Design of molecular solids: utility of the hydroxyl functionality as a predictable design element

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In order to design a new molecular solid one needs a library of functional groups that will self assemble into predictable structural patterns. To test the utility of the hydroxyl group for this purpose, a series of ureas and oxalamides with side-arm substituents containing the hydroxyl functionality were prepared. X-Ray crystallographic analysis of five such compounds revealed a variety of structural features indicating that the hydroxyl group alone was not a predictable design element. However, when a pair of co-crystals of dihydroxyl substituted oxalamides with dipyridyl compounds were prepared, supramolecular structures were prepared consistent with predictions. This suggests that the hydroxyl group coupled to a pyridine hydrogen-bond acceptor is a useful design element for the preparation of molecular networks.

A design leading to the successful preparation of a new molecular solid depends upon an understanding of the intermolecular forces between the constituent molecules of the solid. To prepare a crystal containing a supramolecular structure of interest one must first identify molecular functionalities that will generate predictable intermolecular interactions.[1] One must then synthesize and crystallize a molecule or combination of molecules containing these identified structure-generating functionalities. The success of the preparation not only depends upon the persistence of these intermolecular interactions, but also upon the compatibility of the interactions and the molecular packing with the rules of crystallographic symmetry.

We have attempted to develop a library of structure-generating functionalities that can be combined together in a single molecule to produce supramolecular features of interest,[2] most notably one-dimensional α-networks and two-dimensional β-networks.[3] Our library of functionalities includes the ureas and oxalamides which generate one-dimensional α-networks with predictable symmetries and intermolecular spacings. Dicarboxylic acids and diamides have been used to generate one-dimensional α-networks *via* a linear array of centrosymmetric dimerizations. Orthogonal combinations of two sets of α-network-generating functionalities generate two-dimensional β-networks. The β-network formed by the oxalamide of glycine, **1**, is shown in Fig. **1**. Work with various heterocyclic vinyl ureas has given similar results, but with a different range of possible intermolecular repeat distances.[4]

These studies show that single molecules that incorporate suitable functionalities can be effective for the preparation of designed supramolecular structures. Another, potentially even more powerful, strategy for the design and preparation of structures, is the use of a combination of molecules instead. An advantage of this approach is that it is convergent at the supramolecular level and requires considerably less molecular synthesis for the preparation of complex structures. The major difficulty of this approach is that it requires more sophistication at the supramolecular design step.

Using the pyridine–carboxylic acid hydrogen-bond interaction we have demonstrated that dicarboxylic acids and bipyridines reliably form co-crystals producing one-dimensional α-networks. A combination of this pyridine–carboxylic acid pair-wise interaction, with the urea and with the oxalamide functionality, was used successfully for the preparation of a variety of co-crystals containing two-dimensional β-networks. This co-crystal approach was employed to prepare layered solids of various diacetylenes with the proper orientation and spacing needed for a topochemical polymerization.[5]

The continued development of strategies for the preparation of designed supramolecular structures requires functional groups whose interactions can be predicted with a high degree of certainty. In this paper we evaluate the utility of the hydroxyl functionality as a predictable hydrogen-bonding unit. Alcohols and phenols are potentially of great interest as supramolecular building blocks. They are readily obtainable, and at first glance, the simple hydroxyl group would seem to be a useful hydrogen-bonding unit. However when it comes to

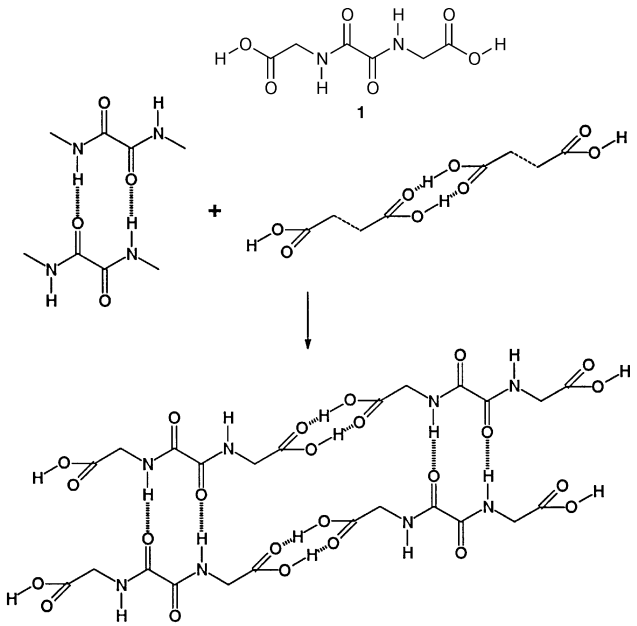


Fig. 1 Oxalamides and dicarboxylic acids can form self complementary hydrogen bonds and will independently generate one-dimensional α-networks. Molecules that contain both of these structure-generating functionalities will self assemble into two-dimensional β-networks. The specific β-network shown here is formed by the oxalamide of glycine, **1**

