Design of Molecular Solids.[1] Application of 2-Amino-4(1*H*)-pyridones to the Preparation of Hydrogen-Bonded α- and β-Networks[2]

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Crystallographic studies have demonstrated 2-amino-4(1*H*)-pyridones to be effective analogs of ureas for the design of molecular solids. This ring system is capable of producing persistent hydrogen-bonded α-networks with a molecular repeat distance of 6.7 Å compared to 4.7 Å for urea. The addition at C-5 of nitrile function to the 2-amino-4(1*H*)-pyridone ring system was sufficient to form a second α-network using the syn hydrogen of the NH_2 group. The presence of two α-network-forming functionalities in the same molecule resulted in a β-network ultimately producing a layered molecular crystal.

Introduction

An essential element of any comprehensive strategy for the synthesis of new materials is the control of solid-state structure. The synthesis of a molecular solid-state structure is a very difficult problem requiring the control of intermolecular interactions leading to the preparation of a specific solid-state goal structure. Important solid-state goals are low-dimensional structures such as one-dimensional rods and two-dimensional layers. A one-dimensional rod structure consists of parallel α-networks where the molecules within the α-network are held together by strong intermolecular forces whereas the α-networks are held together by weak forces such as van der Waals forces. Similarly, a two-dimensional layered structure consists of parallel β-networks where the molecules within the β-network[1] are held together by strong intermolecular forces, whereas the β-networks are held together by weak forces. Because of their anisotropic properties, these solid-state structures have played an important role in the development of materials science.[3]

Layered structures are more complex than rod structures requiring a more complex design strategy. A key component of our approach to the design and preparation of solid-state structure is the identification of features and functionalities[4] capable of producing predictable α-networks. Our strategy for preparing a β-network is to incorporate *two* functionalities, capable of forming α-networks, into the same molecule. If both α-networks in this molecule persist, then there is a very high probability of producing a β-network and, as a consequence, a layered solid-state structure.

The N,N′-disubstituted ureas have proven to be reliable functionalities for molecular self-assembly into α-networks.[5] We have successfully used this functionality, in combination with dicarboxylic derivatives and molecular chirality, for the preparation of β-networks.[5] Because of the different molecular structures, all of the layered compounds had different solid-state structures. However, one structural element they all possessed in common was the 4.6–4.7-Å molecular repeat distance in the plane of the β-network and along the urea hydrogen-bonded network. Although the urea molecular repeat distance has a potential application to the solution of certain problems,[6] the ability to alter this supramolecular structural feature would be a valuable addition to our synthetic strategy. Clearly, it is an important objective to identify other functionalities capable of forming persistent and predictable α-networks for the control of supramolecular structure.

The persistency of urea hydrogen-bonded networks suggest its analogs as possible functionalities for the preparation of designed materials. For example, the vinylogous ureas possess the possibility of forming a hydrogen-bonded network analogous to ureas but with a different molecular repeat distance (Figure 1).

Results and Discussion

To evaluate the utility of the vinylogous urea functionality for the preparation of molecular solids, suitable molecular systems for synthesis are necessary. A suitable molecular structure, incorporating the vinylogous urea functionality, is the 2-amino-4-pyridone ring system (see Scheme 1). This ring system is relatively simple and should be synthetically accessible. Because of problem of tau-

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(1) For the previous paper in this seies see: Chang, Y.-L.; West, M. A., Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 5991.

(2) The α- and β-networks are supramolecular structural features processing translational symmetry in one and two directions, respectively. These networks, together with descrete assemblies and γ-networks represent the four fundamental supramolecular structures. These terms are discussed further in ref 1.

(3) For example, see: *Physics and Chemistry of Materials with Low-Dimensional Structures*; D. Reidel: Dordrecht, The Netherlands.

(4) Two examples of structural features useful for the preparation of materials are chirality[1] and persistent, polymeric hydrogen-bonding networks.

(5) (a) Etter, M. C.; Zofia, U.-L.; Zia-Ebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415. (b) Zhao, X.; Chang, Y.-L.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 6627. (c) Reference 1.

