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Template-Directed Synthesis of 1:1 Layered Complexes of α,ω-Dinitriles and Urea: Packing Efficiency versus Specific Functional Group Interactions

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When urea is crystallized from MeOH in the presence of α,ω-dinitriles of the formula $NC(CH_2)_nCN$, it forms layered 1:1 cocrystals when $n = 3$–5, and channel inclusion compounds (commensurate or incommensurate) when $n = 6$, 8, 10, and 12. Our analysis suggests that this "homologous polymorphism" is the result of a competition between hydrogen bonding (which is favored in the 1:1 complexes) and packing efficiency (which is greater for the channel type inclusion compounds of the long chain guests). One measure of packing efficiency is the relationship between average electron density per unit cell (D_e) and the average atomic number (z(ave)). For a collection of 338 organic crystal structures, plots of D_e versus z(ave) give different least-squares lines for crystals with intermolecular hydrogen bonds and those without them. For the 1:1 cocrystals, donor–acceptor complementarity favors an inefficient packing mode, and successive addition of CH_2 units decreases D_e more rapidly than predicted from the relationships obtained for the other two data sets. The switch from cocrystal to inclusion compound is accompanied by a dramatic increase in packing efficiency. To circumvent the packing efficiency problem and to extend the range of dinitrile structures that form layered complexes, a template effect was employed. Thus, bis(5-cyanopentyl)urea forms 1:1 layered cocrystals with urea either from solution or by grinding. (This differs from the molecular crystal of bis(5-cyanopentyl)urea, which contains *gauche* nitriles that pack in a herringbone fashion.) All of the 1:1 cocrystals exhibit favorable interlayer nitrile–nitrile contacts, as supported by atom–atom potential calculations. Crystal data for structures reported in this paper are as follows: pimelonitrile/urea (1:1 cocrystal): monoclinic, space group $P2/c$, $Z = 2$, $a = 7.196(2)$, $b = 4.583(3)$, $c = 15.973(4)$ Å, $\beta = 98.679(21)°$, $R = 0.051$ at $T = 296$ K; glutaronitrile/urea (1:1 cocrystal): orthorhombic, space group $Pmmn$, $Z = 2$, $a = 6.5020(16)$, $b = 13.712(3)$, $c = 4.5693(10)$ Å, $R = 0.058$ at 213 K; bis(5-cyanopentyl)urea: orthorhombic, space group $P2_12_12$, $Z = 2$, $a = 6.9991(11)$, $b = 21.552(3)$, $c = 4.5747(7)$ Å, $R = 0.071$ at $T = 99$ K; bis(5-cyanopentyl)urea/urea (1:1 cocrystal): monoclinic, space group $P2/n$, $Z = 2$, $a = 13.708(3)$, $b = 4.5879(12)$, $c = 13.964(3)$ Å, $\beta = 112.335(10)°$, $R = 0.038$ at 111 K.

Introduction

Although the "engineering" of molecular crystals has been possible for several series of related compounds, the field of crystal engineering remains more or less in the empirical stage. At a minimum, the successful design of an organic crystal with desired physical and chemical properties is a thorough understanding of both specific interactions between functional groups and crystal packing efficiency. Pioneering work by Kitaigorodskii,[1] Gavezzotti,[2] and others has now placed overall packing efficiency of organic solids on a quantitative footing, but accurate potential energy functions for interactions between different functional groups are sorely needed. At this stage, the successful design and synthesis of organic solids requires intuition and a knowledge of trends in packing for related molecules, as well as the willingness to try different approaches when nature conspires to find a crystal packing mode that was not predicted by the imperfect models that we use.

Our interest in layered materials originated with our initial discovery that urea forms 1:1 complexes with pimelonitrile (1,5-dicyanopentane), and with a large amount of ensuing encouragement by Peggy Etter, who saw in our work parallels with her own research[3] on the use of hydrogen-bonded arrays to form noncentrosymmetric cocrystals. Peggy Etter's "rules" for hydrogen bonding serve as starting points for the design of new solids,[4] and the graph set methods that she helped to develop[5] allow one to recognize patterns and motifs in existing structures. Once a series of related structures is

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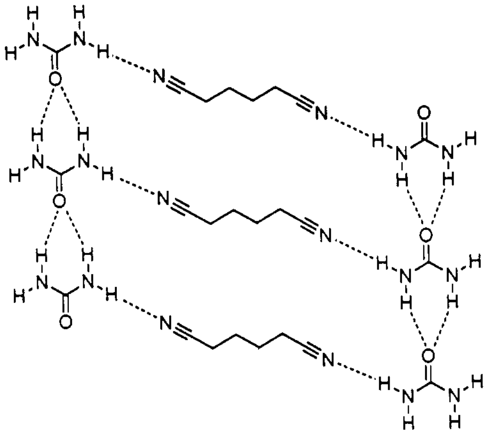
identified, an in-depth study of the packing should reveal the inherent strengths and weakness in the packing arrangement that is controlled by a certain hydrogen-bonding motif, and the differences in hydrogen bonding that one might expect for certain changes in the molecular structure. These, in turn, will allow certain "boundaries" or "limits" to be placed on the ability of a certain hydrogen-bonding motif to control the packing. With these delimiting characteristics in mind, a more finely tuned approach to molecular engineering becomes feasible.

In a recent communication, we reported the crystal structure of one member of a new series of hydrogen-bonded cocrystals of aliphatic α,ω-dinitriles and urea.[6]



These specific complexes, which involve hydrogen bonding between the nitrile groups and the *syn* hydrogens of urea, stand in contrast with the channel inclusion compounds[7,8] that are formed when urea is crystallized in the presence of longer chain dinitriles. For nitriles of the formula NC-$(CH_2)_n$CN, specific complexes are formed when n = 3, 4, or 5, whereas channel inclusion compounds are formed when n = 6, 8, 10, or 12. As elaborated below, our inability to form 1:1 complexes of the longer chain dinitriles and urea is due, in large part, to the inefficient packing of the alkyl chains in these specific complexes. Within a layer, the 4.58 Å spacing along the carbonyl axis is controlled by the hydrogen-bonding requirements of the urea, and the methylene groups are beyond van der Waals contact.

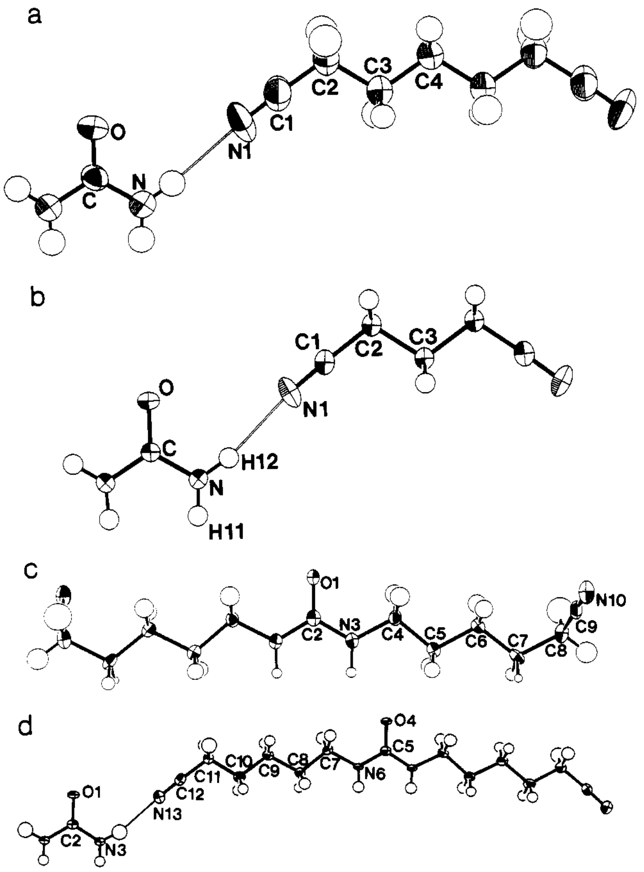


Figure 1. ORTEP[10] diagrams showing atom labeling schemes used for structures reported in this paper: (a) 1/urea, (b) 3/urea, (c) 4, (d) 4/urea. (Those for 2/urea are given in ref 6.) Ellipsoids are drawn at the 50% probability level. Selected bond lengths (angstroms) and angles (degrees) for structures discussed in this paper are given here. 1/urea: N1–C1 1.132(3), C1–C2 1.456(3), O–C 1.238(3), C–N 1.342(2), N1–C1–C2 177.1(2), O–C–N 121.3(1). 3/urea: N1–C1 1.137(2), C1–C2 1.463(2), O–C 1.245(2), C–N 1.345(2), N1–C1–C2 177(4), O–C–N 121.4(1). Compound 4: N10–C9 1.137(6), C9–C8 1.476(4), O1–C2 1.250(8), C2–N3 1.342(5), N10–C9–C8 177.4(5), O1–C2–N3 121.4(3). 4/urea: N13–C12 1.151(4), C11–C12 1.467(4), O1–C2 1.251(4), C2–N3 1.344(3), O4–C5 1.251(4), C5–N6 1.348(3), N13–C12–C11 178(6), O–C–N 121.4(2), O4–C5–N6 121.5(2).

Because the network of hydrogen bonds within a layer is predicted so reliably by simple models, it should be possible to elaborate this framework to form either polar or nonpolar layers. This becomes immediately evident from the structures of the layered complexes containing odd and even numbers of methylenes in the chains. Unfortunately, the range of dinitriles that form hydrogen-bonded complexes with urea is severely limited, and crystal engineering techniques must be used to overcome the packing efficiency problems within this series. This paper explores some simple methods of using packing efficiency as a guide to predicting cocrystal or complex stability, including a statistical analysis of packing efficiency for crystals with hydrogen bonds and those without them, and demonstrates the utility of template effects as a way of overcoming packing efficiency limitations. In the present case, the "template" is the urea moiety itself: incorporation of this group into the middle of an α,ω-dinitrile allows the range of structures to be extended.

Experimental Section

Infrared spectra were obtained with Nicolet 7199 or Mattson Galaxy 4020 FTIR spectrometers. NMR spectra were collected on either Bruker WH-200 or Varian XL-400 spectrometers. Differential scanning calorimetry scans were recorded with a Perkin-Elmer DSC-2C. Melting temperatures are uncorrected. Powder X-ray diffraction patterns were obtained on a Rigaku powder diffractometer (Co Kα, Fe filter, λ = 1.790 26 Å) or on a Scintag XDS-2000 Powder Diffractometer (Cu Kα, graphite monochromator, λ = 1.5406 Å). At the University of Alberta (structures 1/urea and 3/urea), X-ray intensity data were collected on an Enraf-Nonius CAD-4 automated diffractometer. At Indiana University Molecular Structure Center (structures 4 and 4/urea), the diffractometer utilized for data collection was

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Table 1. Crystallographic Data for Structures Reported in This Paper

crystal system	1/urea	3/urea	4	4/urea
crystal habit	plates	plates	flat needles	flat needles
formula	$C_8H_{14}N_4O$	$C_6H_{10}N_4O$	$C_{13}H_{22}N_4O$	$C_{14}H_{26}N_6O_2$
formula weight	182.20	154.17	250.34	310.4
system	monoclinic	orthorhombic	orthorhombic	monoclinic
space group	$P2/c$	$Pmmn$	$P2_12_12$	$P2/n$
a (Å)	7.196(2)	6.5020(16)	6.9991(11)	13.708(3)
b (Å)	4.583(3)	13.712(3)	21.552(3)	4.5879(12)
c (Å)	15.973(4)	4.5693(10)	4.5747(7)	13.964(3)
β (deg)	98.769(21)	90	90	112.35(10)
V(Å^3)	520.6	407.5	690.1	812.3
temp (°C)	23	−60	−174	−162
Z	2	2	2	2
D_{calc} (g cm^{-3})	1.163	1.257	1.205	1.269
radiation, λ (Å)	Mo Kα, 0.710 73	Mo Kα, 0.710 73	Mo Kα, 0.710 69	Mo Kα, 0.710 69
monochromator/filter	graphite/none	none/Zr	graphite/none	graphite/none
μ (cm^{-1})	0.90	0.86	0.743	0.829
crystal dimensions (mm)	0.12 × 0.54 × 0.86	0.5 × 0.5 × 0.7	0.25 × 0.25 × 0.25	0.25 × 0.20 × 0.30
total unique reflections	1253	949	956	1053
reflections used	748 with $I > 3\sigma(I)$	648 with $I > 1.50\sigma(I)$	742 with $I > 2.33\sigma(I)$	886 with $I > 2.33\sigma(I)$
R_{merge}	0.058	0.050	0.051	0.035
no. of variables	89	46	126	149
R	0.051	0.058	0.071	0.038
R_w	0.064	0.069	0.058	0.043
goodness of fit	2.23	2.42	1.08	1.052
θ_{max} (deg)	28	34	27.5	22.5
data collection index range	$\pm h, k, \pm l$	$h, \pm k, \pm l$	$\pm h, k, l$	$\pm h, k, \pm l$
final Δelectron density (e Å^{-3})	0.30 (5)	0.31 (7)	0.21	0.23
absorption correction	none	empirical surface[13]	none	none
structure det package	MITHRIL[11]	MITHRIL[11]	MULTAN78[17]	MULTAN78[17]

designed and constructed locally, as described in ref 9. Miller planes containing the hydrogen bonded sheets were determined by calculating least-squares planes, or by using CERIUS molecular modeling software (Molecular Simulations Inc.).

Pimelonitrile/urea 1:1 Complex (1/Urea). Pimelonitrile (**1**) was used as received from Eastman–Kodak (98+%). Crystals of **1**/urea were grown from methanol under a wide variety of conditions, including evaporation of solvent at room temperature and slow cooling of saturated solutions from room temperature to 5 °C. 200-MHz ^{1}H NMR (DMF-d_7) δ 1.45–1.78 (om, 6H, H_β, H_γ), 2.55 (t, 4H, J = 7 Hz, H_α), 5.60 (br s, 4H, urea). (Melts with decomposition of complex at 124–132 °C.)

