Development of Strategies for the Preparation of Designed Solids. An Investigation of the 2-Amino-4(1*H*)-pyrimidone Ring System for the Molecular Self-Assembly of Hydrogen Bonded α- and β-Networks

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The 2-amino-4(1*H*)-pyrimidone (isocytosine) ring system has been explored as a molecular functionality for the supramolecular synthesis of hydrogen-bonded rod and layered organic materials. Advantages of this ring system are its ability to form complementary hydrogen-bonding patterns in both one and two dimensions with a molecular repeat distance of approximately 6.6 Å. Disadvantages of this ring system are its susceptibility to tautomerism and its conformational requirements for the formation of strong hydrogen bonds. Various isocytosine derivatives were prepared, and their crystal structures determined in order to evaluate the advantages and disadvantages of this ring system for the development of strategies for supramolecular synthesis.

Introduction

The development of strategies for the preparation of designed materials is an exciting challenge for modern chemistry. A fascinating aspect of the solid state is that the properties of a material depend not only upon the constituent molecules but also upon their relative orientation with respect to each other. In principle, a single molecular structure can give rise to a range of materials with different properties that arise simply because of different molecular orientations. It is clear that the development of strategies for the preparation of designed materials must be concerned with both the problems of molecular and supramolecular structure.[1]

An approach to the preparation of a designed material is to first identify a molecular fragment that possesses the solid-state property of interest.[2] The next step is to incorporate this molecular functionality into a supramolecular structure[3] that will best express the solid-state property of interest. This last step can be difficult because there is currently no general solution to the problem of predicting a crystal structure from a knowledge of molecular structure.[4] Fortunately, the preparation of a designed material does not usually require the complete control over supramolecular structure but just control the supramolecular structure of the molecular fragment of interest. Although this is a difficult goal, it is less difficult than the complete control of supramolecular structure.

Supramolecular structures of interest[5] in materials chemistry are two dimensional molecular layers. Layered materials are compounds where each of the constituent molecules are held within a two-dimensional layer by forces that are greater than those that occur between the layers. We have developed an approach to the preparation of two-dimensional layers using hydrogen-bonded β-networks.[6] A key element of our approach was to first identify two functional groups each independently capable of self-assembling molecules into one-dimensional α-networks[7] and to then incorporate these two functional groups into the same molecule. If the two predicted α-networks persist, then there is an extremely high probability that a two-dimensional β-network will be produced. This approach proved to be successful for the preparation of a number of layered compounds.[8]

The success of the above approach for the control of supramolecular structure critically depends upon the availability of functional groups that persistently produce predictable solid-state structures. Among the weak intermolecular interactions that have been employed for the control of supramolecular structure, hydrogen bonding has played an important role.[9] One

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(1) The control of supramolecular structure is a difficult problem with few solutions. In contrast to molecular structure where strong bonding forces play an important role, supramolecular structure is usually determined by factors such as weak intermolecular interactions and molecular shape.

(2) For example, molecular fragments of interest may be those that either display interesting optical properties or can participate in an interesting topochemical controlled reaction.

(3) Useful solid-state structures may be either those that have the dipoles of the molecular fragment aligned along one axis or precisely spaced at a required positions.

(4) "One of the continuing scandals in the physical sciences is that it remains in general impossible to predict the structure of even the simplest crystalline solids from a knowledge of their chemiscal composition." Maddox, J. *Nature* **1988,** *335,* 201.

(5) *Physics and Chemistry of Materials with Low-Dimensional Structures*; D. Reidel: Dordrecht, The Netherlands. The interest in low-dimensional solids, one-dimensional rods, and two-dimensional layers is due primarily to the high degree of anisotropy of their solid state properties.

(6) Chang, Y.-L.; West, M.-A.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **1993,** *115,* 5991.

(7) Two examples being the *N,N'*-disubstituted ureas and dicarboxylic acid derivatives.

(8) (a) Zhao, X.; Chang, Y.-L.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **1990,** *112,* 6628. (b) Lauher, J. W.; Chang, Y.-L.; Fowler, F. W. *Mol. Cryst. Liq. Cryst.* **1992,** *211,* 99. (c) Chang, Y.-L.; West, M.-A.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **1993,** *115,* 5991.

(9) *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H.-J., Dürr, H., Eds.; VCH: New York, 1991.

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of the reasons for the interest in hydrogen bonding is that it is one of the strongest intermolecular interactions and hydrogen bonding is restricted to a limited number of functional groups.[10]

The urea functionality has proven to be quite reliable with respect to producing predictable hydrogen bonding motifs. It has the additional advantage of reliably producing an intermolecular spacing of 4.6–4.7 Å. A practical application of this intermolecular spacing is its ability to align diacetylene functionalities for a topochemical polymerization to give a polydiacetylene. Numerous polydiacetylenes have been prepared and studied because they possess conjugated π-systems with interesting optical and electrical properties.[11]

The next member in the family of acetylene polymers[12] is polytriacetylene. Although attempts have been made to polymerize triacetylenes, these have to date not met with success.[13] The apparent failure of these studies was the inability to achieve the required intermolecular spacing necessary for topologically controlled polymerization.[13a] We have been interested in vinylogous analogs of the urea functionality because they should also be useful for preparation of designed supramolecular structures and should posses an intermolecular spacing for appropriate polytriacetylene polymerization.[13]

We recently demonstrated that the 2-aminopyridone ring (**1**) system is an excellent analogue of the ureas with respect to self-assembly,[14] extending the intermolecular spacing from 4.5 to approximately 6.8 Å. This success led us to explore the utility of the isocytosine (2-amino-4(1*H*)-pyrimidone) ring system for supramolecular synthesis. Because of the additional heterocyclic nitrogen atom this functionality has the potential for participating in an additional hydrogen bonding interaction that could be utilized in the preparation of supramolecular structures.

The crystal structures of only two simple isocytosine derivatives have been reported previously.[15] The first report[15a] concerned the parent ring system whose crystal structure was of interest because it shows the presence of two tautomers in the solid state, the 1*H* tautomer **2** shown in Figure 1 and the 3*H* tautomer. The presence of both tautomers in the crystal lattice prevents the formation of the simple α-network shown in Figure 1. This early observation suggests that isocytosine ring system would not be a useful functionality for the preparation of α- and β-networks.