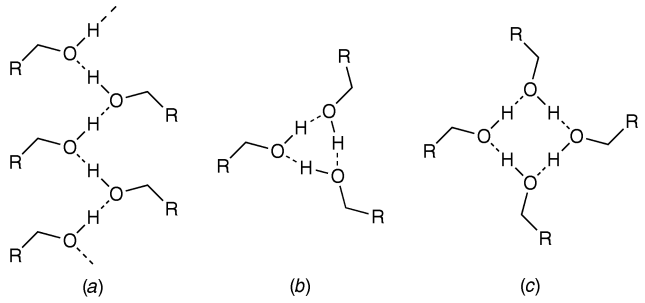


Fig. 2 Common supramolecular structures found in monoalchols. In (*a*) the alcohols form an α-network. Most commonly these α-networks form about a 2_1 screw axis, but many examples are also known with glide-plane symmetry. Similar examples about higher order, 3_1 or 4_1 axes are also known. In (*b*) and (*c*) the alcohols form discrete assemblies about a three- or four-fold symmetry axis. Simple dimers are not commonly found

crystallography, sometimes the simplest systems are quite complex. This is quite true when one examines the crystallography of alcohols.

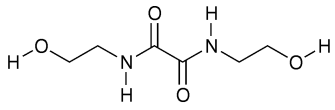
Brock and Duncan[6] have published an analysis of 'anomalous space-group frequencies for monoalcohols.' They found that the spatial requirements of the hydroxyl OH···O hydrogen bonds led to a disproportionately high number of chiral space groups, a larger than expected number of structures with high order axes and many structures with multiple molecules in the asymmetric unit. Hydroxyl groups were found to form either chains or high ordered rings. Trimers and tetramers were relatively common, Fig. 2, discrete dimers were not common.

Despite this warning from the literature about the complexity of hydroxyl hydrogen-bond associations we felt that the hydroxyl functionality could prove to be a useful element for supramolecular design, particularly so when combined with a second structure generating functionality, one known to be a persistent building unit. To carry out this evaluation we have prepared a number of new oxalamide and urea molecules with alcohol or phenol substituents.

Results and Discussion

Single molecule approach

The compounds **2**–**6** were prepared and crystals suitable for



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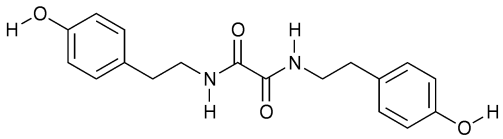

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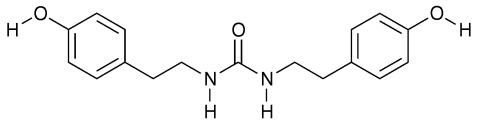

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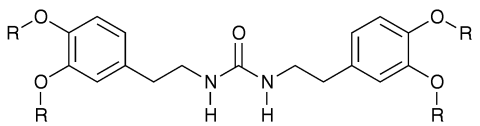


5 R = CH_3
6 R = H

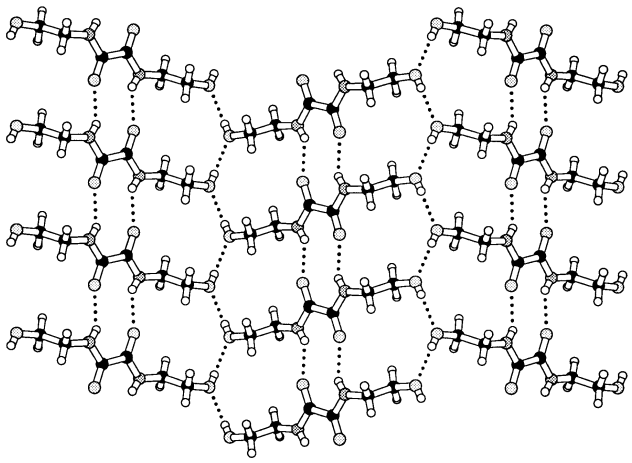


Fig. 3 β-Network formed by compound **2**. The oxalamide functionalities each sit on a set of inversion centers and form hydrogen bonds to the molecule above and below about a second set of inversion centers. The vertical α-networks thus have $P\bar{1}$ rod symmetry. These vertical α-networks are brought together by the hydroxyl hydrogen bonds which form along a 2_1 screw axis. Adding an external 2_1 screw axis to the $P\bar{1}$ rod group generates the layer groups $P2_1/c$

X-ray diffraction were grown. Each of the hydroxyl compounds seemed capable of forming a β-network analogous to the structure shown in Fig. 1 for a dicarboxylic acid. Compound **5**, which lacks the hydroxyl functional group was expected to form a one-dimensional α-network only.