X-ray crystal structure: Systematic absences of $h0l$, l odd led to the choice of space group $P2/c$. Data collection and refinement parameters are described in Table 1, and are presented in more detail in the supplementary material (see paragraph at end of paper). In the final cycles of refinement, non-hydrogen atoms were refined with anisotropic Gaussian displacement parameters, and hydrogen atoms were refined with isotropic B's and no constraints to give a solution with a featureless difference Fourier map. Table 2 contains the atomic coordinates and the B_{iso} values for **1**/urea. The atom labeling scheme for this structure and others reported in this paper are shown in Figure 1.

Glutaronitrile/Urea 1:1 Complex (3/Urea). In our hands, cocrystals of **3**/urea could not be grown from solution without the presence of seed crystals of the complex. To form the seeds, we ground a 1:1 mixture of **3** and urea for approximately 20 min in a Wig-L-Bug.[6] This solid, which had a powder diffraction pattern that was virtually identical to that of the cocrystals later formed from solution, was added to a solution of **3** (Eastman Kodak, 99.4%, 1.57 g) and urea (26 mL of 1.8 M in MeOH) that had already yielded a first crop of tetragonal urea after cooling from 25 to 5 °C. Evaporation of MeOH at 5 °C yielded flat plates suitable for diffractometry. (Melts with decomposition of complex at 113–114 °C.) Over a period of several hours at room temperature, these crystals decomposed to give polycrystalline urea and **3**. 400-MHz ^{1}H NMR (DMF-d_7) δ 1.88 (qi, 2H, H_β), 2.58 (t, 4H, J = 7.2 Hz, H_α), 5.38 (br s, 4H, urea).

Table 2. Fractional Atomic Coordinates (×10^4) and Gaussian Parameters of 1/Urea[a]

atom	x	y	z	B_{iso} (Å^2)
O	0	2077(3)	2500	5.1
C	0	4778(5)	2500	3.8
N	676(2)	6300(3)	3198.1(9)	4.8
N1	2205(3)	−2034(5)	−303.8(10)	7.7
C1	2625(3)	−550(4)	259.9(10)	5.6
C2	3225(3)	1239(4)	1005.6(11)	5.2
C3	4210(2)	−585(4)	1744.2(10)	4.5
C4	5000	1273(5)	2500	4.4

[a] The equivalent isotropic Gaussian parameter $B_{iso} = (8\pi^2/3)\sum_i\sum_j U_{ij}a^*_ia^*_j\mathbf{a}_i\cdot\mathbf{a}_j$.[14] Those positional parameters without esd values were fixed by crystallographic symmetry.

X-ray crystal structure: The automatic peak search and reflection indexing programs generated an orthorhombic unit cell with dimensions given in Table 1. Because the approximate unit cell parameters could also be deduced quite readily from the metric properties of monoclinic **1**/urea structure (by removing an ethylene unit from each of the pimelonitrile chains and then reattaching it to the nitrile), several precautions were taken to ensure that the structure was truly orthorhombic, and that the crystallographic constraints imposed by the $Pmmn$ space group were valid (see supplementary material). Refinements in $P2/c$ and $Pmmn$ space groups were nearly identical, so the space group with higher symmetry was chosen.[12] In the final cycles, hydrogen atom coordinates were refined with isotropic B's fixed, whereas all other atoms were refined with anisotropic Gaussian displacement parameters. The coordinates and B_{iso} values for **3**/urea are given in Table 3.

Bis(5-cyanopentyl)urea (4). In a three-necked round-bottomed flask, a mixture of 6-aminocapronitrile (Aldrich, 99%, 5.996 g, 53.45 mmol), water (30 mL) and potassium carbonate (7.551 g, 54.63 mmol) was cooled to 0 °C before aqueous potassium carbonate (11.463 g (82.94 mmol) in 30 mL of water) and triphosgene (Aldrich, 98%, 8.949 g, 30.16 mmol in 60 mL of toluene) were added simultaneously over 15 min, while keeping

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Table 3. Fractional Atomic Coordinates ($\times 10^4$) and Isotropic Gaussian Parameters[14] of 3/Urea

atom	x	y	z	B_{iso} (Å^2)
O	−2500	−7500	−2726(3)	2.38(4)
C	−2500	−7500	−1(4)	1.58(4)
N	−2500	−8337(1)	1533(3)	2.15(3)
N1	−2500	−54.7(11)	−2864(4)	4.02(5)
C1	−2500	−708.8(11)	−4395(4)	2.54(3)
C2	−2500	−1578.8(11)	−6247(4)	2.32(3)
C3	−2500	−2500	−4367(5)	1.92(4)

[a] Those positional parameters without esd values were fixed by crystallographic symmetry.

Table 4. Fractional Atomic Coordinates ($\times 10^4$) and Isotropic Gaussian Parameters[14] of Compound 4[a]

atom	x	y	z	B_{iso} (Å^2)
O1	5000	5000	9736(11)	2.3
C2	5000	5000	12468(16)	1.8
N3	3637(6)	4707(2)	13997(9)	1.8
C4	2046(7)	4400(2)	12511(11)	1.6
C5	646(6)	4123(2)	14676(11)	1.6
C6	−1011(7)	3806(2)	13129(10)	1.7
C7	−2480(6)	3541(2)	15205(11)	1.7
C8	−4095(7)	3191(2)	13670(12)	2.2
C9	−3376(6)	2645(2)	12061(11)	2.0
N10	−2761(6)	2226(2)	10879(10)	2.6

[a] Those positional parameters without esd values were fixed by crystallographic symmetry.

Table 5. Fractional Atomic Coordinates ($\times 10^4$) and Isotropic Gaussian Parameters[14] of Compound 4/Urea[a]

atom	x	y	z	B_{iso} (Å^2)
O1	7500	12271(5)	12500	2.0
C2	7500	14998(8)	12500	1.6
N3	7016(2)	16525(5)	11625(2)	1.9
O4	2500	4765(5)	2500	2.3
C5	2500	7491(7)	2500	1.6
N6	2875(2)	9026(5)	3390(1)	1.6
C7	3379(2)	7561(5)	4381(2)	1.7
C8	3764(2)	9702(5)	5270(2)	1.6
C9	4330(2)	8170(5)	6298(2)	1.8
C10	4758(2)	10240(6)	7210(2)	1.7
C11	5252(2)	8616(5)	8233(2)	2.0
C12	5694(2)	10619(5)	9111(2)	2.0
N13	6025(1)	12272(5)	9777(2)	2.6

[a] Those positional parameters without esd values were fixed by crystallographic symmetry.

the reaction mixture at 0 °C.[15] (See ref 16 for triphosgene precautions). After an additional 30 min at 0 °C, the mixture was stirred for 17.5 h at room temperature and then saturated with methanol to precipitate the potassium salts. The solution was condensed to approximately half its volume, and H_2O was added to precipitate the product, which was washed with water and toluene to give 4.24 g of crude product (mp 112–114 °C). Solvent evaporation or cooling yielded an extra 1.15 g of product (5.38 g total, 81.3%). Recrystallization (2:1 (v:v) MeOH:H_2O, 36 mL) of 1.62 g of this white solid yielded 1.10 g of crystals suitable for X-ray diffraction: mp 114–114.5 °C; IR (KBr) 3324 (NH), 2951, 2922 (CH), 2242 (CN), 1609 (CO), 1575 (NH), 1481 (CH_2), 1464 (CH_2), 1423 (CH_2), 1377 (CN) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.22 (t, 4H, J = 7 Hz; NH–CH_2–), 2.48 (t, 4H, J = 7 Hz; CH_2CN), 1.71 (qi, 4H, J = 7 Hz, CH_2–CH_2CN), 1.53 (om, 8H, H_3, H_4). Anal. Calcd for $C_{13}H_{22}N_4O$: C, 62.35; H, 8.87; N, 22.38; O, 6.39. Found: C, 62.29; H, 9.20; N, 22.58: O, 5.93.

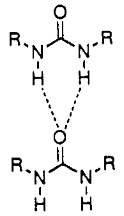
X-ray crystal structure: A search of a limited hemisphere of reciprocal space located a set of diffraction maxima with orthorhombic symmetry and systematic absences corresponding to space group $P2_12_12$. The structure was solved by direct methods (MULTAN78)[17] and difference Fourier techniques, and refined with full-matrix least-squares techniques. In the final cycles, non-hydrogen atoms were refined with anisotropic Gaussian displacement parameters, whereas the hydrogen atoms were freely refined with isotropic B's and no restraints to give a solution with no unusual features in the final difference Fourier map. The coordinates and B_{iso} values are given in Table 4.

Bis(5-cyanopentyl)urea/urea 1:1 Complex (4/Urea). Compound 4 (0.206 g, 0.823 mmol) and urea (0.279 g, 4.65 mmol) were dissolved in MeOH (11.0 mL) at 40 °C, suspended in a Dewar containing H_2O at 40 °C and cooled to 5 °C overnight to yield clear, flat needles that melted in two stages (135–137 and 144–146 °C). Anal. Calcd for $C_{14}H_{26}N_6O_2$: C, 54.16; H, 8.46; N, 27.08; O, 10.31. Found: C, 54.57: H, 8.48: N, 26.62: O, 10.33. (A small excess of 4 may be present.) IR (KBr): 3436, 3320 (NH); 2950, 2919, 2914, 2856 (CH_2), 2247 (C≡N), 1669 (urea CO); 1609 (dialkylurea CO), 1573 (NH), 1457 (CH_2); 1377 (C–N) cm^{-1}. The cocrystals formed by grinding together a 1:1 mixture of urea and 4 gave the following infrared peaks (KBr): 3439, 3324 (NH); 2926, 2858 (CH_2), 2248 (C≡N), 1670 (urea CO); 1608 (dialkylurea CO), 1578 (NH), 1457 (CH_2); 1377 (C–N) cm^{-1}. Except for biases due to preferred orientation of the cocrystals grown from solution, the powder diffractograms for the cocrystals grown from solution and by grinding are nearly identical (see supplementary material).

X-ray crystal structure of 4/urea: Although most of the crystals were heavily twinned, a suitable fragment was found for data collection. A search over a limited sphere of reciprocal space located at set of diffraction maxima with monoclinic symmetry and systematic absences of $h0l$ for $h + l = 2n + 1$. Subsequent solution and refinement confirmed the space group to be $P2/n$. Structure solution and refinement were carried out as with 4 to give a final solution with a featureless difference Fourier map. The coordinates and B_{iso} values for 4/urea are given in Table 5.

Results and Discussion

Work by Etter,[18] Lauher and Fowler,[15,19] and others[20] has shown that dialkylureas and diarylureas have strong tendencies to form polar hydrogen-bonded chains in which the urea carbonyl is tethered in a six-membered ring to the two *anti* urea hydrogens of an adjacent molecule:



The graph set pattern[5] for this first order network is termed C(4)[$R_2^1(6)$] to indicate that repeating chains of four atoms are interwoven with six-membered rings containing two donors and one acceptor. Although numerous exceptions have been observed, especially for systems that contain strong hydrogen-bond acceptors, this mode of association occurs in a large number of urea structures. Within this class of structures, the vast majority exhibit dihedral angles that are close to 0° for adjacent urea groups. These are to be expected from the strong tendency for N–H groups to approach the carbonyl oxygen in the plane

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defined by the lone pairs.[21,22] Notable exceptions include urea,[23] with its perpendicular arrangement of donors and acceptors,[24] and certain hindered diarylureas,[18b] in which steric interactions prohibit a coplanar arrangement of adjacent molecules. For dialkylureas with no unusual steric requirements for the alkyl groups, the coplanar (or nearly coplanar) form of this hydrogen-bonded network should therefore be quite a reliable one for forming flat ribbons or tapes[25] that are not twisted. By tethering these ribbons or tapes together, it should be possible to form two-dimensional layered compounds quite reliably.

This approach has been explored, with great success, in parallel studies by Lauher and Fowler,[15,19] who have used the primary hydrogen-bond network of dialkylureas and a secondary network of hydrogen bonds from carboxylic acid dimers to form two-dimensional layered structures of specified structure. Although the goal of our present study is similar in that we are attempting to find new ways of engineering two-dimensional layered compounds, it is different in that we have focused on specific hydrogen-bonded complexes of urea and have used the homologous polymorphism of the present series to explore the competing roles of packing efficiency and hydrogen bonding in complex formation.

Layered Structures of Dinitriles and Urea. Figure 2 shows the two-dimensional layer structures of **1**, **2**, and **3** with urea. The metric properties of the hydrogen-bonded contacts for these systems and others described below are summarized in Table 6. Interlayer interactions in these complexes will be discussed after the hydrogen-bonded sheet structures and their symmetry relationships to each other are discussed in turn.

Pimelonitrile/Urea (1/Urea). Once the 1:1 stoichiometry and cell constants for **1**/urea had been determined, it was fairly straightforward to predict the two-dimensional layer structure of this complex. Just as in all of the other layered complexes in this series, the urea molecules are tethered to each other by the C(4)[$R_2^1(6)$] network, and the *syn* hydrogens from urea are ideally situated for hydrogen bonding with the dinitrile (Figure 2a). These nitrile–urea interactions make up the second type of first-order network in this layer, a $C_2^2(14)$ chain. The hydrogen bonds, which have lengths that are typical for this sort of interaction,[26] show only small deviations from linearity, as shown by the C≡N- - -N angle of 178°. Together, the two first-order networks generate a second-order $R_6^6(30)$ network, which includes four urea molecules and two nitriles, and which has as its repeating unit the elements of two nitriles and two ureas. The urea carbonyl and C_4 of the nitrile lie on sites of C_2 symmetry, with the symmetry axis along *b*. This gives this hydrogen-bonded sheet a layer group symmetry of *P*2.[19a] Space-filling models displaying the sheet structure of **1**/urea show that the methylene chains of the nitriles are well beyond van der Waals contact with each other (see below), and that the C(4)[$R_2^1(6)$] hydrogen-bonded network controls the spacing along the *b* axis. The polar layer structure that results is a simple consequence of the odd chain parity of the dinitrile and the geometric constraints imposed by the two hydrogen-bonded systems.