(6) For example, the urea repeat distance of 4.7 Å has been useful for the preparation of diacetylenes. (a) Bloor, D, Chance, R. R., Eds. *Polydiacetylenes: Synthesis, Structure and Electronic Properties*; Martinus Nijhoff: Dordrecht, The Netherlands, 1985. (b) *Nonlinear Optical Properties of Organic Molecules and Crystals*, Chemla, D. S., Zyss, J., Eds.; Academic Press: Orlando, FL, 1987. (c) Prasad, P. N.; Williams, D. J. *Introduction of Nonlinear Optical Effects in Molecular and Polymers*; John Wiley & Sons: New York, 1991; p 231. (d) Enkelman, V. *Adv. Polym. Sci.* **1984**, *63*, 91. (e) *Nonlinear Optics of Organics and Semiconductors*, Kobayashi, T., Ed.; Springer-Verlarg: Berlin, 1989.

(7) The molecular repeat distances were calculated using MacroModel version 4.0. W. C. Still, Columbia University, 1993.

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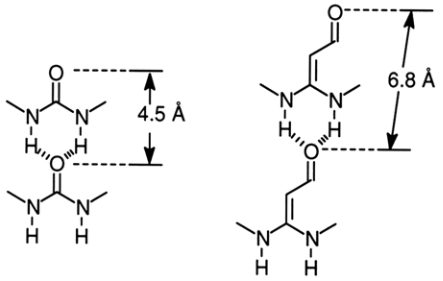
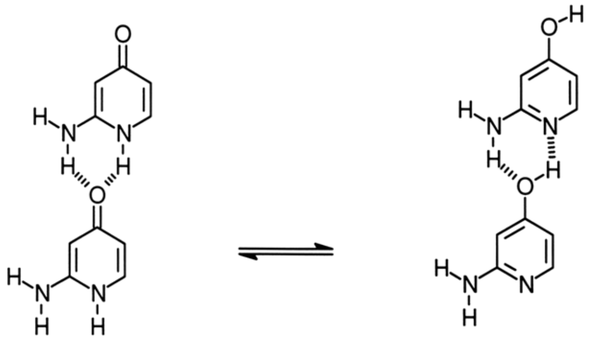
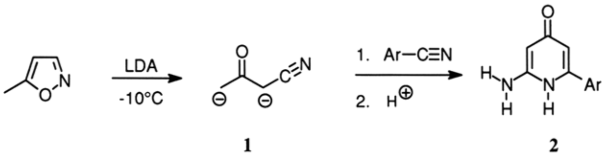


Figure 1. α-networks of a urea and a vinylogous urea with the calculated repeat distances.[7]

Scheme 1. α-Networks of 2-Amino-4(1*H*)-pyridone and 2-Amino-4-hydroxypyridine



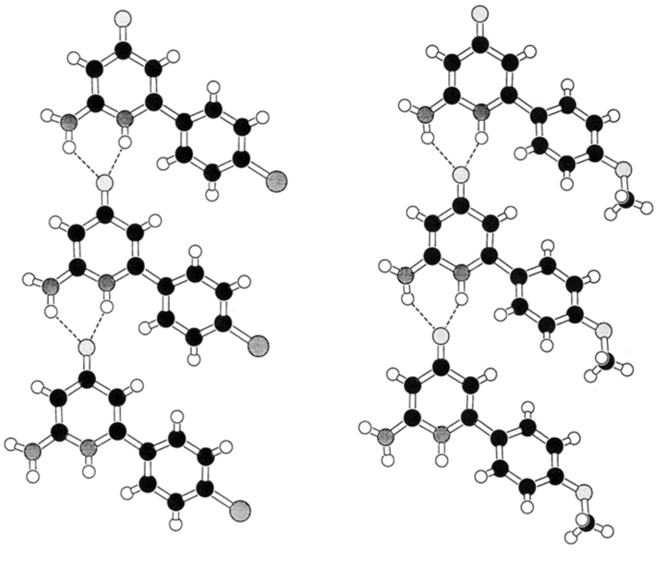
Scheme 2. Preparation of Aminopyridones 2a and 2b



tomerization,[8] caution must be exercised when using heterocyclic rings for the design of hydrogen-bonded networks. In this case, however, either the 4-hydroxypyridine or the 4-pyridone tautomer can give rise to the desired α-network.

