

# The C–H···O Hydrogen Bond: Structural Implications and Supramolecular Design

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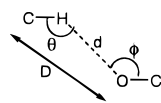
## Introduction

The C–H···O hydrogen bond is so well-established in structural chemistry that it seems difficult now to believe that when Sutor proposed the existence of this type of hydrogen bond in the early 1960s,<sup>1,2</sup> her suggestion was drowned in scepticism, if not outright hostility.<sup>3</sup> It was only two decades later, with Taylor and Kennard's paper, that the subject was properly revived.<sup>4</sup> Shortly thereafter, an Account appeared from this laboratory describing the role of the C–H···O interaction in crystal engineering.<sup>5</sup> Subsequently, one felt confident enough to term these erstwhile "interactions" hydrogen bonds, in a second Account.<sup>6</sup> A recent invitation to contribute another Account and the many recent efforts in this direction by my students and postdoctorals have led to the present paper.

It is clearly no longer necessary to justify the relevance of C–H···O hydrogen bonds, so widely invoked are they in small-molecule and biological crystallography. The presence of O-atoms in a large majority of organic molecules means that this hydrogen bond is widespread, even if not identified in many cases. However, other questions concerning these weak hydrogen bonds could be posed: (1) What is their upper distance limit? (2) Are very short, bent bonds significant? (3) Why do C–H···O bonds sometimes disturb the strong O–H···O and N–H···O network? Alternatively, why do hydrogen bond donors and acceptors not always pair in descending order of strength? (4) How important is cooperativity for weak hydrogen bonds? (5) Are C–H···O hydrogen bonds responsible for crystal packing, or are they the forced consequences of packing? (6) Are weak hydrogen bonds robust enough for supramolecular synthesis and crystal engineering? (7) Does the C–H···O hydrogen bond have any biological significance? These difficult questions cannot be answered fully. This Account attempts to address some of them, but better answers can only follow from further work.

## C–H···O Lengths and Angles

The usual convention for the representation of lengths ( $D$ ,  $d$ ) and angles ( $\theta$ ,  $\phi$ ) is followed here.

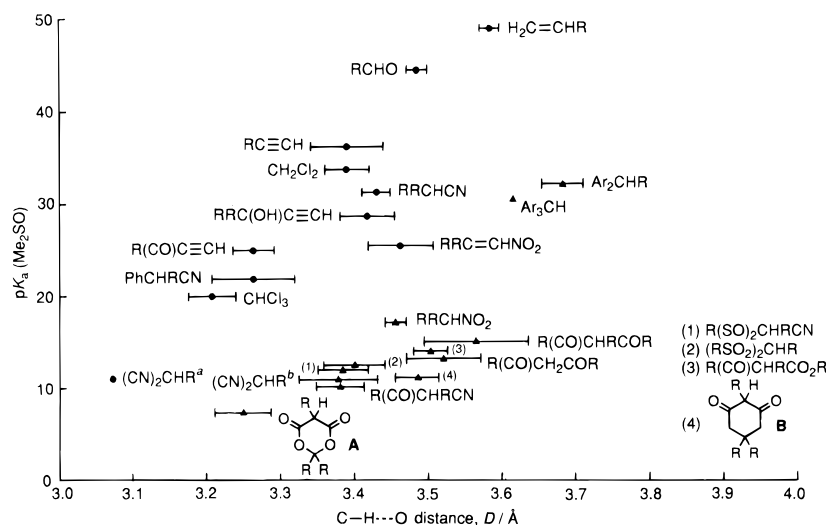


Gautam R. Desiraju was born in Madras in 1952 and received his B.Sc. at the University of Bombay in 1972. He obtained his Ph.D. from the University of Illinois at Urbana-Champaign in 1976 and is now a Professor of Chemistry at the University of Hyderabad. He has worked in the research laboratories of Eastman Kodak (1976–1978) and Dupont (1988–1989). His present research interests include crystal engineering, supramolecular chemistry, solid state reactions, and drug design. The topic of C–H···O hydrogen bonding is threaded through all these areas and has been the subject of previous Accounts in 1986 and 1991.

In any hydrogen bond X–H···O (X = C, N, O), the length,  $D$ , of X···O depends on the acidity of the X–H group and to a somewhat lesser extent on the basicity of the O-atom. That C···O bond lengths are affected by C–H group acidity was shown earlier for the series  $\text{Cl}_3\text{C–H}$ ,  $\text{Cl}_2\text{RC–H}$ ,  $\text{CIRR}'\text{C–H}$ ,  $\text{RR}'\text{R}''\text{C–H}$ .<sup>7</sup> These and further studies on simple alkynes and alkenes confirmed that the more acidic a particular type of C–H group, the shorter are the C–H···O bonds it forms.<sup>8</sup> We used the Cambridge Structural Database (CSD);<sup>9</sup> with a weak hydrogen bond such as C–H···O, a statistical approach is necessary to evaluate a standard  $D$  length for a particular type of C–H group because of the deforming effects of other interactions in the crystal. Now, almost any H-atom, ranging from those in weakly acidic methyl groups to those in strongly acidic alkynes<sup>8</sup> and cyclopropanes,<sup>10</sup> forms C–H···O hydrogen bonds. So, we extended our studies to a large variety of carbon acids, to obtain the results illustrated in Figure 1.<sup>11</sup>  $D$  values span the range 3.00–4.00 Å, and this sets a reasonable upper limit for a C–H···O hydrogen bond. The data, however, are not distributed randomly; rather, mean  $D$  values for chemically distinct C–H groups correlate well with mean  $\text{p}K_a$  values in DMSO for representative compounds within each of the functional groups considered. Interestingly, this correlation extends to C···O distances as long as 4.00 Å, and such an observation follows from the electrostatic nature of the C–H···O hydrogen bond.

Another feature to emerge from Figure 1 is that solid state acidity depends on both electronic and steric factors. There are two broad categories of carbon acids. In the first category the C–H groups have single atoms as  $\alpha$ -substituents ( $\text{CHCl}_3$ ,  $\text{CH}_2\text{Cl}_2$ ), are part of an  $\text{sp}^2$  system ( $\text{RR}'\text{C}=\text{CH–NO}_2$ ,  $\text{H}_2\text{C}=\text{CHR}$ ), or are otherwise sterically unhindered ( $\text{RC}\equiv\text{C–H}$ ,  $\text{RCHR}'\text{CN}$ ,  $\text{RCHO}$ ; ● in Figure 1). Here, mean  $D$  values are well-correlated with  $\text{p}K_a$  values for the respective substituent group. This correlation is as good as that between DMSO and gas phase acidities. In the second category, the C–H group is part of a bulkier moiety and mean  $D$  values are restricted to a narrow range between 3.38 and 3.52 Å [ $(\text{RSO}_2)_2$ -