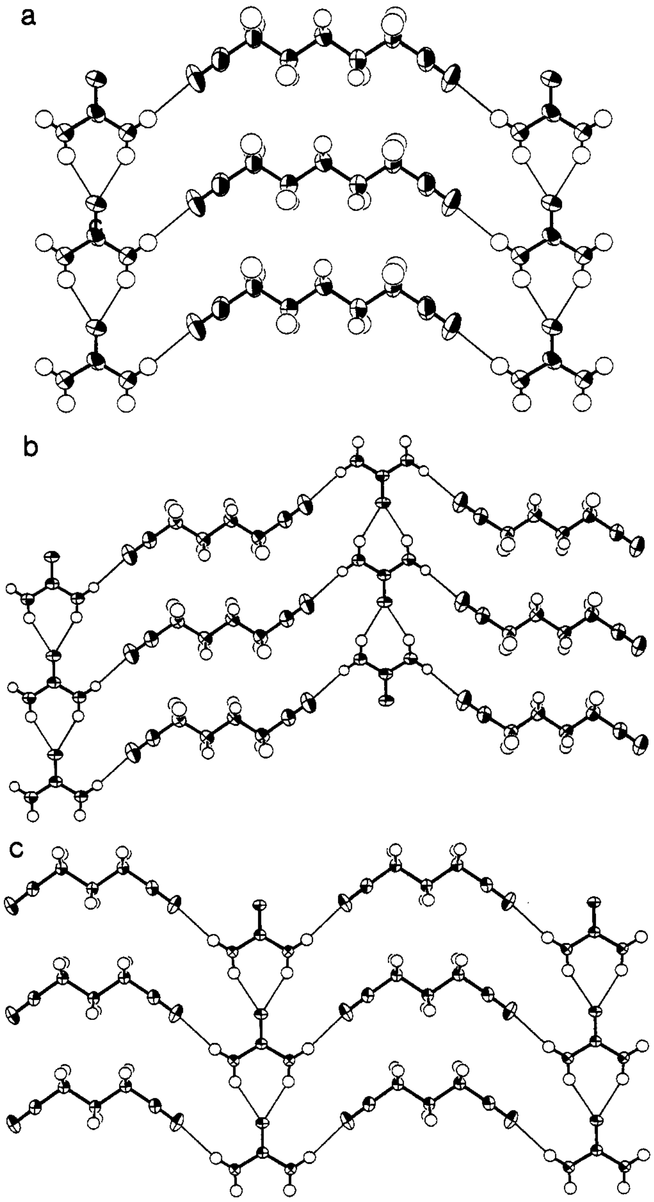

Figure 2. ORTEP[10] diagrams showing projections of two-dimensional layers in complexes of **1**–**3** with urea. (a) (10$\bar{1}$) plane of **1**/urea. (b) (103) plane of **2**/urea. (c) (100) plane of **3**/urea. Ellipsoids are drawn at the 50% probability level. Note that the chain parity of the dinitrile determines whether or not the layer has a dipole moment.

Although they are not perfectly flat, the hydrogen-bonded sheets in **1**/urea form the (20$\bar{2}$) planes of the unit cell; these sheets are related to one another by inversion, with interlayer spacings of 3.45 Å at 20 °C. This inversion center results in a centrosymmetric crystal, with space group *P*2/*c*.

Adiponitrile/Urea (2/Urea). Although the structures of **1**/urea and **2**/urea share the same types of hydrogen-bond interactions and give similar graph sets for their secondary networks,[27] the even chain parity of **2** and the propensity to form linear C≡N---H—N hydrogen bonds gives rise to a layer structure that contains urea molecules

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(24) With urea, the "lone pairs" are satisfied by hydrogen bonding with a second set of neighbors through their *syn* hydrogens.

(25) Zerkowski, J. A.; Seto, C. T.; Wierda, D. A.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 9025–9026.

(26) See, for example: (a) Legon, A. C.; Millen, D. J.; Rogers, S. C. *Proc. R. Soc. London, Ser. A* **1980**, *A370*, 213. (b) Bevan, J. W.; Legon, A. C.; Millen, D. J.; Rogers, S. C. *Proc. R. Soc. London, Ser. A* **1980**, *A370*, 239.

Table 6. Hydrogen-Bonding Interactions in Nitrile/Urea Cocrystals and in Compound 4[a]

	nitrile–urea contacts					urea–urea contacts			
system	$d(N_n - H_u^s)$	$d(N_n–N_u)$	$a(C_n - N_n - H_u^s)$	$a(C_n–N_n–N_u)$	$a(N_u - H_u^s - N_n)$	$d(O - H_u^a)$	$d(O–N_u)$	$a(C_u - O - H_u^a)$	$a(N_u - H_u^a - O)$
1/urea	2.20(2)	3.096(2)	174(5)	178(4)	168(8)	2.06(2)	2.863(2)	148(1)	151(4)
2/urea	2.21(1)	3.105(2)	174(3)	177(2)	171(1)	2.07(2)	2.877(1)	148.7(9)	153(3)
3/urea	2.27(2)	3.155(3)	174(4)	175(2)	174(12)	2.09(2)	2.885(2)	148.6(10)	152(3)
4/urea (1)	2.23(3)	3.106(4)	177(16)	177(5)	164(9)	2.15(3)	2.875(3)	147(2)	146(4)
4/urea (2)						2.10(3)	2.873(3)	147.7(15)	150(4)
4 (2)						2.00(4)	2.864(6)	146(2)	148(5)

[a] Subscripts n and u refer to nitrile and urea. Superscripts s and a refer to *syn* and *anti* hydrogens on urea or dialkylurea molecules. Distances (4d) are in angstroms and the angles (*a*) are in degrees. (1) Urea portion of crystal. (2) Dialkylurea portion of crystal.

that alternate in their orientations. This layer lies in the (103) plane of the crystal and contains centers of symmetry and 2-fold axes perpendicular to the plane (Figure 2b). Its layer group symmetry is therefore *P*2/*a*, and the layer has no net dipole moment. The hydrogen bonding parameters for **2**/urea area are almost identical to those of its higher homologue, as shown in Table 6. Within a unit cell of **2**/urea, layers are connected by a diagonal glide translation, with an interlayer distance of 3.35 Å. This structure, which exists in space group *P*2/*n*, is described in more detail in ref 6.

Glutaronitrile/Urea (3/Urea). From the two structures shown above, in which the parity of the methylene chain of the dinitrile controls the polarity and packing within a hydrogen-bonded sheet, it was fairly straightforward matter to predict the layer packing in **3**/urea. In this orthorhombic structure, the urea molecules stack along the *c* axis, and the hydrogen-bonded layers lie in the (200) planes (Figure 2c). Both urea and dinitrile have the C_{2v} symmetry predicted by their idealized molecular structures, and all of the heavy atoms in the asymmetric unit have *a* coordinates of |0.25|. The two extra mirror planes give the sheet structure a layer symmetry of *Pmm*2, which makes it polar. However, just as with **1**/urea, adjacent layers are related by inversion, with an interlayer distance of 3.25 Å at –60 °C, and the crystal is centrosymmetric, with space group *Pmmn*.

Although the dinitrile chain lengths differ, the hydrogen-bonding topologies for **1**/urea and **3**/urea are identical. The most notable difference in the sheet structures of **1**/urea and **3**/urea lies in the slightly longer hydrogen bond between the nitrile and the *syn* hydrogen of urea in **3**/urea. (The N---N distance differs from that in **1**/urea by 0.059 Å.) The exact reason for this difference is not known, but it is probably related to the constraints imposed by interlayer interactions, as discussed below.

Interlayer Interactions and Nitrile–Nitrile Pairing. For layered systems held together in two dimensions by hydrogen bonds, the most difficult task for the "crystal engineer" is to predict the interlayer stacking, which is typically governed by a multitude of van der Waals and Coulombic interactions. Thus far, our lattice energy calculations using commonly available atom–atom potential parameters have not adequately reproduced the crystal packing parameters of the nitrile–urea complexes. We are continuing to search for potential functions that will better characterize the fine balance between hydrogen bonding, packing efficiency and Coulombic interactions present in these structures. At this time, however, we have simply attempted to identify the most salient features of the interlayer stacking.

One of the most striking features of the dinitrile/urea crystal structures lies in the many similarities of their interlayer interactions. These common features are most easily visualized by viewing projections of two adjacent layers in the three structures (Figure 3). As mentioned earlier, the polar layers of **1**/urea and **3**/urea are related by inversion centers to give centrosymmetric crystals (Figures 3a and 3c). In **1**/urea, the presence of two different inversion centers between the layers requires a more extended set of molecules to show all of the interlayer contacts. With **2**/urea, the centers of symmetry exist within the layers, and the hydrogen-bonded sheets are related by diagonal glide translations.

A cursory view of the three pairs of layers shown in Figure 3 might suggest that there is something special about the disposition of the β-CH_2 of the dinitrile and the urea carbonyl in the adjacent layer. In each plane projection, there is an almost perfect meshing of the β-CH_2 group in one layer with the gap between urea carbonyl groups in the next. (This feature is shared by another structure in this same series, as shown later in this paper.) Absent any special interaction between β-CH_2 and the carbonyl, it seemed appropriate to look further afield for interactions that would favor the overlap of β-CH_2 groups and carbonyls in all three structures. Although the plane projection views are somewhat suggestive of C–H---N interactions between the α-CH_2 groups and the urea nitrogens,[28] no such short contacts were observed in any of the structures.

A much more likely source of the common interlayer contacts are the nitrile–nitrile interactions. For **1**/urea there are two types of nitrile–nitrile contacts, as required by the two sets of inversion centers between the layers. In the first type (labeled 1 in the figure) the nitriles are related by simple inversion, whereas in the second (labeled 2), there exists an additional translation element along *x*. The structure of **2**/urea exhibits nitrile–nitrile pairs related by C_2 axes (type 3) and by inversion (type 4); the former sets of nitriles are arranged in a crisscross pattern that brings them in close contact. In **3**/urea, the pairs have structures that are very similar to the first set of contacts in **1**/urea. Thus, with the exception of the type 3 pair in **2**/urea, all of the nitrile pairs have antiparallel structures and are related by inversion centers.

Table 7 summarizes the structural properties of the nitrile–nitrile pairs found in the structures described in this paper. To facilitate comparison with other studies,[29,30] we find it convenient to report two sets of internal coordinate systems, one using normal atom-centered reference points, the other using reference points based upon the centers of the C≡N bonds. The structural

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(27) The primary networks for **2**/urea are $C(4)[R_2^1(6)]$ and $C_2^2(13)$, whereas the secondary network is $R_6^6(28)$.

(28) Taylor, R.; Kennard, O. *J. Am. Chem. Soc.* **1982**, *104*, 5063–5070.

(29) Gavezzotti, A. *J. Phys. Chem.* **1990**, *94*, 4319–4325.

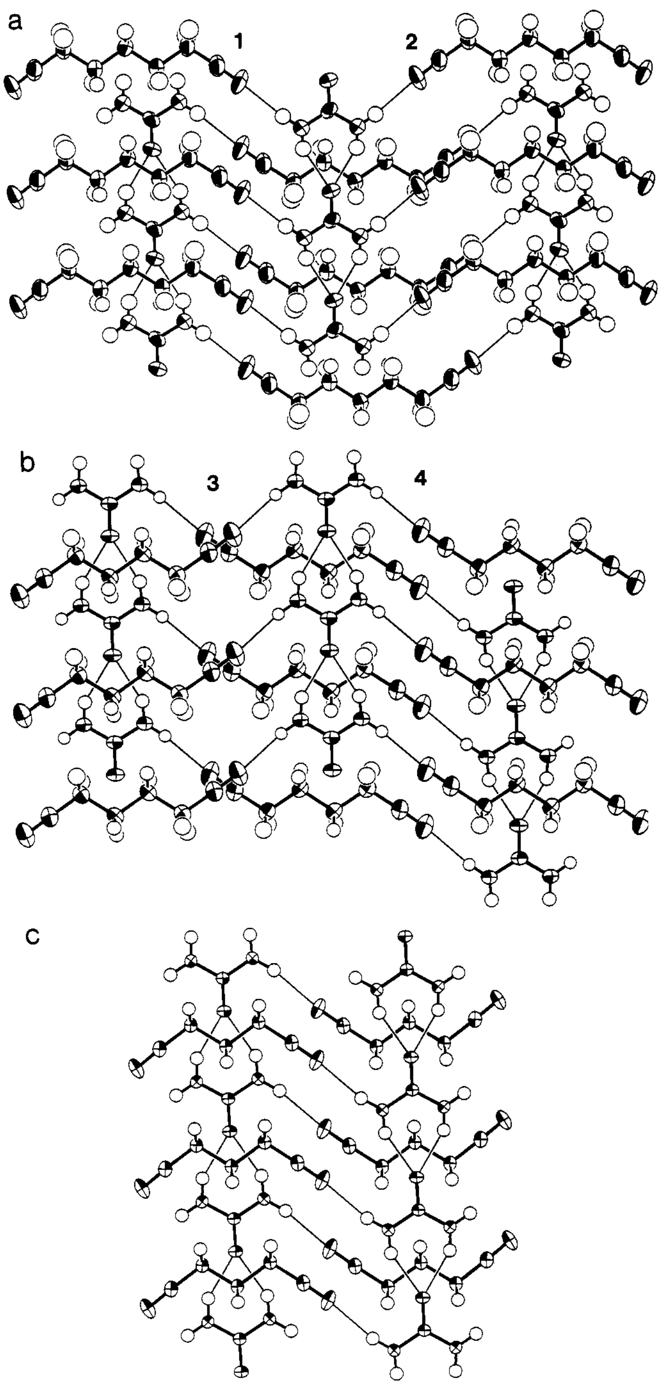

Figure 3. ORTEP[10] diagrams showing interlayer interactions in complexes of **1**–**3** with urea. In each case, the vertical axis is defined by the urea carbonyl, and the viewing plane is defined by the O, C, and N of the urea. (a) **1**/urea. Note the difference in overlap of nitrile groups in the nitrile–nitrile pairs designated with '1' and '2'. (b) **2**/urea. The two different sets of nitrile–nitrile pairs are related by 2-fold axes (3) and inversion (4). (c) **3**/urea. Molecules are related by inversion symmetry to give just one type of interlayer contact. In all three structures, the β-CH_2 group is aligned with the urea carbonyl of the next layer. Ellipsoids are drawn at the 50% probability level.

parameters listed for the nitrile pairs in **1**–**3**/urea can be compared with an analytical potential energy surface for acetonitrile dimers, which has been constructed by La Manna using SCF *ab initio* methods on 165 molecular pairs.[30] His study uses van Duijneveldt's (7,3/3) minimal basis set[31] contracted[32] to (2,1/1), counterpoise methods[33] to remove basis-set superposition errors, and a correction for dispersion energy as outlined by Claverie and Kølos.[34] The interaction energies of the acetonitrile dimers were fit to a Lennard-Jones potential, with a Coulombic term that uses the Mulliken charges on the atoms of acetonitrile:[35]

$$E = -\sum A_{ij} r^{6} + \sum B_{ij} r^{-12} + \sum C_{ij} q_i q_j r^{-1} \qquad (1)$$

Wide variation in the coefficients for the attractive and repulsive terms of La Manna's Lennard-Jones expression suggested that it would be unwise to use this potential for anything except acetonitrile itself, so we have refrained from appending alkyl groups to the cyanomethylene unit. Instead, we have used the crystallographic coordinates to define the positions of $N{\equiv}C{-}CH_2$ groups in the nitrile pairs, and have then added hydrogens at the idealized sp^3 hybridized positions to generate CH_3CN dimers for use in the energy calculations (Table 8). Although La Manna's potential was derived from *ab initio* calculations that overestimate the bond lengths in CH_3CN by significant amounts,[36] we find that for structures in which close contacts are avoided, the interaction energies are not very sensitive to bond length alterations. (This insensitivity is caused by the relatively shallow distance dependence of the Coulombic terms, which tend to dominate the lattice sums.) Thus, we have chosen not to artificially alter the bond lengths in our structural models.