Oxalamide of enthanolamine, 2. Compound **2** forms the β-network shown in Fig. 3. The structure combines the structural features well established previously for each set of hydrogen-bond functionalities. The oxalamide functionalities generate a one-dimensional α-network of $P\bar{1}$ rod symmetry. Neighboring α-networks are then united by hydroxyl hydrogen bonds about 2_1 screw axes, [see Fig. 5(*a*)]. The union of these two symmetry operators generates the layer group $P2_1/c$. The oxalamide functionality commonly yields an intermolecular spacing of 5.062(3) Å corresponding to the *b* axis of the monoclinic unit cell.

Oxalamide of tyramine, 3. One might expect this compound to form a β-network analogous to the one formed by **2**. Instead the compound forms a β-network of $P\bar{1}$ layer symmetry, Fig. 4. The hydrogen bonds between the oxalamide functionalities normally generate an inversion center and are compatible with the observed $P\bar{1}$ layer symmetry. However, this is not the usual case with hydroxyl groups. A centro-

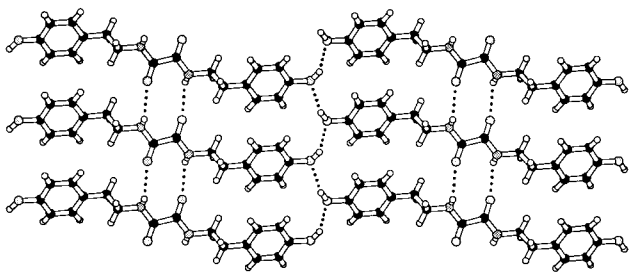


Fig. 4 β-Network formed by compound **3**. The oxalamide functionalities each sit on a set of inversion centers and form hydrogen bonds to the molecule above and below about a second set of inversion centers. The vertical α-networks thus have $P\bar{1}$ rod symmetry. These vertical α-networks are brought together from the hydroxyl hydrogen bonds which form about yet another set of inversion centers. There are actually two hydroxyl hydrogen-atom positions, each with a multiplicity of 0.5, see Fig. 5. Only one set of these two hydrogen-atom positions is shown in this figure. The layer symmetry of this β-netowrk is $P\bar{1}$ and intermolecular repeat distance along the oxalamide α-network is 5.159(3) Å

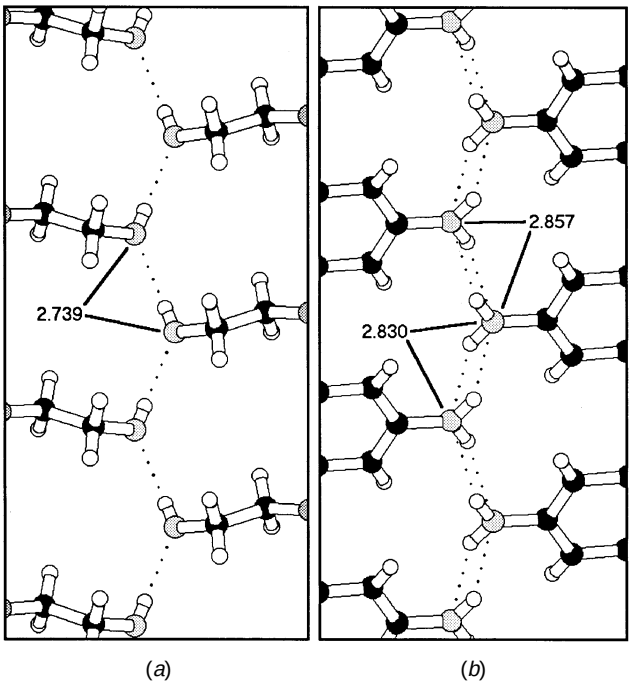


Fig. 5 The hydroxyl chains formed by compounds **2** (*a*) and **3** (*b*). Compound **2** has neighboring molecules related by a 2_1 screw axis. Compound **3** has neighboring molecules related by inversion centers. There are two disordered hydrogen positions each with fifty percent occupancy. For any given hydroxyl there will actually be only one hydrogen atom. The distances (Å) between the neighboring oxygen atoms are shown

