal 4.60 Å urea and 5.05 Å oxamide distances.

the oxamide carbonyl oxygen atoms and the neighboring oxamide amide hydrogen atoms are 2.74 Å. Instead, the molecules adopt an unusual conformation, Figure 8, which maximizes intramolecular hydrogen bonding at the expense of the intermolecular alternative. Classic Ramachandran angles can be calculated for these glycine derivatives. In this particular case, both Ramachandran dihedral angles are near 180°, maximizing internal intramolecular hydrogen bonding. In all of the other

structures reported in this paper, the **gly-ox** and **gly-ur** all have at least one Ramachandran angle that deviates significantly from 180°. This allows intermolecular hydrogen bonding to take place.

When all four of the mixed urea/oxamide structures are examined, one can see that the 3-pyridyl compounds, **gly-ox/3py-ur** and **gly-ur/3py-ox**, both crystallized with layer symmetry  $P2/c$  in complete accordance with our expectations as illustrated in Figure 5. The 4-pyridyl isomers did not. The **gly-ur/4py-ox** structure formed a layer similar to the predicted one, but with the pyridine rings of the oxamide twisted such that the expected inversion center is lost. In the **gly-ox/4py-ur** structure, the **4py-ur** molecule is disordered and the layer structure is a totally unexpected one. What is the problem with the 4-pyridyl compounds? It is likely a molecular conformation problem. The 3-pyridyl isomers essentially have one more internal degree of freedom than do their 4-pyridyl isomers. Rotation of a 3-pyridyl substituent about its principal axis allows a wide range of positions of the nitrogen hydrogen bond acceptor position. Rotation of a 4-pyridyl substituent does not change the position of its nitrogen atom. Perhaps there are simply too many imposed constraints on the **gly-ox/4py-ur** and **gly-ur/4py-ox** cocrystals.

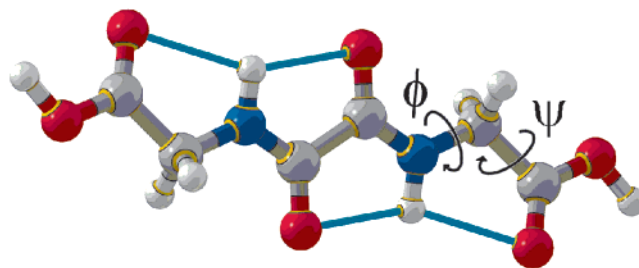


**Figure 7.** Crystal structures of gly-ox with 3py-ur (a) and of gly-ox with 4py-ur (b). The  $\beta$ -network of a is in accordance with the anticipated structure shown in Figure 5; it has  $P2/c$  layer group symmetry. The crystal structure of b is disordered. The 4py-ur molecule sits on a inversion center; in half of the molecules urea carbonyls point up, and in the other half they point down. Only the upward orientation is shown. The oxamide, gly-ox, adopts a conformation that maximizes intramolecular hydrogen bonds; the amide groups do not participate in intermolecular hydrogen bonds. The layer symmetry of this disordered  $\beta$ -network is  $P1$ .

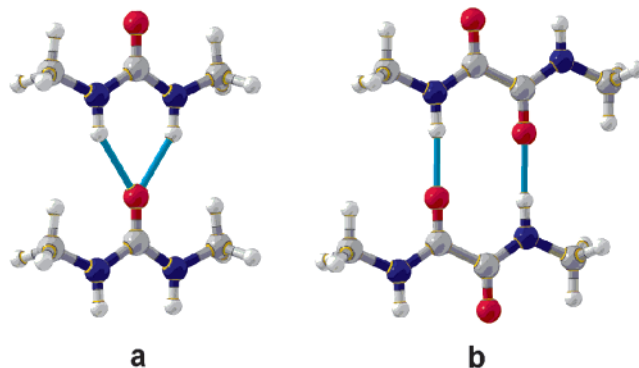
**Energetics.** The series of eight cocrystals presented in this paper provide a unique set of data to map the potential energy surfaces of two related, but different, hydrogen bond functionalities. We have performed a series of simple energy calculations using Jorgensen's OPLS model.<sup>14</sup> The OPLS model includes simple point charge Coulomb interactions plus 6–12 terms; it has been used by Jorgensen to model successfully many important hydrogen-bonded systems.<sup>15</sup> We calculated the energy of the best translational related dimers of dimethylurea and dimethyloxamide, Figure 9. In the calculations,<sup>16</sup> the first molecule was placed at the origin and the second placed with the same orientation at the end of a vector of varying length.

(14) Jorgensen, W. L.; Triandorides, J. *J. Am. Chem. Soc.* **1988**, *110*, 1666–1671.

(15) Pranata, J.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 2810–2819.