(1) Sutor, D. J. *Nature* **1962**, *68*, 195.(2) Sutor, D. J. *J. Chem. Soc.* **1963**, 1105.(3) Donohue, J. In *Structural Chemistry and Molecular Biology*; Rich, A., Davidson, N., Eds.; W. H. Freeman: San Francisco, 1968; pp 459–463.(4) Taylor, R.; Kennard, O. *J. Am. Chem. Soc.* **1982**, *104*, 5063.(5) Sarma, J. A. R. P.; Desiraju, G. R. *Acc. Chem. Res.* **1986**, *19*, 222.(6) Desiraju, G. R. *Acc. Chem. Res.* **1991**, *24*, 290(7) Desiraju, G. R. *J. Chem. Soc., Chem. Commun.* **1989**, 179.(8) Desiraju, G. R. *J. Chem. Soc., Chem. Commun.* **1990**, 454.(9) Allen, F. H.; Davies, J. E.; Galloy, J. J.; Johnson, O.; Kennard, O.; Macrae, C. F.; Watson, D. G. *J. Chem. Inf. Comput. Sci.* **1991**, *31*, 204.(10) Allen, F. H.; Lommerse, J. P. M.; Hoy, V. J.; Howard, J. A. K.; Desiraju, G. R. *Acta Crystallogr., Sect. B*, in press.(11) Pedireddi, V. R.; Desiraju, G. R. *J. Chem. Soc., Chem. Commun.* **1992**, 988.



**Figure 1.** A crystallographic scale of carbon acidity as represented by a plot of  $C\cdots O$  distances,  $D$ , vs  $pK_a$ (DMSO) for several functional groups. Sterically unhindered carbon acids are marked with  $\bullet$ , while for those marked  $\blacktriangle$ , the approach of the C–H and O groups is more difficult. For  $(CN)_2CHR$  compounds, a single unclathrated structure is indicated with a superscript  $a$ , while the average of all structures is indicated with a superscript  $b$ .

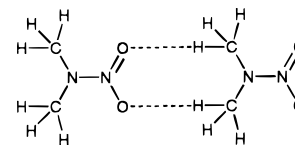
CHR,  $RR'CH-NO_2$ ,  $(RCO)_2CHR$ ;  $\blacktriangle$  in Figure 1]. These observations suggest that mean  $C\cdots O$  distances in crystals are a good measure of carbon acidity when there is little or no steric hindrance to the approach of an O-atom to a C–H group. When such steric hindrance exists, the mean approach of O does not fully reflect the group acidity. This steric factor seems to be all-pervasive. Recent studies show that it can become dominating in the case of  $M-H\cdots O$  hydrogen bonding, in which the hydrogen ligands are bound to the metal core and are often completely embedded within the ligand sheath.<sup>12</sup>

Our results therefore constitute a crystallographic scale of carbon acidity, a property of fundamental importance in physical organic chemistry. Our new scale is of general applicability and can be used for compounds that cannot be measured by the traditional gas phase and solution methods—compounds containing unstable anions, reactive substances, organometallics, and cluster compounds. It is also interesting to view our crystallographic scale of carbon acidity in a more historical perspective. In the early days of NMR, Gutowsky observed that the proton chemical shifts of  $RCOOH$  and  $RCHO$  are not very different. That observation generated the question as to whether the acidities of the two classes of compounds are similar.<sup>13</sup> While it was sensed, even at the time, that NMR chemical shifts do not correlate with group acidity, our results on mean  $D$  values show that such crystallographically derived information does.

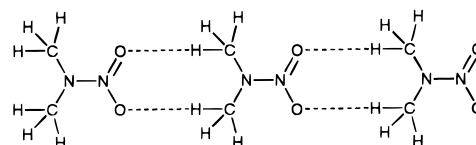
The effect of O-atom basicity on the  $C-H\cdots O$  bond length is far less noticeable than that of C–H group acidity. However, Steiner has shown that basicity effects are revealed when acidity effects are held constant, in other words when very homogeneous and limited sets of compounds are considered. For example, the mean  $D$  value for 13  $C-H\cdots O$  bonds formed by carbonyl O to  $CH_2Cl_2$  is 0.22 Å less than for 17  $C-H\cdots O$  bonds formed by ether O to  $CH_2Cl_2$ .<sup>14</sup> We have approached this issue differently. By using a

very large number of compounds, variations in C–H group acidity cancel out. Accordingly, we found that while the mean  $D$  value for 4205  $C-H\cdots O$  bonds, formed by terminal CO-ligands in Fe-atom organometallics, is 3.51(0.002) Å, the corresponding value for 285 bonds formed by bridging CO-ligands is 3.45(0.009) Å.<sup>15</sup> That the bridged CO-ligand is more basic than the terminal CO-ligand is well-known, and the shortening in the mean  $D$  value of 0.06 Å is just detectable but real.

Interaction cooperativity also increases hydrogen bond strength<sup>16</sup> and is conveniently illustrated with reference to *N,N*-dimethylnitroamine. The crystal structure<sup>17</sup> consists of an infinite ribbon of molecules, but let us concentrate on the hydrogen-bonded dimer **I**. The pair of hydrogen bonds in **I** render the free nitro group more basic and the free methyl groups more acidic, and the hydrogen bonds formed in the trimer **II**, the tetramer, and the pentamer are succes-



**I**



**II**

sively stronger. AM1 calculations show that the average  $C-H\cdots O$  bond energy (per dimer unit) is 3.2, 3.6, 3.8, and 3.9 kcal mol<sup>-1</sup> for **I**, **II**, the tetramer, and

(12) Braga, D.; Grepioni, F.; Tedesco, E.; Biradha, K.; Desiraju, G. R. *Organometallics* **1996**, *15*, 2692–2699.

(13) Parshall, G. W. Personal communication.

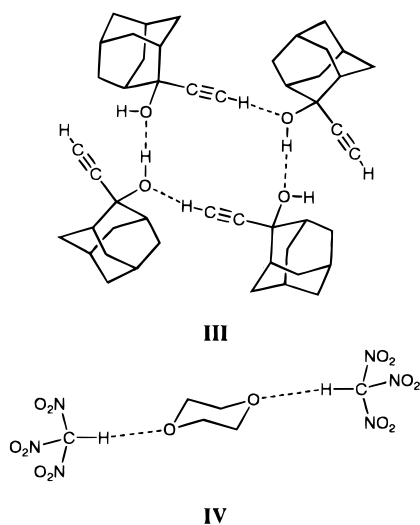
(14) Steiner, T. *J. Chem. Soc., Chem. Commun.* **1994**, 2341.

(15) Braga, D.; Grepioni, F.; Biradha, K.; Pedireddi, V. R.; Desiraju, G. R. *J. Am. Chem. Soc.* **1995**, *117*, 3156.

(16) Jeffrey, G. A.; Saenger, W. *Hydrogen Bonding in Biological Structures*; Springer-Verlag: Berlin, 1991.