The report on the 6-methyl derivative **3**[15b] was more encouraging to our studies. This compound crystallized

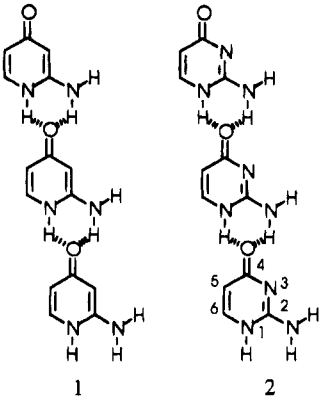


Figure 1. Proposed vinylogous urea hydrogen-bonding motifs for the 2-aminopyridinone and pyrimidone ring systems (α-networks).

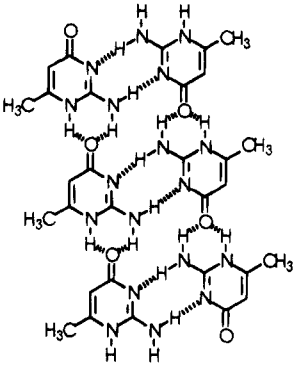


Figure 2. Reported[15b] packing of 6-methylisocytosine (an α-network).

in $P\bar{1}$ space group with the molecules self-assembled into a vinylogous urea α-network along a crystallographic translation axis as shown in Figure 1. Using the syn NH_2 hydrogen and the nitrogen atom at position 3, two of these α-networks dimerized about a center of symmetry (Figure 2).

Thus, the previous literature is ambiguous regarding the potential utility of the isocytosine ring system for the design and preparation of molecular solids. It is possible that the first member of this series, like the first member of other hydrogen-bonding functionalities, is unique and is not a representative member of other isocytosines. Alternatively, the accessibility of two tautomers[16] could present a serious problem for the application of this functionality for supramolecular synthesis. To determine the utility of the isocytosine ring system for the orientation of molecules into predictable solid-state structures, we have prepared specific derivatives of this ring system and determined their crystal structures.

Results

X-ray Diffraction Studies. Crystals of eight compounds **4**–**11** 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

(10) For a recent and extensive discussion of hydrogen bonding see: *Hydrogen Bonding in Biological Structures*; Jeffrey, G. A., Saenger, W., Eds.; Springer-Verlag: Berlin, 1991.

(11) Bloor, D., Chance, R. R., Eds.; *Polydiacetylenes: Synthesis, Structure and Electronic Properties*; NATO ASI E 102; Natinus Nijhoff Publishers: Dordrecht, 1985.

(12) Anthony, J.; Boudon, C.; Diederich, F.; Gisselbrecht, J.-P.; Gramlich, V.; Gross, M.; Hobi, M.; Seiler, P. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 763.

(13) (a) Enkelmann, V. *Chem. Mater.* **1994**, *6*, 1337. (b) Okada, S.; Hayamizu, K.; Matsuda, H.; Masaki, A.; Nakanishi, H. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 857. (c) Kiji, J.; Kaiser, J.; Wegner, G.; Schulz, R. C. *Polymer* **1973**, *14*, 433. For a recent report on some small oligomers possessing the polytriacetylene backbone, see ref 12.

(14) Toledo, L. M.; Lauher, J. W.; Fowler, F. W. *Chem. Mater.* **1994**, *6*, 1222.

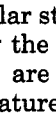
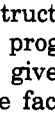
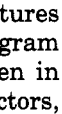
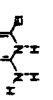
(15) (a) Sharma, B. D.; McConnell, J. F. *Acta Crystallogr.* **1965**, *19*, 797. (b) Lowe, P. R.; Schwalbe, C. H.; Williams, G. J. B. *Acta Crystallogr.* **1987**, *C43*, 330.

(16) It is interesting to note that in aqueous solution both the 1*H* and 3*H* have about the same stability being present in about a 1:1 ratio. Bühlmann, P.; Simon, W. *Tetrahedron* **1993**, *49*, 7627.

using graphite-monochromated Cu radiation. The unit cells were determined by a least-squares analysis of the setting angles of 25 high-angle reflections. Data were collected as indicated in the tables, and the structures were solved and refined using the TEXSAN crystallographic program package of the Molecular Structure Corp. All non-hydrogen atoms were refined with anisotropic temperature factors except for compound 10, which was refined with isotropic temperature factors. All hydrogens were located from the electron density maps except in the case of compounds **5**, **9**, **10**, and **7**, where selected hydrogens were placed in calculated positions. All hydrogen atoms were fixed with isotropic temperature factors except for those of compound **6** which were refined. The data obtained for some compounds were less than ideal due to crystal imperfections. Compounds **9** and **11** were refined in the centric space groups $P2_1/c$ and $P2_1/n$, respectively. In both cases two tautomers were found in the crystal lattice, the neutral 4(1*H*)-pyrimidone and the zwitterion. Two hydrogens have 0.5 multiplicity. The hydrogen at N3 of the pyrimidone ring and the hydrogen of the acid sit on or near two crystallographic inversion centers. Dropping the symmetry to $P2_1$ gave ordered structures presenting a 1:1 mixture of both tautomers in the asymmetric unit. The ordered structures were refined to equally good R factors but had high correlation coefficients and bond distances that deviated from the expected values. Similarly, compound **7** was refined in the space group $C2/c$, with 8 molecules in the unit cell. This requires the structure to be disordered with two hydrogens of 0.5 multiplicity sitting near a crystallographic 2-fold axis and an inversion center. Here too the crystal lattice must be populated by both pyrimidone tautomers. Dropping the symmetry to Cc gave an ordered structure with an equally good refinement but with high correlation coefficients and inadequate bond lengths. In all three cases the disordered structures are considered better models. The refinements obtained for compounds **9**, **11**, and **10** were less than ideal because of inadequate data due to poor crystal quality. For instance, with our best crystal of compound **10** only 224 of 831 unique reflections collected had intensities greater than $3\sigma(I)$. Numerous attempts at growing better-quality crystals proved futile. Although in some of the structures, less than adequate refinements and thus, poor accuracy of bond lengths, did not allow for an unambiguous determination of the molecular structure, we assigned the tautomeric structures on the basis of the solid-state structure and hydrogen bond patterns. For a given solid-state structure, only certain molecular structures are possible. Figures were drawn using the program CHARON. Full crystallographic details are given in Table 1. Tables of coordinates, temperature factors, bond lengths, bond angles, and intermolecular contacts are provided in the supporting information.