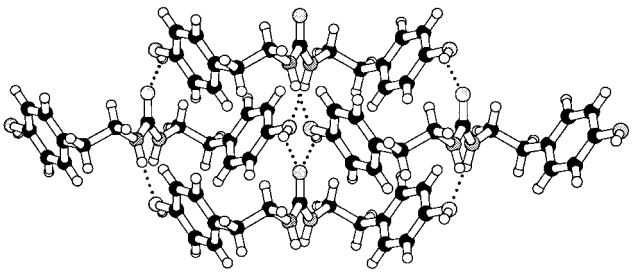


Fig. 6 β-Network formed by compound **4**, the urea of tyramine. The urea functionalities each sit on a two-fold axis and form hydrogen bonds to the hydroxyl groups of molecules above and below. These molecules are related by a 2_1 screw axis. The resulting β-network has *C*2 layer symmetry. Neighboring layers are related to each other by inversion centers yielding a space group of *C*2/*c* for the crystal

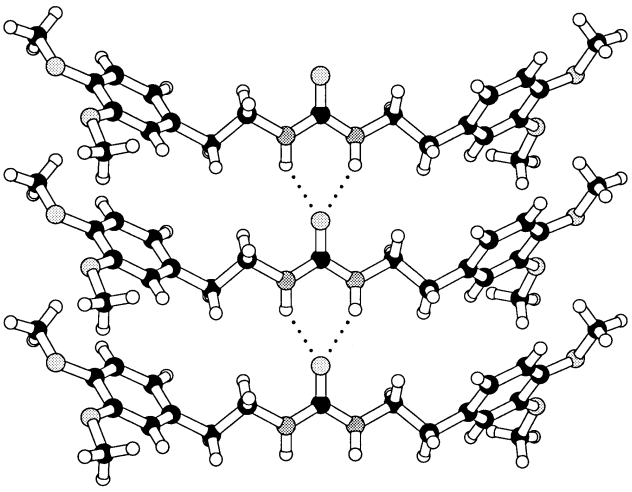


Fig. 7 α-Network formed by compound **5**, the urea of dimethyldopamine. This α-network has *P*2 rod group symmetry and an intermolecular spacing of 4.724(3) Å

symmetric hydroxyl dimer formed about an inversion center is not a commonly observed motif for hydroxyl groups. The actual structure is a chain structure with two disordered hydrogen atoms, each with a fifty percent occupancy, Fig. 5(*b*). Any given hydroxyl group would have only one hydrogen atom present. In a given local domain of the crystal one would expect the hydrogen occupancies to be ordered giving a local hydroxyl structure very similar to the structure found for **2**. The intermolecular spacing along the oxalamide direction is 5.159Å(3) Å in accordance with other oxalamide structures.[8]

Urea of tyramine, 4. In the structure of **4**, Fig. 6, the predicted hydrogen bond patterns are broken with the urea and hydroxyl groups alternating to form a unique chain structure about a two-fold axis. The hydroxyl group of the tyramine is inserted within the amide chain of the ureas. The resulting structure is a two dimensional β-network, but certainly not one that was designed. Since the hydroxyl group has disrupted the normal urea α-network the intermolecular spacing of 6.387(3) Å is considerably longer than the 4.5–4.7 Å repeat distance commonly found for other ureas.[3]

Urea of dimethyldopamine, 5. Compound **5**, the urea of dimethyldopamine (dopamine = 3-hydroxytyramine), has only one set of hydrogen-bond functionalities and as expected forms an α-network only, Fig. 7. The rod symmetry of the α-network is *P*2 and the intermolecular spacing of 4.724(3) Å is in the range found for other urea structures.[3]

Urea of dopamine, 6. With the methyl groups of **5** removed the catechol functionalities would be expected to form additional hydrogen bonds uniting the α-networks of **5** into a more complex network. Unfortunately we have been unable to grow an anhydrous crystal of compound **6**. Instead a hydrated crystal with two molecules of water per molecule of **6** has been isolated, Fig. 8. The resulting structure still contains the urea α-network, but there are no hydrogen bonds between any of the hydroxyl groups of **6**. Instead each hydroxyl group is involved in two hydrogen bonds with a water molecule, one as a donor and one as an acceptor, Fig. 8.

These structural studies of the five compounds **2**–**6** discussed above indicate that the hydroxyl group can be used to assemble molecules into supramolecular structures, but that it is not a very dependable or predictable interaction. For the purpose of design one desires a more dependable interaction. For this we turn to a co-crystal strategy. The hydroxyl group would seem to be a better hydrogen bond donor than it is an acceptor. Using the Etter principle[7] that the good hydrogen bond donor will always seek out the best hydrogen bond acceptor, one can predict that hydroxyl groups should readily co-crystallize with compounds that have a good hydrogen bond acceptor site.

