Structural Consequences of a Molecular Assembly that is Deficient in Hydrogen-bond Acceptors

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The X-ray crystal structure of **1**, a molecular assembly that is deficient in H-bond acceptors relative to the number of H-bond donors, illustrates two methods by which this unfavourable situation can be accommodated: (*i*) through the formation of weak N–H···π hydrogen-bonds and (*ii*) through a change in hybridisation.

H-Bonding and π–π interactions are two of the principal forces which determine three-dimensional structure, self-assembly and recognition in chemical and biological systems.[1] The directionality and specificity associated with these interactions is electrostatic in origin,[2,3] and simple rules have been developed for interpreting and predicting the properties and occurrence of both types of interaction.[2,3a] Recently, some examples of interactions at the interface between H-bonds and π–π interactions have been reported.[4,5] This communication is concerned with such intermediate strength electrostatic interactions (Fig. 1).

Etter has proposed methods for predicting packing arrangements in crystal structures based on H-bonding patterns.[2] The underlying principle is that the strongest H-bond acceptor should be paired up with the strongest H-bond donor. This procedure can be repeated until all the H-bonding functionalities are suitably matched. However, what happens when the H-bond requirements of a particular molecule cannot be satisfied because it contains an excess of donors or acceptors?

The case of an excess of H-bond acceptors has been well-studied.[4,6] Generally the superfluous H-bond acceptors find the next most acidic hydrogens and form weak C–H···X hydrogen-bonds. The acidic C–H hydrogens are often found on the edge of aromatic rings. C–H···O interactions occur frequently in both the small molecule and protein crystal structures.[4] Another common structural motif, which can relieve a deficiency in H-bond donors, is the bifurcated

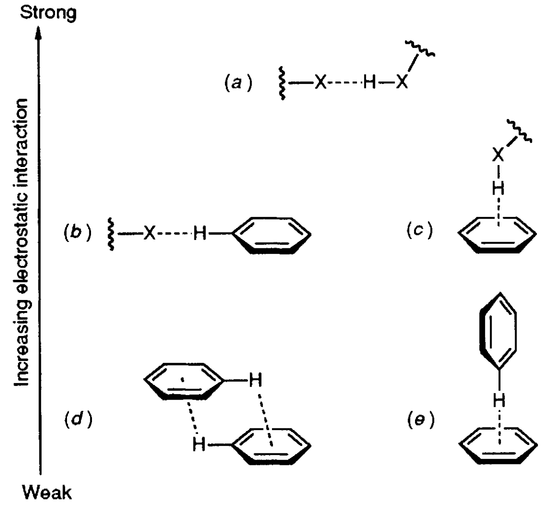

Fig. 1 Hierarchy of intermolecular interactions. (*a*) H-bond. (*b*) Weak C–H···O H-bond. (*c*) Weak N–H···π H-bond. (*d*) Offset π–π interaction. (*e*) Edge-to-face π–π interaction. X is a heteroatom.

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Table 1 H-Bonding properties of various functional groups

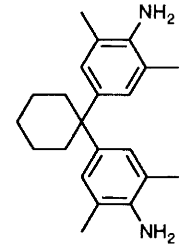
Hybridisation	(No. of donors) – (no. of acceptors)			
	Nitrogen		Oxygen	
sp^3	>N–	−1	-O-	−2
	-NH-	0	-OH	−1
	$-NH_2$	+1		
sp^2	>N–	0	-O-	−1
	-NH-	+1	-OH	0
	$-NH_2$	+2		
sp^2	=N–	−1	=O	−2
	=NH	0		
sp	≡N	−1		

three-centre H-bond in which one H-bond donor is shared between two H-bond acceptors.[2]

In contrast, the case of molecular assemblies that are deficient in H-bond acceptors has not been examined in any detail. Table 1 suggests a reason for this somewhat surprising observation. The functional groups commonly involved in H-bonding in organic molecules and proteins are listed along with a classification of their H-bonding capacity. There is clearly an imbalance between the number of H-bond donors and the number of H-bond acceptors. For a random distribution of these functional groups, we would expect to find an excess of H-bond acceptors: hence the frequent observation of weak C–H···O hydrogen-bonds. Table 1 suggests that the case of an excess of H-bond donors should be less common.

