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The Application of the 2-Amino-4-Pyrimidones to Supramolecular Synthesis.

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Abstract: A strategy for preparation of two dimensional layered compounds is introduced. This strategy explores the possibility of using the 2-amino-4(*H*)-pyrimidone ring system as a host for dicarboxylic acids guests. This strategy is successful for the orientation of adipic acid into a two dimensional β-network with a molecular repeat distance of 6.5 Å.

Supramolecular structures or molecular assemblies are fundamental to biological function and are responsible for all the properties of known materials. Advances in biology and materials science will require the preparation of new supramolecular structures. A significant challenge for modern chemistry is the development of strategies for the preparation of designed supramolecular structures. Meeting this challenge will expand and enrich the discipline of chemistry as well as have important applications in biotechnology and materials science.

Compared to the preparation of designed molecular structures, the preparation of designed supramolecular structures is a more difficult problem.[1] Whereas the atoms in a molecule are held together by strong covalent bonds, the molecules in a supramolecular structure are held together by numerous and relatively weak forces such as hydrogen bonding and van der Waals interactions. Also, other factors such as molecular shape and symmetry play a role in determining supramolecular structure.

Supramolecular synthesis is currently an active area of research[2] and strategies for the preparation of designed supramolecular structures are beginning to develop. In our own work,[3] we have focused on the development of strategies for the preparation of low dimensional solids[4] such as one dimensional rods and two dimensional layers.[5] An essential element of our strategies is the identification of molecular features that form predictable solid state structures. Examples are the N,N'-disubstituted urea and dicarboxylic acid functionalities. We have observed that these functionalities reliably self assemble into one dimensional α-networks. The combination of two functional groups capable of self-assembling into orthogonal α-networks results in a molecule with a high probability of producing a two dimensional β-network and a layered solid. We have observed that this is a simple yet powerful strategy for the preparation of layered solids.

Generalization of this strategy requires other functional groups capable of producing predictably supramolecular structures. Analogs of the urea functionality are the 2-amino-4(1H)-pyridones and the, potentially

more versatile, 2-amino-4(1H)-pyrimidones (isocytosines). We have observed that the 2-amino-4(1H)-pyridone ring system is an excellent analog of mono substituted ureas, readily self-assembling into α-networks.[3c] In contrast to the ureas, which all have a molecular repeat distance of about 4.7Å, the analogous pyridones have repeat distances of about 6.7Å (Figure 1). The ability to control the molecular repeat distance is important in a number of applications such as topochemically controlled solid reactions.

Simple 2-amino-4(1H)-pyrimidones also self-assemble in an analogous manner as the 2-amino-4(1H)-pyridones. However, this latter ring system is more versatile because of the presence of the additional nitrogen atom (N-3)

Figure 1. The one dimensional self-assembly of the 2-amino 4-pyridone and 4-pyrimidone ring systems into α-networks.

in the ring. This nitrogen atom along with the amino hydrogen atom produces a donor-acceptor functionality capable of self-dimerization or hydrogen bonding to other donor-acceptor functionalities such as acids and amides. This hydrogen bonding motif is illustrated by the solid state structure of some simple 2-amino-4(1H)-pyrimidones.[6]
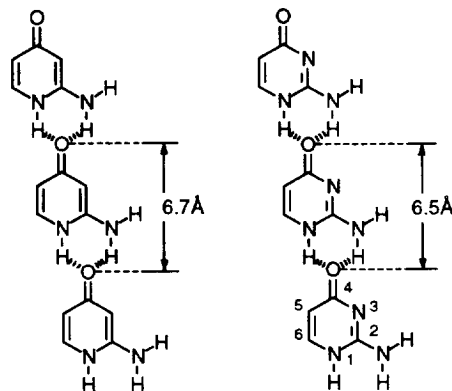
All that is required to apply the 2-amino-4(1H)-pyrimidone ring system for the formation of a β-network is the addition of a second functionality to the ring that can hydrogen bond to N-3 and the amino group. We have demonstrated that this is a successful strategy by the preparation of the 5-substituted propionic acid derivative **1**. Investigation of the crystal structure of this compound demonstrated it had self-assembled into a β-network and a layered solid.[6] These preliminary studies suggest the pyrimidine ring is a potentially useful heterocycle for supramolecular synthesis.

