

The C-H...O Hydrogen Bond in Crystals: What Is It?

GAUTAM R. DESIRAJU

School of Chemistry, University of Hyderabad, Hyderabad 500 134, India

Received May 28, 1991 (Revised Manuscript Received September 17, 1991)

The concept of a C-H...O hydrogen bond, which is becoming increasingly important for our understanding of how molecules align themselves in crystals, dates back to Pauling's observation that the boiling point of acetyl chloride (51 °C) is substantially higher than that of trifluoroacetyl chloride (<0 °C). He ascribed this discrepancy to hydrogen-bond formation even though the expected hydrogen-bonding groups are not present.¹ In other early studies, Glasstone suggested that complexes of haloforms with ketones ($X_3C-H...O=C<$) have a definite existence,² while Jeffrey correlated the relatively high melting point of dimethyl oxalate (54 °C) with methyl...carbonyl interactions in the crystal.³ The ever-growing literature on C-H...O bonds, the increasing interest in molecular and crystal engineering,⁴ and the work carried out in our laboratories during the last three years has prompted the writing of the present Account.

Posing the question in the title of this Account in a provocative article,⁵ Donohue gave a derisive answer: "It isn't". His remark proved to be the nemesis of structural chemists, who for more than a decade thereafter shunned the idea of a C-H group forming a hydrogen bond with electronegative atoms. Donohue's comment was a rebuttal to Sutor, who assumed a van der Waals distance of 2.6 Å for the H...O contact and claimed that C-H...O hydrogen bonds exist in caffeine (H...O, 2.07 Å), theophylline (2.25 Å), and other compounds.^{6,7} Donohue, however, argued that the 2.6-Å value was inappropriate. Quoting Ramachandran's values for "normally allowed" (2.4 Å) and "outer limit" (2.2 Å) O...H distances,⁸ he claimed that no special bonding effects are needed to explain Sutor's C-H...O geometries. In retrospect, it is interesting to note that Ramachandran always believed that C-H...O hydrogen bonds exist and that they contribute significantly to the stability of biomolecules!⁹ The distance ranges were apparently mentioned by him merely to alert crystallographers about different types of O...H contacts. In the hiatus that followed, a solitary article by Cohen on the structural chemistry of quinones is noteworthy¹⁰ because it hints that C-H...O bond strengths need not be well-correlated with O...H distances and because it identifies C-H...O interactions as "lateral" in crystal structures of planar molecules.

A landmark study by Taylor and Kennard in 1982 provided conclusive evidence of the existence of C-H...O hydrogen bonds in crystals.¹¹ These authors showed that C-H...O contacts are electrostatic and that they occur within certain distance (C...O, 3.0-4.0 Å) and angle (C-H...O, 90-180°) ranges. We identified these directional preferences in several crystal structures of planar oxygenated compounds,¹² and an Account pub-

lished in 1986 delineates the role of these C-H...O interactions in crystal engineering.¹³ The choice between several competing 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.

Today, there is a consensus that C-H...O bonds have significant implications in many diverse areas of structural chemistry. These interactions are no longer considered an esoteric phenomenon with little practical importance or as a mere hunting ground for crystallographic disputes. Owing to the frequent occurrence of oxygen in organic compounds (68% of 1991 Cambridge Database¹⁴ entries), thousands of crystal structures must contain short C...O distances, many of which could arise from C-H...O bonds. 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. Further, 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. Accordingly, a preferred molecular conformation in an organic solvent may yield to an "unfavorable" conformation in aqueous media because of additional C-H...O stabilization, while an appropriate C-H...O bond may clinch the site of protein folding. C-H...O interactions seem to determine the ordering of CO and alkylidyne molecules in a mixed adsorbate on a clean Pt(111) surface,¹⁵ and to specify the stereochemistry of CH₃OH inclusion within ZSM-5 zeolite channels.¹⁶

In this Account, an attempt has been made to understand the significance of C-H...O hydrogen bonds in organic crystals and to evaluate them more rigorously

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Gautam R. Desiraju was born in Madras in 1952, obtained his Ph.D. in 1976 at the University of Illinois at Urbana-Champaign, and is now a Professor of Chemistry at the Central University of Hyderabad. His research interests are in the area of crystal engineering, molecular recognition, and materials chemistry.

