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Supramolecular synthons based on N–H···N and C–H···O hydrogen bonds. Crystal engineering of a helical structure with 5,5-diethylbarbituric acid

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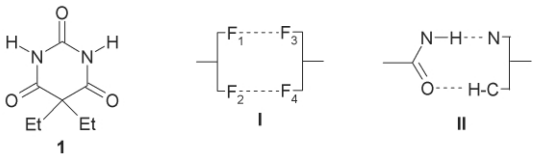
Received (in Columbia, MO, USA) 7th May 2002, Accepted 3rd July 2002
First published as an Advance Article on the web 18th July 2002

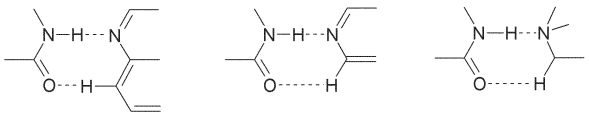
5,5-Diethylbarbituric acid is a convenient molecular precursor for a newly identified N–H···N/C–H···O synthon, which is robust enough for the design of a helix architecture.

The central aim of crystal engineering is a general protocol for the construction of crystal structures from molecular structures.[1] Since there is no direct correspondence between molecular functional groups (F_n) and crystal packing features, a realistic approach to crystal engineering is to identify particular combinations of molecular functionality that preferentially yield particular supramolecular synthons, which in turn are more easily related to the packing features.[2] Along these lines, several groups of investigators have identified two-point hydrogen bonded synthons with the general structure **I**. A number of these have been identified by Allen *et al.* from the Cambridge Structural Database (CSD),[3] while Jones and co-workers have shown that a strong/weak combination† such as O–H···N/C–H···O for $F_1\cdots F_3/F_2\cdots F_4$ is sufficiently reliable in crystal design.[4] Other related examples of strong/weak synthons are well known.[5] In this communication, we show that 5,5-diethylbarbituric acid, **1** (barbital),‡ is an effective tecton in the generation of the hitherto unreported N–H···N/C–H···O strong/weak supramolecular synthon **II**, which is endowed with sufficient robustness for effective crystal engineering.



1 **I** **II**

When barbital and acridine were taken in an equimolar ratio in EtOAc, crystals of the 1:2 molecular complex (mp 175 °C, *C*2/*c*), § shown in Fig. 1, were obtained. Notice the 'bifurcated' arrangement of two acridine molecules about the central barbital molecule and the two-fold symmetry equivalent synthons **IIa** (N–H···N: 1.92 Å, 177°; C–H···O: 2.49 Å, 157°). Similarly, when equimolar amounts of **1** and 1,10-phenanthroline were taken in EtOAc, the result was the 1:1 molecular complex (mp 160 °C, $P2_1/c$)§ shown in Fig. 2. Here too the N–H···N/C–H···O arrangement is seen (as synthon **IIb**, N–H···N: 1.83 Å, 172°; C–H···O: 2.85 Å, 114°), but additionally there is a centrosymmetric N–H···O dimer (1.83 Å, 176°) that effectively acts as a spacer. Why acridine gives the 1:2 complex with **1** while 1,10-phenanthroline gives the 1:1 complex is another matter because equimolar amounts of the components were taken for recrystallisation in both experiments, and there appeared to be no special problem with compound solubility in either case. Perhaps the approach of two molecules of phenanthroline towards the barbital molecule is sterically disfavoured. In any event, what is significant is the formation of the N–H···N/C–H···O synthon **II** in both cases.