Co-crystal approach

In previous work we demonstrated that dicarboxylic acids readily co-crystallized with various bipyridines. A similar approach should work with dihydroxyl compounds as well. To test this idea we prepared a 1 : 1 co-crystal of compound **3** with the bipyridine **7**. As expected the phenol hydroxyl group forms a hydrogen bond to the pyridine nitrogen atom. The resulting structure is shown in Fig. 9. In the **3**–**7** co-crystal, molecule **3** forms the same α-network *via* oxalamide hydrogen bonds that it forms in its pure crystal, Fig. 4. In the structure of the pure compound the hydroxyl groups were disordered about a chain of inversion centers. In the co-crystal the hydroxyl groups of the urea host form hydrogen bonds to the bipyridine guest which sits on an inversion center. Thus the hydroxyl groups of neighboring α-networks are still related by inversion centers, but now in an ordered environment, one mediated by the bipyridine guest. The basic pyridine nitrogen atom is a much better hydrogen bond acceptor than is the

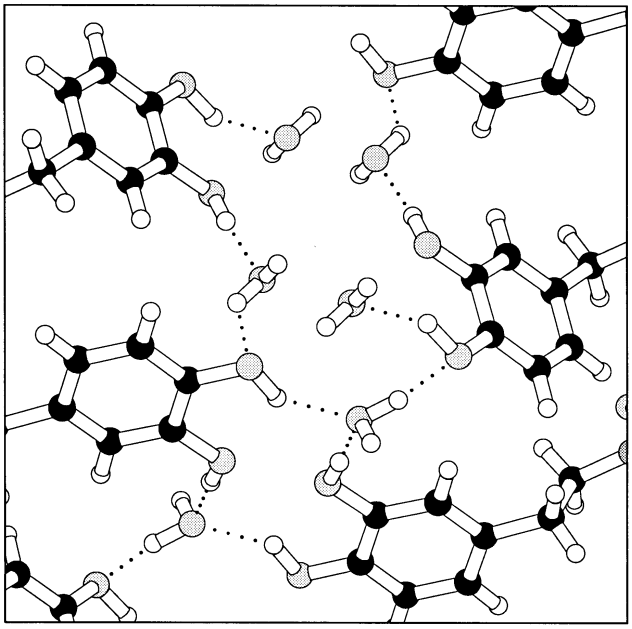
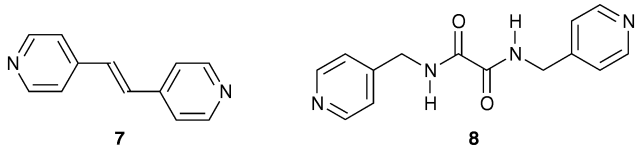


Fig. 8 The hydrated catechol groups of compound **6**. Both hydroxyl groups form two hydrogen bonds to water molecules, one as a donor and one an acceptor

hydroxyl oxygen atom. Thus the hydroxyl–pyridine hydrogen bond would seem to be a more reliable and persistent design element, generating a specific structure in a manner much more predictable than a hydroxyl group alone.



7 **8**

A checkerboard pattern *versus* stripes. As a second test of the hydroxyl–pyridine co-crystal approach we prepared the oxalamide of 4-aminomethylpryidine, **8**, and co-crystallized the compound with the oxalamide of ethanolamine, compound **2**. Since both compounds are oxalamides, there were two possible β-networks that could be envisioned, Scheme 1.

The first candidate β-network, the 'stripes' pattern, would have two independent vertical oxalamide-based α-networks, one formed from the dihydroxyl compound, the second from the bipyridine. The second candidate β-network, the 'checkerboard' pattern, would have the two compounds alternating to form one vertical α-network. In each case the parallel vertical α-networks would be brought together *via* the

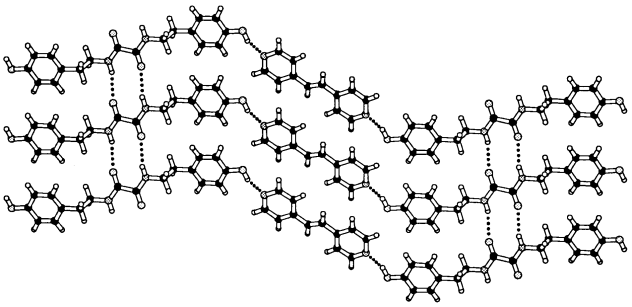
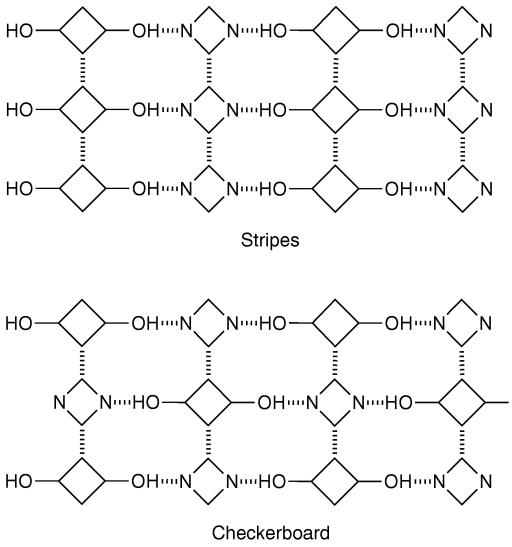