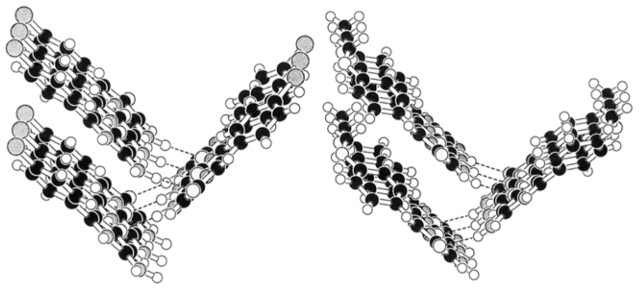
Although the 2-amino-4-pyridone ring system is known, it is not common. There are no crystallographic studies reported, and there are only a few syntheses that would be suitable for our investigations.[9] One attractive method for the preparation of 6-aryl derivatives[9a] begins with the commercially available 2-methylisoxazole. Initial treatment of the isoxazole with LDA gives the dianion **1**. Addition of an aromatic nitrile followed by neutralization produces the desired 2-amino-4(1*H*)-pyridone. Although this method has limitations, it was successful for the preparation of two 2-amino-4(1*H*)-pyridones (Ar = *p*-chlorophenyl (**2a**) and *p*-anisyl (**2b**)) which gave crystals of sufficient quality for X-ray diffraction studies (Scheme 2).

Compound **2a** (Ar = *p*-chlorophenyl) crystallized in the monoclinic noncentrosymmetric space group $P2_1$ with one molecule in the asymmetric unit. All of the hydrogen atoms were located from the electron density difference maps and the bond length and angles indicated that the pyridone and not the hydroxypyridine tautomer was obtained. Compound **2b** (Ar = *p*-anisyl) crystallized in the noncentrosymmetric orthorhombic space group $P2_12_12_1$ with one molecule in the asymmetric unit.



2a **2b**

Figure 2. Hydrogen-bonded α-networks of compounds **2a** and **2b**. The neighboring molecules in each network are related by a simple translation operator with a repeat distance of 6.693(1) Å in **2a** and 6.688(1) Å in **2b**.



2a 2b

Figure 3. Hydrogen-bonded β-networks of compounds **2a** and **2b**. The α-networks shown in Figure 2 assemble into β-networks via the syn NH_2 hydrogen atom. Each figure shows "end on" views of three α-networks each related by a 2_1 screw axis to its neighbors.

Both **2a** and **2b** self-assembled into the α-network, depicted in Scheme 1, with *P*1 rod symmetry (Figure 2). These α-networks both possessed a molecular repeat distance of 6.7 Å, in close agreement with the calculated value.

Interestingly, both of the α-networks in **2a** and **2b** also associate with each other in the same way ($P2_1$ layer symmetry) through hydrogen bonding using the syn[10] NH_2 hydrogen and the carbonyl oxygen atom. The resulting β-networks of both **2a** and **2b** have exactly the same hydrogen-bonded networks (Figure 3). The only supramolecular structural difference between these crystals is the relationship of the layers with respect to each other. In compound **2a** the β-networks are related by translational

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[8] Elguero, J.; Marzin, C.; Katritzky, A. R.; Lindia, P. *The Tautomerism of Heterocycles. Advances in Heterocyclic Chemistry, Supplement* 1; Academic Press: New York, 1976.

[9] (a) Binick, F. J.; Pan, Y.; Gschwend, H. W. *Tetrahedron Lett.* **1978**, 4221. (b) Kappe, T.; Stelzel, H. P.; Ziegler, E. *Monatsh. Chem.* **1983**, *114*, 953.

[10] For convenience, the designation of syn and anti to be the two NH_2 hydrogen atoms is analogous to that used for amide groups. That is, the hydrogen atom toward the C═O group is syn and the hydrogen atom away from the C═O group is anti.