Synthesis. The substituted isocytosines were prepared according to the following general procedure.[17] *General method A*: Guanidine carbonate (0.025 mol), the β-keto ester (0.025 mol), and 50 mL of absolute ethanol were combined and stirred at reflux for 18 h. The reaction mixture was cooled, and the precipitate was removed by filtration. The precipitate was redissolved in a minimum amount of hot water and neutral-

Table 1. Crystallographic Data

molecular structure											
compound	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**			
formula	$C_6H_9N_3O$	$C_{10}H_9N_3O$	$C_6H_7N_3O_3{\cdot}H_2O$	$C_5H_7N_3O$	$C_6H_8N_4O_2$	$C_7H_9N_3O_3$	$C_8H_9N_3O_3$	$C_9H_{11}N_3O_3$			
a (Å)	6.5723(2)	6.574(1)	18.659(3)	11.584(2)	5.298(2)	4.898(2)	18.766(4)	5.710(1)			
b (Å)	7.028(2)	25.363(6)	10.582(2)	7.546(2)	14.685(2)	13.169(3)	6.542(2)	9.527(1)			
c (Å)	7.926(3)	16.344(2)	7.741(1)	14.108(1)	9.284(1)	12.046(1	6.542(2)	16.774(2)			
α (deg)	105.22(3)										
β (deg)	91.43(3)	99.22(1)		106.62(2)	92.95(3)	95.83(2)		92.501(5)			
γ (deg)	105.41(2)										
vol (Å^3)	338.8(2)	2690(1)	1528.4(7)	1181.7(2)	722.30(2)	773.0(6)	803.1(8)	911.8(4)			
crystal size (mm)	0.4 × 0.2 × 0.2	0.5 × 0.2 × 0.2	0.5 × 0.2 × 0.1	0.40 × 0.4 × 0.3	1.5 × 0.1 × 0.1	0.4 × 0.1 × 0.1	0.2 × 0.1 × 0.1	0.3 × 0.2 × 0.2			
space group	$P\bar{1}$	$P2_1$	*Pbca*	$C2/c$	$P2_1/c$	$P2/c$	*Pnma*	$P2_1/n$			
Z	2	12	8	8	4	4	4	4			
D_{calc} (g/cm^3)	1.364	1.387	1.627	1.406	1.548	1.574	1.515	1.436			
2θ (deg) (max)	148	95.9	129.7	84	130	120	128	100			
temp (°C)	23	23	23	23	23	23	23	23			
reflns collected (unique)	658	2610	1531	899	1287	1218	831	1015			
observations ($I > 3\sigma$)	532	1222	1018	312	1004	333	224	657			
R	0.055	0.055	0.052	0.041	0.038	0.079	0.074	0.061			
R_w	0.069	0.058	0.072	0.047	0.047	0.080	0.077	0.069			

(17) Worrall, D. E. *J. Am. Chem. Soc.* **1943**, *65*, 2053.

ized with aqueous ammonia. If necessary, additional water was added to redissolve any precipitate. Hot filtration followed by slow cooling precipitated the isocytosine derivative. To obtain the acid derivatives directly from the ester, 2 equiv of guanidine were used for hydrolysis of the ester group. The product was obtained by acidification with glacial acetic acid.

6-Ethylisocytosine (4). Using *general procedure A*, 2.5 g of ethyl propionylacetate (aldrich Chemical Co.) gave 1.92 g of **4** (82%): mp 248–250 °C; ^{1}H NMR (DMSO-d_6) δ 10.0 (br s, 1H, N_1-H), 6.69 (br s, 2H), 5.39 (s, 1H, H_5), 2.53 (d, J = 7.5 Hz, 2H, CH_2), 1.06 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C NMR 164.2, 164.1 (C_6, C_2), 155.6 (C_4), 98.9 (C_5), 29.6 (CH_2), 12.13 (CH_3); IR (KBr pellets) 3337, 3073, 2986, 2949, 1664, 1649, 1507, 1499, 1491, 1453, 1421, 1384 cm^{-1}.

6-Phenylisocytosine (5). Using *general procedure A*, 3.84 g of ethyl benzoylacetate (Aldrich Chemical Co.) gave 2.19 g of **5** (78%): mp 298–300 °C; ^{1}H NMR (DMSO-d_6) d 10.8 (br s, 1H, N_1–H), 7.91 (d, J = 6 Hz, 2H), 7.47 (s, 1H) 7.42 (d, J = 6 Hz, 2H), 6.60 (br s, 2H), 6.10 (s, 1H); ^{13}C NMR 162.6, 163.3 (C_6, C_2), 155.4 (C_4), 137.3, 137.3, 129.9, 128.30, 126.6 (phenyl H), 97.5 (C_5); IR (KBr pellets) 3348, 3085, 2956, 1658, 1504, 1476, 1379 cm^{-1}.

Isocytosine-6-acetic Acid (6). Using two equivalents of guanidine carbonate according to *general procedure A*, 10.0 g of diethyl acetone dicarboxylate (Aldrich Chemical Co.) gave 6.4 g of **6** (77%): mp 297–300 °C; ^{1}H NMR (DMSO-d_6) δ 6.84 (br s, 2H, NH_2), 5.48 (s, 1H, H_5) 3.33 (H_2O), 1.97 (s, 2H, CH_2); ^{13}C NMR 171.40 (CO_2), 165.1, 163.7 (C_6, C_2), 155.7 (C_4), 100.6 (C_5), 22.7 (CH_2); IR (KBr pellets) 3482, 3302, 3233, 3225, 3099, 3089, 3067, 3056, 2985, 2751, 1704, 1657, 1584, 1480, 1584, 1358, 905 cm^{-1}.

Isocytosine-6-acetamide (8). Using *general procedure A*, 5.0 g of diethyl acetone dicarboxylate (Aldrich Chemical Co.) and 2.22 g of guanidine carbonate gave 4.86 g (66% yield) of ethyl isocytosine-6-acetate: mp 188 °C; ^{1}H NMR (DMSO-d_6) δ 10.86 (br s, 1H, N_1–H), 6.64 (br s, 2H, NH_2), 5.50 (s, 1H, H_5), 4.649 (q, J = 5.4 Hz, 2H, CH_2), 3.314 (s, 2H, CH_2), 1.156 (t, J = 5.4 Hz, 3H, CH_3); ^{13}C NMR 177.2 (CO_2Et), 167.57 (C_2), 163.25 (C_6), 154.01 (C_4), 99.98 (C_5), 58.592 (Et CH_2), 41.04 (CH_2), 12.36 (Et CH_3); IR (KBr pellets) 3393, 3319, 3096, 2985, 2907, 1726, 1700, 1680, 1684, 1680, 1675, 1670, 1647, 1636, 1609, 1486, 1388, 1193 cm^{-1}.