Fig. 9 The β-network formed by co-crystallizing the oxalamide of tyramine, **3**, with the bipyridine, **7**. The oxalamide hosts form an α-network completely analogous to the α-network formed in the pure crystal, Fig. 4. The hydroxyl groups form hydrogen bonds to the pyridine nitrogen atoms of the bipyridine guest molecules. Both the oxalamide and the bipyridine molecules sit on inversion centers, the symmetry of the layer is thus $P\bar{1}$



Scheme 1

hydroxyl–pyridine hydrogen bonds to form a β-network. In the **3**–**7** co-crystal, the checkerboard pattern is not possible, because the simple bipyridine **7** lacks the hydrogen bond functionalities needed to form an independent α-network. However in the **2**–**8** structure, Fig. 10, the checkerboard pattern is found. So what is wrong with a stripes pattern for the **2**–**8** co-crystal? The problem is that it requires that the two independent oxalamide based α-networks must be exactly commensurate, that each of the two must have exactly the same intermolecular spacing. While indeed both molecules are oxalamides and should have similar favored spacings, the necessity for precisely identical intermolecular spacing is a stringent requirement. The checkerboard pattern on the other hand has only one oxalamide hydrogen bond α-network and the requirement for commensurate structures does not occur.

A second 'checkerboard' structure has also been prepared with the same bipyridine, **8**. This is the co-crystal between the bipyridine, **8**, and the dicarboxylic acid, **1**. The structure is isomorphous with the **2**–**8** co-crystal (Fig. 10), illustrating the similar nature of the hydroxyl–pyridine hydrogen bond to the carboxylic acid–pyridine hydrogen bond. Both the molecular and supramolecular structures are very similar, with identical space groups and similar cell constants, Table 1. The density of the dicarboxylic acid derived co-crystal, **1**–**8**, is considerably

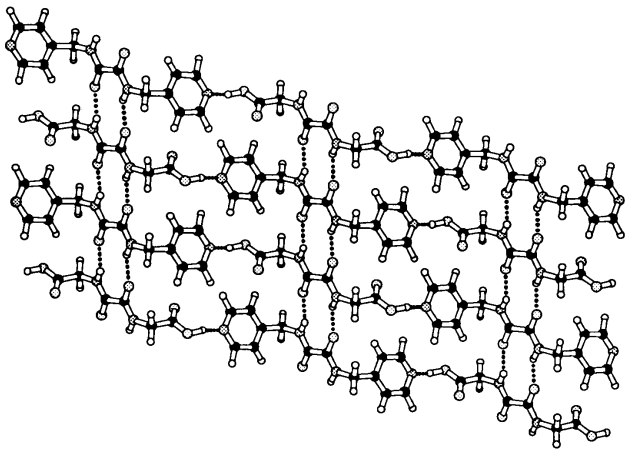


Fig. 10 The co-crystal of the oxalamide of ethanolamine, **2**, with the bipyridyl oxalamide derivative, **8**. The compound forms a β-network with a checkerboard pattern. Each molecule sits on an inversion center, the symmetry of the layer is $P\bar{1}$. The co-crystal of the oxalamide of glycine, **1**, with **8**, is isomorphic with this structure

greater and the volume actually smaller than that of the diol-derived co-crystal, **2**–**8**. Presumably this reflects the greater strength of the carboxylic acid–pyridine hydrogen bond [N···O, 2.607(2) Å] over the hydroxyl–pyridine hydrogen bond [N···O, 2.826(2) Å].

Conclusion

For the purposes of supramolecular design the hydroxyl functionality by itself is a highly variable group, that will form hydrogen bonds, but with patterns that will show considerable variation. As a design element, the hydroxyl group alone may not be very reliable. The hydroxyl–pyridine hydrogen bond however, is a good one, meaning that this pairwise interaction should be highly persistent. High persistence and predictability is the key requirement of a good design element for generating desired structures. Thus our conclusion, a hydroxyl alone is not a particularly good design element, but paired with a good hydrogen bond acceptor such as a pyridine, it works very well.

Experimental

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 were 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 were collected as indicated in Table 1, and the structures were solved and refined using the TEXSAN crystallographic program package of the Molecular Structure Corporation. The quality of the structures varied due to the quality of the available single crystals. In the best cases, hydrogen atoms were located in difference maps and refined. In the cases with poorer data sets, the hydrogen atoms were placed in calculated positions and added as fixed contributions.

CCDC reference number 440/010.