**Figure 8.** Molecular structure of gly-ox as found in the gly-ox/4py-ur cocrystal. The Ramachandran-like dihedral angles  $\phi$  and  $\psi$  are  $167^\circ$  and  $175^\circ$ , respectively. This leads to the formation of an intramolecular hydrogen bond between the carboxylic acid carbonyl oxygen and the amide hydrogen.



**Figure 9.** Best calculated dimers of dimethylurea (a) and dimethyl-oxamide (b). In the calculations which used Jorgensen's OPLS model, the first molecule was fixed and the second was allowed to take any position allowed by a simple translation. The calculated best spacing is 4.63 Å for a and 4.94 Å for b.

The orientation of this translational vector was minimized at each distance. For the dimethylurea the best translational vector always corresponds to the molecule's 2-fold axis; for the oxamide the orientation of the translation vector varies with distance, and the minimized structure is shown in Figure 9.

The best dimethylurea dimer has a lower energy minimum,  $-10.64$  kcal, than does the best dimethyloxamide dimer,  $-9.72$  kcal, Figure 10. This is due to the unfavorable cross term interactions in the oxamide hydrogen bond dimer that are absent in the urea dimer. In the oxamide case there are oxygen–oxygen and hydrogen–hydrogen repulsive contacts in addition to the attractive oxygen–hydrogen interactions. This also results in a 0.3 Å longer calculated minimum distance, 4.94 Å, for the oxamide system versus the shorter 4.63 Å distance calculated for the urea dimer. Experimental values for these dimers are unknown, but the values calculated for the dimers are in reasonable agreement with experimental repeat distances found in the actual crystal structures, which of course contain full  $\alpha$ -networks of molecules. Crystalline dimethylurea<sup>17</sup> has an experimental repeat distance of 4.57 Å, and dimethyloxamide<sup>18</sup> has an experimental repeat of 5.08 Å. Although these dimer calculations are crude, it is still interesting to speculate about the differences between the calculated and observed values. The experimental repeat distance for crystalline dimethylurea is shorter than the distance calculated for the dimer. Since the

(16) Standard OPLS charges were modified to fit dimethylurea and dimethyl-oxamide: C, +0.39; O,  $-0.39$ ; N,  $-0.40$ ; H, +0.33; CH<sub>3</sub>, +0.07. The  $\sigma$  and  $\epsilon$  parameters were taken from the literature: Duffy, E. M.; Severance, D. L.; Jorgensen, W. L. *Isr. J. Chem.* **1993**, *33*, 323–330.

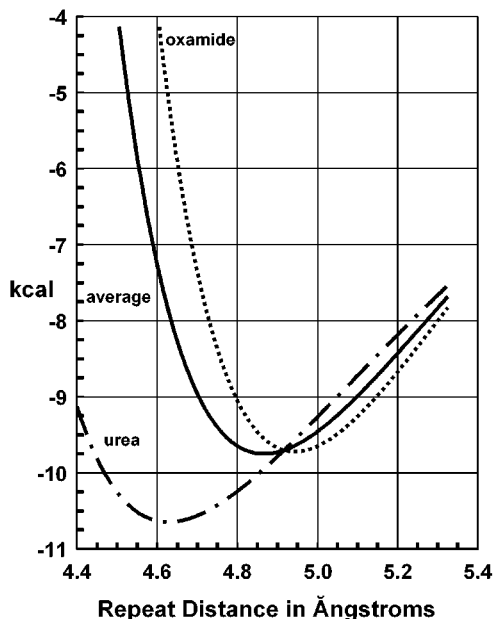
(17) Perez-Folch, J.; Subirana, J. A. *J. Chem. Cryst.* **1997**, *27*, 367–369.

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**Table 1.** Crystallographic Information for Various Cocrystals