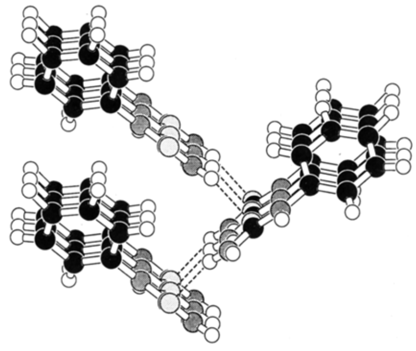


Figure 4. Crystal structure of *N*-phenylurea.[12] This structure is very similar to the structures of compound 2a and 2b as shown in Figures 2 and 3. Each *N*-phenylurea molecule forms an α-network via a simple translation of 4.66(1) Å using the hydrogen bonds shown in Figure 1. These α-networks assemble into β-networks via the syn NH_2 hydrogen atoms. The figure "end on" views of three α-networks each related to a 2_1 screw axis to its neighbors.

symmetry whereas in **2b** the β-networks are related by a screw axis along the crystallographic *b* axis.

An inspection of the Cambridge Crystallographic Database[11] reveals that **2a** and **2b** are not only structural analogs of monosubstituted ureas at a molecular level but also at a supramolecular level. That is, selected monosubstituted ureas self-assemble into α-networks and these α-networks, using the syn NH_2 hydrogen atom and the carbonyl oxygen atom, further assemble into a β-network. For example, Figure 4 shows three α-networks of *N*-phenylurea and their assembly into a β-network.[12]

The crystal structures of **2a** and **2b** illustrate that the vinylogous ureas are excellent analogs of ureas. Their ability to predictably produce α-networks should be of considerable value for the design and preparation of solid-state materials.

It is one of our goals to prepare layered compounds by a careful design of β-networks. Our strategy for the preparation of β-networks is to incorporate two functionalities into a single molecule capable of forming two α-networks. If these two α-networks persist, then there is a very high probability of producing a layered material. Although both **2a** and **2b** technically formed β-networks, they used the carbonyl oxygen to form *three* hydrogen bonds. A more predictable hydrogen bonded network would be desirable for the formation of an α-network.

A strategy for the design of a more reliable α-network would be to explicitly add a functionality to the 2-amino-4(1*H*)-pyridone ring system capable of accepting the syn hydrogen of the NH_2 group. A possible candidate for a functional group that will only behave as an hydrogen bond acceptor is a nitrile. Nitriles are known hydrogen-bond acceptors[13] and, more importantly, Hollingsworth[14] has demonstrated that dinitriles and urea can be used to produce layered structures using the syn urea hydrogen atom and the nitrile functionality to form hydrogen bonds. For example, nitrile **3** can be envisioned to assemble into an α-network according to Scheme 3.

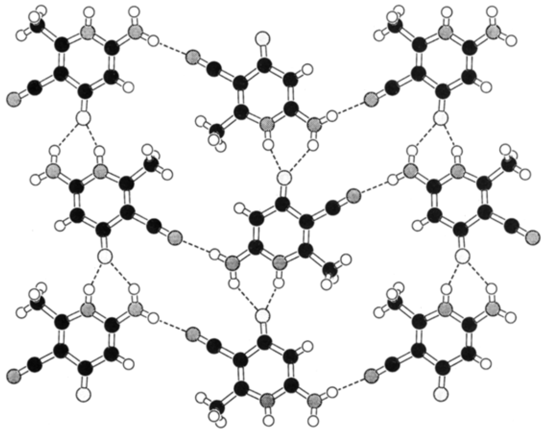
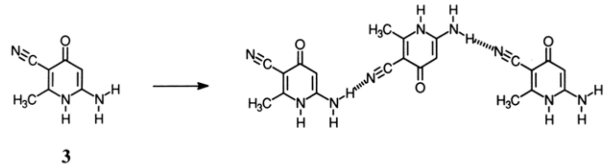
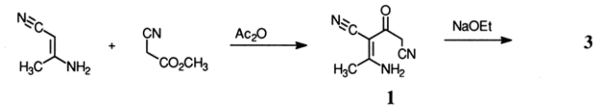


Figure 5. β-network of compound **3**. The layer symmetry of this β-network is $P2_1/a$ with the 2_1 screw axis relating neighboring molecules in the vertical direction and the glide plane relating the molecules in the horizontal direction.