In a molecular assembly with a deficiency of H-bond acceptors, π-electrons should represent the next best acceptor as far as the superfluous H-bond donors are concerned. By analogy with the C–H···X hydrogen-bonds, one might expect to find weak X–H···π hydrogen-bonds in such cases (Fig. 1). Recently, the first observations of O–H···π hydrogen-bonds were reported.[5] We now report the first example of an N–H···π hydrogen-bond, confirming that X–H···π interactions occupy an important place in the hierarchy of electrostatic interactions shown in Fig. 1. We also report another mechanism by which a deficiency in H-bond acceptors may be accommodated: through a change in hybridisation.[7]

Table 1 suggests that molecular structures that contain sp^3 NH_2, sp^2 NH_2 or sp^2 NH groups are likely to be deficient in H-bond acceptors. Two classes of molecule that fit these requirements and contain π-systems are pyrroles and anilines. Compound **1** represents a molecular structure that contains four H-bond donors but no obvious H-bond acceptors.[6] Its crystal structure illustrates two ways in which this situation can be accommodated.‡



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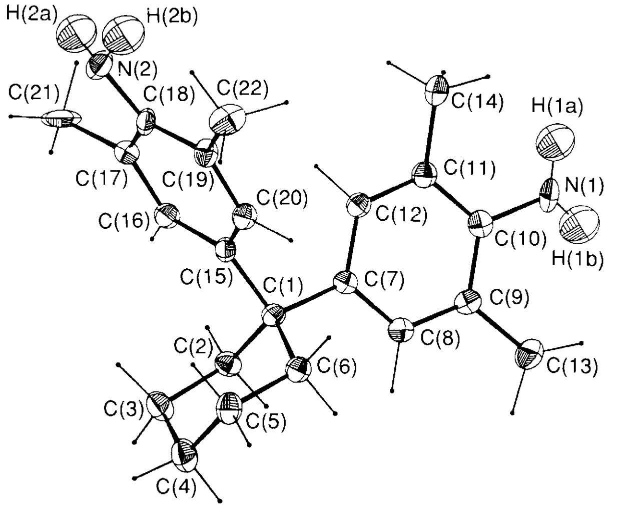

Fig. 2 Molecular structure of **1** (crystallographic numbering). Selected distances (Å) and angles (°): N(1)–H(1a) 0.88(2), N(1)–H(1b) 0.92(2), N(2)–H(2a) 0.96(3), N(2)–H(2b) 0.95(3), N(1)–C(10) 1.389(2), N(2)–C(18) 1.410(2); C(7)–C(1)–C(15) 108.8(1).

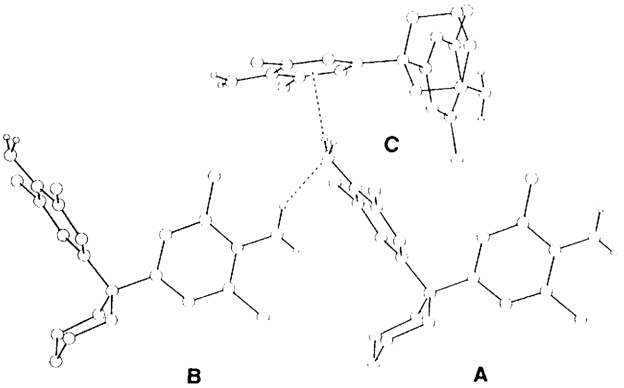

Fig. 3 Intermolecular interactions observed in the crystal structure of **1**. H-Bonds are shown as dotted lines.