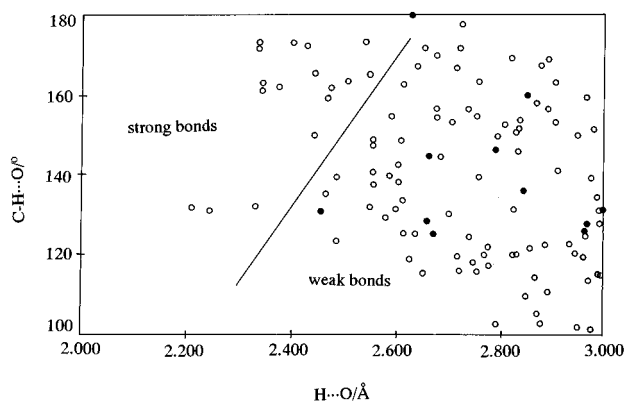
(17) Filhol, A.; Bravic, G.; Rey-Lafon, M.; Thomas, M. *Acta Crystallogr.* **1980**, *B36*, 575.

the pentamer, at which stage the cooperativity effect begins to level off.<sup>18</sup> Again in 2-ethynyladamantan-2-ol, neutron analysis shows that the C–H···O and O–H···O bonds form a cooperative network, **III**, containing one of the shortest ( $d = 2.070$  Å,  $D = 3.135$  Å) and most linear ( $\theta = 173.3^\circ$ ) C–H···O hydrogen bonds known.<sup>19</sup> O–H···O cooperativity affords a C–H···O bond strengthening comparable to that obtained in the 1:2 complex **IV** of dioxane with the very acidic trinitromethane ( $d = 2.01$  Å,  $D = 2.93$  Å), but this bond is much more bent ( $\theta = 143^\circ$ ).<sup>20</sup>



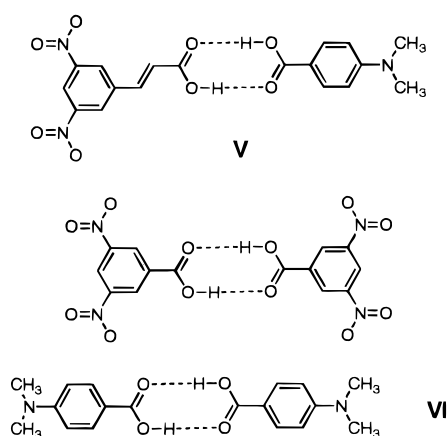
Any analysis of hydrogen bond angles  $\theta$  and O-atom bending angles  $\phi$  must be preceded by a correction of H-atom positions to neutron normalized values because these positions are often determined to only limited accuracy by X-ray diffraction.<sup>16</sup> Additionally, in statistical surveys, these angles should be corrected for the solid angle factor ( $\sin \theta$  or  $\sin \phi$ ) because there is a greater probability for the occurrence of a hydrogen bond at lower values of  $\sin \theta$  (or  $\sin \phi$ ) for purely geometrical reasons.<sup>21</sup> There is a general consensus that linear bonds ( $150^\circ < \theta < 180^\circ$ ) are structurally significant because of the dipole–monopole and dipole–dipole contribution to the electrostatic energy which is a maximum at  $\theta = 180^\circ$  and zero at  $\theta = 90^\circ$ . Therefore, we always use a lower limit of  $110^\circ$  while accepting a C–H···O geometry as a hydrogen bond. Conversely, a very short  $D$  value accompanied by a very bent geometry ( $90^\circ < \theta < 110^\circ$ ) should be regarded with some suspicion. Such a geometry, when *intramolecular*, may not make any bonding contribution to the cohesive energy and may even be repulsive.

So while there is little disagreement regarding very linear and very bent C–H···O geometries, the majority of situations lie somewhere between. Here, a more cautious approach is required. It is helpful to jointly consider bond lengths and angles graphically. Figure 2 is a scatter plot of  $\theta$  angle versus  $d$  (H atom position normalized) for all C–H···O bonds in a series of nine carboxylic acid complexes formed from dimethylami-



**Figure 2.** Scatterplot of C–H···O angles,  $\theta$ , vs H···O distances,  $d$  (C–H normalized to 1.08 Å) for C–H···O hydrogen bonds in nine benzoic acid–cinnamic acid molecular complexes. Bonds marked ● arise from the homodimer complex **VI**.

no-, methoxy-, and nitro-substituted cinnamic and benzoic acids.<sup>22</sup> In eight cases, heterodimers such as **V** are formed by O–H···O hydrogen bonding between dissimilar acid molecules. The ninth, **VI**, is a 1:1



molecular complex of 4-(*N,N*-dimethylamino)benzoic acid and 3,5-dinitrobenzoic acid and contains hydrogen-bonded homodimers. This unexpected homodimer is formed because C–H···O hydrogen bonding in **VI** is much poorer than in the eight heterodimer complexes. Figure 2 contains both strong and weak C–H···O hydrogen bonds as defined by their length and linearity attributes. C–H···O bonds in complex **VI** are shown as filled circles. It is clear that these bonds are neither the shortest nor the most linear in the group. Further, all eight heterodimer complexes contain at least a few C–H···O bonds in the strong bond region.

The angle  $\phi$  is commonly considered to provide information on O-atom lone-pair directionality. Generally  $\phi \approx 120$ – $140^\circ$  for ketonic acceptors, but there are many cases of multiple approaches by C–H groups. Sometimes, as many as four C–H groups form contacts with a carbonyl O-atom (Figure 3).<sup>23</sup> Naturally,  $\phi$  values deviate from  $120^\circ$  in these cases. The formation of multiple C–H···O contacts is not unexpected in such donor-rich systems and could arise from electrostatic factors. The presence of these variable effects indicates that the spread of  $\phi$  angles

(18) Sharma, C. V. K.; Desiraju, G. R. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2345.

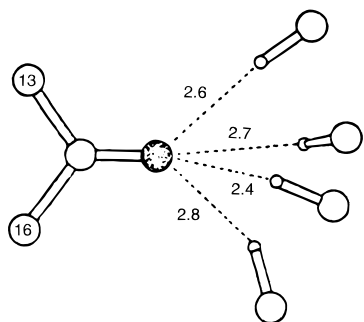
(19) Allen, F. H.; Howard, J. A. K.; Hoy, V. J.; Desiraju, G. R.; Reddy, D. S.; Wilson, C. C. *J. Am. Chem. Soc.* **1996**, *118*, 4081.

(20) Bock, H.; Dienelt, R.; Schodel, H.; Havlas, Z. *J. Chem. Soc., Chem. Commun.* **1993**, 1792.

(21) Kroon, J.; Kanters, J. A.; van Duijneveldt-van de Rijdt, J. G. C. M.; Vliegenhardt, J. *J. Mol. Struct.* **1975**, *24*, 109.

(22) Sharma, C. V. K.; Panneerselvam, K.; Pilati, T.; Desiraju, G. R. *J. Chem. Soc., Perkin Trans. 2* **1993**, 2209.

(23) Desiraju, G. R.; Kashino, S.; Coombs, M. M.; Glusker, J. P. *Acta Crystallogr.* **1993**, *B49*, 880.



**Figure 3.** Multiple C–H···O hydrogen bonds to a single carbonyl O-atom in 7-methyl-15,16-dihydrocyclopenta[*a*]phenanthren-17-one. The atoms are numbered according to steroid nomenclature. The H···O distances ( $d$ ) are shown.

is perhaps larger for C–H···O bonds than it is for O–H···O bonds.