Scheme 3. Favorable Hydrogen-Bonded Network Involving the Nitrile Functionality



Scheme 4. Synthesis of 2-Amino-5-cyano-6-methyl-4(1*H*)-pyridone



Nitrile-substituted 2-amino-4(1*H*)-pyridone **3** should be accessible using an enaminonitrile and cyanoacetic acid.[15] This method was successful leading to the preparation of 2-amino-5-cyano-6-methyl-4(*H*)-pyridone (**3**) according to Scheme 4.

Crystals of **3** suitable for X-ray crystallography were grown from water. The compound crystallizes in the centrosymmetric monoclinic space group $P2_1/a$ with one molecule per asymmetric unit. The structure revealed the β-network shown in Figure 5.

The β-network contains two perpendicular α-networks. One of the α-networks is analogous to that shown in Scheme 3 and the other is a result of the vinylogous urea hydrogen bonded network. Although this second hydrogen bonded network involves the vinylogous urea, it is not the same network as is shown in Scheme 1. In Scheme 1, each of the molecules along the vinylogous urea direction is related by simple transitional symmetry whereas each of the molecules in the actual lattice of **3** is related by a 2-fold screw axis.

Simple model building demonstrates that a β-network cannot be formed by combining the two hydrogen bonded networks shown in Schemes 1 and 3. The problem is that the hydrogen-bonded network involving the vinylogous urea anti-hydrogens is not perpendicular to the hydrogen-bonded network involving the nitrile. This problem can be rigorously defined using the language of group theory.

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(11) Allen, F. H.; Bellard, S.; Brice, M.; Cartwright, B. A.; Doubleday, A.; Higgs, H.; Hummelink-Peters, B. G.; Kennard, O.; Motherwell, W. D. S.; Rodgers, J. R.; Watson, D. G. *Acta Crystallogr.* **1979**, *B35*, 2331.

(12) Kashino, S.; Haisa, M. *Acta Crystallogr.* **1977**, *B33*, 855.

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

(14) Hollingsworth, M. D.; Santansiero, B. D.; Oumar-Mahamat, H.; Nichols, C. J. *Chem. Mater.* **1991**, *3*, 23.

(15) Kappe, T.; Stelzel, H. P.; Ziegler, E. *Monatsh. Chem.* **1983**, *114*, 953.

Adjacent molecules of the α-network of Scheme 3 are oriented upside down with respect to each other. In a crystal this change in orientation would correspond to either a glide plane or a 2-fold screw axis. Since the α-network is nearly planar, the effect of a glide plane and screw axis would be similar and either is possible. To form a β-network, a second set of hydrogens bonds must be formed in a second direction. To obey the requirements of crystallographic symmetry and to properly fill space, this second translation direction cannot be oblique, it must be perpendicular to the first axis.[16] However the molecular geometry of the aminopyridone molecule, with the hydrogens offset to one side,[17] leads to an inherently oblique translation incompatible with requirements of the α-network of Scheme 3. Since simple translation of the aminopyridone cannot produce an acceptable perpendicular lattice direction, some other symmetry operator is required. Again, due to the near planar nature of the molecule, either a perpendicular glide plane or a perpendicular screw axis would be acceptable. Thus, a lattice very similar to that shown in Figure 5 could be formed in four fundamental ways:[18] two glide planes, two screw axes or two different arrangements of one glide plane and one screw axis.[19] The arrangement experimentally observed has a horizontal glide plane corresponding to the α-network of Scheme 3, and a vertical 2-fold screw axis corresponding to the α-network formed by the vinylogous urea hydrogen bonds. This gives the β-network $P2_1/a$ layer symmetry.

It is important to recognize that both of the α-networks shown in Scheme 3 and Figure 1 are very favorable hydrogen-bonded interactions, but they cannot be used together to form a β-network.[20] This situation illustrates an important principle that can be effectively used in the design and preparation of crystal lattices. *In a crystal lattice, with identical molecules, all intermolecular interactions must also correspond to specific symmetry operations*.[21] Since the specific symmetry operators must be mutually compatible,[22] there will often be cases where otherwise favorable hydrogen-bonding interactions will be forbidden in a crystalline lattice. Thus, crystal designs must rely on both good chemistry and good crystallography.