Scheme 1. Self-assembly a pyrimidone carboxylic acid derivative.[6]
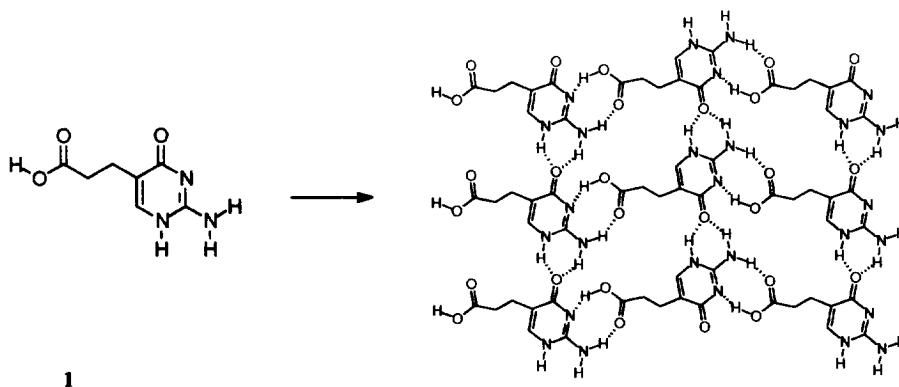
A goal of supramolecular synthesis is to control the orientation in the solid state of molecular functionalities possessing useful optical, electrical, mechanical or chemical properties. One strategy, for the preparation of a specific material, is to attach appropriate groups to a useful functionality such that they will
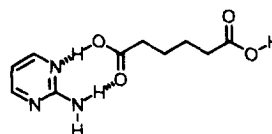
orient the molecular functionality into the desired orientation. Because of the molecular repeat distance of 6.5 Å, the 2-amino-4(1H)-pyrimidone ring system is potentially useful for orienting a triacetylene group for a topochemical polymerization.[7] An obvious approach to test this possibility would be to directly attach a triacetylene functionality to the 2-amino-4(1H)-pyrimidone ring. The general problem with this approach is that the molecular synthesis becomes relatively complex. An alternative approach is to use the 2-amino-4(1H)-pyrimidone ring to form a host-guest complex with a suitably substituted triacetylene derivative. We have found this approach to be remarkably successful using ureas, with a molecular repeat distance of 4.7 Å, to orient diacetylenes for topochemical polymerization.[8] It is of interest to evaluate the ability of the 2-amino-4(1H)-pyrimidone ring for the orientation of functionality by the formation of host-guest complex.

Carboxylic acids are well known to form co-crystals with 2-aminopyrimidine.[9] X-ray crystallography has revealed that a common and remarkably persistent structural feature of these co-crystals is the eight membered hydrogen bonded ring formed between the heterocycle and the carboxylic acid. For example, succinic acid forms a 1:1 complex with 2-aminopyridine whose crystal structure clearly demonstrates the formation of a cyclic hydrogen bonded complex.[9]
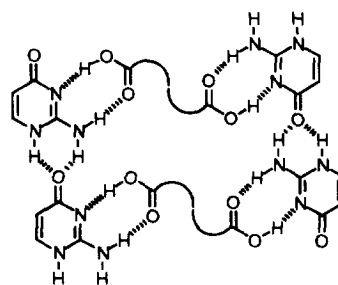
Figure 2. Previously observed 2-aminopyrimidine carboxylic acid co-crystal.[9a]

Encouraged by these results and our previous observation on 2-amino-4-pyrimidone 1, we investigated host-guest[10] formation between the 2-amino-4-pyrimidone ring system and some simple dicarboxylic acids in order to determine whether or not a two molecule approach would be successful for the orientation of a guest molecule with a molecular repeat distance of of 6.5 Å (Figure 3). Using pyrimidone derivatives with succinic, glutaric and adipic acid produced the host-guest shown in Table 1. These complexes were formed by slow evaporation of the reactants in methanol.

Figure 3. Designed host-guest complex.