crystal	layer group	interlayer symmetry	space group	repeat	<i>a</i> (Å)	<i>b</i> (Å)	<i>c</i> (Å)	$\alpha$ (deg)	$\beta$ (deg)	$\gamma$ (deg)	vol (Å <sup>3</sup> )	Z
gly-ur/3py-ur	<i>P2</i>	inversion	<i>P2/c</i>	4.6183(8)	10.634(2)	4.6183(8)	20.641(4)	90	97.23(3)	90	1005.7(3)	2
gly-ur/4py-ur	<i>P2</i>	inversion	<i>P2/n</i>	4.5754(7)	9.919(2)	4.5754(7)	21.788(4)	90	95.324(3)	90	984.6(2)	2
urea/4 <sup>a</sup>	<i>P2</i>	inversion	<i>P2/n</i>	4.588	13.708	4.588	13.964	90	112.35	90	812.2	2
urea/5 <sup>a</sup>	<i>P2/c</i>	screw axis	<i>C2/c</i>	4.620	12.962	9.240	14.514	90	119.33	90	1515.5	4
gly-ur/3py-ox	<i>P2/c</i>	screw axis	<i>C2/c</i>	4.8765(4)	26.593(5)	4.8765(4)	16.788(3)	90	107.93(2)	90	2071.3(6)	4
gly-ur/4py-ox	<i>Pc</i> ( <i>P2/c</i> ) <sup>b</sup>	translation	<i>Pc</i> ( <i>P2/c</i> ) <sup>b</sup>	4.882(1)	12.437(3)	4.882(1)	17.934(4)	90	107.26(1)	90	1039.9(4)	1
gly-ox/3py-ur	<i>P2/c</i>	screw axis	<i>C2/c</i>	4.839(4)	27.401(8)	4.8386(4)	18.104(6)	90	123.47(1)	90	2002.2(9)	4
gly-ox/4py-ur	<i>P1</i>	translation	<i>P1</i>	4.643(1)	4.643(1)	9.704(2)	11.467(2)	99.41(1)	91.79(1)	95.68(1)	506.7(2)	1
gly-ox/3py-ox	<i>P1</i>	screw axis	<i>P2<sub>1</sub>/c</i>	5.030(2)	5.030(2)	24.508(1)	8.625(4)	90	99.54(1)	90	1048.5(7)	2
gly-ox/4py-ox	<i>P1</i>	translation	<i>P1</i>	5.088	4.375(4)	10.175(2)	12.846(1)	97.77(3)	92.65(4)	67.08(3)	521.9(4)	1

<sup>a</sup> Reference 11. <sup>b</sup> In the **gly-ur/4py-ox** cocrystal, the oxamide has a pseudoinversion center. If this center were real, then the layer group and the space group would be *P2/c*.



**Figure 10.** Plot of calculated hydrogen bond energies (kcal/mol) versus translational repeat distance for the best hydrogen-bonded dimer calculated for dimethylurea and dimethyloxamide. Each energy represents two hydrogen bonds. The best urea dimer has a minimum at 4.63 Å with an energy of  $-10.64$  kcal/mol. The best oxamide dimer has a minimum at 4.94 Å with an energy of  $-9.72$  kcal/mol. If the oxamide and urea values are averaged, the curve of the averages has a minimum at 4.87 Å with a minimum energy of  $-9.75$  kcal/mol.

dipoles of all ureas in one  $\alpha$ -network all point in the same direction, one would expect a significant attractive interaction with next-nearest neighbors leading to a shortening of the repeat distance. For the centrosymmetric oxamides there is no alignment of dipoles. Next-neighbor interactions include equal numbers of favorable and unfavorable interactions. Without this extra stabilizing force one might expect the distances in an oxamide crystal to be longer than those in an isolated dimer. The shorter distance and the apparently greater strength of the urea–urea interaction correlates with the observation that the urea  $\alpha$ -networks form in a more reliable manner than do the analogous oxamide  $\alpha$ -networks.

More interesting is the potential curve that results from averaging the calculated potential curves for the dimethylurea and dimethyloxamide dimers, Figure 10. Due to the asymmetric shape of the two individual potential curves, the curve of the averages has a minimum much closer to the oxamide minimum than to the urea minimum. Stretching the urea dimer by 0.3 Å to the oxamide minimum would cost only about 1 kcal; compressing the oxamide dimer by the same amount would cost

more than 6 kcal. Clearly in a mixed crystal one would expect distance values closer to the calculated oxamide minimum. The predicted minimum of 4.87 Å is in very good agreement with the repeat distances found for three of the mixed urea oxamide crystals reported in this paper, **gly-ur/3py-ox** (4.87 Å), **gly-ur/4py-ox** (4.87 Å), and **gly-ox/3py-ur** (4.84 Å). The fourth mixed cocrystal **gly-ox/4py-ur** (4.64 Å) does not have intermolecular oxamide hydrogen bonds and thus has the repeat distance expected for a urea-only structure.

**Interlayer Symmetry.** As mentioned in the introduction, one way to simplify a crystal engineering problem is to simplify the stated goal. We have done this by concentrating our efforts on the preparation of layered  $\beta$ -networks. As we formulated our candidate structures, we anticipated certain repeat distances and particular layer symmetries, but we did not take the last step and predict the space group of the final crystals. This would have been a difficult task, because there are no particular strong interlayer bonding interactions that we can use as a reliable guide for our predictions. Although we did not try to predict the interlayer symmetry, now that we have completed our exercise it is worthwhile for us to examine the data to see how the layers do come together, Table 1.