If the design and preparation of new materials is ever to be a rational process, it is necessary to control supramolecular as well as molecular structure. Layered materials are important supramolecular structures. The essential supramolecular structural feature of a layered material is a β-network. We have developed a strategy for the preparation of β-networks by incorporating, into the same molecule, two functionalities capable of forming α-networks. The 2-amino-4(1*H*)-pyridone ring system has been demonstrated to be a useful functionality for the formation of α-networks and controlling the molecular repeat distance. The addition to this ring system of a nitrile function, as a single hydrogen-bond acceptor, resulted in the formation of a β-network and a layered organic solid.

Experimental Section

General Techniques. Melting points were recorded on a Fisher-Johns melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Nicolet QE-300 spectrometer and tetramethylsilane was used as internal reference. The NMR spectra were recorded on samples dissolved in pure DMSO-d_6. Coupling constants are reported in hertz. All chemical shifts are reported in ppm units from the internal standard and described as being either broad singlet (br s) singlet (s), doublet (d), triplet (t), quartet (q), quintet (q′), or multiplet (m). Infrared spectra for compounds **2a** and **2b** were recorded on a Perkin-Elmer 1600 FT-IR and for compound **3** on a Mattson Galaxy Series FTIR 3000 as KBr pellets without internal reference. Low-resolution mass spectra (MS) were recorded using a Hewlett-Packard 5980A spectrometer. All starting materials were purchased from Aldrich Chemical Co. and were used without further purification.

General Procedure for the Preparation of the Pyridones 2a and 2b.[9] To a mechanically stirred solution of 10.5 mL (0.075 mol) of diisopropylamine in 75 mL of dry THF (−10 °C, N_2 atmosphere) was added dropwise 30 mL (0.075 mol) of 2.5 M *n*-BuLi. After 15 min, 3.06 mL (0.0375 mol) of 5-methylisoxazole was added dropwise. The yellow-orange suspension was stirred at −10 °C for 30 min and then (0.034 mol) of the arylnitrile in 7 mL of THF was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. Water was added and the pH adjusted to ca. 7 approximately with glacial acetic acid, whereupon the pyridone precipitated from solution. The product was collected by filtration, washed with water and ether, and treated with activated carbon in hot methanol. Crystals were obtained from methanol.

2-Amino-6-(*p*-chlorophenyl)-4(1*H*)-pyridone (2a). Recrystallizatioon of the filtrate from a large volume of methanol yielded beige needles of good quality for X-ray crystallography; mp 294–300 °C (dec); ^{1}H NMR (DMSO-d_6) δ 10.10 (br s, 1H), 7.90 and 7.44 (AA′BB′, 2H), 6.52 (s, 1H), 5.86 (s, 1H), 5.79 (s, 2H); IR (KBr pellets) 3368, 3306, 3181, 3115, 2956, 2932, 1639 cm^{-1}; *m/e* (relative intensity) 222 (33), 220 (100), 193 (12), 180 (25), 137 (12), 92 (11), 68 (24).

2-Amino-6-(4-anisyl)-4(1*H*)-pyridone (2b). Recrystallization of the filtrate from a large volume of methanol yielded beige plates of good quality for X-ray crystallography; mp 280 °C (dec) (lit mp 280);[9] ^{1}H NMR (DMSO-d_6) δ 10.00 (br s, 1H), 7.81 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 8.4 Hz, 2H), 6.41 (s, 1H), 5.76 (s, 1H), 5.69 (s, 1H), 3.77 (s, 3H); IR (KBr pellets) 3358, 3308, 3175, 3116, 2966, 1640 cm^{-1}; *m/e* (relative intensity) 216 (100), 201 (14), 108 (6), 77 (5), 68 (9), 66 (6).

2-Amino-5-cyano-6-methyl-4(1*H*)-pyridone (3). Using a procedure analogous to that reported,[15] cyanoacetic acid (2.13 g, 0.025 mol), was added to 3-aminocrotonitrile (2.02 g, 0.025 mol) in 25 mL of acetic anhydride. The mixture was heated at 105 °C for 5 min, and the solvent removed by evaporation *in vacuo*. The brown, oily residue was triturated three times with ice-cold water, and the water discarded. The oil was then triturated with cold methanol until a solid formed. This solid was filtered and washed several times with cold methanol. The orange colored solid was then recrystallized twice from methanol to give 0.275 g, (7.2%) of cyano-2-(3-aminocrotonitrile (4)): mp 177–178 °C; ^{1}H NMR (CDCl$_3$) δ 9.99 (br s, 1H), 9.02 (br s, 1H), 3.47 (s, 2H), 2.00 (s, 3H), IR (KBr pellet) 3393, 3228, 2915, 2259, 2200, 1636, 1478 cm^{-1}.