We think that it is significant that all of the antiparallel nitrile dimer structures observed in **1**–**3**/urea lie within 2 kJ mol^{-1} of the pair configuration calculated to be most stable (−11.3 kJ mol^{-1}) by the *ab initio* methods (see last entry of Table 7 for structural parameters), and that the crossed dimers (type 3) are stabilized by a significant amount. According to La Manna's potential, the most favorable structure observed in the present study is the type 2 contact found in **1**/urea. A view of the (010) plane of this crystal (Figure 4) shows that significant torsions about the C_2–C_3 (174.9(1)°) and C_3–C_4 (174.1(1)°) bonds of **1** twist the nitriles related by the type 2 inversion into this favorable geometry. These torsions distort the $C{\equiv}N{-}{-}{-}H$ hydrogen bond away from linearity by only a small amount, and have the favorable effect of increasing the N_1---C_2 distance and decreasing the N_1---C_1 distance between neighboring nitriles. With the type 1 pairs, the effects of the torsions are not as clear, but the calculated interaction energy is again close to the theoretical limit. The actual Coulombic stabilization caused by the torsions obviously depends upon the partial charges that are assigned to the atoms,[37] but the observed effects are quite suggestive.[38]

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(30) (a) La Manna, G. *Chem. Phys. Lett.* **1983**, *103*, 55–58.[30b] (b) See also Bohm, H. J.; McDonald, I. R.; Madden, P. A. *Mol. Phys.* **1983**, *49*, 347–360 for a Lennard-Jones potential for acetonitrile derived by other methods.

(31) van Duijneveldt, F. B. *IBM Tech. Rept.* RJ945, 1971.

(32) Gianolio, L.; Pavani, R.; Clementi, E. *Gazz. Chim. Ital.* **1978**, *108*, 181–205.

(33) Boys, S. F.; Bernardi, F. *Mol. Phys.* **1970**, *19*, 553–566.

(34) (a) Claverie, P. In *Intermolecular Interactions: From Diatomics to Biopolymers*; Pullman, B., Ed.; Wiley: New York, 1978. (b) Kølos, W. *Theor. Chim. Acta (Berlin)* **1979**, *51*, 219–240.

(35) Prof. La Manna has kindly provided the Mulliken charges, which are given here (in au): N, −0.2321; C1, 0.1097; C2, −0.5765; H, 0.2330.

(36) (a) La Manna's *ab initio* bond lengths (C–C = 1.56 Å, C–N = 1.21 Å, C–H = 1.19 Å) should be compared with the experimental values[36b] obtained from combined electron diffraction and microwave spectroscopy (C–C = 1.46 Å, C–N = 1.15 Å, C–H = 1.09 Å). (b) Karakida, K.; Fukuyama, T.; Kuchitsu, K. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 299–304.

(37) (a) It would be most appropriate to use potential derived multipoles[37b] to probe this effect, but we have not yet done these calculations. (b) Williams, D. E. *J. Comput. Chem.* **1988**, *9*, 745–763.

Table 7. Interlayer Nitrile–Nitrile Contacts in Nitrile/Urea Cocrystals and in Compound 4

	atom-centered coordinates[a]					C≡N bond-centered coordinates			
system	$d(C_1–C_1)$	d(N–N)	$d(N–C_2)$	$a(N–C_1–C_1)$	$a(N–C_1–C_1–N)$	d(+–+)	a(N–+–+)	a(N–+–+–N)	symmetry
1/urea (1)	3.776(3)	3.928(3)	3.914(3)	76.6(2)	180[b]	3.683	94.02	180	$\bar{x}, \bar{y}, \bar{z}$
1/urea (2)	3.673(3)	4.406(3)	3.651(3)	92.7(2)	180[b]	3.895	109.6	180	$\bar{x} + 1, \bar{y}, \bar{z}$
2/urea (3)	3.588(2)	3.665(2)	3.953(2)	80.08(11)	106.6	3.509	92.03	107.8	$^1/_2 - x, y, ^1/_2 - z$
2/urea (4)	3.872(2)	3.901(2)	3.993(2)	73.72(10)	180[b]	3.717	90.77	180	$\bar{x} + 1, \bar{y}, \bar{z}$
3/urea	3.828(1)	3.795(1)	3.969(1)	71.85(9)	180[b]	3.638	89.13	180	$^1/_2 + x, \bar{y}, \bar{z} - 1$
4/urea	3.700(3)	3.736(3)	3.828(3)	72.8(2)	180[b]	3.536	90.95	180	$\bar{x} + 1, \bar{y} + 2, \bar{z} + 2$
4	4.024(7)	3.780(6)	3.424(7)	47.5(6)	162.2	3.759	62.36	163.7	$^1/_2 + x, ^1/_2 - y, \bar{z} + 2$
			4.979(6)[c]	89.0(3)			103.94		
Theory[d]	3.5	4.25	3.517	90	180[b]	3.703	109.1	180	$\bar{x}, \bar{y}, \bar{z}$

[a] The distances (d) are in angstroms and the angles (a) are in degrees. In the C≡N bond-centered set of coordinates, the "+" symbol designates the bond center. [b] Constrained by the space group symmetry to be this value. [c] The second set of entries under structure 4 use the atoms in the second molecule of the dimer as a reference point. These values are required to describe the structure of this skewed dimer. [d] Reference 30a.

Table 8. Interaction Energies for Acetonitrile Dimers with Pair Structures Reported in This Paper[a]

system	E(vdW)	E(rep)	E(Coul)	E(total)	symmetry
1/urea (1)	−3.226	2.017	−8.780	−9.988	$\bar{x}, \bar{y}, \bar{z}$
1/urea (2)	−2.814	3.053	−10.566	−10.327	$\bar{x} + 1, \bar{y}, \bar{z}$
2/urea (3)	−4.196	3.390	−2.913	−3.719	$^1/_2 - x, y, ^1/_2 - z$
2/urea (4)	−3.030	1.845	−8.411	−9.595	$\bar{x} + 1, \bar{y}, \bar{z}$
3/urea (interlayer)	−3.401	2.344	−8.501	−9.557	$^1/_2 + x, \bar{y}, \bar{z} - 1$
3/urea (intralayer)	−1.916	1.295	0.045	−0.574	$x, y, z + 1$
4/urea	−4.038	3.134	−9.156	−10.060	$\bar{x} + 1, \bar{y} + 2, \bar{z} + 2$
4	−1.262	2.487	−6.945	−5.720	$^1/_2 + x, ^1/_2 - y, \bar{z} + 2$

[a] Energies in kJ mol^{-1}.

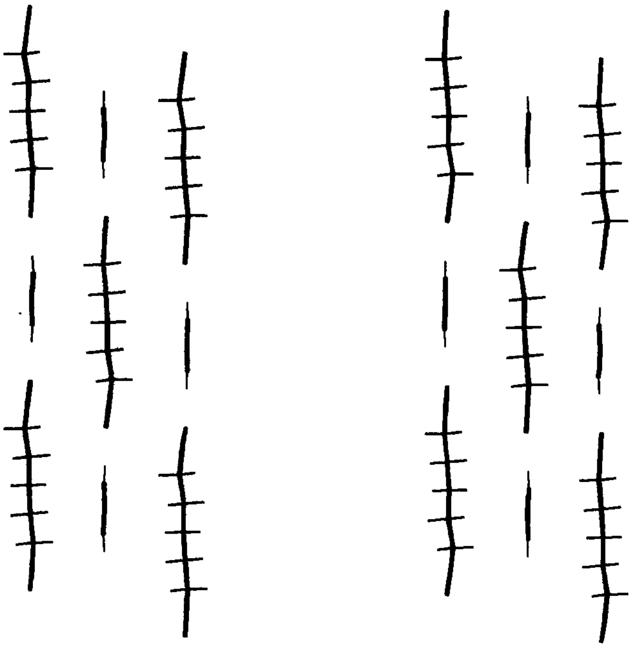

Figure 4. Stereoview of the (010) plane of 1/urea. Nitrile–nitrile pairs in the lower right and upper left are related by type 1 inversion symmetry, whereas those in the lower left and upper right are related by type 2 inversions. Note that in the type 2 pairs, chain torsions twist the α carbons away from the nitrile in the adjacent layer.

The closest approach between nitrile dimers in 1–3/urea occurs in the pairs related by C_2 axes in 2/urea (type 3). Here the nitrile bond centers are separated by only 3.51 Å, and La Manna's potential predicts an interaction of 3.7 kJ mol^{-1}. Thus, it seems that significant stabilization can occur in this pair. The torsion about C_2–C_3 (176.5°) of 2 may have a small effect on the nitrile pair energies, but this has not been explored systematically.

Although the structures of 1/urea and 3/urea exist in different space group classes, it should be evident from the figures and discussion that the two can be classed as homologous isomorphs. As mentioned in the experimental section, it is possible to construct a reasonable model of 3/urea from that of 1/urea by simply removing two methylene groups from 1 and then "reattaching" the nitriles. This reconstruction shortens the repeat length of the layer in 3/urea, but leaves the interlayer contacts between the remaining fragments more or less unchanged. (The nitrile dimers in 3/urea lie within 0.05 Å and 5° of the structure found for the type 1 dimer observed in 1/urea.) The model approximates the orthorhombic symmetry observed for 3/urea, so the *Pmmn* symmetry of the crystal is thought to be a coincidental result of the interlayer interactions. This space group symmetry requires that all of the interlayer nitrile–nitrile contacts are identical, and that the nitriles are planar. Along with the narrower girth of urea (compared to the methylene chains), the planarity of this shorter chain may account for the smaller interlayer separation in 3/urea. The added symmetry constraints and the meshing requirements imposed by the interlayer packing may also be responsible for the comparatively long C≡N---H—N hydrogen bond observed in 3/urea. This seems more likely than an unusual electrostatic effect that weakens this interaction.

For 3/urea, we have used La Manna's potential to calculate the *intra*layer interaction between adjacent nitriles (Table 8), which is more or less the same for all of the layered systems. It should come as no surprise that the van der Waals and repulsive terms for this pair are small, since the nitriles within a layer are beyond van der Waals contact. However, it is notable that the Coulombic interaction between these pairs is close to zero and that the hydrogen bonding between the nitriles and urea need not compensate for a repulsive intralayer interaction between nitriles. Thus, it seems that the dinitriles and urea are well-suited for forming hydrogen bonded complexes.

Higher Homologues and Channel Inclusion Compound Formation. The structural properties of crystals containing homologous dinitriles and urea are remarkably diverse. For mixtures of $NC(CH_2)_nCN$ and urea, at least eight different types of structures can be created with n = 1–8, 10, and 12, even if one counts the structures of

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[38] The torsions may also serve to optimize other types of interlayer contacts, but the multitude of small terms in the lattice sums prevent us from analyzing this with any certainty.

1/urea and **3**/urea as homologous isomorphs. The shortest members of the series, malononitrile and succinonitrile, give the trivial result of no complex formation (by grinding or from solution), perhaps because of unfavorable interlayer interactions in the 1:1 complexes that would be predicted from the structures of **1**–**3**/urea. Suberonitrile (n = 6) forms commensurate inclusion compounds with urea in which the molar ratio of urea to guest is 6:1. Its structure shows no evidence for hydrogen bonding between host and guest, and will be reported in a forthcoming publication.[39] With azelanitrile (n = 7) and urea, a paste-like solid is formed when a 1:1 mixture of the two are ground together, but we have not yet been able to characterize the structure of this material. Methanolic solutions of urea and azelanitrile yield crystals of tetragonal urea. Sebaconitrile (n = 8) and urea form an unusual commensurate inclusion compound[8] (6 urea:1 guest) in which the host and guest are hydrogen bonded to each other, and in which the channel structure is distorted severely away from linearity.[40] With n = 10 and 12, normal channel inclusion compounds are formed, but the interchannel guest ordering and solvent inclusion properties of the two systems are different. With n = 10, there is no inclusion of methanol, and the guests show rhombohedral ordering in which the offset between guests in adjacent channels (Δ_g) is one-third the repeat of the guest molecule ($c_g/3$).[7b,8] With n = 12, the offset between guest molecules in adjacent channels (Δ_g) is zero, and the ratio of solvent (methanol) to guest is 1:3.[42]

This sequence is obviously complicated, but there is a clearly defined break between n = 5 and n = 6, where the crystal system changes from 1:1 complex to channel inclusion compound. Under a variety of conditions, we have attempted to form channel inclusion compounds from short chain dinitriles and urea and 1:1 complexes from longer chain dinitriles and urea but have not succeeded. As reported earlier in our preliminary account of this work,[6] the switch from layered cocrystal to channel inclusion compound most likely reflects the competition between nitrile–urea hydrogen bonding (which favors cocrystal formation) and packing efficiency (which seems to favor inclusion compound formation). However, the different stoichiometries of the 1:1 complexes and channel systems make any strict comparison impossible, and in the absence of reliable potential functions for these very different systems, we must resort to analyses that are simple-minded, but useful, nonetheless.

