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C-H...O HYDROGEN BONDING AND THE DELIBERATE DESIGN OF ORGANIC CRYSTAL STRUCTURES

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Abstract: The C-H...O interaction, though weak, is not van der Waals in nature but electrostatic and resembles O-H...O and N-H...O hydrogen bonds in its geometrical properties. Spectroscopic evidence hints at some degree of covalent bonding between H and O atoms. The long-range, electrostatic character of the C-H...O interaction determines its important role in crystal engineering. Planar aromatic hydrocarbons adopt herringbone structures but if a critical number of O atoms is present, a planar molecule will cross the structural threshold from a C...H stabilised herringbone structure to a C-H...O stabilised layer structure wherein adjacent molecules are parallel and highly overlapped. These ideas have been used to design a family of crystal structures of alkoxyphenylpropionic acids that participate in an intermolecular, solid state Diels-Alder reaction. When the number of C-H...O interactions in a structure is unusually large or small, there is a possibility of distortions in the O-H...O network.

Keywords: C-H...O hydrogen bonds, crystal engineering, intermolecular interactions, cambridge structural database, infrared spectroscopy, crystal packing

The study of intermolecular interactions is of fundamental importance to organic solid state chemistry, because these interactions determine crystal structures while the structures in turn determine most of the important physical and chemical properties of solids.¹ This paper deals with C-H...O hydrogen bonds which have become increasingly useful in the crystal engineering of organic molecules. The existence of a C-H...O interaction itself has been debated in the earlier literature. Sutor² and Ramachandran³ believed that these interactions contribute significantly to crystal stability, but Donohue⁴ disagreed with the concept of a C-

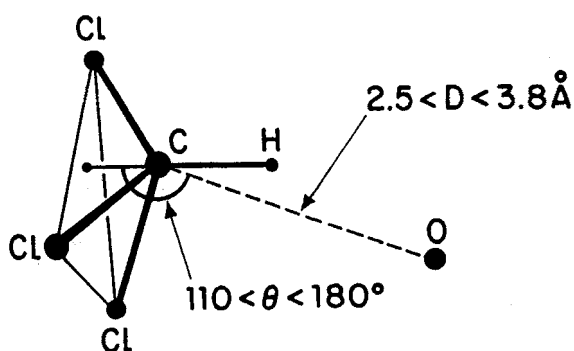
H...O bond. Today many crystallographers and structural chemists accept that these interactions are of significance. There are at least two other areas where the study of C-H...O bonds is likely to prove rewarding: physical organic chemistry and macromolecular crystallography. This is so because the energy of the C-H...O bond (1-2 Kcal/mol) is just in the range where it can compete with conformational forces in small molecules and with forces responsible for the tertiary structure of macromolecules. In this paper an attempt will be made (1) to evaluate C-H...O bonds using criteria which are customary for stronger O-H...O and N-H...O hydrogen bonds: lengths; angles; spectroscopic properties and (2) to understand and apply their role in crystal engineering towards the design of solids with pre-selected properties.

C-H...O LENGTHS

Unlike strong O-H...O and N-H...O hydrogen bonds where O...O and N...O distances cluster within narrow ranges (0.2\AA) of some mean values (say 2.75 and 2.85\AA respectively), C...O lengths in C-H...O bonds are far more variable. Because of the very weakness of the interaction, distortion by other crystal forces results in C...O distances between 3.0 and 4.0\AA . Many will agree that C...O lengths of around 3.2 - 3.3\AA with the C-H group pointing towards the O atom represent good C-H...O interactions. What about C-H...O distances greater than the van der Waals limit, that is where C...O is between 3.5 and 4.0\AA and where there is an equally satisfactory C-H...O angle geometry? In general, it is customary to evaluate the strength of a hydrogen bond on the basis of the shortening of its length from the van der Waals distance, and by this token the longer C...O distances are not significant.