The above ethyl isocytosine-6-acetate (0.80g) was dissolved in 30 mL of anhydrous methanol in a 100 mL thick-walled bottle and flushed with nitrogen. The bottle was sealed tightly with clamped rubber septa and placed in an ice bath. A vigorous stream of ammonia was passed through for a period of 1 h. The ammonia flow was stopped and the bottle placed aside for 72 h. Crystals of the amide (0.42 g), which deposited at the bottom of the container, were collected and recrystallized from methanol to give crystals of good quality for X-ray crystallography; mp 303–304 °C (lit. mp[17] indefinite above 285 °C); ^{1}H NMR (DMSO-d_6) δ 10.40 (br s, 1H, N_1–H), 7.42 (s, 1H, $CONH_2$), 6.98 (s, 1H, $CONH_2$), 6.67 (br s, 2H, NH_2), 5.46 (s, 1H, H_5), 3.08 (s, 2H, CH_2); ^{13}C NMR 170.43 ($CONH_2$), 163.2, 163.5 (C_6, C_2), 155.6 (C_4), 101.4 (C_5), 44.0 (CH_2); IR (KBr pellet) 3354, 3265, 3145, 3133, 3124, 3103, 1681, 1622, 1593, 1486, 1425, 1371 cm^{-1}.

6-Methyisocytosine-5-acetic Acid (9). Using 2 equiv of guanidine carbonate according to *general procedure A*, 5.40 g of diethyl acetylsuccinate (Aldrich Chemical Co.) gave 2.07 g of **9** (39%); mp 320–325 °C (dec); ^{1}H NMR (DMSO-d_6) δ 11.10 (br s, 1H, N_1–H), 6.41 (br s, 2H, NH_2), 3.23 (s, 2H, CH_2), 1.98 (s, 3H, CH_3); ^{13}C NMR 173.909 (CO_2H), 167.7, 165.0 (C_6, C_2), 155.6 (C_4), 99.8 (C_5), 32.697, (CH_3), 22.7 (CH_2); IR (KBr pellets) 3401, 3312, 2907, 1703, 1686, 1613, 1607, 1542, 1501, 1302 cm^{-1}.

6-Methylisocytosine-5-proponic Acid (11). Using 2 equiv of guanidine carbonate according to *general procedure A*, 5.76 g of diethyl acetylglutarate (Aldrich Chemical Co.) gave 3.29 g of **11** (67%); mp 302–303 °C (dec.) (lit. 301–303 °C);[18] ^{1}H NMR (DMSO-d_6) δ 7.06 (br s, 2H, NH_2), 2.50 (t, 2H, CH_2), 2.21 (t, 2H, CH_2), 2.05 (s, 3H, CH_3); ^{13}C NMR 175.9 (CO of CO_2H), 164.5, 159.5 (C_6, C_2), 153.8 (C_4), 110.3 (C_5), 34.8 (CH_2 of Et), 20.7 (CH_2), 20.6 (CH_3); IR (KBr pellets) 3400, 3312, 2920, 1689, 1605, 1565, 1524, 1300 cm^{-1}.

Isocytosine-5-proponic Acid (10). Diethyl 2-formylglutarate was prepared according to a procedure from the literature.[19] To a solution of guanidine carbonate (4.50 g, 0.025 mol) in 15 mL of absolute ethanol was added 5.40 g (0.025 mol) of diethyl 2-formylglutarate. The mixture was refluxed overnight. The solid which precipitated was collected by filtration and recrystallized from water to give 2.47 g (50%) of crystalline product. Crystals of good quality for X-ray crystallography were obtained by slow cooling from water; mp 280 °C (dec); ^{1}H NMR (DMSO-d_6) δ 7.34 (s, 1H, at C6-H), 6.81 (br s, 2H, NH_2), 2.35 (t, 2H, CH_2), 2.29 (t, 2H, CH_2). ^{13}C NMR 175.87 (*CO* of CO_2H), 164.5, 159.52 (C_6, C_2), 156.00 (C_4), 114.2 (C_5), 34.8 (CH_2 of Et), 20.7 (CH_2), 20.6 (CH_3); IR (KBr pellets) 3399, 2901, 1701, 1684, 1672, 1619, 1544, 1513, 1401 cm^{-1}.

6-Methylisocytosine (7).[20] Crystals of isocytosine-6-acetic acid monohydrate (1.0 g) were dissolved in a minimum amount of DMF and boiled for 30 min. The solution was set aside and crystals of 6-methylisocytosine grew overnight; mp 300 °C (dec) (lit. 285–290 °C);[21] ^{1}H NMR (DMSO-d_6) d 10.98 (br s, 1H, N_1–H), 6.69 (br s, 2H), 5.39 (s, 1H, H_5) 2.53 (d, J = 7.5 Hz, 2H, CH_2), 1.06 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C NMR 164.2, 164.1 (C_6, C_2), 155.6 (C_4), 98.9 (C_5), 29.6 (CH_2), 12.1 (CH_3); IR (KBr pellets) 3335, 3075, 2952, 1664, 1525, 1513, 1390, 564 cm^{-1}.

Discussion

The same hydrogen-bonding motifs observed for the 6-methylisocytosine structure reported previously[15b] (Figure 2) were also observed for 6-ethyl- and 6-phenylisocytosine. Curiously, the 6-phenylisocytosine achieves this hydrogen pattern by including three molecules into the asymmetric unit. The primary difference among these three molecules is the dihedral angle between the plane of the phenyl and isocytosine rings. Here, two types of α-networks are present. One network has $P\bar{1}$

(18) Baker, B. R.; Santi, D. V.; Almaula, P. I.; Werkheiser, W. C. *J. Med. Chem.* **1964**, *7*, 25.
(19) Hermes, J. D.; Tipton, P. A.; Fisher, M. A.; O'leary, M. H.; Morrison, J. F.; Cleland, W. W. *Biochemistry* **1984**, *23*, 6263.
(20) The numbers **3** and **7** refer to two different crystal structures. These different crystal structures both consist of 6-methylisocytosine.
(21) Lacey, R. N. *J. Chem. Soc.* **1954**, 839.