To summarize, many longer C–H···O contacts ( $3.50 < D < 4.00$  Å) could be significant, especially when linear. The  $D$  and  $\theta$  values are jointly reflected in the  $d$  value, which is the chemically meaningful distance. In practice, we employ a liberal  $d$  cutoff of 2.80 Å for H-normalized data. Actually the relevant aspect in database surveys is not that this or that cutoff is correct or incorrect but rather that one uses a consistent and high value throughout. While evaluating individual bonds, the greatest weight is given to those contacts wherein short separations ( $2.00 < d < 2.30$  Å) are accompanied by linear geometries ( $150^\circ < \theta < 180^\circ$ ).

### C–H···O and O–H···O Bonds. How Similar Are They?

Hydrogen bonding is generally associated with elevated melting points. The fact that 1,4-benzoquinone ( $C_6H_4O_2$ ; mp  $116^\circ$ ) melts  $5^\circ$  C higher than resorcinol ( $C_6H_6O_2$ ) is an interesting demonstration of the efficacy of C–H···O hydrogen bonding in crystal packing. Of course, benzoquinone has a very efficiently packed layer structure ( $D = 3.338, 3.433$  Å,  $\theta = 161.3^\circ, 166.4^\circ$ )<sup>24</sup> while resorcinol has an unusually open, even anomalous packing. Perhaps quinol (mp  $174^\circ$ ) provides a fairer comparison. In any event, recent studies show many similarities between C–H···O and O–H···O hydrogen bonds.

A hydrogen bond is an attractive, directional interaction with certain spectroscopic attributes, structure-defining effects, and reproducibility of occurrence. The energy of this bond is dominated by electrostatic factors. However, polarization, charge transfer, and exchange repulsion are also significant. The importance of electrostatics is revealed in the definition, provided by Steiner and Saenger, of a hydrogen bond as “any cohesive interaction X–H···Y where H carries a positive and Y a negative (partial or full) charge, and the charge on X is more negative than on H”.<sup>25</sup> Because of the electrostatic nature of C–H···O hydrogen bonds, long-distance cutoffs are necessary. With such a definition, it is not hard to find similarities between C–H···O and O–H···O hydrogen bonds. Steiner noted a small but significant lengthening of the C–H distance by 0.008 Å upon C–H···O hydrogen

bonding<sup>26</sup> and also that the anisotropic displacement parameters (adp's) of the C–H···O atoms are systematically reduced.<sup>27</sup> We have observed similar effects on adp's in C–H···O bonds in organometallic compounds.<sup>15</sup>

Polarization effects in hydrogen bonding have been quantified with charge density studies. Carroll and Bader found a link between the softness of an acid and the increased penetration of its H-atom by the basic atom.<sup>28</sup> Koch and Popelier found that, for C–H···O bonds, the nonbonded charge density on the H-atom is penetrated more than that on the O-atom.<sup>29</sup> This suggests that the C–H group is a soft acid and that the C–H···O hydrogen bond is a soft hydrogen bond. We came to the same conclusion with a totally different analysis. While CO-ligands in organometallic clusters do not act as good acceptors in strong hydrogen-bonding situations, they readily form C–H···O hydrogen bonds.<sup>15</sup> The soft acceptor CO prefers to hydrogen bond with the soft donor C–H, or alternatively the hard donor O–H prefers to form bifurcated or solvated hydrogen bonds with hard acceptors. In such a scheme of things, one can arrange hydrogen bonds in increasing order of softness: F–H···F < O–H···O < N–H···O < N–H···N < C–H···O < C–H···N < O–H··· $\pi$  < N–H··· $\pi$  < C–H··· $\pi$ .

The similarity between C–H···O and N–H···O hydrogen bonds is revealed by the existence of pairs of isomorphous structures such as the complexes of  $\beta$ -cyclodextrin with diethanolamine, HO–(CH<sub>2</sub>)<sub>2</sub>–NH–(CH<sub>2</sub>)<sub>2</sub>–OH, and pentane-1,5-diol, HO–(CH<sub>2</sub>)<sub>2</sub>–CH<sub>2</sub>–(CH<sub>2</sub>)<sub>2</sub>–OH.<sup>30</sup> These and other examples show that the C–H···O hydrogen bonds are not passive bystanders in crystals but may actively direct crystallization patterns.

### C–H···O Bonds in Crystal Structures

There is general consensus that C–H···O bonds determine crystal packing especially when stronger hydrogen bonding is absent.<sup>31</sup> The occurrence of the O-atom in organic molecules is widespread, and the most common O-atom-containing functional group, the carbonyl group, is one of the best C–H···O hydrogen bond acceptors. Many structures simply cannot be rationalized unless C–H···O hydrogen bonding is actively invoked.<sup>32</sup> On occasion, C–H···O bonding also affects intramolecular conformation. Consider the 11-ethyl (VII) and 11-methoxy (VIII) derivatives of 15,16-dihydrocyclopenta[*a*]phenanthren-17-one.<sup>23</sup> In both dimorphs of VII, the anticipated steric hindrance in the bay region of the steroid results in torsional angles between  $5^\circ$  and  $20^\circ$ . Such distortion is absent in VIII, which is planar because of intramolecular C–H···O bonding ( $d = 1.98$  Å).

Intermolecular effects of C–H···O hydrogen bonding are more clearly manifested. The nitro group, though not very basic, acts as a C–H···O acceptor in the crystal structures of a large number of unsaturated

(26) Steiner, T. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1315.

(27) Steiner, T. *J. Chem. Soc., Chem. Commun.* **1994**, 101.

(28) Carroll, M. T.; Bader, R. F. W. *Mol. Phys.* **1988**, 65, 695.

(29) Koch, U.; Popelier, P. L. A. *J. Phys. Chem.* **1995**, 99, 9747.

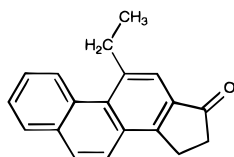
(30) Steiner, T.; Koellner, G.; Gessler, K.; Saenger, W. *J. Chem. Soc., Chem. Commun.* **1995**, 511.

(31) Desiraju, G. R. *Crystal Engineering. The Design of Organic Solids*; Elsevier: Amsterdam, 1989; pp 142–164.

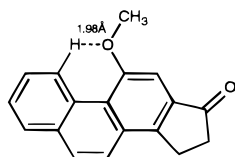
(32) Seiler, P.; Dunitz, J. D. *Helv. Chim. Acta* **1989**, 72, 1125.

(24) Trotter, J. *Acta Crystallogr.* **1960**, 13, 86.

(25) Steiner, T.; Saenger, W. *J. Am. Chem. Soc.* **1993**, 115, 4541.