IIa **IIb** **IIc**

The CSD was now examined to find out the generality of occurrence of heterosynthon **II**. The April 2002 version (5.23, 257162 entries, screens 85, 88, 153) contains 10323 hits with the (C=O)NH fragment. Using accepted ranges for N–H···N (1.5–2.4 Å, 120–180°) and C–H···O (2.0–3.1 Å, 110–180°) hydrogen bonds,[6] we obtained 140 occurrences of synthon **II** containing either 0, 1 and 2 atoms in the tether between the N-atom and the C–H group. Among these, synthon **II** occurs as part of a larger three-point recognition motif in 62 hits. These larger synthons contain not only N–H···N and C–H···O hydrogen bonds but also a third, generally stronger hydrogen bond. Accordingly, these 62 hits were removed so as to obtain 78 genuine occurrences of the two-point synthon **II**. Computations on the model system succinimide–pyridine (Spartan RHF/6-31G*) showed that the stabilisation energy for synthon **IIb** is −8.2 kcal mol^{-1}, which is comparable to the stabilisation

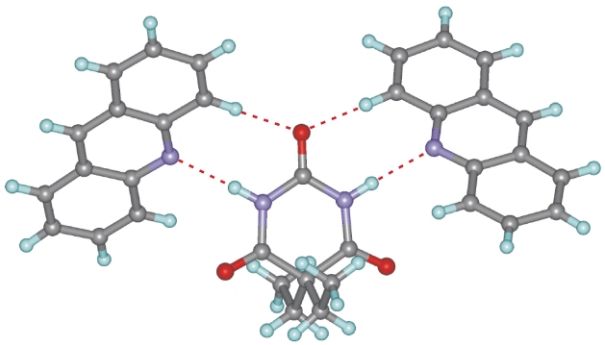


Fig. 1 Barbital and acridine 1:2 complex. Notice synthon **II**.

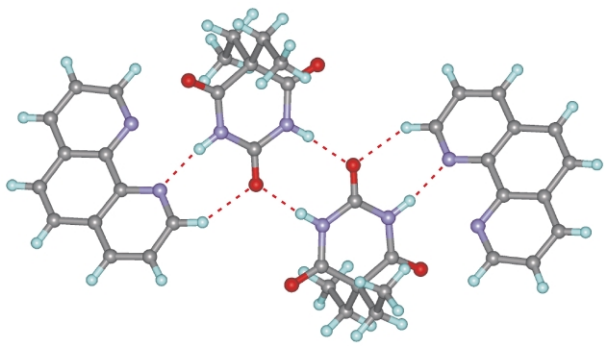


Fig. 2 Barbital and 1,10-phenanthroline 1:1 complex. Notice synthon **II** and the central N–H···O dimer.

DOI: 10.1039/b204388b

provided by a single O–H···O hydrogen bond. These CSD and computational results show that synthon **II** is a reasonably viable structural unit for crystal design.

The next step in the crystal engineering exercise was to test the robustness of synthon **II** in a new system. The molecule selected for co-crystallisation with barbital was urotropine (hexamethylenetetramine). An equimolar mixture of the two components taken in EtOAc yielded a 1:1 molecular complex (Fig. 3). Notice that both barbital and urotropine can be supramolecularly bifunctional with respect to synthon **IIc**. Further, the rigid geometry of both molecules leads *via* the intermediacy of this synthon (N–H···N: 1.88 Å, 169°, 1.84 Å, 168°; C–H···O: 2.50 Å, 124°, 2.89 Å, 115°) to a helix with a pitch of 13.3 Å. The space group is centrosymmetric (*Pbca*) and so both left and right-handed helices are present in the crystal structure. The helix topology is a current target in crystal engineering strategies,[7] but very few all-organic helix structures have been reported.[8] What makes the present example noteworthy is that the helix may be anticipated from the robustness of the N–H···N/C–H···O synthon **II**, the shapes of the constituent molecules, barbital and urotropine, and the firm scaffolding provided by both molecules.

Finally, it is worthwhile to observe that variations of synthon **II** with an overall stabilisation of only around −8 kcal mol^{-1} occur repeatedly in molecular complexes of barbital. As seen from our computations, such stabilisation is comparable to what is provided by a single strong hydrogen bond such as O–H···O or N–H···O. We estimate that the N–H···N hydrogen bond is worth around −6 kcal mol^{-1} and that the C–H···O bond is correspondingly weak. A combination of a moderate to strong interaction and a weak interaction therefore seems to be sufficient to achieve synthon robustness. Such robustness almost surely arises from the two-point nature of synthon **II**. All this augurs well for the reliability of other strong/weak interaction combinations in crystal engineering because of the concomitant predictability of the design exercise.