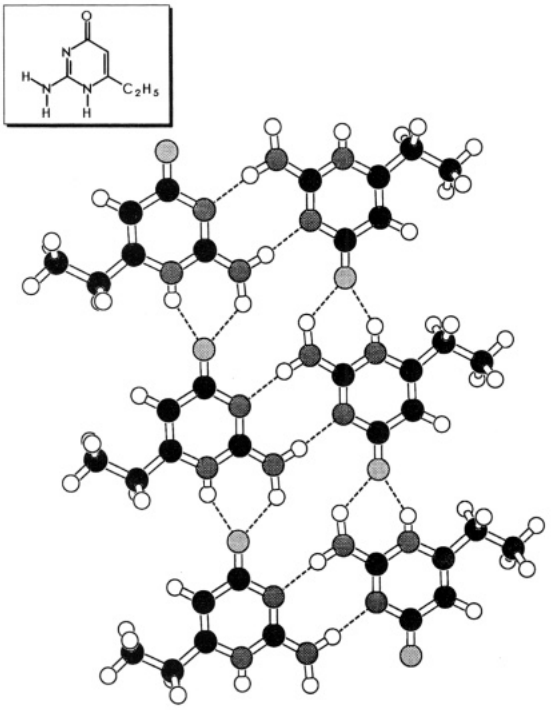


Figure 3. Crystal structures of 6-ethylisocytosine (4) showing the vinylogous urea hydrogen-bonded α-networks and its dimeric structure.

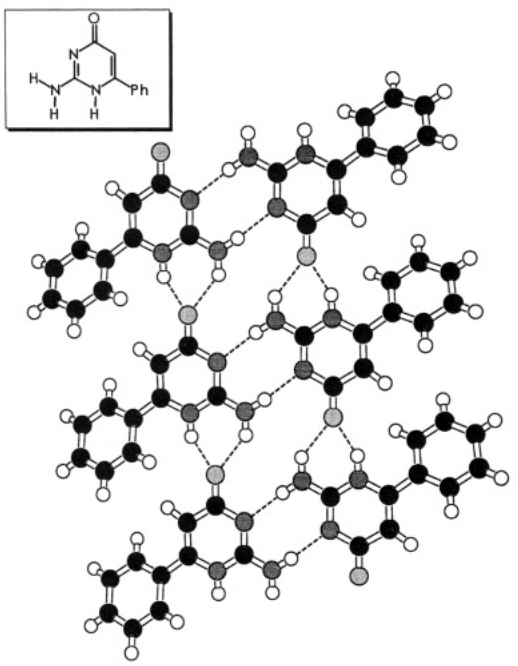


Figure 4. Crystal structures of 6-phenylisocytosine (5) showing the vinylogous urea hydrogen-bonded α-networks and its dimeric structure.

rod group symmetry since it is formed about a center of symmetry. The other is formed by two crystallographically unique molecules about a pseudo center of symmetry and therefore is of $P1$ rod group symmetry. The repeat distance of the primary α-networks in both the 6-ethyl- and 6-phenylisocytosine compounds is 6.57 Å, in reasonably good agreement with our predictions (Figures 3 and 4).

These results suggest that the crystal structure of the parent isocytosine ring system is unique and the solid-state hydrogen-bonded motif shown in Figure 2 will

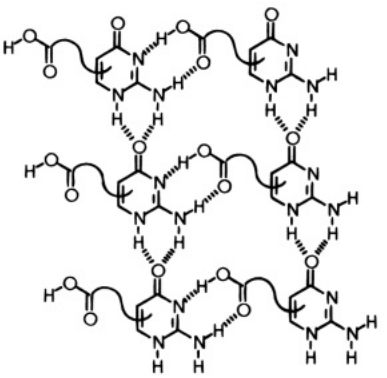


Figure 5. Hypothetical hydrogen-bonding motif derived from an isocytosine carboxylic acid (a β-network).

be common among the more complex isocytosines. Encouraged by these preliminary results, we proceeded to design a layered solid state structure using the α-network of the above vinylogous urea. Our general strategy for designing layered structures is to incorporate, into the same molecule, two functionalities capable of producing independent α-networks. If both α-networks persist, then there is a very high probability that the new molecule will form a β-network producing a layered compound.

The heterocyclic nitrogen atom at position three and the syn amino hydrogen of the isocytosine ring system are not involved in vinylogous urea hydrogen-bonded α-network and possess the necessary structural elements necessary for hydrogen bonding to carboxylic acids. Furthermore, Etter has shown[22] that carboxylic acid functionalities consistently form hydrogen bonded complexes with 2-aminopyrimidine. The attachment of a carboxyl group, or a derivative, to either positions 5 or 6 produces a molecule with the ability to form a β-network. One example of such a β-network is shown in Figure 5. In this example each molecule is related to its neighbors by simple crystallographic translation. Alternative β-networks with neighboring molecules related by screw axes or glide planes are also possible. In some cases this would require alternate molecules in the two component α-networks to be flipped or reflected relative to their immediate neighbors. In principle one could limit these possibilities by controlling molecular shape and by the introduction of chirality.

Alternative hydrogen-bonding patterns, to the one shown in Figure 5, are possible. For example, simple cyclic dimerization of the carboxylic acids and the aminopyridone functionalities would also produce a β-network, but it would be considered less probable because it would violate one of Etter's empirical hydrogen bonding rules.[22,23] This interaction would not involve association between the strongest hydrogen bonding donor (the carboxylic acid) and the strongest hydrogen-bonding acceptor (isocytosine ring).

One potential difficulty with all the β-networks involving the hydrogen pattern shown in Figure 5 is that they all require, for the formation of strong hydrogen bonds, that the isocytosine ring and the hydrogen-bonded carboxyl group from a neighboring molecule in the same β-network lie in the same or

(22) Etter, M. C.; Adsmond, D. *J. Chem. Soc., Chem. Commun.* **1990**, *8*, 589.
(23) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120.