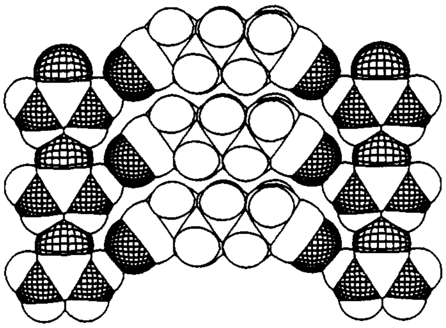

Figure 5. Space filling diagram of **1**/urea. Atomic radii are taken from Bondi.[44] Other cocrystals in this series show the same inefficient packing. The view is the same as in Figure 2.

Within a layer of the 1:1 complexes, the 4.58-Å repeat of the $C(4)[R^{1}_{2}(6)]$ motif dictates the spacing between methylene chains, and places them well beyond van der Waals contact. Space filling diagrams (see Figure 5) and comparison of cell volume increments per methylene for **1**/urea and **3**/urea and for closely packed homologous systems support this view.[6] For assessing the packing efficiency within a layer, however, comparisons of volume increments per methylene should be strictly applicable only if the interlayer separations and the urea spacings are identical for the different crystals.[45] In the present series, the layer separation increases by nearly 0.1 Å as each methylene unit is added to the dinitrile chain. This makes an exact comparison of the structures difficult, since the thermal expansion coefficients of these crystals are such that one would have to compare cell constants for **3**/urea with those of **2**/urea and **1**/urea measured 100–200 K lower. Such a comparison would be artificial, however, since the motional parameters for the methylene chains in **1**–**3**/urea would be very different. A more reasonable approach would be to compare cell constants for the different crystals at the same temperature, bearing in mind that the volume increment includes a component due to layer expansion.[46,47] This simple-minded analysis yields a volume increment of approximately 25 Å^3/CH$_2$ for each pair of crystal structures, which suggests fairly loose packing of the methylene chains in the 1:1 complexes.

Thus, although each of the hydrogen bond donors and acceptors is satisfied in the layered systems, this structure can only be sustained for dinitriles containing up to five methylenes. Beyond that, channel inclusion compound formation is favored, presumably because the methylene chains are stabilized by their surroundings more than in the layered complexes. This argument should certainly hold in the limit of long chain dinitriles (e.g., n = 10, 12), but one might also argue for other more specific effects for dinitriles with n = 6 and 8. Both of these are commensurate inclusion compounds in which the host:guest stoichiometry

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(39) Pertinent data for suberonitrile/urea are reported here: monoclinic, space group $P2_1/n$, ($Z = 4$ for $C_7H_{18}N_7O_3$), $a = 8.192(2)$, $b = 10.935(2)$, $c = 14.472(3)$ Å, $\beta = 94.23(1)°$, $V = 1292.9(7)$ Å^3 at 293 K.

(40) Under appropriate conditions in MeOD,[8] sebaconitrile and urea-d_4 form incommensurate[41] (hexagonal) inclusion compounds instead of the monoclinic form that is ordinarily found with this guest.

(41) By incommensurate, we mean that the repeat distances of host and guest along the channel axis (c_h and c_g) do not satisfy the relationship $n|c_h| \cong m|c_g|$ for reasonably small integers m and n. This is the normal form for urea inclusion compounds. See: Rennie, A. J. O.; Harris, K. D. M. *Proc. R. Soc. London* **1990**, *430*, 615–640.

(42) IR frequencies of nitrile stretching bands (2-cm^{-1} resolution, Nujol mull except as noted) were as follows (cm^{-1}): **3** (neat), 2251.0; **3**/urea cocrystal (grinding), 2257.0; **3**/urea cocrystal (from methanol), 2256.0, 2250.0 (sh); **2** (neat), 2246.7; **2**/urea cocrystal (grinding), 2251.4, **2**/urea cocrystal (from methanol), 2251.4; **1** (neat), 2244.4; **1**/urea cocrystal (grinding), 2250.3; **1**/urea cocrystal (from methanol), 2250.4; suberonitrile (neat), 2244.9; suberonitrile/urea inclusion compound (from methanol), 2249.4 (the origin of this shift is presently being studied); sebaconitrile (neat), 2244.9, sebaconitrile/urea inclusion compound (from methanol), 2243.1, 2257.2 (sh); 1,10-dicyanodecane/urea (from methanol), 2250.8; 1,12-dicyanododecane/urea (from methanol), 2250.6. The higher frequencies for hydrogen-bonded nitriles are typical for nitriles.[43]

(43) Grundnes, J., Klaboe, P. In *The Chemistry of the Cyano Group*; Rappoport, Z., Ed.; Interscience Publishers, New York, 1970; pp 134ff.

(44) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441–451.

(45) In our earlier work, a simple digit transposition led us to believe that the layer separations in **1**/urea and **3**/urea were much closer than they actually are.

(46) Metric data for **3**/urea are given here for the orthorhombic cell. $T = -87$ °C: $a = 6.5020(18)$, $b = 4.5693(11)$, $c = 13.712(3)$ Å, $V = 407.37(16)$ Å^3; $T = -70$ °C: $a = 6.5241(13)$, $b = 4.5734(8)$, $c = 13.721(2)$ Å, $V = 409.40(12)$ Å^3; $T = -55$ °C: $a = 6.5411(8)$, $b = 4.5772(5)$, $c = 13.728(2)$ Å, $V = 411.02(9)$ Å^3; $T = -40$ °C: $a = 6.5584(13)$, $b = 4.5802(7)$, $c = 13.738$ Å, $V = 412.68(12)$ Å^3. These may be compared with the cell constants listed in Table 1.

(47) In as much as the layer expansion is due to the larger width of a methylene (compared to a urea molecule), this seems appropriate.

is 6:1. As mentioned earlier, the inclusion compound of sebaconitrile/urea shows hydrogen bonding between host and guest, so this complicates any argument made solely on the basis of packing efficiency. With suberonitrile/urea, there are no hydrogen bonds between hosts and guests, but there are a number of electrostatic interactions that could favor formation of this inclusion compound. A number of other α,ω-disubstituted hexanes form commensurate inclusion compounds with urea,[48] so at this point it is not possible to rule out specific interactions or shape effects[49] that favor the switch from layer to channel when $n = 6$.[50,51] Other arguments in favor of packing efficiency are given in the next section.

Packing Efficiency in Hydrogen-Bonded and Non-Hydrogen-Bonded Crystal Structures. One goal for crystal engineers is to achieve at least some level of predictability concerning the sorts of dramatic changes in packing that take place on going from 1:1 complex to channel inclusion compound. The volume increments mentioned above are useful indicators that can provide clues about the trends that one might expect, but taken in isolation, they provide little predictive value. We were therefore interested in exploring different criteria for packing efficiency in hydrogen-bonded and non-hydrogen-bonded crystals, with the hopes that these criteria would give us a clearer idea of whether or not a particular homologous series of crystal structures could continue as homologous isomorphs or would have to undergo drastic changes of the sort exhibited here.

Certainly one of the best criteria for packing efficiency is Kitaigorodskii's C_k,[1] which is a measure of the volume of the unit cell that is occupied by the atoms. However, for a reliable comparison, this method requires a series of complete crystal structures measured at similar temperatures. Instead, we sought a method that would require as little input as possible, preferably only cell constants, and the numbers and identities of the atoms in the unit cell. Such a method would ideally make it possible to predict the "breaking point" for a series on the basis of powder diffractograms or diffractometric cell constants alone. It would also allow us to collect the full crystallographic data at any temperature, and then compare values derived from unit cell constants, which could be measured more conveniently at similar temperatures.

One solution to this problem comes from a study by Gavezzotti, who in 1982 published a survey of indices related to packing efficiency for 72 selected organic crystal structures, including a number of plastic crystals.[2a] Among the different measures of packing efficiency, we find the most useful to be the relationship between the average electron density of a crystal (D_e, e Å^{-3}) and the average atomic number (z(ave)) of the unit cell. For $2.5 \leq z(\text{ave}) \leq 8.0$, which covers the bulk of organic crystal structures, and 54 of the 72 in his study, Gavezzotti found a linear relationship between D_e and z(ave) in which the following holds:

$$D_e = 0.0525z(\text{ave}) + 0.1983 \text{ e Å}^{-3} \qquad 2.5 \leq z(\text{ave}) \leq 8.0 \quad (2)$$

At higher values of z(ave), the curvature of the least-squares line becomes significant, but the predictive power of this relationship is quite substantial for $2.5 \leq z(\text{ave}) \leq 8.0$.

Of the 54 crystal structures used to formulate this relationship, only three showed intermolecular hydrogen bonding. The rest of the structures were held together by simple van der Waals and dipolar interactions. In the context of the present study, we wondered if eq 2 would be equally valid for organic crystals exhibiting intermolecular hydrogen bonding, and whether the packing trend in **1**–**3**/urea would deviate from the norm that it establishes. We also realized that it was not at all clear if hydrogen-bonded crystals would be more or less efficiently packed than crystals without hydrogen bonding. The simple example of ice reminds us that hydrogen bonding can support an open architecture, and that it would not be surprising if there were many cases in which packing efficiency is sacrificed so that the crystal can form a larger number of hydrogen bonds.[54] At the same time, it was clear that hydrogen bonding typically translates into closer contacts between molecules and that higher packing efficiencies could result. In light of earlier work by Hagler and Leiserowitz,[55] in which it was shown that several different crystal packing arrangements containing the same number of hydrogen bonds could give packing energies within a few kcal mol^{-1} of one another, it seemed

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(48) See: Otto, J. *Acta Crystallogr.* **1972**, *B28*, 543. Our complete crystal structures of $Br(CH_2)_6Br$/urea, $Br(CH_2)_6Cl$/urea, $Cl(CH_2)_6Cl$/urea, $NC(CH_2)_6CN$/urea, $CN(CH_2)_6NC$/urea, and $Cl(CH_2)_6CN$/urea will be reported shortly.

(49) In their staggered forms, the V-like shapes of pimelonitrile and azelanitrile are probably not well suited for inclusion compound formation.

(50) A number of short chain compounds, including 1,5-dibromopentane, 1,5-dichloropentane and 1,4-dichlorobutane[48] form channel inclusion compounds with urea, so it seems that short chain lengths do not preclude formation of channel inclusion compounds.

(51) Several lines of evidence suggest that isonitriles might be somewhat stronger hydrogen bond acceptors than nitriles,[52] so one might expect from the above that 1,6-diisocyanohexane would form a 1:1 complex with urea instead of a channel inclusion compound. Since 1,6-diisocyanohexane and suberonitrile are nearly isostructural, this would constitute a simple measure of the degree to which hydrogen bonding and packing efficiency are in competition. In our initial efforts with the diisonitrile, however, we have only been able to form channel inclusion compounds. The crystal structure of 1,6-diisocyanohexane/urea is very similar to that of suberonitrile/urea,[53] except that the orientations of the guest molecules and their conformational disorder are somewhat different. Once again, there is no evidence for hydrogen bonding between urea and isonitrile. Formation of a 1:1 complex between the isonitrile and urea would have provided strong evidence for the notion that there is a fine balance between hydrogen bonding and packing efficiency, but the present "negative" result is somewhat ambiguous, since the difference in hydrogen bond strengths are thought to be fairly small.[52f]

(52) For early infrared studies on hydrogen bonding to alcohols and phenols, see: (a) von Rague Schleyer, P.; Allerhand, A. *J. Am. Chem. Soc.* **1962**, *84*, 1322–1324. (b) Allerhand, A.; von Rague Schleyer, P. *Ibid.* **1963**, *85*, 866–870. (c) Ferstandig, L. L. *Ibid.* **1962**, *84*, 3553–3557. (d) Loewenstein, A.; Margalit, Y. *J. Phys. Chem.* **1965**, *69*, 4152–4156. (This solution-phase NMR study suggests a difference of 1.1 kcal mol^{-1} for CH_3CN and CH_3NC with MeOH.) (e) Calculations at the 4-31G level for MeOH with either CH_3CN or CH_3NC yield an extra 0.5 kcal mol^{-1} hydrogen bond stabilization for the latter. See: Tang, T. H.; Fu, X. Y. *Int. J. Quantum Chem.* **1983**, *24*, 317–325. (f) Recent gas-phase studies[52g] indicate that the hydrogen-bond-acceptor abilities of CH_3CN and CH_3-NC toward HCN, HCl and acetylene are nearly identical. These are backed by high level calculations on the HCl complexes,[52h] which suggest a hydrogen-bonding difference of only 0.2 kcal mol^{-1}. (g) See: Legon, A. C.; Lister, D. G.; Warner, H. E. *J. Am. Chem. Soc.* **1992**, *114*, 8177–8180 and references cited therein. (h) Del Bene, J. E. *J. Am. Chem. Soc.* **1993**, *115*, 1610–1611.

(53) Crystal data for 1,6-diisocyanohexane/urea (1:6) inclusion compound are given here: monoclinic, space group $P2_1/n$, $Z = 2$ for $C_{14}H_{36}N_{14}O_6$, $a = 8.189(4)$, $b = 10.922(6)$, $c = 14.504(9)$ Å, $\beta = 94.74(3)°$, $V = 1292.8$ Å^3 at 293 K. (Compare with ref 39.) Our complete crystal structure of this inclusion compound will be reported in another publication.

(54) In a sense, the general rule that molecules will form the maximum possible number of hydrogen bonds is a prescription for inefficient crystal packing. See refs 4 and 55.