The first method is the one outlined above, the formation of weak X–H···π hydrogen-bonds. The basic molecular structure is shown in Fig. 2. Fig 3 illustrates the intermolecular interactions observed in the crystal. Molecules **A** and **C** are involved in an N–H···π hydrogen-bond. The acidic hydrogen H(2a) of **A** lies over the geometric centre of the six-membered aromatic ring of **C** (to within 0.15 Å) and the N(2)–H(2a) bond is inclined at 49° to the plane of the aromatic ring. The distance between the hydrogen and the plane is 2.42(2) Å and the carbon–hydrogen distances range from 2.72(2) to 2.87(2) Å. These values are comparable to those observed for O–H···π hydrogen-bonds.[5]

The second method by which the deficiency in H-bond acceptors is accommodated in this molecular assembly is through a change in the hybridisation of the molecule.[7] Location of the hydrogen atoms in the difference Fourier map and subsequent refinement of positions revealed that the two nitrogen atoms which appear to be chemically identical in **1** are in fact different in the crystalline state (Fig. 2). N(1) is sp^2 hybridised, and N(2), the other nitrogen in the same molecule,

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‡ Crystals of **1** were grown from chloroform–hexane solution. *Crystal structure anlysis* of at 153 K: $C_{22}H_{30}N_2$, space group $P2_1/n$, a = 10.641(4), b = 9.846(5), c = 18.253(7) Å, β = 98.90(3)°, Z = 4, D_m = 1.11(5), D_c = 1.13 g cm^{-3}, μ(Mo-Kα) = 0.71 cm^{-1}, Nicolet P 3 diffractometer: 4333 unique reflections, 3153 observed [$I > 3\sigma(I)$] in range $4 < 2\theta < 55°$ used; positions of amine H atoms located from ΔF map and refined isotropically; R = 0.050, R_w = 0.055 [$w = 2.54/(\sigma^2F + 0.0007F^2)$], 245 parameters. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

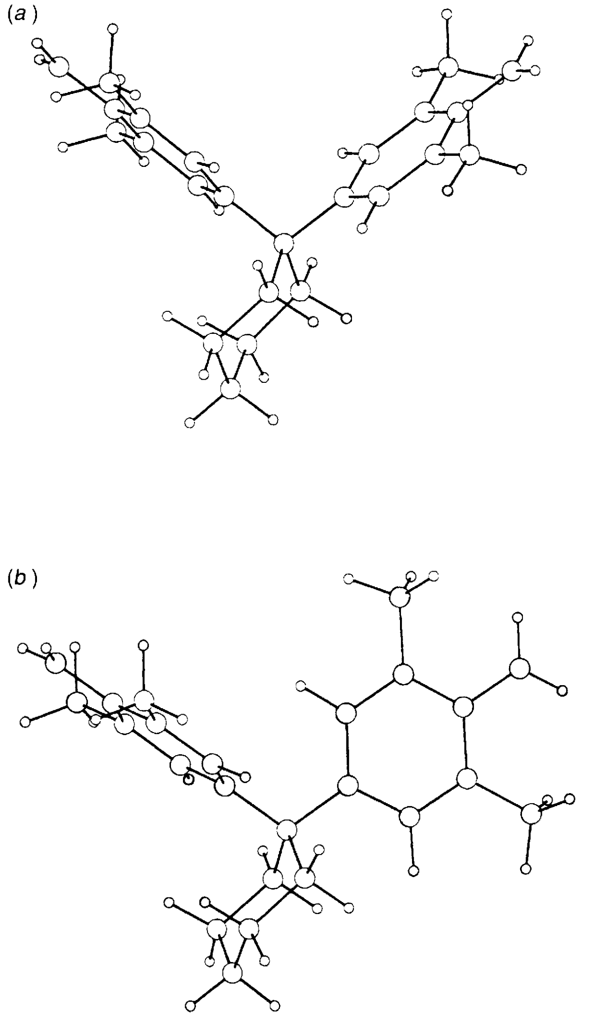

Fig. 4 The conformational energy minima calculated using the CHARMm force-field. (*a*) 'Open' conformation: CHARMm energy = −31.3 kJ mol^{-1}. (*b*) 'Closed' conformation: CHARMm energy = −24.4 kJ mol^{-1}.