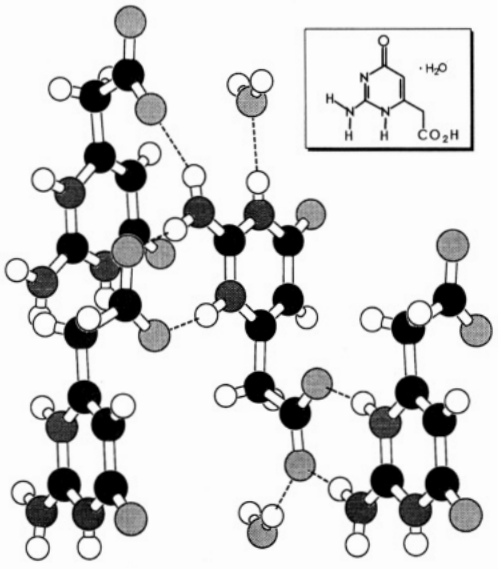


Figure 6. Crystal structure of isocytosine-6-acetic acid (**6**).

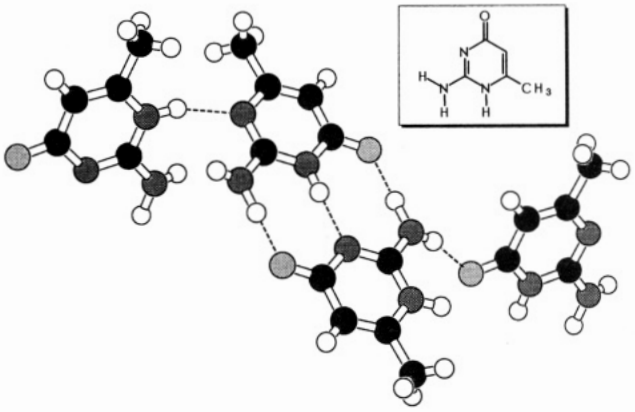


Figure 7. The second polymorph of 6-methylisocytosine. The single hydrogen atom at N-1 of the two molecules in the upper left of this figure is shared by the two molecules and is disordered about a 2-fold axis. Similarly, the single hydrogen atom at N-3 of the two molecules in the center of this figure is shared by those two molecules and is disordered about a center of symmetry.

parallel planes. Because the adjacent hydrogen bonded isocytosine rings also must be related by a translational symmetry element, the isocytosine carboxylic acids as a molecular tool for the supramolecular synthesis of β-networks are fundamentally more constrained for the assembly of β-networks than the ureylene dicarboxylic acids we have previously studied.[8]

A reasonable starting point to explore the above concept for the design of materials would be to add a carboxyl group at position 5 or 6 of the isocytosine ring. We prepared 6-isocytosine acetic acid (**6**) according to known literature procedures.[17] However, we have been unable to obtain a solvent-free single-crystal suitable for diffraction studies. We have determined the solid-state structure of **6** as a hydrate, and the best interpretation of the crystallographic data has the proton being transferred from the carboxylic acid to the basic nitrogen at position 3 producing a zwitterionic molecule. In the crystal the carboxylate forms a cyclic hydrogen bonded structure with the guanidinium functionality involving the amino substituent and the hydrogen attached to N-1. The syn hydrogen of the amino group hydrogen bonds to one of the oxygen atoms of the carboxylate ion a neighboring molecule. The hydrogen of N-3 hydrogen bonds to the water oxygen while the carbonyl oxygen of the ring accepts two protons from water. The result is a complex 3-dimensional hydrogen bonded network (Figure 6).

To obtain crystals without water in the lattice, attempts were made to recrystallize 6-isocytosine acetic acid **6** from anhydrous, hot DMF. Interestingly, this process resulted in decarboxylation of **6** giving 6-methylisocytosine.[20]

The crystal structure of this compound was determined and we were surprised to observe that is not the same as had been previously reported in the literature[15b] and discussed above. The structure of the 6-methylisocytosine **3** obtained above was solved using a disordered model in the space group *C*2/*c*. This disorder arose from the presence of both the (1*H*) and (3*H*) tautomers of the isocytosine ring in the lattice. The hydrogen-bonded pattern is very similar to that previously reported[15a] for isocytosine, the parent ring system. Two molecules dimerize in the style of the Watson–Crick guanine: cytosine base pair with a proton of multiplicity 0.5 sitting on the center of symmetry. The second disordered proton sits on a 2-fold axis bonding to the nitrogen at position 1 of two different dimers. The anti-hydrogen of the amine group is involved in hydrogen bonds to the carbonyl oxygen of neighboring dimers (Figure 7).

The potential complication of tautomerization, suggested by the reported crystal structure of isocytosine, appears to be a problem. In a continuation of our studies of producing the β-network shown in Figure 5, we investigated the possibility of employing an amide rather than a carboxylic acid on the isocytosine ring. Primary amides, like carboxylic acids, form cyclic dimeric structures[24] and are useful functionalities for the preparation of β-networks.[8c] The amide derivative of carboxylic acid **6** was prepared and its crystal structure determined. Although it is chemically unreasonable for the amide to form a zwitterionic structure that was observed for the acid derivative **6**, this compound also failed to form the vinylogous urea hydrogen-bonded motif previously shown by compounds **4** and **5**. In fact, the isocytosine ring system has undergone an isomerization from the 1*H* tautomer (the vinylogous urea) to the 3*H* tautomer completely precluding the formation of the β-network shown in Figure 5. Instead the compound forms a complex three-dimensional γ-network as shown in Figure 8.

Because of the above results with the 6-substituted carboxylic acid and amide, we turned our attention to position 5 of the isocytosine ring. We prepared the 6-methylisocytosine-5-acetic acid (**9**). The X-ray crystal structure of this compound demonstrated that it did not produce the β-network. The structure exhibited crystallographic disorder about a center of symmetry caused by the presence of a zwitterionic and a neutral molecule in the crystal lattice. The carboxylates hydrogen bond about another center of inversion with the proton sitting halfway between two oxygen atoms. The short O···O distance of only 2.42 Å is consistent with the presence of a very strong hydrogen bond.[25] The second oxygen of the carboxylate group is involved in hydrogen bonds

(24) Leisowitz, L.; Schmidt, G. M. J. *J. Chem. Soc. A* **1969**, 2372.
(25) Emsley, J.; Jones, D. J.; Lucas, J. *Rev. Inorg. Chem.* **1981**, *3*, 105.