Syntheses

Compound **1** was prepared according to literature procedures.[8] Compound **7** was purchased from Aldrich Chemical Company.

***N,N′*-Bis(2-hydroxyethyl)oxalamide, 2.** Diethyl oxalate (240 mg, 1.6 mmol) was added neat to ethanolamine (200 mg, 3.2 mmol). The addition yielded a yellow solid. Recrystallization of the solid from methanol afforded *N,N′*-bis(2-hydroxyethyl) oxalamide as colorless crystals in 71% yield: mp. 164–165 (lit[9] m.p. 166–167 °C).

***N,N′*-Bis(4-hydroxyphenylethyl)oxalamide, 3.** Tyramine (520 mg, 3.8 mmol) and diethyl oxalate (280 mg, 1.9 mmol) were dissolved in methanol (30 mL) at 30 °C and stirred for 1 h. Evaporation of the methanol produced a colorless solid which was isolated by filtration. Recrystallization from methanol afforded **3** as a colorless crystalline solid in 52% yield: m.p. 245–248 °C; ^{1}H NMR [$(CD_3)_2SO$]: δ 9.19 (s, 1H), 8.68 (t, 1H), 6.95 (d, 2H, J = 7.5), 6.64 (d, 2H, J = 7.5), 3.26 (q, 2H, J = 7.0), 2.63 (t, 2H, J = 7.2 Hz); IR (KBr) 3300 (N—H), 1654 (C=O) cm^{-1}. X-Ray quality crystals were obtained by recrystallization in methanol.

***N,N′*-Bis(4-hydroxyphenylethyl)urea, 4.** Tyramine hydrochloride (0.017 mol) and of 6.25 N NaOH (8.26 mL, 0.051 mol) were added to water (50 mL). The reaction mixture was cooled in an ice bath. Triphosgene (0.85 g, 2.87 mmol) was dissolved in methylene chloride (20 mL). This solution was added at once to the tyramine solution and stirred for 0.5 h. The reaction was allowed to warm to room temperature and stir for 3 h. The reaction mixture was again cooled in an ice bath and the pH adjusted to *ca.* 2 with 12 N HCl. The product precipitated was collected by vacuum filtration. Recrystallization from methanol–ethyl acetate gave **4** (2.25 g, 42%); m.p. = 226–227 °C. ^{1}H NMR [$(CD_3)_2SO$]: δ 9.14 (s, 2H), 6.93 (d, 4H, J = 8.1), 6.62 (d, 4H, J = 8.4), 5.81 (t, 2H, J = 5.4 Hz), 3.1 (m, 4H), 2.51 (m, 4H); ^{13}C NMR [$(CD_3)_2SO$]: 158.1, 155.6, 129.8, 129.5, 115.1, 41.3, 35.4; IR (KBr): 3396 (O—H), 3333 (N—H), 1617 (C=O), 1607 (ring stretch) 1514 (C—N—H), 1442 (ring stretch), 1227 (C—O), 823 cm^{-1} (C—H bend).

***N,N′*-Bis(3,4-dimethoxyphenylethyl)urea, 5.** 3,4-Dimethoxyphenylethylamine (4.0 ml, 23.7 mmol) was dissolved in water (25 mL) followed by slow addition of 6.25 M NaOH (3.8 mL). The mixture was cooled in an ice bath and stirred for 0.5 h. Triphosgene (1.2 g, 3.95 mmol) was dissolved in a minimum amount of toluene and added to the reaction mixture. Precipitation started after 5–10 min. After 0.5 h the reaction mixture was allowed to warm to room temperature and stirred for another 2.5 h. A colorless solid was isolated by vacuum filtration and recrystallized from ethyl acetate–methanol (3 : 1), to give colorless crystals (2.52 g, 55%), m.p. 143–144 (lit.[10] m.p. 149 °C).

***N,N′*-Bis(3,4-dihydroxyphenylethyl)urea, 6.** Compound **5** (1.4 g, 3.6 mmol) was dissolved in dry methylene chloride (100 mL) under N_2. Boron tribromide (4.51 g, 18 mmol) was added slowly to the reaction mixture over a period of 2 h yielding a yellow solution and a precipitate. The solution was then stirred for 24 h and the precipitate dissolved. The solution was extracted (3 × 75 mL) with nitrogen-flushed water. After each fraction of water was added, the solution was allowed to stand under nitrogen to allow the precipitate that formed to dissolve into the aqueous layer. The combined water extracts were evaporated in a 40 °C water bath under a heavy stream of nitrogen. After almost complete removal of water, a yellow oily substance began to form which was placed in a ice bath followed by vacuum filtration yielding a yellow flaky solid. Recrystallization from ethyl acetate–methanol (3 : 2) yielded long rod-like crystals (0.40 g, 35%): m.p. 100–110 °C. The subsequent X-ray diffraction study showed that these crystals corresponded to the dihydrate. ^{1}H NMR [$(CD_3)_2SO$]: 6.63 (d, 2H, J = 7.9), 6.57 (s, 2H), 6.44 (d 2H, J = 8), 4.78 (s, 4H), 3.12 (t, 4H, J = 7.1Hz), 2.37 (m, 4H); IR (KBr) 3444–3146 (O—H), 3316 (N—H), 1579,1607 (C=O), 1528 (C—N—H), 1444 (ring stretch), 1370 (O—H in-plane bend), 1234 (C—O), 646 cm^{-1} (O—H out of plane).