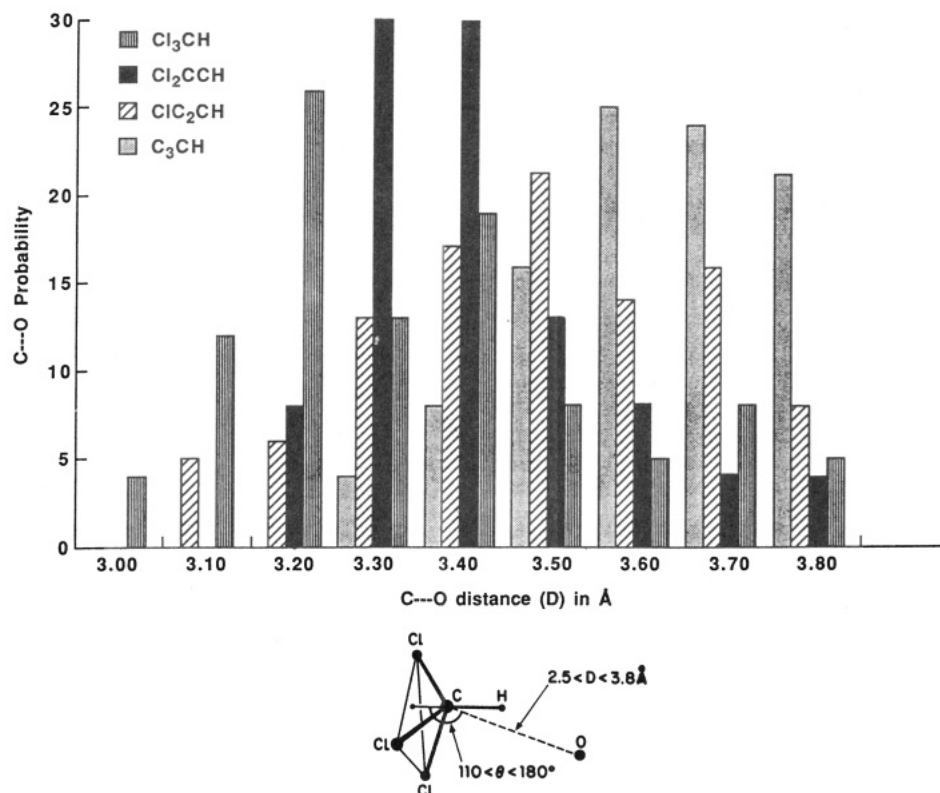
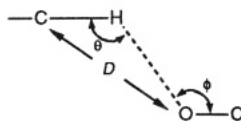


Figure 1. Schematic view of a C-H...O interaction in the compounds $(Cl_{3-n}R_n)CH$ showing chosen limits for distances (D) and angles (θ) along with histograms of C...O distances for the four compound categories ($n = 0, 1, 2, 3$). Note that the histograms are offset according to C-H acidity. C, C₂, and C₃ refer to any alkyl or aryl groups R which are not electron-withdrawing.

using criteria which are customary for the stronger N-H...O and O-H...O hydrogen bonds: lengths, angles, and effects on physical, spectroscopic, and crystallographic properties. One may ask: (a) Are certain intermolecular C-H...O lengths and angles characteristic of certain donor and acceptor groups? (b) Do C-H...O interactions resemble van der Waals forces or O-H...O and N-H...O hydrogen bonds? (c) Are some organic crystal structures defined and controlled by C-H...O interactions, or do structures merely accommodate the C-H...O geometry within the overall framework of van der Waals forces and strong hydrogen bonds?

C-H...O Lengths

The length, D , of a hydrogen bond is one of its most characteristic attributes. For strong bonds, O...O and N...O distances are centered around 2.75 and 2.85 Å, respectively, and cluster within a narrow range (0.2 Å).



These nonbonded distances are significantly shorter than the conventional van der Waals separations.¹⁷ The value of D is more sensitive to the nature of the H atom than to the nature of the basic acceptor: the more acidic the hydrogen, the shorter the bond. For C-H...O bonds, the situation is far less clear-cut. Because of the very weakness of the interaction, C-H...O

bonds can be distorted by other crystal forces and C...O distances with $3.0 < D < 4.0$ Å are common. Here, van der Waals radii are not so helpful.