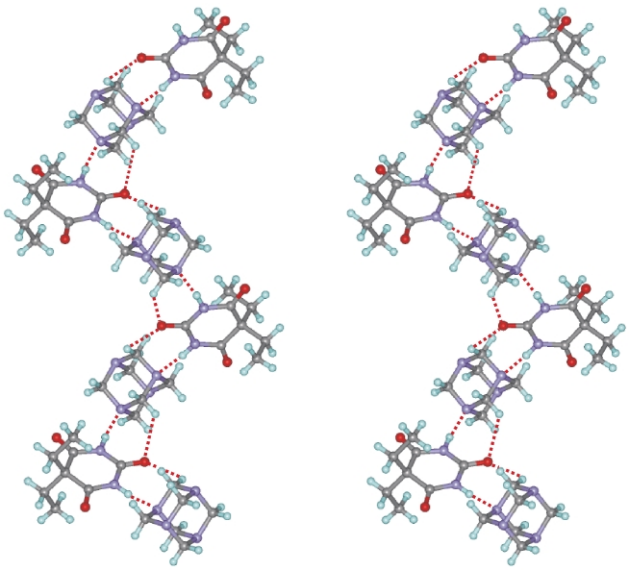


Fig. 3 Stereoview of the helix structure in 1:1 complex of barbital and urotropine.

P. V. thanks the CSIR, New Delhi for the award of an SRF. G. R. D. and M. J. thank the DST-KBN for a collaborative grant (INT/POL/008/00). The research of M. J. was partially supported by the HHMI. G. R. D. acknowledges continuing cooperation from the Cambridge Crystallographic Data Centre and Accelrys Inc.

Notes and references

† While there is some subjectivity in the use of the terms 'strong' and 'weak' as applied to hydrogen bonds, the convention used here is as described in ref. 6.

‡ The compounds were purchased and used as such in the complexation experiments.

§ *Crystal data*: **1**·acridine: $C_8H_{12}N_2O_3{\cdot}2(C_{13}H_9N)$, M = 542.62, monoclinic, space group $C2/c$, a = 18.249(4), b = 16.260(3), c = 10.053(2) Å, β = 111.47(3)°, V = 2776.0(10) Å^3, Z = 4, D_c = 1.298 Mg m^{-3}, T = 100 K, 3138 unique reflections, $R1$ = 0.043, $wR2$ = 0.106. CCDC 186035. **1**·1,10-phenanthroline: $C_8H_{12}N_2O_3{\cdot}C_{12}H_8N_2$, M = 364.40, monoclinic, space group $P2_1/c$, a = 12.656(3), b = 7.014(1), c = 20.665(4) Å, β = 98.31(3)°, V = 1815.1(6) Å^3, Z = 4, D_c = 1.333 Mg m^{-3}, T = 100 K, 4096 unique reflections, $R1$ = 0.060, $wR2$ = 0.124. CCDC 186036. **1**·urotropine: $C_8H_{12}N_2O_3{\cdot}C_6H_{12}N_4$, M = 324.39, orthorhombic, space group *Pbca*, a = 10.866(2), b = 13.263(3), c = 22.634(5) Å, V = 3262.0(11) Å^3, Z = 8, D_c = 1.321 Mg m^{-3}, T = 100 K, 3736 unique reflections, $R1$ = 0.065, $wR2$ = 0.119. CCDC 186037. See http://www.rsc.org/suppdata/cc/b2/b204388b/ for crystallographic data in .cif or other electronic format. KUMA CCD detector, ω scan mode. Structure solution and refinement with standard methods (SHELX97); H-atoms refined isotropically.

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