VII



VIII

compounds because its conjugation enhances its acceptor ability via cooperativity effects.<sup>33–35</sup> We have already mentioned the anomalous homodimer VI of 3,5-dinitrobenzoic acid and 4-(*N,N*-dimethylamino)-benzoic acid.<sup>22</sup> In solution, both homo- and heterodimers must exist, but because of difficulties in C–H···O bond formation, stacking interactions become significant. We showed that these interactions are much better for homodimers than for heterodimers wherein atom charges within an O–H···O hydrogen-bonded dimer are dissipated because of resonance assistance.<sup>36</sup> Therefore, stacking of aromatic rings can prevail over other types of interactions such as C–H···O and even O–H···O, and such effects should be included when the structures of biomolecules are modeled.<sup>37</sup>

It is important that different types of intermolecular interactions be considered jointly in structure analysis and prediction.<sup>38</sup> This is because the vast majority of crystals are best considered as an interplay between the medium-range isotropic forces (van der Waals) and the long-range anisotropic forces (hydrogen bonding). It is erroneous to think that forces like O–H···O and N–H···O can *solely* control crystal packing and simplistic to try to design crystal structures on the basis of only a single type of intermolecular interaction. Formulation of rules may achieve a certain superficial simplification, but in the long run, one may encounter more exceptions than examples. Against such a backdrop, we have been using a new method, NIPMAT, for the visualization of organic crystal structures.<sup>39</sup> A pictorial matrix is formed using the atoms of a molecular skeleton ( $A_1, A_2, \dots, A_m, \dots, A_n$ ), and the matrix element  $A_m A_n$ , which is defined by the shortest intermolecular contact  $A_m \cdots A_n$  is shown as a gray scale. The shorter the contact, the grayer the square which represents that particular contact. Therefore, the plot obtained is a *simultaneous visual representation of all the intermolecular interactions*. It is possible that two atoms,  $A_m$  and  $A_n$ , may sometimes have more than one short intermolecular contact, and our inability to show more than one  $A_m \cdots A_n$  contact is a limitation of the method.

In the context of C–H···O hydrogen bonding, Figure 4 shows NIPMAT plots for 1,4-benzoquinone<sup>24</sup> and fluoranil.<sup>40</sup> In benzoquinone, the C–H···O bonds are revealed as dark regions in the upper and right

extremities. However, there is an overall grayness to the plot especially in the carbon region, revealing that stacking interactions are also important. The utility of this sort of analysis is confirmed on inspecting the NIPMAT plot of fluoranil. Here, and in the absence of H-atoms, the dominant feature is the dipolar C···O interaction, whose geometry leads to the skewed arrangement of rings, revealed as a pale area in the carbon region (no stacking). A comparison of these NIPMAT plots shows that the packings of benzoquinone and fluoranil are fundamentally different. Consideration of a single NIPMAT plot allows a simple but elegant visual assessment of intermolecular interactions in a crystal that is almost impossible otherwise.

### The C–H···O Bond: Crystal Engineering and Supramolecular Design

A major motivation underlying our studies of the C–H···O hydrogen bond has been its utilization in crystal engineering—the deliberate design of organic crystal structures toward solids with predesired aesthetic and functional properties.<sup>31</sup> Crystal engineering proceeds through the stages of observation of structural families, rationalization of observed packings, prediction of new structures, and the testing of predictions in actual structure design. With the realization that the crystal is one of the best examples of a supermolecule,<sup>41,42</sup> crystal engineering is now part of the supramolecular mainstream and may be properly defined as the supramolecular equivalent of organic synthesis. In this context, it is possible to define a supramolecular synthon as *a structural unit within a supermolecule which can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interactions*.<sup>38</sup> Supramolecular synthons are of significance in crystal engineering because they relate molecular and supramolecular structure. They are the smallest structural units which contain all the information inherent in the recognition events through which molecules assemble into supermolecules.

Supramolecular construction may be achieved not only with strong hydrogen bonds such as O–H···O and N–H···O but also with weak C–H···O bonds. This is so because of the electrostatic and therefore long-range character of *all* hydrogen bonds. In this context, a few generalizations are useful: (i) H-atom acidity, bond cooperativity, and a rigid molecular geometry are important for the establishment of C–H···O-based synthons. (ii) Molecules which have the possibility of forming C–H···O bonds and no other directional interaction are preferable choices for supramolecular construction. The absence of O–H···O- and N–H···O-forming functional groups is an advantage. (iii) The number of hydrogen bond donors and acceptors should be matched so that bifurcation is avoided. This is difficult in donor-rich C–H···O systems. (iv) Molecular symmetry may be transformed into supramolecular symmetry using C–H···O directionality. (v) Multiple matching of recognition sites is distinctly advan-

(33) Desiraju, G. R.; Pedireddi, V. R. *J. Chem. Soc., Chem. Commun.* **1989**, 1112.

(34) Pécaut, J.; Masse, R. *J. Mater. Chem.* **1994**, *4*, 1851 and references cited therein.

(35) Masse, R. *Nonlinear Opt.* **1995**, *9*, 113.

(36) Gilli, G.; Bellucci, G.; Ferretti, V.; Bertolasi, V. *J. Am. Chem. Soc.* **1989**, *111*, 1023.

(37) Pascard, C. *Acta Crystallogr.* **1995**, *D51*, 407.

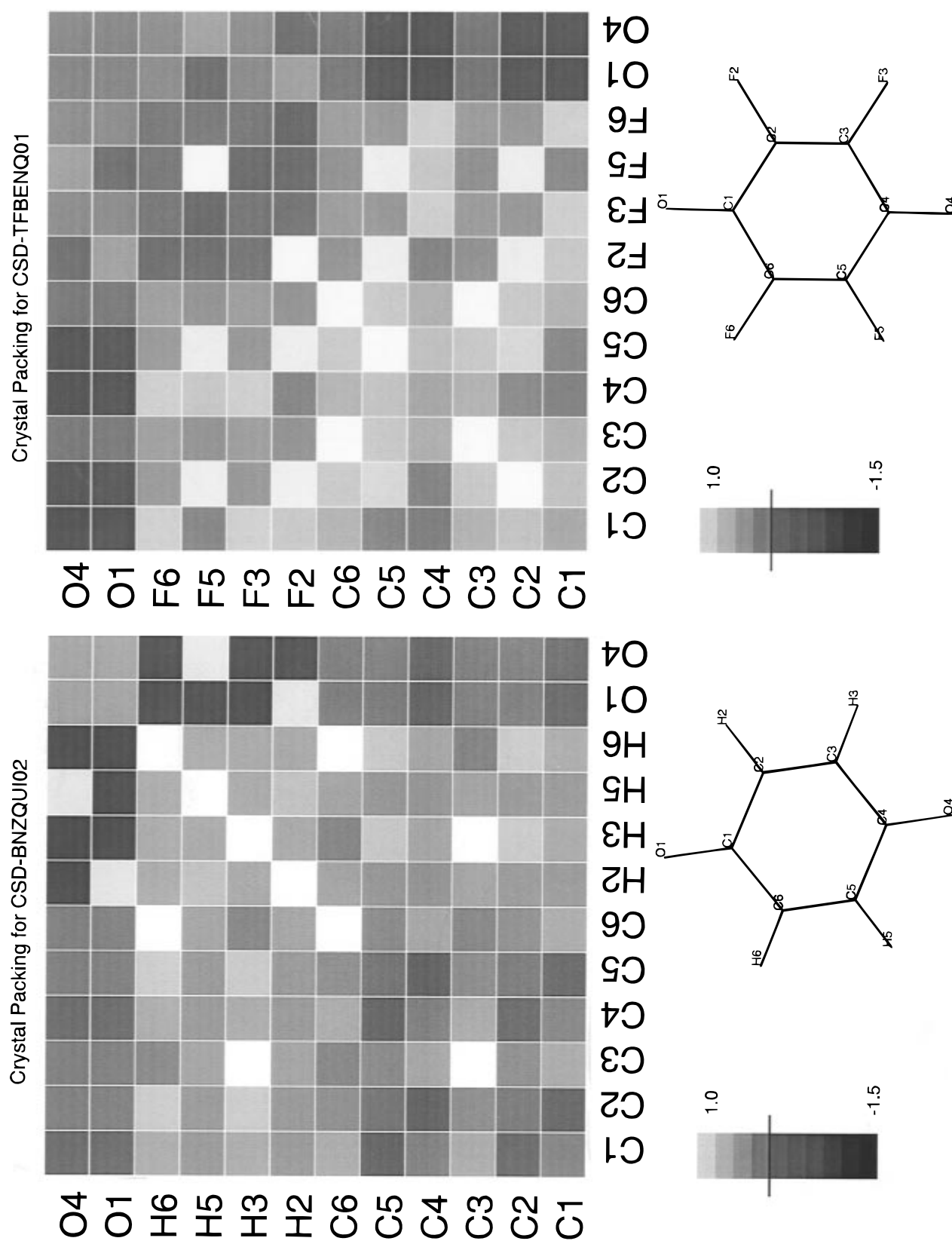
(38) Desiraju, G. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2311.