The stoichiometry was determined by dissolving the co-crystal in a suitable solvent, such as DMSO-d_6, and analyzing the ratio of the diacid to the 2-amino-4-pyrimidone. Except for the host-guest complex of 6-methyl-2-amino-4-pyrimidone with glutaric acid, all of these complexes formed in the ratio of two molecules of the host to one molecule of the guest, the stoichiometry predicted by Figure 3.
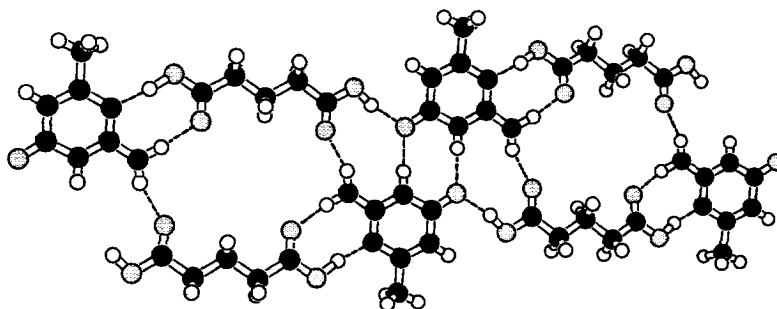
The results presented in Table 1 would indicate we were remarkably successful in the preparation of the host-guest complex shown in Figure 3. In order to obtain more direct information on the structures of these co-crystals we proceeded to determine their crystal structures using x-ray crystallography. We were successful growing crystals suitable for x-ray crystallography for five of the seven co-crystals shown in Table 1 (6-methyl-2-amino-4-pyrimidone (2) with glutaric acid and adipic acid and 6-ethyl-2-amino-4-pyrimidone (3) with succinic acid and glutaric acid and 6-phenyl-2-amino-4-pyrimidone (4) with adipic acid.

The designed hydrogen bonded motif (Figure 3) requires a 2:1 ratio of the host to guest molecules. The co-crystal of compound 2 and glutaric acid was unique being formed in a 1:1 ratio

Table 1. 2-Amino-4-pyrimidone/dicarboxylic acid host/guestcomplexes.

Host	Guest	Ratio Host/Guest	melting point (°C)
(structure) **2**	succinic acid	2:1	230-3
2	glutaric acid	1:1	203-6
2	adipic acid	2:1	276-8
(structure) **3**	succinic acid	2:1	215-7
3	glutaric acid	2:1	238-40
3	adipic acid	2:1	217-8
(structure) **4**	adipic acid	2:1	293-5

of host to guest. This ratio is inconsistent with the hydrogen bonding motif present in Figure 3 and we anticipated that this hydrogen bonded motif was not formed. Inspection of the crystal structure (Figure 4) of this co-crystal demonstrates that the heterocycle is present as the (3H) tautomer and not as the (1H) tautomer required by Figure 3. Although one of the anticipated eight membered ring hydrogen bond motifs formed between the carboxylic acid and the aminopyrimidine functionality, the hydrogen bonds formed by the other two acidic hydrogens were not predicted.

Figure 4. The crystal structure of 6-methyl-2-amino-4(3H)-pyrimidone (2) and glutaric acid co-crystal.

The ratio of the co-crystal formed between compound **2** and adipic acid has the correct stoichiometry (2:1) for the designed solid shown in Figure 3 but inspection of its crystal structure (Figure 5) also demonstrates that it is the (3H) tautomer present and not the required (1H) tautomer. Interestingly, the hydrogen bond patterns shown in Figure 3 are similar to those in this crystal structure. There is a pair of N-H groups chelating the pyrimidine carbonyl oxygen atom and there is an eight membered hydrogen bonded ring formed by the carboxylic acid and the aminopyrimidine ring. However, the structure is formed using the (3H) tautomer rather than the (1H) tautomer shown in Figure 3. This results in the primary α-network, formed by the pyrimidine ring, being kinked instead of the linear array shown in Figure 3. The final structure is a two dimensional β-network (Figure 5).