(55) Hagler, A. T.; Leiserowitz, L. *J. Am. Chem. Soc.* **1978**, *100*, 5879–5887. This study of adipamide is analogous to the present study in that the normal hydrogen-bonding arrangement for amides was "sacrificed" for an alternative arrangement with higher packing efficiency.

that hydrogen-bonded systems would exhibit greater packing efficiency.

We set out to formulate a relationship similar to eq 2 for crystals containing intermolecular hydrogen bonds[56] and to compare the packing efficiency relationship for this set with that for crystals without them. Using Gavezzotti's data base as a starting point,[57] we selected an additional 276[58] structures from the literature as well as nine from our own work. The bulk of these structures were selected at random from issues of *Acta Crystallographica* published during 1948 to 1994. (See the Appendix for references.) By choosing structures from literature spanning a spread of years, we sought to avoid any bias in molecular complexity that might occur for structures reported in a narrower time frame. A smaller subset of hydrogen-bonded crystals was selected nonrandomly so that certain classes of molecules would be included. These include structures containing urea groups, a small number of carbohydrate crystals, and a number of nitrated aromatic crystals studied by Etter[59] and others. Exclusion of these subsets of crystals was found not to alter the general conclusions reached in this study.

Our combined data base of 338 structures contained 169 structures that exhibited intermolecular hydrogen bonding and 169 that did not. The combined set of structures yields the following least-squares relationship between D_e and z(ave):

$$D_e = 0.0553(19)z(\text{ave}) + 0.1943 \text{ e Å}^{-3} \qquad (r^2 = 0.702) \quad (3)$$

which is quite similar to the relationship given in eq 2. When the two sets of data are separated, however, the following least-squares lines are obtained:

H-bonded:

$$D_e(1) = 0.0638(30)z(\text{ave}) + 0.1703 \qquad (r^2 = 0.733) \quad (4)$$

not H-bonded:

$$D_e(2) = 0.0507(21)z(\text{ave}) + 0.2027 \qquad (r^2 = 0.768) \quad (5)$$

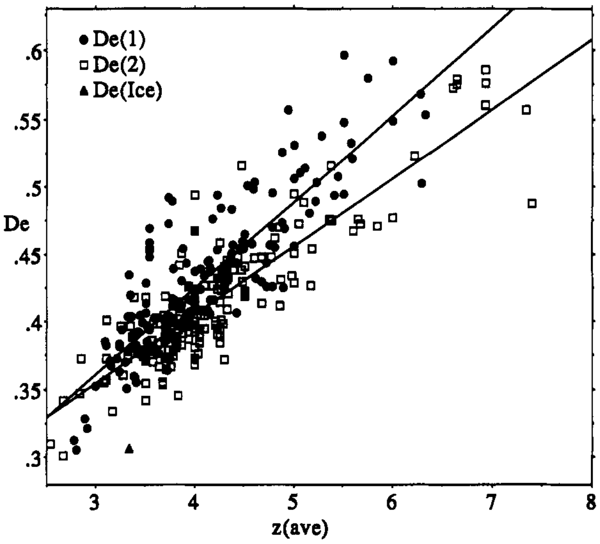

Figure 6. Correlation between D_e and z(ave) for crystal structures containing intermolecular hydrogen bond (circles, $D_e(1)$) and those without them (squares, $D_e(2)$). The triangle shows the value for ice at 273 K.

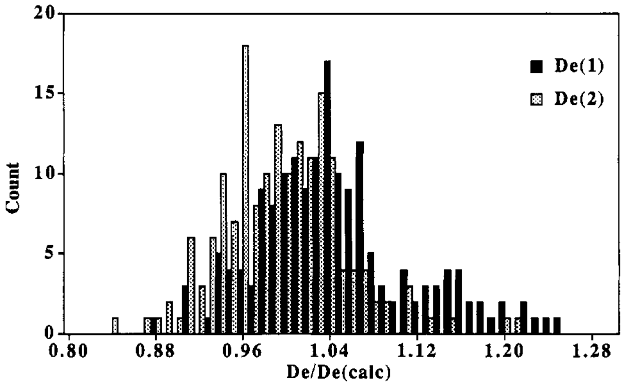

Figure 7. Distributions of packing efficiencies of hydrogen-bonded and non-hydrogen-bonded crystals. For each data set, the observed values of D_e have been normalized by dividing by the value of D_e predicted by the least-squares line for the non-hydrogen-bonded set. Heavily shaded columns: hydrogen bonded crystals ($D_e(1)$); lightly shaded columns: non-hydrogen-bonded set ($D_e(2)$).

These relationships are shown graphically in Figure 6, which shows that only 22 (13%) of the data points for the non-hydrogen-bonded crystals lie above the least-squares line for the hydrogen-bonded set, and that only 38 (22%) of the points for hydrogen bonded crystals lie below the line for the non-hydrogen-bonded set. The dissimilarity in slopes is evident upon inspection, but the significant overlap of the two data sets (Figure 7) requires that we find a statistical test that gives a measure of the probability that the slopes are different. One such method involves introduction of a "dummy variable" (called ID) that codes the data according to the type of intermolecular contact.[60] In the present case, we set ID = 1 for the hydrogen bonded set and ID = 2 for the non-hydrogen-bonded set. Multiple regression on all of the data using the following relationship:

$$D_e = \beta_0 + \beta_1 z(\text{ave}) + \beta_2 \text{ID} + \beta_3 \text{ID}z(\text{ave}) \quad (6)$$

can show if introduction of the terms containing ID are significant factors in explaining the variance within the data. Of particular interest is the "interaction" between ID and z(ave), and the probability that β_3 is nonzero. This so-called "homogeneity of slopes" test gives a 99.97% probability that IDz(ave) is a significant factor in explaining the variance ($r^2 = 0.755$), and that the slopes are in fact different. (See footnote 61 for statistical parameters.) A similar treatment of Gavezzotti's non-hydrogen-bonded

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[56] Although they are obviously important,[28] we have not attempted to identify short C–H---X contacts for possible consideration as hydrogen bonds.

[57] Of the 54 structures used by Gavezzotti[2a] to formulate eq 2, we found parameters for 53. The remaining structure (3.25, tetracyclohexylcyclotetraphosphine) remains unpublished.

[58] Of the crystal structures that we chose, approximately 93% were derived from data collected within 10 K of room temperature. The rest were done between 110 and 253 K. The temperatures for the structures used in Gavezzotti's data base are given in ref 2a.

[59] Panunto, T. W.; Urbánczyk-Lipkowska, Z.; Johnson, R.; Etter, M. C. *J. Am. Chem. Soc.* **1987**, *109*, 7786–7797.

[60] (a) Sokal, R. R.; Rohlf, F. J. *Biometry: The Principles and Practices of Statistics in Biological Research*, 2nd ed.; W. H. Freeman and Co.: New York; pp 499–509. (b) Montgomery, D. C.; Peck, E. A. *Introduction to Linear Regression Analysis*; John Wiley and Sons: New York, 1992; pp 131–137.

[61] Coefficients with standard errors, partial F (pF) values and probabilities (p) are as follows for the three way multiple regression (df = 3, 334). z(ave): $\beta_1 = 0.0769(60)$, $pF = 163.6$, $p = 0.0001$; ID: $\beta_2 = 0.032(15)$, $pF = 4.459$, $p = 0.0355$; IDz(ave): $\beta_3 = -0.0131(36)$, $pF = 13.071$, $p = 0.0003$.

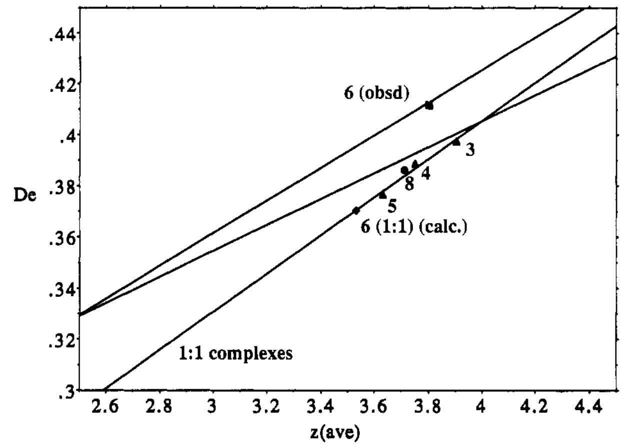

Figure 8. Comparison of observed and predicted packing efficiency of cocrystals and inclusion compounds. The upper two lines are for hydrogen-bonded and non-hydrogen-bonded crystals, as in Figure 6. The number next to each point designates the number methylene groups in the chain of the dinitrile. The line labeled "1:1 complexes" is the least-squares line for 1–3/urea (triangles labeled 3, 4, and 5). The diamond on that same line (6) gives the calculated value for the 1:1 complex of 1,6-dicyanohexane (suberonitrile) and urea. The square (6, obsd) and circle (8) are the observed values for the urea inclusion compounds of suberonitrile and sebaconitrile.

crystals (ID = 2) and the crystals without hydrogen bonding that we chose (ID = 1) showed no significant difference in the slopes for those two data sets. (The probability is 86.6% that IDz(ave) is *not* a significant factor in explaining the variance.)[62]

For this limited set of structures, at least, these data confirm the notion that molecules with the ability to form intermolecular hydrogen bonds *can* typically form crystals in which packing efficiency is not sacrificed. Presumably this is done by choosing the best or one of the best of several packing arrangements, each of which satisfies the donor and acceptor requirements of the functional groups in the molecule, as suggested by Hagler and Leiserowitz.[55] Although a number of compounds that form hydrogen bonds can form loosely packed structures,[63] the open structure of ice seems to be the exception, not the rule (see Figure 6). In that structure, the perfect complementarity of the hydrogen bond donors and acceptors makes the open structure accessible.

In the case of the 1:1 cocrystals, perfectly matched donor–acceptor complementarity again seems to favor a packing mode that is inefficient. This is seen most readily by comparing the observed and predicted packing efficiencies of the 1:1 cocrystals with the least-squares lines established for hydrogen-bonded and non-hydrogen-bonded crystals (Figure 8). As anticipated by the above discussion, successive addition of methylene groups to the dinitrile decreases the value of D_e more rapidly than predicted from the relationships for either of the other sets of data.[64] Perhaps most importantly, the extrapolated value for the 1:1 complex of suberonitrile/urea (labeled 6 (1:1)(calc)) has a D_e value that is only 93.6% as large as the one predicted by the least-squares line for hydrogen-bonded crystals. This places the predicted packing efficiency of this complex among the lowest 15% of the hydrogen bonded structures in this survey. The inclusion compound that is actually formed lies almost exactly on the line for the hydrogen-bonded structures.

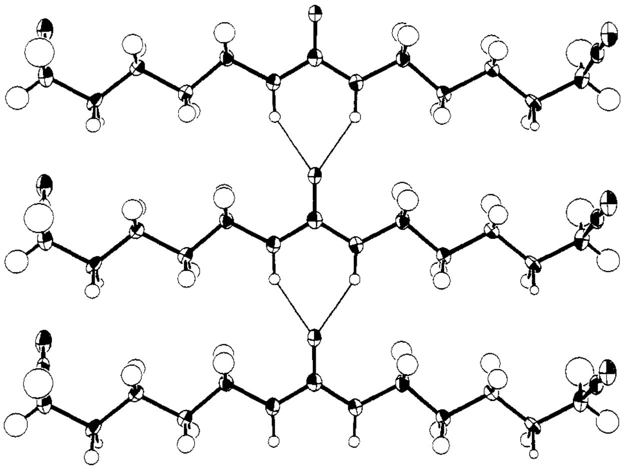

Figure 9. ORTEP[10] diagram showing hydrogen-bonded ribbon structure of compound 4. (Ellipsoids are drawn at the 50% probability level.) The *c* axis is vertical, and the main chain lies close to the (150) plane. Note the *gauche* conformation of the terminal nitrile group.

Template-Directed Engineering of Layered Complexes. Although the foregoing discussion points strongly to packing efficiency as the key to understanding the switch from layer to channel, the issue is clouded somewhat by the fact that the two lowest members of the inclusion compound series are commensurate structures. Nevertheless, the fact remains that 1:1 complexes of longer chain nitriles and urea are inaccessible. Since one goal of this work is to find ways of engineering layered systems, it became clear that in order to form layered systems of longer chain dinitriles and urea, the dinitrile would have to be "preorganized" into the correct packing arrangement. One approach is to insert the urea moiety into the middle of the dinitrile, in the hopes that the $C(4)[R_2^1(6)]$ translation motif would generate a ribbon of hydrogen-bonded dinitriles that would be preorganized for complexation with urea. This approach allows the desired flexibility of chain length for the dinitriles and thus allows formation of polar layers via complexation. Our work with bis(5-cyanopentyl)urea (4) and its complex with urea (4/urea) shows that this strategy is a viable one.

Crystal Structure of Bis(5-cyanopentyl)urea (4) and Its 1:1 Complex with Urea. Although the crystal structure of 4 (without urea) exhibits the ribbon-like array of hydrogen-bonded urea molecules and the concomitant 4.6-Å axis repeat (along *c*) that was expected for the $C(4)[R_2^1(6)]$ translation motif (Figure 9), this was one of the only features of the structure that was readily predicted from molecular models. Unlike the 1:1 complexes, this molecular crystal does not contain simple, flat layers. Instead, the dialkylurea molecules exist in chiral conformations containing 2-fold rotation axes along the carbonyl groups. The chirality is generated by *gauche* conformations at the chain ends that allow the nitrile groups to mesh well with each other. In this orthorhombic structure (space group $P2_12_12$), the hydrogen-bonded ribbons stack

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(62) With ID = 1 for our data and ID = 2 for Gavezzotti's data (no intermolecular hydrogen bonds), the multiple regression gave the following for (df = 3, 165). z(ave): β_1 = 0.0498(66), pF = 56.42, p = 0.0001; ID: β_2 = 0.0028(187), pF = 0.0226, p = 0.8808; IDz(ave): β_3 = 0.0007(43), pF = 0.0284, p = 0.8664.

(63) Many of the most loosely packed structures in our survey of hydrogen-bonded compounds were amides that contained the typical 5.1-Å short axis. For cases in which interleaving of groups is not possible, this large separation keeps molecules from packing efficiently.