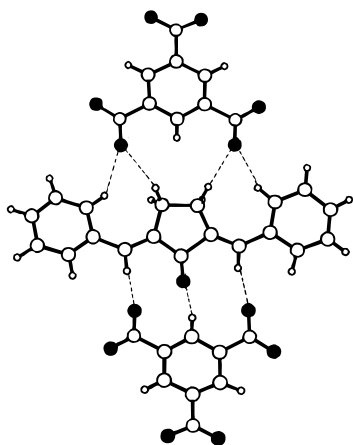
(39) Rowland, R. S. *Am. Cryst. Assoc. Abstr.* **1995**, *23*, 63 (Abstract 2a.5.B, Montreal Meeting).

(40) Hagen, K.; Nicholson, D. G.; Saethre, L. J. *Acta Crystallogr.* **1987**, *C43*, 1959.

(41) *Perspectives in Supramolecular Chemistry: The Crystal as a Supramolecular Entity*; Desiraju, G. R., Ed.; Wiley: Chichester, 1996; Vol. 2.

(42) Desiraju, G. R. In *Comprehensive Supramolecular Chemistry*; MacNicol, D. D., Toda, F., Bishop, R., Eds.; Pergamon: Oxford, 1996; Vol. 6.

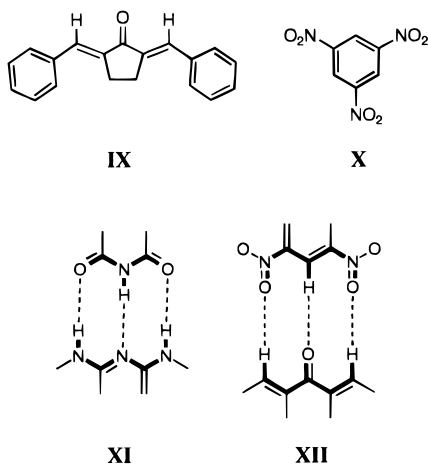




**Figure 5.** C–H···O-mediated 2:1 molecular complex of 1,3,5-trinitrobenzene and 2,5-dibenzylidenecyclopentanone. The O-atoms are shaded. The C–H···O bonds are indicated as dashed lines.

tageous. (vi) All possible interactions of a molecule must be considered, because no one type of interaction controls crystal packing entirely.

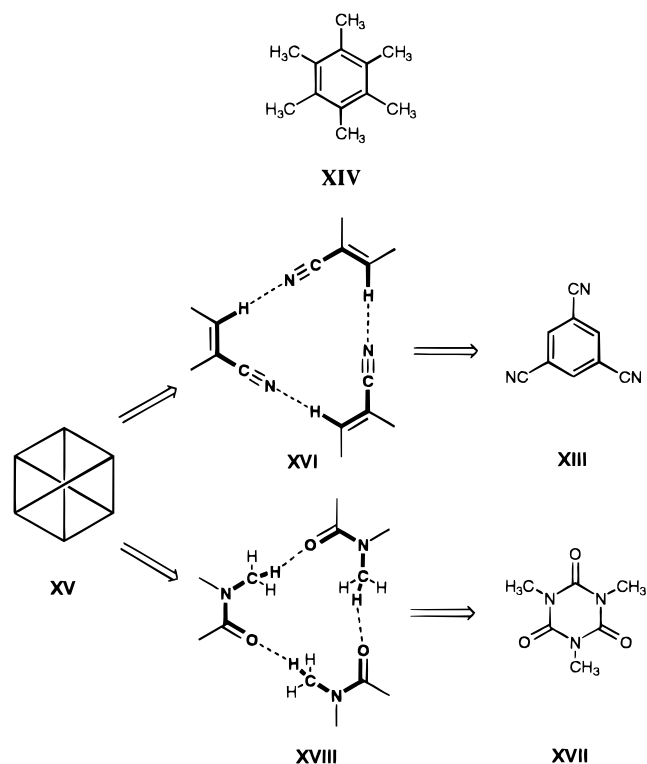
The 1:2 molecular complex of 2,5-dibenzylidenecyclopentanone, **IX**, and 1,3,5-trinitrobenzene, **X**, illustrates some of these ideas (Figure 5).<sup>43</sup> The N–H···O- and N–H···N-based synthon **XI** is well-known.<sup>44,45</sup> By replacing the strong hydrogen bonds in **XI** with C–H···O bonds, the new target **XII** was



obtained. The choice of **X** as a precursor was then quite deliberate. The H-atoms in this molecule are very acidic, and the nitro group is a good acceptor in these cooperative situations. The choice of **IX** as the second molecular component of the supermolecule was made by matching complementary groups. There are seven moderate to strong C–H···O bonds with  $2.30 < d < 2.84 \text{ \AA}$ ,  $3.18 < D < 3.60 \text{ \AA}$ , and  $122^\circ < \theta < 160^\circ$ . Interestingly, **IX** presents an alternative recognition face for the **X** molecule.