However, the C-H...O contact is not really a van der Waals interaction but is electrostatic in nature, falling off much more slowly with distance. Therefore van der Waals radii are not the best indicators of bond strengths and even 'long' C...O separations (3.50 - 4.00 Å) may have to be considered seriously.

Geometrical properties of weak intermolecular forces are conveniently studied with crystallographic databases because a statistical study of several crystal structures can partly eliminate the distorting effects of other strong interactions, which may differ from structure to structure. In other words, the 'signal-to-noise' ratio for the interaction is enhanced because the 'noise' - the effect of other interactions - is reduced. Such studies may be performed conveniently for C-H...O bonds because of the frequent occurrence of O in organic compounds (68% of 1990 Cambridge Database⁵ entries). Thousands of crystal structures must contain short C...O distances and many of these could arise from C-H...O bonds.



The Cambridge Database was used to retrieve all ordered structures of chloroform solvates which have non-bonded contacts from the C-H group of CHCl_3 to an O atom.⁶ The mean C...O length for the 100 retrieved

contacts with $D < 3.90 \text{ \AA}$ is $3.32(2) \text{ \AA}$. When contacts from C-H groups in compounds of the type RCHCl_2 , R_2CHCl and R_3CH to intermolecular O were also retrieved, the mean C...O lengths obtained for 23, 87 and 868 contacts respectively are $3.40(3)$, $3.46(2)$ and $3.59(1) \text{ \AA}$. Additionally the histograms for each of these four groups of compounds are offset in a stepwise manner showing that shorter C-H...O contacts are obtained for more acidic C-H groups, a typical 'hydrogen-bond' property. The database is useful for such studies - this information could not have been obtained from a few structures, since the histograms overlap almost in the entire range $3.00\text{--}4.00 \text{ \AA}$. Similar results were obtained when C-H...O distances for alkenes ($>\text{C}=\overset{|}{\text{C}}\text{--H...O}$) and the more acidic alkynes ($\text{--C}\equiv\text{C--H...O}$) were compared.⁷

C-H...O ANGLES

The important angular attributes of the C-H...O bond are the C-H...O bending angle, θ and the H...O-C angle ϕ . Observed θ values cluster in the range $150\text{--}160^\circ$, but purely from geometrical considerations and excluding energy factors, the number of A-H...B bonds whose bending angle lies in the range θ to $\theta + d\theta$ is proportional to $2\pi \sin\theta d\theta$.⁸ This geometrical correction leads to a distribution which is clearly indicative of a linear interaction. This tendency towards linearity is shared by both strong and weak C-H...O bonds. In the study of alkene and alkyne C-H...O bonds mentioned above, there is a 50% (alkyne) and 60% (alkene) probability that θ lies in the range $165\text{--}180^\circ$.

Still, the C-H...O bond is essentially electrostatic in character since the H atom tends to point towards the lone pairs of the O atom rather than be repelled by them. So, for carbonyl acceptors, the H...O=C angle ϕ is distributed around 120° and the C-H

group lies in the plane defined by the oxygen lone pairs. For ethereal acceptors, the C-H bond tends to be in the plane of the oxygen lone pairs, but the directional preferences within this plane, say towards the conventional lone pair directions, are far less apparent.

SPECTROSCOPIC STUDIES

If the C-H...O interaction is to be termed a hydrogen bond, appropriate spectroscopic measurements should reveal the effects of such bonding. IR spectroscopy is usually the method of choice. However, the weakness of the C-H...O bond causes problems. Sim attempted to correlate IR spectral shifts (solution-solid state) of the C(sp)-H bond in a pair of terminal alkynes with the corresponding C...O length in the crystal.⁹ However, this work was inconclusive in that the two C-H...O bonds have more or less identical geometrical properties (D , θ , ϕ) and yet have significantly different spectral shifts. Such anomalies are owing to the fact that C...O geometries are easily perturbed by stronger interactions. A statistical approach is again preferable. Sim's work was repeated with nine terminal acetylenes and a good correlation was noted between the solid state C(sp)-H stretching frequencies and intermolecular C...O distances.¹⁰ One of the two compounds studied by Sim now appears to be an outlier. A closer approach of the O atom progressively weakens the acetylenic C-H bond suggesting that the C-H...O contact is a bonding interaction. In general, however, a sufficiently activated C-H group is required to observe consistent spectral shifts, and most spectroscopic studies of C-H...O bonding deal with compounds such as acetylenes, quinones and heterocycles. The lack of