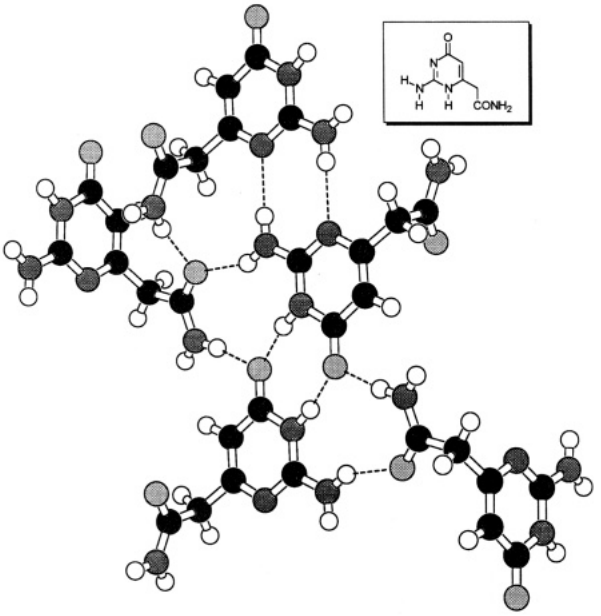


Figure 8. Crystal structure of isocytosine-6-acetamide (**8**), showing the complex three-dimensional γ-network formed by these molecules.

Figure 9. Crystal structure of 6-methylisocytosine-5-acetic acid (**9**). The hydrogen atom at N-1 is disordered about a center of symmetry as shown by the two molecules on the right-hand side of the figure.

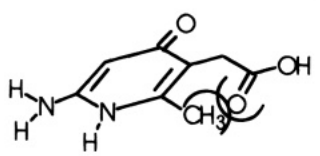


Figure 10. Nonbonded interaction of 5-isocytosine acetic acid.

to the hydrogen of N-1 of neighboring molecules (Figure 9).

To test the validity of this disorder model, we reduced the symmetry from $P2_1/c$ to $P2_1$. This removes the crystallographic disorder and places both the neutral and the zwitterionic species in the asymmetric unit. The refinement obtained was equally good, but the correlation coefficients were large and the bond distances deviated from the expected values. We are confident that the structure is indeed disordered.

The acetamide **8** and the acetic acid **9**[26] failed to produce the designed supramolecular structure shown in Figure 5. A possible reason for this observation is the restricted conformation mobility of the isocytosine ring with respect to the carboxyl or carboxamide group

(26) Compound **6** is also an isocytosine carboxylic acid but we were unable to obtain single crystals of the anhydrous compound. Thus, the crystal structure of the anhydrous compound is unknown.

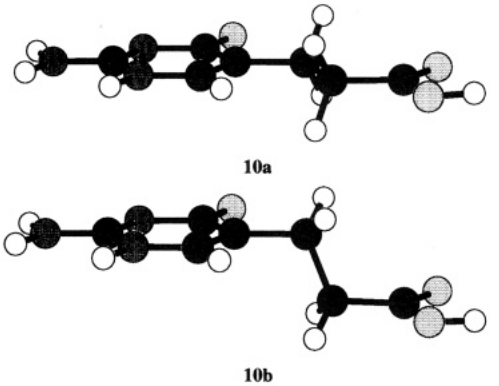


Figure 11. Two conformational energy minima of 5-isocytosinepropionic acid (**10**).

(Figure 10). To form strong hydrogen bonds, the isocytosine ring of one molecule and the hydrogen bonded carboxyl or carboxamide group of the neighboring molecule must lie in the same plane. If the neighboring molecule is related to the first by simple crystallographic translation as shown in Figure 5, this means that all isocytosine rings and all carboxyl or carboxamide groups must lie in the same or parallel planes. This crystallographic symmetry requirement restricts the possible conformations of the side chains within a molecule to those which can meet this coplanarity requirement. Inspection of molecular models and molecular mechanics calculations of 5-isocytosine acetic acid indicate that unfavorable nonbonded interactions occur in all possible coplanar conformations of the carboxyl and isocytosine functionalities. The molecules cannot self-assemble into the designed network, because the necessary molecular conformation is energetically unfavorable.

Extension of the tether connecting the carboxyl group to the isocytosine ring by one methylene group would allow more conformation mobility and possibly facilitate the formation of the designed β-network shown in Figure 5. In contrast to the 5- and 6-substituted acetic acid derivatives of the isocytosine ring, there exist a family of conformations for the 5 and 6 propionic acid derivatives which allow for the isocytosine ring and the carboxyl group to lie in the parallel planes. Two conformations that represent energy minima, which would allow for the β-network formation, are shown in Figure 11. The primary difference in these conformations is that in conformation **10a** the isocytosine ring lies in the same plane whereas in conformation **10b** these two functionalities lie in different but parallel planes.

We prepared the 5-isocytosine propionic acid **10** and its 6-methyl derivative **11**. A comparison of these two compounds is of interest because compound **10** has available both low-energy conformations shown above in Figure 11, whereas compound **11** would be predicted to experience severe nonbonded interactions between the methyl group and the connecting chain in the planar conformation. Indeed, X-ray crystallography demonstrated that the molecular conformation of 5-isocytosine propionic acid **10** is essentially that shown above in **10a** (Figure 11), whereas the connecting chain of the 6-methyl derivative **11** is rotated from the plane of the isocytosine ring as depicted in **10b**.

We were gratified to observe that 5-isocytosine propionic acid (**10**) self-assembled into the designed β-net-

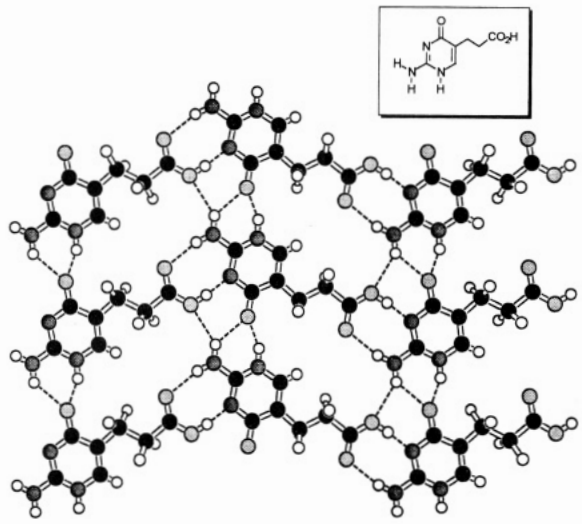


Figure 12. Crystal structure of 5-isocytosinepropionic acid (**10**) showing the hydrogen-bonded β-network. This β-network is planar and lies on the mirror plane of the *Pnma* space group.