Another example is provided by the 1:1 complex of 1,3,5-tricyanobenzene, **XIII**, and hexamethylbenzene, **XIV**. This complex was obtained by retrosynthetic

analysis of the trigonal network **XV**, leading to synthon **XVI**, which in turn leads to the molecular precursor **XIII**.<sup>46</sup> Such an analysis follows from the known linearity of C–H···N hydrogen bonds.<sup>47</sup> Pure **XIII** contains a slightly modified form of network **XV**<sup>48</sup> while recrystallization of a 1:1 mixture of **XIII** and **XIV** leads to the desired network (Figure 6).<sup>46</sup> Conceivably, the presence of **XIV** leads to a certain amount of structural insulation which is conducive to the formation of the lamellar structure. This type of insulation is enhanced in the 1:1 molecular complex of **X** with trimethylisocyanurate, **XVII**, the design of which was accomplished retrosynthetically via synthon **XVIII** (Figure 7).<sup>49</sup> Unlike the layers of **XIII** and



**XIV**, which are offset because of donor–acceptor complexation (leading to a reduction of crystal symmetry to monoclinic), the molecular symmetries of **X** and **XVII** are carried over into the crystal (space group  $P6$ ). The molecular layers are rotated therefore by  $60^\circ$  to yield a honeycomb structure.

It is still unclear when this kind of carryover of molecular symmetry into the crystal is effective, contradicting, as it seems to, Kitaigorodskii's laws of close-packing.<sup>50</sup> However, when it occurs, it allows for the construction of elaborate supramolecular structures. The 1:2 complex of 1,3,5-tetrabromoadamantane, **XIX**, and hexamethylenetetramine, **XX** (Figure 8), is face-centered cubic, with **XIX** molecules at the cell corners and **XX** molecules tetrahedrally situated in alternating octants (as in cubic ZnS).<sup>51</sup> These

(46) Reddy, D. S.; Goud, B. S.; Panneerselvam, K.; Desiraju, G. R. *J. Chem. Soc., Chem. Commun.* **1993**, 663.

(47) Dhurjati, M. S. K.; Sarma, J. A. R. P.; Desiraju, G. R. *J. Chem. Soc., Chem. Commun.* **1991**, 1702.

(48) Reddy, D. S.; Panneerselvam, K.; Desiraju, G. R.; Carrell, C. J.; Carrell, H. L. *Acta Crystallogr.* **1995**, C51, 2352.

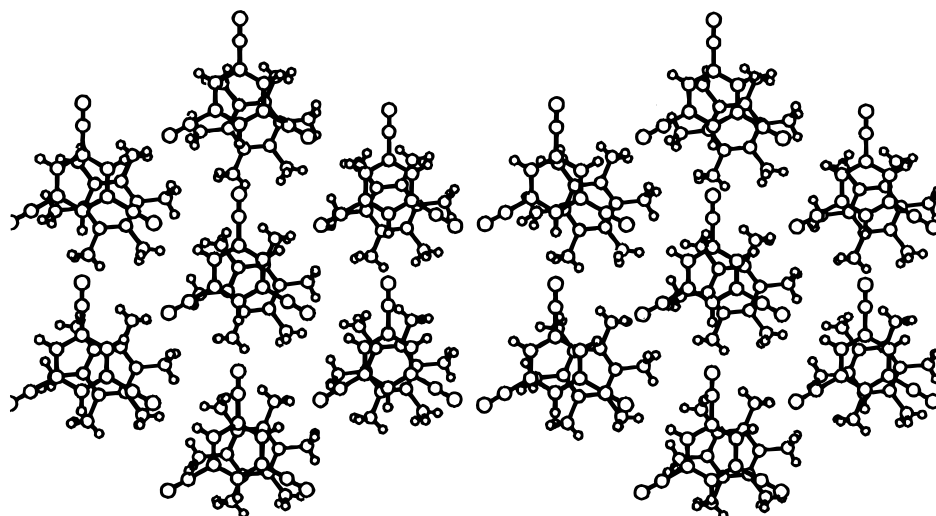
(49) Thalladi, V. R.; Panneerselvam, K.; Carrell, C. J.; Carrell, H. L.; Desiraju, G. R. *J. Chem. Soc., Chem. Commun.* **1995**, 341.

(50) Kitaigorodskii, A. I. *Molecular Crystals and Molecules*; Academic: New York, 1973.

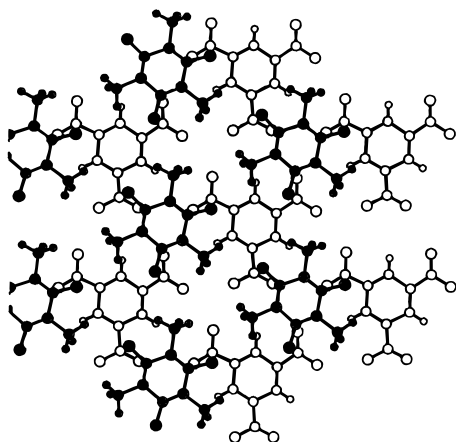
(43) Biradha, K.; Sharma, C. V. K.; Panneerselvam, K.; Shimoni, L.; Carrell, H. L.; Zacharias, D. E.; Desiraju, G. R. *J. Chem. Soc., Chem. Commun.* **1993**, 1473.

(44) Lehn, J.-M.; Mascal, M.; DeCian, A.; Fischer, J. *J. Chem. Soc., Perkin Trans. 2* **1992**, 461.

(45) Zimmerman, S. C.; Kwan, W.-S. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 2404.

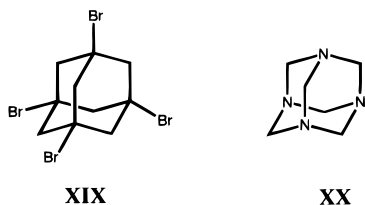


**Figure 6.** Stereoview of the lamellar structure of the 1:1 molecular complex 1,3,5-tricyanobenzene-hexamethylbenzene. Only the former molecules are C-H...N hydrogen bonded. Note the stacking interactions between layers.



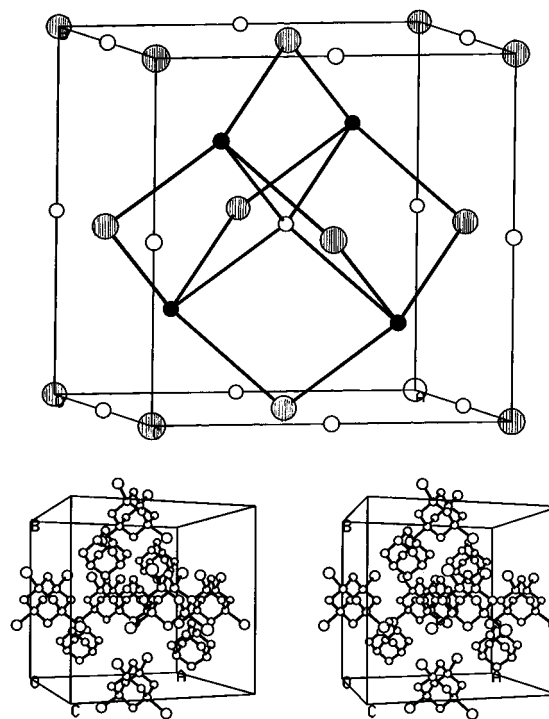
**Figure 7.** Lamellar structure of the 1:1 molecular complex trimethylisocyanurate-1,3,5-trinitrobenzene. Only the former molecules (shaded) are C-H...O hydrogen bonded. Note the hexagonal packing.

molecules are held by four sets each of three equivalent C-H...N hydrogen bonds ( $D = 3.77 \text{ \AA}$ ,  $\theta = 151^\circ$ ), forming a large adamantoid cavity containing the second (disordered) molecule of **XX**. Such "organic zeolites" allow for the study of host-guest and other properties.