(64) Because the cell constants were measured at different temperatures (3/urea = 233 K, 2/urea = 253 K, 1/urea = 296 K) the observed slope (0.0748) is even shallower than it would have been otherwise.

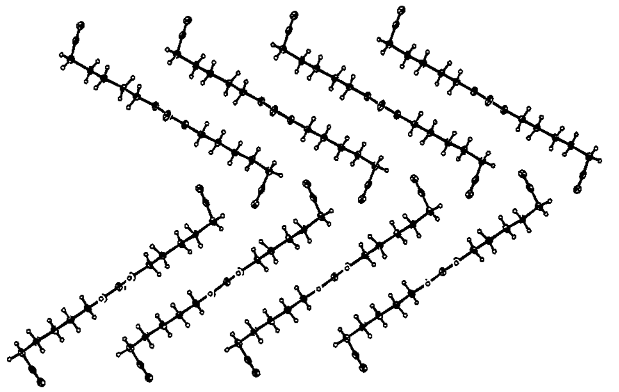

Figure 10. ORTEP[10] diagram (50% probability ellipsoids) of compound 4 showing herringbone packing pattern and interdigitation of *gauche* nitriles from adjacent layers. In this view along the (2-fold) *c* axis, the *a* axis is horizontal, and the 2-fold screw axes along *a* and *b* are evident.

to form layers along the *a* axis (Figure 10). These layers are related by 2-fold screw axes (along *a* and *b*) to give a familiar herringbone pattern[65] in which the alkyl chains within the alternating layers lie close to the (150) and $(1\bar{5}0)$ planes. At the interface between these layers (the (010) plane), the nitrile groups are twisted to be *gauche* to the alkyl chains that bear them ($\angle C_6–C_7–C_8–C_9 = 62.5°$). This conformation allows the layers to interdigitate in such a way that the nitrile–nitrile interactions are moderately favorable (see Tables 7 and 8). Since the *anti* and *gauche* conformers of aliphatic nitriles are thought to be within 1 kcal mol^{-1} of each other,[66] the conformational penalty for this torsion is not large enough to preclude it.[67]

Cocrystals of 4/urea can be formed either from methanol solution or by grinding together a 1:1 mixture of urea and 4.[6] Powder X-ray diffraction shows that formation of the 1:1 cocrystal is essentially complete after less than 10 min of grinding and that the cocrystal formed by grinding is the same as that grown from solution. Just as expected from the structures of 1–3/urea, the 1:1 cocrystal of 4/urea contains highly planar dinitriles that are hydrogen bonded to the urea molecules (Figure 11). The chain length of the dialkylurea and the hydrogen-bonding requirements of the nitrile and urea give rise to polar layers that lie in the $(40\bar{2})$ planes of this $P2/n$ crystal. The separation of 3.43 Å between these layers is nearly identical to the separation in 1/urea, but just as with that system, the layers alternate directions along *b* to form a centrosymmetric cocrystal.

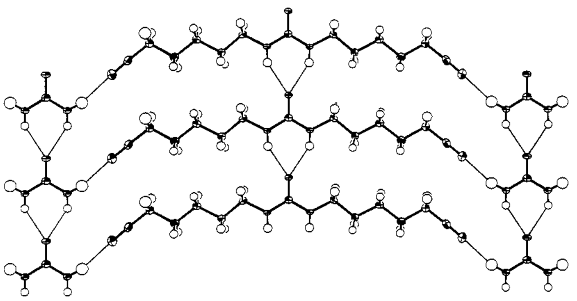

Figure 11. ORTEP[10] diagram (50% probability ellipsoids) showing the layer structure of 4/urea. The *b* axis is vertical, and this polar hydrogen bonded sheet lies close to the $(40\bar{2})$ plane of the crystal.

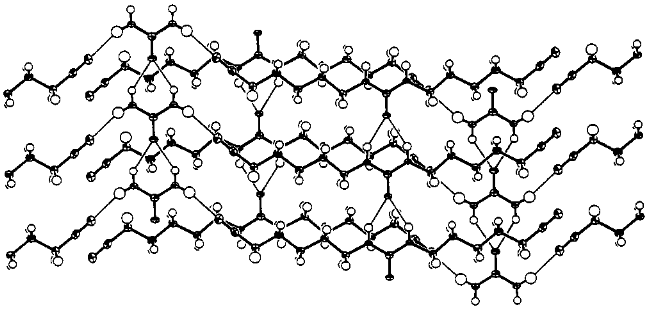

Figure 12. ORTEP[10] diagram showing interlayer stacking in 4/urea. Note the antiparallel alignment of nitriles in adjacent layers. Ellipsoids are drawn at the 50% probability level.

We were encouraged to find that the interlayer packing of 4/urea could be understood in terms of the same sorts of interactions observed for the simpler systems described above. Inspection of Figure 12 shows that adjacent layers are aligned so as to generate antiparallel nitrile dimers of high stability. According to the calculational method used above, these dimers lie within 0.3 kJ mol^{-1} of the type 2 dimer observed in 1/urea (see Tables 7 and 8). In addition to the nitrile–nitrile contact, each nitrile is flanked on its opposite side by the urea portion of the dialkylurea in a third layer. Similar interlayer interactions are expected for lower and higher homologues in the same series, but the putative stability of the "crisscross" dimer (type 3 in 2/urea) lends some measure of unpredictability to the interlayer stacking of these 1:1 cocrystals.

Prospects for Template-Directed Design of Other Cocrystals. Given an understanding of the packing efficiency constraints and the hydrogen bonding preferences of the dinitrile–urea systems, it should be possible to engineer a variety of different cocrystals containing layers of the desired polarity. Prediction of the interlayer interactions is obviously much more difficult, but the steps taken here provide at least a starting point for further synthetic efforts. Elaboration of the template-directed design approach to aromatic systems is a realistic goal, but other modes of complexation can complicate matters significantly. Our recent crystal structure[68] of the 1:1 cocrystal of urea with bis(4-cyanophenyl)urea exhibits an alternative packing mode in which the urea molecules are no longer tethered to each other in the $C(4)[R_2^1(6)]$ translation motif. Instead, the *anti* hydrogens of urea are hydrogen bonded to the diaryl urea carbonyl while the *syn* hydrogens undergo the predicted hydrogen bonding to the nitrile. This packing arrangement, which is reminiscent of many of the structures reported by Peggy Etter,[18] exhibits the same hydrogen-bonding complementarity as in the other 1:1 complexes. In addition, however, it

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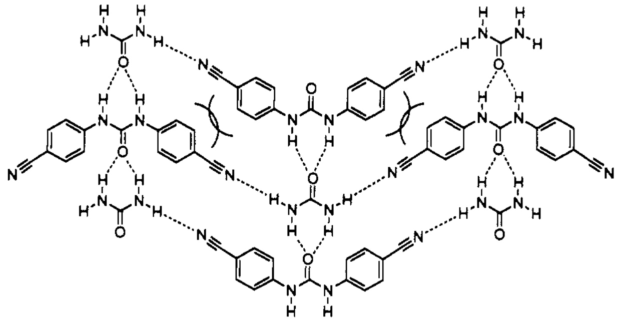
(65) For example, see: (a) Jaffe, A. B.; Malament, D. S.; Slisz, E. P.; McBride, J. M. *J. Am. Chem. Soc.* 1972, *94*, 8515–8521. (b) Filippakis, S. E.; Leiserowitz, L.; Schmidt, G. M. J. *J. Chem. Soc. B* 1967, 305–311. (c) Gleason, W. B.; Britton, D. *Acta Crystallogr.* 1983, *C39*, 1253–1255.

(66) (a) Hirota, E. *J. Chem. Phys.* 1962, *37*, 2918–2920. (b) Crowder, G. A. *J. Mol. Struct.* 1987, *158*, 229–236.

(67) A number of crystal structures exhibit nitriles in *gauche* conformations. For example, see: (a) Kitano, Y. *Acta Crystallogr.* 1983, *C39*, 1547–1549. (b) Pahor, N. B.; Attia, W. M.; Geremia, S.; Randaccio, L. *Ibid.* 1989, *C45*, 561–566. (c) Baumeister, U.; Hartung, H. *Ibid.* 1988, *C44*, 1295–1297. (d) Czerwinski, E. W.; Ponnuswamy, M. N. *Ibid.* 1988, *C44*, 862–865. (e) Yeh, M. C. P.; Knochel, P.; Butler, W. M.; Berk, S. C. *Tetrahedron Lett.* 1988, *29*, 6693–6696. (f) Elbasyouny, A.; Brugge, H. J.; von Deuten, K.; Dickel, M.; Knochel, A.; Koch, K. U.; Kopf, J.; Melzer, D.; Rudolph, G. *J. Am. Chem. Soc.* 1983, *105*, 6568–6577. (g) Our structure of suberonitrile/urea[39] consists of a mixture of *gauche* conformers at 103 K.

(68) To be published. Crystal data for this complex is given here: $C_{15}H_{10}N_4O{\cdot}CH_4N_2O$, monoclinic, space group $C2/c$ ($Z = 4$) $a = 12.962(4)$, $b = 9.240(3)$, $c = 14.514(5)$ Å, $\beta = 119.33(1)°$, $V = 1515.45$ Å^3 at −170 °C.



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provides more space for the aryl rings, which are not well-accommodated by the typically observed 4.58-Å repeat. As it stands, the aryl rings are twisted out of coplanarity with the urea groups by interactions with their neighbors (see I), but this interaction can be used to our advantage as we try to engineer crystals and cocrystals that conform to the packing mode exhibited for **4**/urea. Presently, these efforts are focused on the use of shape and dipole complementarity between layers to form polar crystals and cocrystals.

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Supplementary Material Available: Tables of crystal data for 287 compounds used in the analysis of packing density of crystals with and without hydrogen bonding, including structural drawings, cell volumes, space groups, molecular formulas, z(ave), D_e(obsd), and the value of D_e(calc) predicted by Gavezzotti's study, histograms showing the distribution of z(ave) values for hydrogen-bonded and non-hydrogen-bonded sets of crystals, powder diffractograms and peak assignments for **4**/urea formed by grinding and from solution, descriptions of X-ray data collection procedures, anisotropic Gaussian displacement parameters, bond distances and angles, and selected least-squares planes (107 pages); tables of observed and calculated structure factors (19 pages). Ordering information is given on any current masthead page.

Appendix

The following is a listing of compound numbers (in parentheses), names, and references for the crystal structures used in the packing efficiency study. They are organized by journal name.

From *Acta Chem. Scand. Ser. B* (57) D-Erythronic acid 3,4-carbonate (−150 °C): Moen, T. O. **1982**, *36*, 345–347.

From *Acta Crystallogr.* (5) *p*-Methyl-*m*-nitro-*N*-methylaniline: Chiaroni, A. **1971**, *B27*, 448–458. (7) γ-*o*-Nitroaniline: Dhaneshwar, N. N.; Tavale, S. S.; Pant, L. M. **1978**, *B34*, 2507–2509. (9) 4′-Nitro-2-biphenylamine: Sutherland, H. H.; Ali-Adib, Z. **1986**, *C42*, 432–433. (11) *p*-(*p*-Nitroanilino)phenyl isothiocyanate: Hardgrove, G. L., Jr.; Einstein, J. R.; Wei, C. H. **1983**, *C39*, 616–620. (12) 2,4-Dinitroaniline: Prasad, L.; Gabe, E. J.; LePage, Y. **1982**, *B38*, 674–675. (13) *N*-Methyl-2,6-dinitro-4-(trifluoromethyl)aniline: Brown, J. N.; Towns, R. L. R. **1977**, *B33*, 149–151. (19) *p*-Bromo-*m*-nitro-*N*-methylaniline: ref 5. (22) 2,3,4,6-Tetranitroaniline: Dickinson, C.; Stewart, J. M.; Holden, J. R. **1966**, *21*, 663–670. (24) 1,3-Diamino-2,4,6-trinitrobenzene (form I): Holden, J. R. **1967**, *22*, 545–550. (25) 1,3,5-Triamino-2,4,6-trinitrobenzene: Cady, H. H.; Larson, A. C. **1965**, *18*, 485–496. (26) 3,5-Diamino-2,4,6-trinitrophenol: Bhattacharjee, S. K.; Ammon, H. L. **1981**, *B37*, 2082–2085. (27) 5-Fluoro-2,4,6-trinitro-1,3-benzenediamine: Ammon, H. L.; Bhattacharjee, S. K.; Holden, J. R. **1982**, *B38*, 1851–1854. (30) (*p*-Methylphenoxy)acetic acid: Gopalakrishnan, T.; Rao, L. M. **1981**, *B37*, 2085–2087. (31) 2-Amino-1,3-oxazole: Albinati, A.; Marcon, M. G.; Traldi, P.; Cavoli, P. **1981**, *B37*, 2090–2092. (32) Procaine: Kashino, S.; Ikeda, M.; Haisa, M. **1982**, *B38*, 1868–1870. (33) 4-((Ethylthio)methyl)-5-methylimidazole: Bouwman, E.; Driessen, W. L. **1989**, *C45*, 1792–1794. (34) 3-Azetidinol: Gajhede, M.; Anthoni, U.; Christophersen, C.; Nielsen, P. H. **1989**, *B45*, 562–566. (35) Urea/5,5-diethylbarbituric acid 1:1 complex: Gartland, G. L.; Craven, B. M. **1974**, *B30*, 980–987. (37) Oxalic acid/urea 1:1 complex: Harkema, S.; ter Brake, J. H. M.; Helmholdt, R. B. **1984**, *C40*, 1733–1734. (38) Urea/oxalic acid 2:1 complex: Harkema, S.; Bats, J. W.; Weyenberg, A. M.; Feil, D. **1973**, *B29*, 143. (39) Phenol/urea 2:1 complex: MacDonald, A. L.; Murray, A.; Townsley, S. **1987**, *C43*, 676–678. (40) Quinol/urea 1:1 complex: Mahmoud, M. M.; Wallwork, S. C. **1975**, *B31*, 338–342. (41) 2,6-Lutidine/urea 1:1 complex: Lee, J. D.; Wallwork, S. C. **1965**, *19*, 311. (42) *N,N′*-Bis(3,4-dichlorophenyl)urea: Stankovic, S.; Andreetti, G. D. **1978**, *B34*, 3787–3790. (43) *N,N′*-Dicyclohexylurea: Coiro, V. M.; Giacomello, P.; Giglio, E. **1971**, *B27*, 2112–2119. (46) *N,N′*-Di-*n*-hexyl-4-oxoheptanediamide: Rueda, D. R.; Fayos, J. **1983**, *C39*, 766–768. (48) *N,N′*-Diphenylhexanediamide: Harkema, S.; Gaymans, R. J.; van Hummel, G. J. **1983**, *C39*, 385–387. (50) *N,N′*-Heptamethylenedibenzamide: Brisson, J.; Brisse, F. **1982**, *B38*, 2663–2667. (52) 5-Hydroxy-6-methyl-3,4-pyridinedimethanol (pyridoxime): Longo, J.; Franklin, K. J.; Richardson, M. F. **1982**, *B38*, 2721–2724. (53) Cyclohexyl-(4-pyridyl)methanol: Galesic, N.; Matijasic, I.; Leban, I. **1982**, *B38*, 2275–2277. (61) 2-Acetyl-4(3*H*)-quinazolinone: Chadwick, D. J.; Easton, I. W. **1983**, *C39*, 454–456. (68) 2,2′-(*p*-Phenylene)di-2-propanol: Koritsanszky, T.; Menczel, G. **1982**, *B38*, 1617–1619. (69) 1-(Isopropylamino)-3-(1-naphthylamino)propan-2-ol: Laguerre, M.; Leger, J.-M.; Merlet, D.; Colleter, J.-C.; Dubost, J.-P. **1982**, *B38*, 2291–2293. (72) α-Furildioxime (benzene solvate): Stenkamp, R. E.; Jensen, L. H.; Murphy, T. B.; Rose, N. J. **1982**, *B38*, 1169–1172. (73) 4-Acetamidobut-2-ene-4-olide: Ruzic-Toros, Z.; Kojic-Prodic, B. **1982**, *B38*, 1664–1666. (85) Parabanic acid/thiourea 1:1 complex: Weber, H.-P.; Craven, B. M. **1987**, *B43*, 202–209. (86) 6-Azauracil: Singh, P.; Hodgson, D. J. **1974**, *B30*, 1430–1435. (87) 2-Oxazolidinone: Turley, J. W. **1972**, *B28*, 140–143. (88) Uric acid: Ringertz, H. **1966**, *20*, 397–403. (89) Cyclopropanecarboxamide: Long, R. E.; Maddox, H.; Trueblood, K. N. **1969**, *B25*, 2083–2094. (90) *N*-Methylpropiolamide: Leiserowitz, L.; Tuval, M. **1978**, *B34*, 1230–1247. (91) *N*-Methyltetrolamide: *Ibid.* (92) *N*-Methylbenzamide: *Ibid.* (93) *N*-Methylcinnamide: *Ibid.* (94) *N*-Methylsorbamide: *Ibid.* (95) Cyanuric acid: Verschoor, G. C.; Keulen, E. **1971**, *B27*, 134–145.