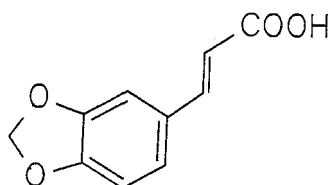
proper spectroscopic evidence for C-H...O bonds formed by weakly acidic C-H groups could arise from the fact that the spectral shifts are just not large enough or that alternatively, C-H...O interactions of weakly and strongly acidic C-H groups may be fundamentally different.

C-H...O BONDS AND CRYSTAL ENGINEERING

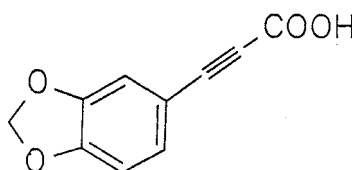
Since C-H...O interactions are electrostatic and effective at long C...O separations, they play an important role in crystal engineering. The significance of these C-H...O interactions in a particular structure increases with their number relative to the stronger O-H...O and N-H...O interactions. The angular properties of the interactions also lead to certain directional preferences, which have been identified previously in crystal structures of planar oxygenated compounds like quinones, coumarins, methylenedioxy and furyl heterocycles^{11,12}. These preferences in turn lead to particular crystal motifs such as a short axis of ca. 4Å. To summarise, the packing arrangements of these planar compounds may be understood only by a consideration of the directional properties of weak C-H...O bonds present in these structures.

Progress has been made in the design of crystal structures of planar oxygenated aromatics, which are determined by an interplay of C...H interactions (which steer to herringbone structures, characterised by adjacent inclined molecules) and C-H...O bonds (which being lateral, steer to stacked sheet structures with short axes of 3.8-4.2Å). Planar aromatic hydrocarbons generally adopt the herringbone structure (or its variants) since C...H interactions predominate,¹³ but their oxygenated derivatives show a pronounced tendency to adopt the stack structure. The O atoms are involved in short

C-H...O contacts which being lateral, can serve in organising the molecules into two-dimensional motifs such as sheets or ribbons. The number of O and H atoms in the molecule seem to determine if a herringbone or stack structure will be formed for a particular compound. To summarise, the stack structure is favoured by higher C:H ratios and these ratios are effectively raised by an increasing number of O atoms.



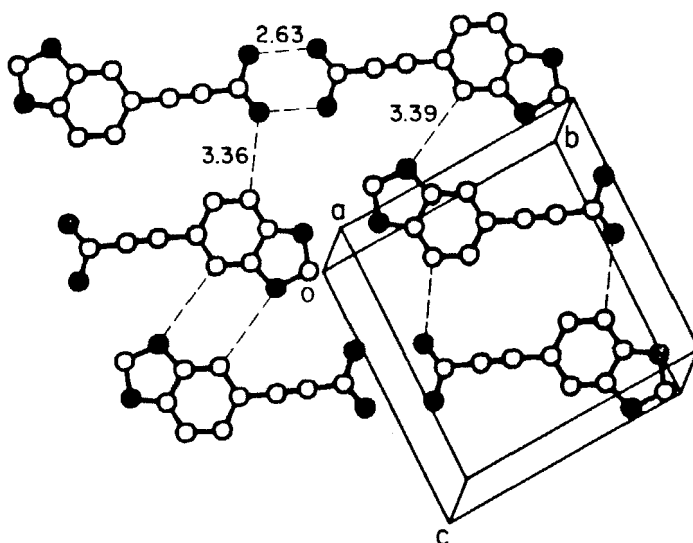
(1)