First to be considered are the three urea  $\beta$ -networks with *P2* layer symmetry, **gly-ur/3py-ur**, **gly-ur/4py-ur**, and **urea/4**. If these chiral layers packed via simple translation, then the resulting space group would have been the polar group *P2*. Not surprisingly, the layers stack via inversion instead giving opposing dipoles, and the final space group for all three structures is *P2/c*.<sup>19</sup> The **urea/5** structure and two of the mixed urea–oxamide  $\beta$ -networks, **gly-ur/3py-ox** and **gly-ox/3py-ur**, have *P2/c* layer symmetry. There are two good ways for such layers to pack, either via simple translation, generating space group *P2/c*, or by a screw axis between the layers, generating space group *C2/c*. The screw axis brings about a natural “bump to hollow” packing, and thus *C2/c* seems a bit more probable; *C2/c* is indeed the observed space group for all three structures. The **gly-ur/4py-ox** structure has *Pc* layer symmetry; the layers are related by simple translation, and the space group is thus also *Pc*. The final three structures, **gly-ox/4py-ur**, **gly-ox/3py-ox**, and **gly-ox/4py-ox**, form  $\beta$ -networks with *P1* layer symmetry. In *P1* the two axes are nonorthogonal, and the simplest interlayer packing would be via simple translation in a third nonorthogonal direction to give the *P1* space group. Two of the structures adopt this motif, but the layers of **gly-ox/3py-ox** pack via a screw axis instead to generate space group *P2<sub>1</sub>/c*.

### Experimental Details

The urea and oxamides were synthesized using previously published methods.<sup>5,6,10</sup> The eight cocrystals were all grown by dissolving

(19) In two cases the alternate setting, *P2/n*, is adopted.

millimolar quantities of each molecule in methanol/water solution. Each solution was then allowed to evaporate to dryness, giving crystals in a quantitative yield. Although each cocrystal was easy to prepare, the quality of each of the crystals was generally less than ideal for X-ray diffraction. Most crystals were obtained as elongated plates or needles with a small cross section, often with striations or cracks parallel to the principal axis of the crystal. In each case this principal axis corresponded to the molecular repeat distance, Table 1.

## Conclusions

In the eight structures we examined, the carboxylic acid–pyridine hydrogen bonds always formed. We were counting on this strong intermolecular interaction to bring about the cocrystallization in the first place; it seems to be very reliable. In all six crystals containing the urea functionality, the urea  $\alpha$ -network always formed. This is consistent with previous work in our group; the urea functionality is very reliable. In five of the six oxamide structures, the anticipated oxamide  $\alpha$ -network formed, but in the **gly-ox/4py-ur** crystal the oxamide molecules formed intramolecular hydrogen bonds instead. This is also consistent with our previous work; oxamide  $\alpha$ -networks are reliable, but not quite as reliable as urea  $\alpha$ -networks.

The anticipated  $C_2$  molecular symmetry of the disubstituted urea molecules was crystallographically imposed in four of the six urea structures; in the **gly-ur/4py-ox** structure, there is a strong  $C_2$  pseudosymmetry. The exception is the **gly-ox/4py-ur** structure, which has a disordered urea sitting on an inversion center. The anticipated  $C_i$  molecular symmetry of the oxamides was found in all structures with the lone exception of the **gly-ur/4py-ox** structure, in which the inversion symmetry is broken by the orientation of the pyridine substituents. Overall, the molecular symmetry elements seem to be reasonably persistent and can be expected to be carried over into a crystal in most cases. Molecular conformation is also important. The 3-pyridyl compounds formed structures in accordance with expectations;

the two exceptions both involved 4-pyridyl substituents, which have less conformational freedom.

The incommensurate urea oxamide hydrogen bonds forced the molecules to adopt unusual repeat distances. In one case the oxamide avoided the problem by adopting an unusual molecular conformation that maximized intramolecular hydrogen bonds. In the other three mixed urea–oxamide structures both the urea and oxamide  $\alpha$ -networks assumed an intermediate repeat distance averaging 4.87 Å, a value closer to the calculated value for oxamides. The usual urea hydrogen bonds were stretched; the normal oxamide repeat was compressed. The observed oxamide repeat distances are the shortest ever observed, showing that a hydrogen-bonded  $\alpha$ -network can be compressed when forced to adapt to unusual environments.

This exercise presents a clear example of one feature of molecular packing that is often overlooked. Abnormally short intermolecular distances are often ascribed to unusually favorable intermolecular interactions. But sometimes this may not be a correct interpretation. Abnormally short distances, such as the short oxamide repeat distances found in this work, may be forced contacts and repulsive.<sup>20</sup> One should not forget that molecular packings are a compromise between attractive and repulsive forces throughout the entire crystal.

**Acknowledgment.** We thank the National Science Foundation for their support of this work, CHE 9980350.

**Supporting Information Available:** Full crystallographic information for the eight cocrystals discussed in this paper (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA016635V

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