(96) Tripropylacetamide: Cohen-Addad, C.; Grand, A. **1974**, *B30*, 186–192. (97) *N*-Propyltripropylacetamide: *Ibid.* (98) *N*-Propyldipropylacetamide: Cohen-Addad, C.; Grand, A. **1974**, *B30*, 1342–1346. (99) Dibutylacetamide: *Ibid.* (100) β-Pyrazine-2-carboxamide: Rø, G.; Sørum, H. **1972**, *B28*, 991–998. (101) δ-Pyrazine-2-carboxamide: Rø, G.; Sørum, H. **1972**, *B28*, 1677–1684. (102) α,α,α′,α′-Tetramethyl-β-ketoglutaric acid: Avitabile, G.; Ganis, P.; Martuscelli, E. **1969**, *B25*, 2378–2385. (103) 2-Acetyl-3-indazolinone: Smith, D. L.; Barrett, E. K. **1969**, *B25*, 2355–2361. (104) DL-Acetylleucine *N*-methylamide: Ichikawa, T.; Iitaka, Y. **1969**, *B25*, 1824–1833. (105) *N*-Acetyl-*N*′-phenylselenourea: Perez-Rodriguez, M.; Castro, L. **1969**, *B25*, 532–540. (106) 3′-*O*-Acetyl-4-thiothymidine: Saenger, W.; Suck, D. **1971**, *B27*, 2105–2112. (107) Adenosine: Lai, T. F.; Marsh, R. E. **1972**, *B28*, 1982–1989. (109) Allitol: Azarnia, N.; Jeffrey, G. A.; Shen, M. S. **1972**, *B28*, 1007–1013. (110) D-Iditol: *Ibid.* (111) D-Glucitol, form A: Park, Y. J.; Jeffrey, G. A.; Hamilton, W. C. **1971**, *B27*, 2393–2401. (112) Xylitol: Kim, H. S.; Jeffrey, G. A. **1969**, *B25*, 2607–2613. (113) Glucitol/pyridine 1:1 complex: Kim, H. S.; Jeffrey, G. A.; Rosenstein, R. D. **1971**, *B27*, 307–314. (114) Ribitol: Kim, H. S.; Jeffrey, G. A.; Rosenstein, R. D. **1969**, *B25*, 2223–2230. (115) D-Mannitol, β-form: Berman, H. M.; Jeffrey, G. A.; Rosenstein, R. D. **1968**, *B24*, 442–449. (116) D-Mannitol, α′-form: *Ibid.* (117) Galactitol: Berman, H. M.; Rosenstein, R. D. **1968**, *B24*, 435–441. (118) *allo*-Purinol: Prusiner, P.; Sundaralingam, M. **1972**, *B28*, 2148–2152. (119) *p*-Aminobenzoic acid, α-form: Jarchow, V. O.; Kuhn, L. **1968**, *B24*, 222–224. (120) 2-Amino-5-bromotoluene: van der Meer, H. **1972**, *B28*, 3098. (121) DL-α-Aminobutyric acid, form A: Ichikawa, T.; Iitaka, Y. **1968**, *B24*, 1488–1501. (122) DL-α-Aminobutyric acid, form B: Ichikawa, T.; Iitaka, Y. *Ibid.* (123) 2-Amino-3-chloropyrazine: Morrow, J. C.; Huddle, B. P. **1972**, *B28*, 1748–1753. (124) 4-Hydroxy-4-phenylhexanamide: Castellano, E. E.; Schpector, J. Z.; Carvajal, G. **1981**, *B37*, 284–286. (125) Pivaloyl-L-Prolyl-*N*′-isopropylglycinamide: Aubry, A.; Protas, J.; Boussard, G.; Marraud, M. **1980**, *B36*, 2822–2824. (126) (*tert*-Butoxycarbonyl)-D-alanyl-D-glutamic acid monohydrate: Aubry, A.; Boussard, G.; Marraud, M. **1981**, *B37*, 1474–1477. (127) Phenylurea: Kashino, S.; Haisa, M. **1977**, *B33*, 855–860. (128) Suberamide: Hospital, M.; Housty, J. **1966**, *20*, 368–373. (131) *N*,*N*′-Bis(β-chloroethyl)pimelamide: Ciajolo, M. R.; Pavone, V.; Benedetti, E. **1977**, *B33*, 1295–1297. (135) Adipamide: Hospital, M.; Housty, J. **1966**, *20*, 626–630. (136) *N*,*N*′-Ethylenedibenzamide: Palmer, A.; Brisse, F. **1980**, *B36*, 1447–1452. (138) *N*,*N*′-Tetramethylenedibenzamide: Harkema, S.; van Hummel, G. J.; Gaymans, R. J. **1980**, *B36*, 3182–3184. (140) *N*,*N*′-Hexamethylenedibenzamide: Pinneault, C.; Brisse, F. **1983**, *C39*, 1434–1437. (141) *N*,*N*′-Diacetylhexamethylenediamine: Bailey, M. **1955**, *8*, 575. (143) *N*,*N*′-Hexamethylenebispropionamide: Jensen, L. H. **1962**, *15*, 433–440. (145) *N*,*N*′-Octamethylenedibenzamide: Pineault, C.; Brisse, F. **1983**, *C39*, 1437–1439. (146) *N*,*N*′-(*p*-Phenylene)dibenzamide, form I: Harkema, S.; Gaymans, R. J. **1977**, *B33*, 3609–3611. (147) *N*,*N*′-Dibenzoyl-*p*-phenylenediamine, form II: Adams, W. W.; Fratini, A. V.; Wiff, D. R. **1978**, *B34*, 954–956. (148) *N*,*N*′-Diphenylterephthalamide: Harkema, S.; Gaymans, R. J.; van Hummel, G. J.; Zylberlicht, D. **1979**, *B35*, 506–508. (149) Bis(4-hydroxybutyl)-4,4′-methylenebis(phenylcarbamate): Forcier, P. G.; Blackwell, J. **1981**, *B37*, 286–289. (151) Dilactylamide: Mazzarella, L.; Pedone, C.; Puliti, R. **1973**, *B29*, 2699–2702. (152) Triphenylphosphine oxide (3,4-dichlorophenoxy)acetic acid (1:1 complex): Lynch, D. E.; Smith, G.; Byriel, K. A.; Kennard, C. H. L. **1993**, *C49*, 718–721. (153) (*S*)-(+)-Ibuprofen: Freer, A. **1993**, *C49*, 1378–1380. (154) *cis,anti,cis*-8-Methoxytricyclo[6.3.0.0]undecan-2,3-diol: Ianelli, S.; Nardell, M. **1993**, *C49*, 1388–1392. (155) 4-[(3-(Methoxyphenyl)imino)methyl]phenol: Yeap, G.-Y.; Teo, S.-B. **1993**, *C49*, 1396–1398. (156) 1,4-Diethyl-3,5-dimethoxy-1,4-dihydrobenzoic acid: Silva, A. L.; Maldonado, L. A. **1993**, *C49*, 1404–1406. (157) (*R*)-2-Hydroxy-3-iodo-2-methylpropyl 4-nitrobenzenesulfonate: Sun, G.; Fronczek, F. R.; Gandour, R. D. **1993**, *C49*, 1507–1509. (158) 1,3-(2,2-Dimethylpropyl)-2-[1-hydroxy-3-phenyl-(*E*)-2-propenyl]-2,3,3a,4,5,6,7,7a-octahydro-1*H*-1,3,2-benzodiazaphosphole 2-oxide: Koeller, K. J.; Rath, N. P.; Spilling, C. D. **1993**, *C49*, 1547–1549. (159) 2,4-Dinitrophenylhydrazine: Okabe, N.; Nakamura, T.; Fukuda, H. **1993**, *C49*, 1678–1680. (160) 2-Methyl-4-oxo-3*H*,5*H*-6-imidazo[3,4-*b*]-[1,2,4]triazepinecarbonitrile: Booth, B. L.; Pritchard, R. G.; Freitas, A. P.; Proenca, M. F. J. R. P. **1993**, *C49*, 1693–1694. (161) Ethyl 3-(5-amino-4-cyano1-imidazolylamino)-2-butenoate: Booth, B. L.; Pritchard, R. G.; Freitas, A. P.; Proenca, M. F. J. R. P. **1993**, *C49*, 1695–1696. (163) *b*-Cytidine: Ward, D. L. **1993**, *C49*, 1789–1792. (166) 1-Naphthoic acid: Fitzgerald, L. J.; Gerkin, R. E. **1993**, *C49*, 1952–1958. (167) 2-Naphthoic acid: *Ibid.* (168) N^{α}-Benzyloxycarbonyl-L-prolyl-C^{α}-methyl-D-phenylalanine: Valle, G.; Formaggio, F.; Crisma, M.; Toniolo, C.; Kamphitis, J. **1993**, *C49*, 2003–2005. (169) *cis,transoid,cis*-7,8-Dihydroxytricyclo[7.5.0.0^{2,8}]tetradec-1-yl acetate: Ianelli, S.; Nardelli, M.; Bellitti, D. **1993**, *C49*, 2022–2027. (170) *cis,cisoid,cis*-8,9-Dihydroxytricyclo[6.5.0.0^{2,7}]tridec-2-yl acetate: *Ibid.* (171) 2-(2,3-Dimethoxyphenyl)-6-hydroxy-4*H*-1-benzopyran-4-one: Wallet, J.-C.; Gaydou, E. M.; Molins, M. M. F.; Miravitlles, C. **1993**, *C49*, 2030–2032. (172) Methyl-4-(benzylamino)-6-methyl-2-oxo-3-cyclohexene-1-carboxylate: Kubicki, M.; Codding, P. W. **1993**, *C49*, 2045–2046. (173) Ethyl 2-cyano-3-(4-hydroxy-3-methoxyphenyl)propenoate: Jainqui, S.; Genbo, S.; Youping, H. **1993**, *C49*, 2137–2139. (174) 10-Hydroxy-4-methoxy-5,9-dimethyltricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-13-one: Soriano-Garcia, M.; Iribe, R. V.; Covarrubias, A.; Olguin, J. S.; Maldanado, L. A. **1993**, *C49*, 2140–2141. (175) *N*,*N*′-(1,2-Ethynylenedi-2,2′-phenylene)bis(4-methylbenzenesulfonamide): Davis, D. S.; Stubbs, J. L.; Fronczek, F. R.; Gandour, R. D. **1993**, *C49*, 2148–2149. (176) (*E*)-Acetophenone oxime/benzoic acid (1:1 complex): Maurin, J. K.; Winnicka-Maurin, M.; Paul, I. C.; Curtin, D. 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Structures reported in this paper: (191) Bis(5-cyanopentyl)urea. (194) Glutaronitrile/urea (195) adiponitrile/urea. (196) Pimelonitrile/urea. (197) Bis(5-cyanopentyl)urea/urea.

Unpublished structures from this laboratory: (188) 1,6-Dicyanohexane/urea. (192) Bis(4-cyanophenyl)urea/urea (1:1). (193) Bis(3-cyanophenyl)urea/urea (1:1).