(2)

These ideas have been applied to the design of crystal structures that permit an intermolecular solid-state Diels-Alder reaction.¹⁴ The strategy involved identification of substances that may act as either diene or dienophile, and further, crystallise in a structure that permits a topochemical 4+2 conversion. Accordingly, substituted phenylpropionic acids were considered, and the starting point in this crystal engineering exercise, the 4Å stack structure of 3,4-methylenedioxycinnamic acid, (1), was chosen deliberately. The crystal structure is layered, the layers being constructed by linking O-H...O bonded centrosymmetric dimers with C-H...O bonds. As described above, other factors being constant, a planar aromatic having a higher C:H ratio prefers the stack structure. Accordingly, one may extrapolate from the stack structure of (1), C₁₀H₈O₄, that of 3,4-methylenedioxyphenylpropionic acid, (2), C₁₀H₆O₄. Both (1) and (2) are planar mole-

cules with similar volumes, shapes and functionalities. The smaller number of H atoms in (2) was expected therefore to enhance the tendency for adoption of a stacked structure.



View of the crystal structure of 3,4-methylenedioxyphenylpropionic acid, (2), down the 4 short axis. O atoms are shaded. C-H...O and O-H...O bonds are shown.

This prediction was confirmed; acids (1) and (2) are isomorphous and the figure above shows that (2) molecules form a compact sheet characterised by O-H...O ($\text{O}\cdots\text{O}$ 2.63 Å) and C-H...O ($\text{C}\cdots\text{O}$, 3.36, 3.39 Å) bonds. These bonds stabilise the sheet motif, and with it, the stack structure. This study was extended to 3,4-dimethoxy and 3,4,5-trimethoxyphenylpropionic acids, both of which are efficiently C-H...O bonded, and both of which form stacked 4 Å-structures. Almost predictably, the unsubstituted phenylpropionic acid $\text{C}_6\text{H}_5\text{C}\equiv\text{CCO}_2\text{H}$ crystallises as an O-H...O hydrogen bonded dimer in the herringbone pattern since the lack of a suffi-

cient number of O atoms results in a dovetailing of terminal phenyl groups so as to optimise C...H interactions. It appears therefore that the presence of a critical number of O atoms will permit a planar aromatic molecule to cross the structural threshold from a C...H stabilised herringbone structure to a C-H....O stabilised stack structure.

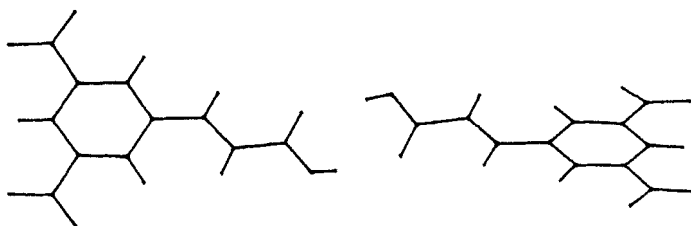
It is known that when phenylpropionic acids (such as (2)) are refluxed with acetic anhydride, they are converted into anhydrides of the corresponding 1-phenylnaphthalene-2,3-dicarboxylic acids.¹⁵ The chemical expedient of forming the symmetrical anhydride, $\text{Ph}(\text{C}\equiv\text{CCO})_2\text{O}$, in situ, brings diene and dienophile components together for a Diels-Alder reaction. By constructing a $4\overset{\text{O}}{\text{\AA}}$ short axis, a similar geometry is achieved in the crystal. Therefore, when crystalline acid (2) is heated (80°C , 1 week) the corresponding Diels-Alder anhydride is produced in fair yields. The other acids with stack structures react similarly, while the unsubstituted acid, which does not have a stack structure, is stable to heating below the melting point.