is sp^3 hybridised.§ There are H-bonds between the sp^2 NH$_2$ hydrogens and the sp^3 NH$_2$ lone pairs (between molecules **B** and **A** in Fig. 3). The N(2)–H(1b) distance is 2.26(2) Å and the N(2)–H(1b)–N(1) angle is 150°. The C(18)–N(2)–H(1b), H(2a)–N(2)–H(1b) and H(2b)–N(2)–H(1b) angles all deviate significantly from the tetrahedral angle which suggests that the H-bond is distorted by additional N-H···π interactions.¶

Thus, the H-bonding requirements of this system are so strong that they induce a change in hybridisation. Such a switch in hybridization caused by intermolecular H-bonding could play an important role in enzyme catalysis. Clearly, appropriately placed H-bonding functionality is capable of inducing a change in the hybridisation state of a bound substrate and substantially modifying its reactivity.

The rules discussed above for predicting H-bonding patterns can be successfully applied to the interactions in this system.[2] The best H-bond donors, the sp^2 NH$_2$ hydrogens, are paired with the best H-bond acceptors, the sp^3 NH$_2$ lone pairs. The other H-bond donors, the sp^3 NH$_2$ hydrogens, are paired with the next best H-bond acceptor, the π-electrons of the aromatic rings. In addition, the N–H···π hydrogen-bond is formed with the best π facial acceptor. In the aromatic ring that contains the sp^2 NH$_2$ group, the nitrogen lone pair is delocalised over the whole ring giving an electron-rich π-system. This aromatic ring is, therefore, a better H-bond acceptor than the other one in which this delocalisation does not occur.[3a]

In addition to N–H···N and N–H···π hydrogen-bonds, this structure also contains an example of the third class of interaction in Fig. 1, π–π interactions. In this case, the interaction is intramolecular rather than intermolecular. The two aromatic rings are at 98° to each other, adopting an edge-to-face arrangement as expected on the basis of simple electrostatic arguments (Fig. 2).[3a] We investigated the conformational preferences of **1** using the CHARMm force-field.[8] Conformational searching predicted that an 'open' conformation should be the lowest energy structure (Fig. 4). The experimentally observed 'closed' conformation is predicted to be 5.8 kJ mol^{-1} higher in energy. In the open conformation, the π-systems adopt a face-to-face arrangement, which should lead to unfavourable electrostatic interactions. These interactions are not adequately handled by the CHARMm force-field.[3a] Calculations using our own force-field, which allows for out-of-place π-electron density, indicate that the difference in energy between the two conformers is only 0.5 kJ mol^{-1}.[3a]

In conclusion, this unusual crystal structure illustrates the three classes of intermolecular interactions depicted in Fig. 1. It demonstrates two mechanisms by which molecular assemblies can accommodate an excess of H-bond donors, through the formation of X–H···π hydrogen-bonds and through changes in hybridisation.

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§ The H–N(1)–H bond angle is 116(2)°, the average H–N(1)–C bond angle is 120(1)°, and the maximum deviation of the N(1) hydrogens from the plane of the aromatic ring is 0.07 Å. The H–N(2)–H bond angle is 109(2)°, the average H–N(2)–C bond angle is 114(1)°, and the maximum deviation of the N(2) hydrogens from the plane of the aromatic ring is 0.20 Å. In addition, the N(1)–C(10) distance is 0.021 Å shorter than the N(2)–C(18) distance reflecting the delocalisation of the nitrogen lone pair over the aromatic ring in the former sp^2 hybridised system.

¶ Angles are C(18)–N(2)–H(1b) = 84(2), H(2a)–N(2)–H(1b) = 118(2) and H(2b)–N(2)–H(1b) = 114(2)°.