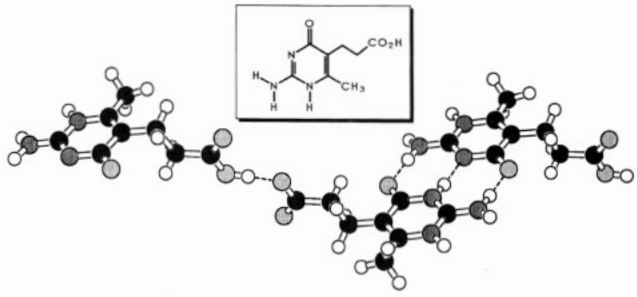


Figure 13. Crystal structure of 6-methylisocytosine-5-propionic acid (**11**). The hydrogen atom at N-1 is disordered about a center of symmetry as shown by the two molecules on the right-hand side of the figure. Note the similarity of this structure to 6-methylisocytosine-5-acetic acid as shown in Figure 9.

work illustrated in Figure 5. The space group for the crystal is *Pmna* with the molecule lying on a mirror plane. Thus, all non-hydrogen atoms in **10** lie completely within the same plane with a mirror plane passing through the molecule.

However, crystallography demonstrated that the 6-methyl derivative **11**, which can have a low-energy conformation with coplanarity between the isocytosine ring and the carboxyl group in parallel planes, did not self-assemble into the designed β-network.

The most obvious difference between **10** and its 6-methyl derivative **11** is that **11** does not have low-energy molecular conformation with the isocytosine ring and the carboxyl group lying in the same plane. It can however adopt a conformation with the two groups in parallel planes. This subtle difference changes the symmetry of the molecule and the nature of the predicted β-network. If the planes of the two functionalities are the same as is possible for molecule **10**, then the β-network can be planar as shown in Figure 14a.

If, however, the two functionalities are merely parallel, then the resulting β-network would be pleated as shown in Figure 14b. Each molecule in the direction of hydrogen-bonded carboxyl group cannot be related by a screw axis but must be related by a glide plane. Although there is no inherent crystallographic problem with a "pleated β-network" it might be anticipated that the stacking of pleated layers might be less efficient

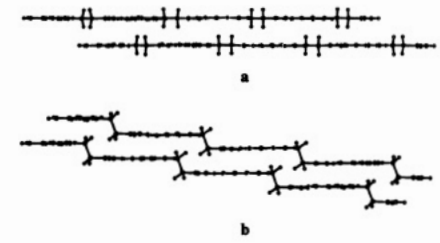


Figure 14. Two possible β-networks for different conformations of the isocytosine-6-propionic acid (**10**).

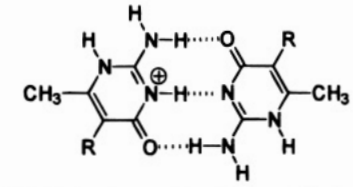


Figure 15. Triple hydrogen-bonded motif observed for **9** (R = $-CH_2CO_2H$) and **11** (R = $-CH_2CH_2CO_2H$). The persistence of this triple hydrogen-bonded motif suggests it as a possible hydrogen-bonded assembly for supramolecular synthesis.

than the packing of a planar network. For example, the planar layers have available a range of interlayer intermolecular relationships by simple translation of the layers with respect to each other allowing for the layers to pack in order to minimize all intermolecular forces such as van der Waals and electrostatic interactions. However, close packing of the pleated layers results in locking the restricting the layers in one dimension and only allows translation parallel to the pleat. This restriction reduces the possibilities of interlayer intermolecular relationships possibly resulting in inefficient packing of the layers.

The crystal structures of the two isocytosine carboxylic acids, which did not display the formation of the designed α- and β-networks (**9** and **11**),[26] showed similarities in their intermolecular interactions that are worthy of note. They both form an interesting triple hydrogen bonded AAD·DDA motif[27] with one-half of the isocytosine rings being protonated by one-half of the carboxylic acid functionalities. This triply hydrogen bonded motif has also previously been found with the cytosine-5-acetic acid[28] and cytosine hemitrichloroacetate.[29] Recently, this same hydrogen-bonded motif has been observed a deoxycytidylyl-(3′,5′)-deoxycytidine analogue[30] (Figure 15).

Summary

The goal of this research program is the development of strategies for the preparation of designed materials. A key element in these strategies requires the identification of functionalities with the ability to form strong and predictable intermolecular interactions in the solid state. The isocytosine ring system with its ease of synthesis and three hydrogen-bonding acceptor and donor sites is an attractive functionality for supramo-

(27) (a) Murray, T. J.; Baloga, M. H.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1992**, *114*, 4010. (b) Murray, T. J.; Baloga, M. H.; Zimmerman, *Philos. Trans. R. Soc. London, Ser. A* **1993**, *345:1674*, 49. Jorgensen, W. L.; Pranata, J. *J. Am. Chem. Soc.* **1990**, *112*, 2008.

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(29) Gdaniec, M.; Brycki, B.; Szafran, M. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1775.

(30) Egli, M.; Lubini, P.; Bolli, M.; Dobler, M.; Leumann, C. *J. Am. Chem. Soc.* **1993**, *115*, 5855.

lecular synthesis. We have demonstrated that the isocytosine ring system can behave as a vinylogous urea and self-assemble into an α-network with a repeat distance of approximately 6.6 Å. Extension of this strategy for the formation of a hydrogen-bonded β-network can be accomplished by the addition of a single carboxyl group to the isocytosine ring.

However, the accessibility of two tautomers (e.g., the two different solid-state structures for 6-methylisocytosine, Figures 2 and 7) can complicate the application of the isocytosine ring as a molecular functionality for supramolecular synthesis. Furthermore, the rather severe molecular conformational requirements for the β-network further restrict the incorporation of isocytosine carboxylic acids into a strategy for the preparation of layered organic solids. Nevertheless, it is clear that an understanding of intramolecular and intermolecular interactions along with a careful consideration of crystallography can be employed to prepare specific supramolecular structures. As our understanding of these phenomena increases, we will become nearer to the goal of precisely controlling supramolecular structure.

Supporting Information Available: Tables of crystallographic data (42 pages); tables of observed and calculated structure factors (41 pages). Ordering information is given on any current masthead page.

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