Figure 5. The crystal structure of 6-methyl-2-amino-4(3H)-pyrimidone (2) and adipic acid co-crystal.
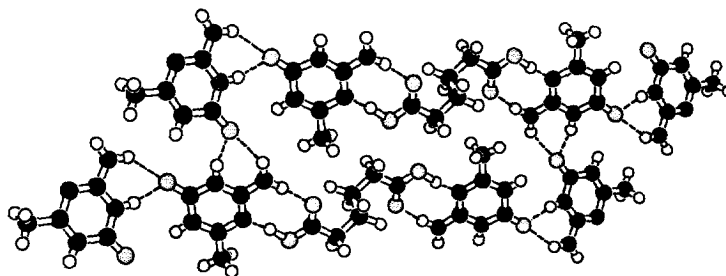
In contrast to pyrimidone **2**, a co-crystal of pyrimidone **3** and succinic acid, suitable for crystallography, was obtained. This co-crystal also had the required stoichiometry for the designed structure shown in Figure 3, but inspection of the crystal structure (Figure 6) demonstrated that the heterocycle, consistent with the above two structures, was again present as the (3H) isomer. Although none of the hydrogen bonded motifs shown in Figure 3 are present in this structure, the ones found are all are reasonable and precedented in the literature.
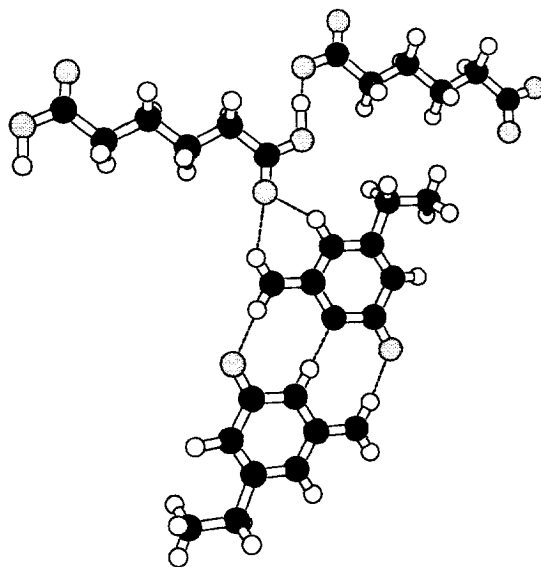
Figure 6. The crystal structure of 6-ethyl-2-amino-4(3H)-pyrimidone (3) and succinic acid co-crystal.
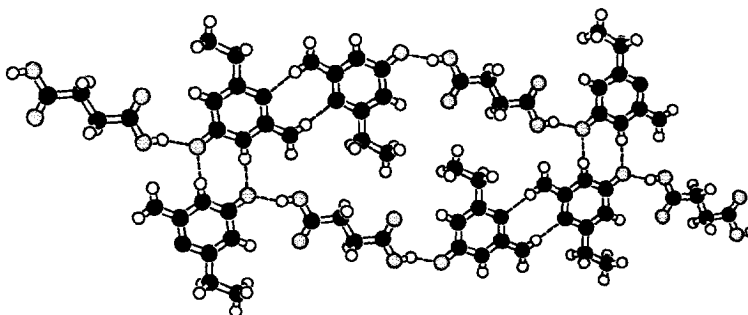
Compound **3** and compound **2** both formed co-crystals with adipic acid in a 2:1 stoichiometry. These two heterocycles have identical hydrogen bond donors and acceptors. Since they differ only by the substituent at position six, methyl vs. ethyl, similar hydrogen bonding motifs in the solid state could be anticipated. This proved not to be the case. The crystal structure of the adipic acid co-crystal with **3** demonstrates that proton transfer has occurred from one of the carboxylic acid groups to the heterocyclic nitrogen of one of the 2-amino-4-pyridones (Figure 7). This protonated heterocycle forms a triple hydrogen bond motif with a neutral heterocycle.[11] Conversely, the carboxylate group forms a hydrogen bond with the carboxylic acid of an adjacent molecule. Both of these hydrogen bonded motifs between donors and acceptors with the same acidity constants would be anticipated to be very strong. In both cases the hydrogen atom is disordered about a crystallographic inversion center, meaning that all of the pyrimidines as well as all of the carboxyl groups are identical in the crystallographic refinement. The remaining two proton donors of the heterocycle form more classical hydrogen bonds to the carbonyl of the carboxyl group.

Attempts were made to produce co-crystals of compound **4** with either succinic, glutaric or adipic acid. Only co-crystals with adipic acid suitable for x-ray crystallography

Figure 7. The crystal structure of 6-ethyl-2-amino-4-pyrimidone (3) and adipic acid co-crystal.