C-H...O BONDS AS CRYSTAL STRUCTURE DIRECTORS

Usually, the directional preferences of C-H...O bonds are maintained within the framework of stronger forces such as O-H...O and N-H...O hydrogen bonding, $\pi\pi$ stacking and donor-acceptor interactions. However, C-H...O bonds may also be able to discriminate between alternative O-H...O (or other) networks which, though geometrically reasonable are structurally, quite distinct. In this respect, C-H...O bonds may be termed 'crystal-structure-determining'.

An interesting example is provided by 3,5-dinitrocinnamic acid, (3), a molecule which contains several

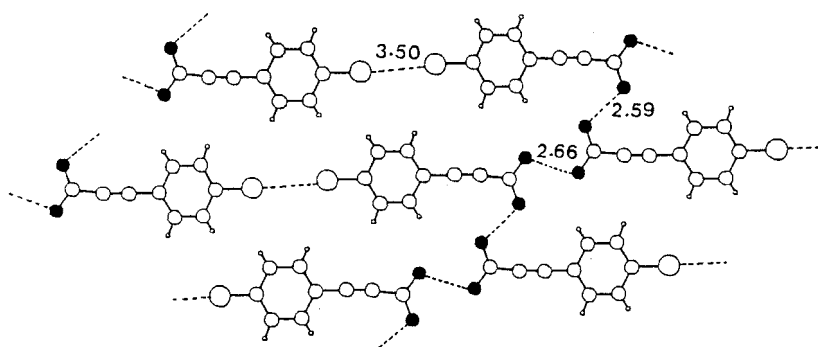
activated H and acceptor O atoms. Acid (3) crystallises as an O-H...O dimer wherein the hydrogen bonded molecules are related, not by an inversion centre as is usual, but by a two-fold rotation axis.¹⁶ Both inversion and two-fold dimers are equienergetic and in principle, both are reasonable possibilities. However, inspection of the crystal structure of acid (3) above shows that there is an extensive C-H...O bond network (7 contacts with $C...O < 3.75\text{\AA}$). These C-H...O bonds dominate the structure, and their combined directional requirements appear to be incompatible with an O-H...O inversion dimer.



Dimer structure of 3,5-dinitrocinamic acid, (3). Notice that the two molecules are related by a 2-fold axis.

In other carboxylic acids such as trans-cinnamic acid, a smaller number of C-H...O bonds stabilise the inversion dimer. In the extreme, there are cases such as 4-chlorophenylpropionic acid, (4), where the complete absence of C-H...O interactions leads to an unexpected hydrogen bonded catemer motif rather than the dimer.¹⁷ It is known that the O-H...O catemer is intrinsically more stable than the dimer. Therefore, if the dimer is to be formed it must be stabilised additionally by C-H...O bonds or in some other manner. Conversely, if the C-H...O bond-forming ability is reduced, the catemer is favoured. Failure of acid (4),

$C_9H_5ClO_2$ to form C-H...O bonds could arise from adverse C:H:O ratios because the crystal structures of 4-chlorobenzoic and 4-chlorocinnamic acids contain C-H...O bonds and the molecules crystallise as dimers.



Crystal structure of 4-chlorophenylpropionic acid, (**4**), down the short axis to show O-H...O and Cl...Cl interactions. Oxygen atoms are shaded. Molecular layers such as shown here are stacked along the short axis. Notice the catemer O-H...O network and the absence of C-H...O interactions.

CONCLUSIONS

C-H...O hydrogen bonds have been largely overlooked in the past, but a critical examination of the crystallographic literature shows that they are not only very common but that they may actually control and direct the crystallisation pathway of organic molecules. Therefore it is in order to re-examine older ideas about crystal packing in this new light. For instance, there is every indication that phenomena such as three-centre-bonding (bifurcation), resonance-assisted and co-operative hydrogen bonding exist for C-H...O networks. It is therefore suggested that chemists will find it worthwhile to consider all interactions, weak (C-H...O, O-H...C(?)) and strong (O-H...O, N-H...O),

while attempting to understand hydrogen bond arrangements and indeed crystal packing itself. In turn, this would enable a more general control over solid state properties.

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