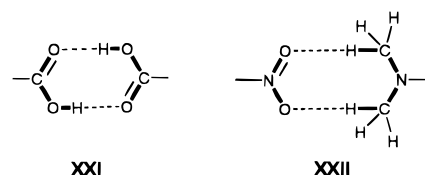
A crystal then may be thought of as a retrosynthetic target, and retrosynthetic thinking is accordingly of great importance in solid state supramolecular synthesis because it could be the basis of new and interesting approaches to crystal design. The ribbon-based structure of terephthalic acid is well-known and consists of a linear array of phenyl rings and carboxyl

(51) Reddy, D. S.; Craig, D. C.; Rae, A. D.; Desiraju, G. R. *J. Chem. Soc., Chem. Commun.* **1993**, 1737.



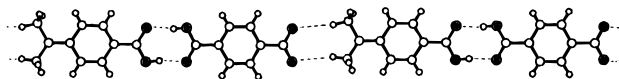
**Figure 8.** (a, top) Schematic view of the crystal structure of the 1:2 complex 1,3,5,7-tetrabromoadamantane-hexamethylenetetramine. Molecules are shown as spheres. The large spheres are  $\text{AdBr}_4$ ; the small shaded and unshaded spheres are hmt at crystallographically distinct sites. (b, bottom) Actual structure showing molecular detail.

dimer synthons, **XXI**. By replacing alternating synthons with the nitrodimethylamino synthon, **XXII**,



encountered already in *N,N*-dimethylnitroamine, the crystal structure of the 1:1 complex of 4-nitrobenzoic





**Figure 9.** Ribbon structure of the 1:1 complex 4-nitrobenzoic acid–4-(*N,N*-dimethylamino)benzoic acid. O-atoms are shaded. Note that both C–H···O and O–H···O hydrogen bonds are present.

acid and 4-(*N,N*-dimethylamino)benzoic acid is readily realized (Figure 9).<sup>18,52</sup>

### A Look to the Future

As one obtains strong and weak covalent bonds, one obtains strong and weak hydrogen bonds, and studies of C–H···O hydrogen bonding have, in turn, led to much work on other weak hydrogen bonds, to an appreciation of polarization effects in hydrogen bonding and the concept of softness of a hydrogen bond, and to the consideration of this bond as a general three-center–four-electron interaction.<sup>53</sup> In effect, the C–H···O bond has emerged as the archetype of the weak hydrogen bond. The C–H···N bond is very common,<sup>46</sup> but more unusual are O–H··· $\pi$ ,<sup>19,54</sup> C–H··· $\pi$ ,<sup>55</sup> O–H···M, and M–H···O bonds.<sup>53</sup> Whether a C–H···F hydrogen bond<sup>56</sup> (with its soft donor–hard acceptor combination) exists is an open question. Also the C–H···Cl bond, if it exists, appears to be sufficiently different from a C–H···O bond.<sup>29</sup> Yet, there is evidence for C–H···S and C–H···Se hydrogen bonds.<sup>57,58</sup>

The importance of C–H···O hydrogen bonding in biological systems has received recent attention.<sup>37,59</sup> The incomplete coordination capabilities of water in biomolecules are often satisfactorily fulfilled with C–H···O bonds.<sup>60</sup> C–H···O hydrogen bonds in nucleic

(52) Sharma, C. V. K.; Panneerselvam, K.; Pilati, T.; Desiraju, G. R. *J. Chem. Soc., Chem. Commun.* **1992**, 832.

(53) Brammer, L.; Zhao, D.; Ladipo, F. T.; Braddock-Wilking, J. *Acta Crystallogr.* **1995**, *B51*, 632 and references cited therein.

(54) Viswamitra, M. A.; Radhakrishnan, R.; Bandekar, J.; Desiraju, G. R. *J. Am. Chem. Soc.* **1993**, *115*, 4869.

(55) Steiner, T. *J. Chem. Soc., Chem. Commun.* **1995**, 95.

(56) Shimoni, L.; Carrell, H. L.; Glusker, J. P.; Coombs, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 8162.

(57) Novoa, J. J.; Rovira, M. C.; Rovira, C.; Veciana, J.; Tarrés, J. *Adv. Mater.* **1995**, *7*, 233.

(58) Iwaoka, M.; Tomoda, S. *J. Am. Chem. Soc.* **1994**, *116*, 4463.

(59) Glusker, J. P. *Acta Crystallogr.* **1995**, *D51*, 418.

(60) Steiner, T. *Acta Crystallogr.* **1995**, *D51*, 93.

(61) Leonard, G. A.; McAuley-Hecht, K.; Brown, T.; Hunter, W. N. *Acta Crystallogr.* **1995**, *D51*, 136.

(62) Derewenda, Z. S.; Lee, L.; Derewenda, U. *J. Mol. Biol.* **1995**, *252*, 248.

(63) Lehn, J.-M. *Supramolecular Chemistry*; VCH: Weinheim, 1995.

(64) Robertson, J. M. *Organic Crystals and Molecules*; Cornell University Press: Ithaca, NY, 1953; p 239.

acid and protein structures are only now being documented.<sup>61,62</sup> Their implication in substrate–receptor recognition and drug design strategies is imminent. A major conclusion from these studies is that the factors which control hydrogen bond strength in small organic molecules, that is, H-atom acidity, cooperativity, resonance assistance, and the presence and absence of proximal groups, are the *only* ones important in macromolecules. So important are these weak bonds that it is felt that crystallographic refinement programs with stereochemical or energy restraints that treat nonbonded C···O separations as exclusively repulsive should be revised;<sup>62</sup> clearly small-molecule and macromolecular crystallography are closely related.

In conclusion, the major realization from a study of C–H···O hydrogen bonding is that crystal structures cannot be rationalized and predicted from considerations of strong hydrogen bonding alone. The formation of strong and weak hydrogen bonds in crystals of even deceptively simple organic molecules is governed by a complex hierarchy of electrostatic and polarization preferences. This is in keeping with general trends in chemistry, which is now concerned more than ever with systems of increasing delicacy and complexity.<sup>63</sup> However, the past is always implicit in the present, and as we look to the future, it is sobering to note that so much that is known today about C–H···O hydrogen bonding is encapsulated in this more than 40 year old extract from the work of J. Monteath Robertson who stated that “Another generalisation derived from a study of these various crystal structures is what may be termed the principle of maximum hydrogen bonding. All the available hydrogen atoms attached to electronegative groups, are generally employed in hydrogen bond formation. Some of the bonds formed may be weaker than others, but the molecular packing is generally capable of adjustment in such a way as to permit the fulfilment of this condition.”<sup>64</sup>

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