Figure 8. The crystal structure of 6-phenyl-2-amino-4(1H)-pyrimidone (4) and adipic acid co-crystal.
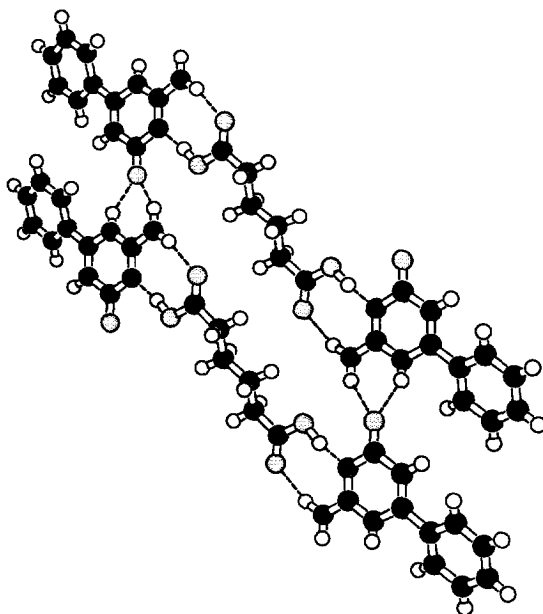
could be obtained. Much to our surprise, crystal structure of this co-crystal (Figure 8) proved to be the designed host-guest complex shown in Figure 3. The aminopyrimidine formed an α-network similar to the one shown in Figure 1 with a molecular repeat distance of 6.51 Å. This molecular scaffold serves as a host for an array of adipic acid guest molecules. The final α-network has a ribbon like structure with $P\overline{1}$ rod symmetry similar to that shown in Figure 3.

The 2-aminopyrimidine ring system readily forms co-crystals with dicarboxylic acids with an almost exclusive 2:1 stoichiometry. In the crystal structures that could be studied it is remarkable is that this ring system does not use the same hydrogen bonding motifs to form these 2:1 complexes. This observation is in sharp contrast to co-crystals of the 2-aminopyrimidine ring system with carboxylic acids where the solid state hydrogen bonding patterns are remarkably consistent. One obvious problem with the 2-amino-4-pyrimidone ring system is the accessibility of two tautomers. In aqueous solution the (1H) and (3H) tautomers are believed to be present in nearly a 1:1 ratio[12] with the (3H) tautomer becoming more favorable in dipolar aprotic solvents. Since the environment of a crystal may be more like a dipolar aprotic solvent, the dominance of the (3H) tautomer in the above structures would be appear to be consistent with this observation. Although the energy difference between the two tautomers must play a role in the kinetics of crystal formation, it would be anticipated to be relatively small compared to the total energy of the lattice forces.

Another factor that can play a role in the solid state structure of co-crystals of 2-aminopyrimidine ring system and dicarboxylic acids is proton transfer between the carboxylic acid and heterocyclic base. When this occurs it would be anticipated that there is a lower probability of producing the designed structure. Previous investigations[13] of co-crystals between acids and bases have considered that a pKa difference of about 3 is required to form an ionic complex (proton transfer from the acid to base). The relevant pKa values for the carboxylic acids are succinic acid = 4.16, glutaric acid = 4.31 and adipic acid = 4.43. The pKa values for the 6-methyl and 6-ethyl 2-amino-4-pyrimidinones have not been determined. The pKa for the 2-amino-4-pyrimidinone has been reported to be 4.01.[14] These data would indicate that ionic complex should not form in the solid state and yet proton transfer did occur between adipic acid and 6-ethyl-2-amino-4-pyrimidone (3, Figure 7). Furthermore, proton transfer did not occur between adipic acid and 6-methyl-2-amino-4-pyrimidone (2, Figure 6). Since these two heterocycles must have pKas similar to each other and 2-amino-4-pyrimidone, the relative acidities of the acid and base determined in water cannot be playing a dominant role on the solid state structure.

In summary, heterocycles will continue to play an important role in supramolecular synthesis. They can have a high density of hydrogen bond donors and acceptors along with a relatively simple conformational energy surface. These two factors both facilitate the development of strategies for the preparation of designed solids. This study demonstrates that the application of heterocycles to supramolecular synthesis can be a difficult problem. The high density of hydrogen bond donors and acceptors can result in numerous hydrogen

bond motifs.[15] However, nature also has the same problems and effectively uses similar heterocycles for supramolecular synthesis. With more knowledge we will have a greater understanding of the "rules" of supramolecular chemistry and will become more successful in the preparation of designed supramolecular structures.