***N,N′*-Bis(pyridin-4-ylmethyl)oxalamide, 8.** The addition of 4-(aminomethyl)pyridine (2.2 g, 20 mmol) to diethyl oxalate (1.5 g, 10 mmol) gave **8** immediately as a colorless solid. Recrystallization of the product from methanol gave plate-like crystals in 77% yield: m.p. 213–214 °C; ^{1}H NMR [$(CD_3)_2SO$]: δ 4.39 (d, 2H, J = 6.5), 7.27 (d, 2H, J = 5.5), 8.51 (d, 2H, J = 5.5), 9.50 (t, 2H, J = 6.3 Hz); IR (KBr) 3325 (N—H), 1669 (C=O) cm^{-1}.

Table 1 Selected crystallographic data

Compound	**2**	**3**	**4**	**5**	**6** · $2H_2O$	**3–7**	**2–8**	**1–8**
Empirical formula	$C_6H_{12}N_2O_4$	$C_{18}H_{20}N_2O_4$	$C_{17}H_{20}N_2O_3$	$C_{21}H_{28}N_2O_5$	$C_{17}H_{24}N_2O_7$	$C_{30}H_{30}N_4O_4$	$C_{20}H_{26}N_6O_6$	$C_{20}H_{22}N_6O_8$
Formula weight /g mol^{-1}	176.2	328.4	300.4	388.5	368.4	510.6	446.5	474.4
a/Å	4.483(2)	11.042(2)	33.615(8)	34.516(8)	34.678(7)	16.619(7)	4.359(2)	4.315(2)
b/Å	20.453(10)	5.159(1)	15.051(4)	4.724(2)	4.563(2)	5.582(3)	9.490(4)	9.595(3)
c/Å	5.062(4)	14.354(3)	6.387(3)	12.601(4)	11.154(3)	14.338(6)	13.071(4)	12.845(3)
α/°	—	—	—	—	—	—	96.28(5)	96.48(6)
β/°	111.25(5)	101.47(5)	—	100.98(6)	92.08(4)	101.53(7)	93.40(5)	92.65(5)
γ/°	—	—	—	—	—	—	93.93(5)	95.52(5)
U/$Å^3$	432.6	801.4	3231.6	2016.9	1763.7	1303.2	535.0	532.4
Space group	$P2_1/c$ (no. 14)	$P2_1/c$ (no. 14)	*Fdd*2	*C*2/*c* (no. 15)	*C*2/*c* (no. 15)	$P2_1/c$ (no. 14)	$P\bar{1}$ (no. 2)	$P\bar{1}$ (no. 2)
Z	2	2	8	4	4	2	1	1
Calculated density /g cm^{-3}	1.352	1.361	1.235	1.279	1.387	1.301	1.386	1.480
Observations collected	876	1187	796	1442	1867	2765	2004	1546
Observations ($I > 3\sigma$)	479	429	523	725	1236	1715	1457	838
Variables	79	117	104	128	119	232	197	162
R	0.044	0.046	0.042	0.068	0.062	0.031	0.050	0.057
R_w	0.050	0.047	0.046	0.073	0.068	0.035	0.036	0.062

3–7 Co-crystal. A minimum amount of methanol was added to a 1 : 1 molar ratio of compounds **3** and **7** to produce a saturated solution. Slow evaporation resulted in crystal formation: m.p. 254–255 °C; IR (KBr) 3335 (N—H), 1656 cm^{-1} (C=O).

2–8 Co-crystal. Compound **2** (20 mg) and compound **8** (32 mg) were dissolved in water (20 mL). Slow evaporation yielded thick, colorless, rectangular crystals: m.p. 230–232 °C (sublimation of one component occurred at 200–205 °C); IR (KBr) 3292 (N—H), 1652 cm^{-1} (C=O).

1–8 Co-crystal. Compound **1** (22 mg) and **8** (27 mg) were dissolved in water (50 mL). Slow evaporation yielded long, thin, colorless crystals: m.p. 290–295 °C, IR (KBr) 3397 (N—H), 1659 cm^{-1} (C=O).

Acknowledgements

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