The above cyanoacetyl-2-(3-aminocrotonitrile) (4, 0.25 g, 0.0017 mol) was used without purification and was dissolved in absolute ethanol containing 1 equiv of NaOEt. This solution was refluxed for 2 h during which time a yellowish precipitate formed. The solvent was removed by evaporation *in vacuo*. The residue was

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[16] A translational axis, oblique to a glide plane or screw axis will not properly fill space. This is illustrated by the fact that a triclinic cell, with only oblique axes cannot possess either a glide plane or a screw axis.

[17] Note that this does not happen in the urea system, where the urea anti-hydrogens are centered beneath the urea carbonyl. The molecular structure leads naturally to a perpendicular translation.

[18] If the molecules actually crystallized on a mirror plane then you could have coincident glide planes and screw axes.

[19] In one arrangement observed experimentally the horizontal axis corresponds to the glide plane and the vertical axis corresponds to a screw axis. A similar structure could be imagined with the orientations of the two symmetry operators switched.

[20] Although hydrogen-bonded networks of the vinylogous ureas can be envisioned that are mutually perpendicular, these would require hydrogen-bonded networks considerably distorted from those shown.

[21] Lauher, J. W.; Chang, Y. L.; Fowler, F. W. *Mol. Cryst. Liq. Cryst.* **1992**, *211*, 99.

[22] By mutually compatible we mean that the symmetry operators must form a proper symmetry group.

Table 1. Crystallographic Parameters

compound	**2a**	**2b**	**3**
a (Å)	6.693(1)	4.827(2)	7.047
b (Å)	4.094(3)	6.688(1)	13.050
c (Å)	15.586(3)	33.080(1)	7.851
β (deg)	100.69(2)		91.09
volume (Å^3)	502.8(5)	1067.9(7)	967.8(5)
crystal size (mm)	0.5 × 0.3 × 0.1	0.3 × 0.3 × 0.2	0.4 × 0.3 × 0.2
space group	$P2_1$	$P2_12_12_1$	$P2_1/a$
Z	2	4	4
d_{calc} (g/cm^3)	1.457	1.345	1.347
2θ (deg) range, radiation	0–120, –Cu	0–120, –Cu	0–50, –Mo
temperature (°C)	23	23	23
observations collected (total)	889	990	1644
observations ($I > 3\sigma$)	804	527	312
variables	135	145	100
R	0.039	0.071	0.049
R_w	0.051	0.079	0.044

dissolved in a minimum amount of water and acidified to ca. pH 4.5 with glacial acetic acid. A solid precipitated and was filtered. Recrystallization from hot water gave 0.170 g (62%) of yellowish-beige needles and plates; decomposes above 330 °C; ^{1}H NMR (CDCl$_3$) δ 6.55 (br s, 2H), 5.67 (br s, 1H), 2.29 (s, 3H); IR (KBr pellet) 3409, 3218, 2220, 1640, 1532, 1469 cm^{-1}.

X-ray Diffraction Studies. Crystals of the three compounds **2a**, **2b**, and **3** 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 was 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 structure were solved and refined using the TEXAN crystallographic program package of the Molecular Structure Corp. All non-hydrogen atoms were refined with anisotropic temperature factors with hydrogen atoms added with fixed isotropic contributions. All hydrogens of compound **2a** and all heteroatom hydrogens of compound **2b** were located in electron density maps, all other hydrogens were placed in calculated positions. Table 1 gives crystal data for the three compounds. Full crystallographic details and tables of coordinates, temperature factors, bond distances, and angles are given in the supplementary material.

Acknowledgment. Support for this research was provided by a grant from the National Science Foundation (CHE-9307947) and the honors of the Petroleum Research Fund (PRF-23754AC1).

Supplementary Material Available: Full crystallographic details and tables of coordinates, temperature factors, bond distances, and angles (11 pages). Ordering information is given on any current masthead page.