Table 2. Crystallographic Data

Co-crystal	2+glutaric acid	2+adipic acid	3+succinic acid	3+adipic acid	4+adipic acid
a (Å)	5.048(2)	13.050(3)	5.015(2)	8.236(2)	6.510(1)
b (Å)	8.024(3)	7.589(2)	8.022(2)	12.351(2)	8.273(2)
c (Å)	15.239(7)	9.892(2)	12.000(2)	4.949(1)	12.267(3)
α (deg)	84.13(3)			84.85(2)	98.13(2)	85.28(2)
β (deg)	88.99(3)	107.07(2)	78.31(2)	97.95(2)	84.74(2)
γ (deg)	82.56(3)		74.45(2)	90.20(2)	71.26(2)
Volume (Å³)	608.88	936.58	455.14	493.38	621.98
Space Group	$P\bar{1}$	$P2_1/c$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
Z	2	2	1	1	1
Reflections collected	1764	1861	1679	1284	1608
Observations (I>3σ)	1254	1166	1477	662	929
R	0.056	0.060	0.039	0.037	0.045
Rw	0.069	0.074	0.052	0.036	0.046
Ratio (¹HNMR)	1:1	2:1	2:1	2:1	2:1
M. P. (°C)	203-206	276-278	215-217	217-218	293-295

EXPERIMENTAL SECTION

X-ray Diffraction Studies. Crystals were obtained as described below, selected and mounted on glass fibers using epoxy cement. The crystals were optically centered on an Enraf Nonius CAD4 diffractometer and X-ray data was collected using graphite-monochromated Mo radiation. The unit cells were determined by a least squares analysis of the setting angles of 25 high angle reflections. Data was collected as indicated in Table 2, and the structures were solved and refined using the TEXSAN crystallographic program package of the Molecular Structure Corporation. All refinements were routine except for the co-crystal of **3** and adipic acid. Two hydrogen atoms in the structure (Figure 7) were disordered about a center of symmetry.

6-Methyl-2-amino-4(3H)-pyrimidone (2) and succinic acid. Succinic acid (0.0118 g, 0.1 mmol) and 6-methyl-pyrimidone (0.0125 g, 0.1 mmol) was dissolved in hot methanol following by slow evaporation. The colorless co-crystals were formed in a 1:2 ratio (by ¹H-NMR): Mp 230-233 °C; ¹H-NMR (250 MHz, DMSO-d_6) : δ 1.97 (3H, s), 2.41 (2H, s), 5.38 (1H, s), 6.48 (2H,br s); IR (KBr pellet) 3344(NH), 3104(=C-H), 2924(CH), 1711, 1666 cm⁻¹(C=O).

6-Methyl-2-amino-4(3H)-pyrimidone (2) and glutaric acid. Dissolve glutaric acid (0.0132 g, 0.1 mmol) and 6-methyl-pyrimidone (0.0125 g, 0.1 mmol) in hot methanol following by slow evaporation. Colorless co-crystals were formed in a 1:1 ratio (by ^{1}H-NMR): Mp 203-206°C; ^{1}H-NMR (250 MHz, DMSO-d$_6$) δ 1.69 (2H, m), 1.98 (3H, s), 2.21 (4H, t), 5.38 (1H, s), 6.50 (2H,br s); IR (KBr pellet) 3337 (NH), 3151(=C-H), 2920 (CH), 1713, 1660 cm^{-1} (C=O).

6-Methyl-2-amino-4(3H)-pyrimidone (2) and adipic acid. Adipic acid (0.0146 g, 0.1 mmol) and 6-methyl-pyrimidone (0.0125 g, 0.1 mmol) was dissolved in hot methanol following by slow evaporation. The colorless co-crystals were formed in a 1:2 ratio (by ^{1}H-NMR): Mp 276-278°C; ^{1}H-NMR (250 MHz, DMSO-d$_6$) δ 1.49 (2H, s), 1.96 (3H, s), 2.20 (2H, s), 5.38 (1H, s), 6.45 (2H,br s); IR (KBr pellet) 3440 (NH), 3170 (=C-H), 2905(CH), 1679 cm^{-1} (C=O).

6-Ethyl-2-amino-4(3H)-pyrimidone (3) and succinic acid. Succinic acid (0.0118 g, 0.1 mmol) and 6-ethyl-pyrimidone (0.0139 g, 0.1 mmol) was dissolved in hot methanol following by slow evaporation. Colorless co-crystals were formed in a 1:2 ratio (by ^{1}H-NMR): Mp = 215-217°C; ^{1}H-NMR (300 MHz, DMSO-d$_6$) δ 0.974 (3H, t), 2.15 (2H, q) 2.32 (2H, s) 5.28 (1H, s), 6.37 (2H, br s); IR(KBr pellet) 3441, 3341 (NH), 3071(=C-H), 2902(CH), 1676, 1721 cm^{-1} (C=O).

6-Ethyl-2-amino-4(3H)-pyrimidone (3) and glutaric acid. Glutaric acid (0.0132 g, 0.1 mmol) and 6-ethyl-pyrimidone (0.0139 g, 0.1 mmol) was dissolved in hot methanol following by slow evaporation. The colorless co-crystals were formed in a 1:2 (by ^{1}H-NMR): Mp 238-240 °C; ^{1}H-NMR (250 MHz, DMSO-d$_6$) δ 1.06 (3H, t), 1.69 (1H, quin), 2.23 (4H, m), 2.49 (1H, s) 5.38 (1H, s), 6.50 (2H, br s) ppm. IR (KBr pellet) 3340(NH), 3159(=C-H), 2974, 2948 (CH), 1702, 1663 cm^{-1} (C=O).

6-Ethyl-2-amino-4-pyrimidone (3) and adipic acid. Adipic acid (0.0146 g, 0.1 mmol) and 6-ethyl-pyrimidone (0.0139 g, 0.1 mmol) was dissolved in hot methanol following by slow evaporation. The colorless co-crystals were formed in a 1:2 ratio (by ^{1}H-NMR): Mp = 217-218°C. ^{1}H-NMR (250 MHz, DMSO-d$_6$) : δ 1.07 (3H, t), 1.49 (2H, s), 2.25 (4H, m) 5.38 (1H, s), 6.49 (2H, br s) ppm. IR (KBr pellet) : 3420, 3384 (NH), 3180 (=C-H), 2922 (CH), 1701, 1689 cm^{-1} (C=O).

6-Phenyl-2-amino-4(1H)-pyrimidone (4) and adipic acid. Adipic acid (0.073 g, 0.5 mmol) and 6-phenyl-pyrimidone (0.0186 g, 0.1 mmol) was dissolved in hot methanol followed by slow evaporation. The colorless co-crystals were formed in a 1:2 ratio (by ^{1}H-NMR): Mp = 293-295°C. ^{1}H-NMR (250 MHz, DMSO-d$_6$) : δ 1.49 (2H, br s), 2.20 (2H, br s), 6.10 (1H, s), 6.59 (2H, s), 7.44 (3H, br s), 7.92 (2H, br s); IR (KBr pellet) : 3358, 3242(NH), 3132 (=C-H), 2921 (CH), 1689, 1650 cm^{-1} (C=O).

References and Footnotes

(1)   The ability to predict supramolecular structure from molecular structure is, in general, an unsolved problem (Maddox, J. *Nature* **1988,** *335,* 201). Fortunately, useful supramolecular structures do not require complete control of supramolecular structure, just control of certain molecular functionalities.

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(10) When two molecules of similar complexity are involved in a host-guest complex it can be difficult to identify the host and the guest. Because the α-network of the heterocycle is intact its supramolecular structure is the more complex component and it is more appropriate to call it the host and the dicarboxylic acid the guest. If the α-network is not present then it is more appropriate to call the complex simply a co-crystal.

(11) There are a few examples of this hydrogen bond motif reported in the literature. For example, see reference 6 and previous work cited. Also this motif has recently been observed in the crystal structure of a parallel-stranded duplex of a deoxycytidylyl-(3'-5')-deoxycytidine analogue (Egli, M.; Lubini, P.; Bolli, M.; Dobler, M.; Leumann, C. *J. Amer. Chem. Soc.* **1993**, *115*, 5855-5856).

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(15) For example, a molecule with five different hydrogen bond donors and five different hydrogen bond acceptors can theoretically result in 120 different hydrogen bond motifs.