At this point, it should be emphasized that such radii are empirical quantities that permit only an approximate rationalization of nonbonded distances in crystals. Deviations are marked for weaker interactions. The Sutor-Donohue-Ramachandran controversy arose largely because of the erroneous assumption that a particular set of van der Waals radii are constants of fundamental importance and that interactions may be termed "short" or "long" on this basis. Even anisotropic radii, advocated in recent times,^{18,19} appear to be overparametrized quantities, allowing for good agreement with experiment but offering little by way of chemical insight. In general, the use of any one consistent set of isotropic radii is probably adequate. What is of *chemical* importance is a statistically significant shift toward shorter or longer intermolecular distances within a group of compounds.

The basic problem in evaluating the geometrical attributes of a weak interaction such as the C-H...O hydrogen bond is a high noise-to-information ratio. Since the interaction is so easily deformed, the variation in bond geometry is considerable and even careful crystallographic studies may not lead to sensible conclusions *if the number of structures sampled is small*. If a large number of structures are examined, however, systematic trends in the data may lead to a meaningful chemical result. Chemistry emerges from crystallography. A statistical approach, greatly facilitated by the availa-

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bility of crystallographic databases, is therefore invaluable in the study of weak intermolecular interactions.

Accordingly, let us consider Figure 1, which is a histogram of C...O distances in chloroalkanes (Cl_{3-n}R_n)-C-H...O with 0 ≤ n ≤ 3. The Cambridge Database was used to retrieve all ordered structures of chloroform solvates which have nonbonded contacts from the C-H group of CHCl₃ to an O atom.²⁰ The mean C...O length for the 100 retrieved contacts with D < 3.90 Å is 3.32 (2) Å. When contacts from C-H groups in compounds of the types RCHCl₂, R₂CHCl, and R₃CH to intermolecular O were also retrieved (excluding cases with strongly electron withdrawing substituents, R), the mean C...O lengths obtained for 23, 87, and 868 contacts respectively are 3.40 (3), 3.46 (2), and 3.59 (1) Å. The histograms for these four groups of compounds are offset regularly, showing that, in general, *shorter C-H...O contacts are obtained for more acidic C-H groups*. One must appreciate that this kind of information could not have been obtained from a few structures, since the histograms overlap in almost the entire range 3.00–4.00 Å and, in particular, in the region 3.30–3.80 Å.

A similar analysis was performed for C-H...O bonds involving alkyne (—C≡C—H...O) and alkene (>C=C(R)—H...O) groups.²¹ The mean C...O distance for 105 alkyne geometries is 3.46 (2) Å while that for 622 alkene geometries is 3.64 (1) Å. This large difference cannot be rationalized on the basis of C-H bond length differences but must result from carbon acidity differences between alkyne and alkene C-H groups.

Are C-H...O distances greater than the van der Waals limit significant? The above results show that systematic gradations in C...O distances for different types of very weakly acidic C-H groups extend well beyond the "conventional" van der Waals limit. This means that the C-H...O contact is not really a van der Waals interaction but is primarily electrostatic, falling off much more slowly with distance. Now, electrostatic forces between approaching molecules prior to crystallization (*r*⁻¹ dependence) are effective at distances longer than those at which dispersion forces (*r*⁻⁶) are important. So, even long C...O separations (3.50–4.00 Å) may have to be considered seriously, and C-H...O bonds may have an orienting effect on molecules before the influence is felt of van der Waals forces which will eventually determine the packing of hydrocarbon residues in the crystal. If this is the case, the surprising constancy of the C-H...O angular geometry is readily explained.

C-H...O Angles

The relatively fixed angular geometries of C-H...O bonds are striking because intermolecular angles are usually deformed more easily than lengths. 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). While observed θ values cluster in the range 150–160°, Ramachandran and others have shown that, 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 $2\pi \sin \theta d\theta$.^{11,22,23} This geometrical correction leads to a

distribution that is clearly indicative of a linear interaction.

Curiously, this tendency toward linearity is shared by both strong and weak C-H...O bonds. In the study of 622 alkene and 105 alkyne C-H...O bonds discussed above, there is a 50% (alkyne) and 60% (alkene) probability that θ lies in the range 165–180°. It is interesting that the longer alkene contacts are as linear as (or even more linear than?) the shorter alkyne contacts. In contrast, it appears that, for O-H...O and N-H...O hydrogen bonds, O...O and N...O nonbonded repulsions tend to straighten out the shorter bonds; in other words, the stronger the bond, the more linear it is likely to be.²⁴ That both strong and weak C-H...O bonds are linear would suggest that analogous C...O repulsion is not a major factor in determining bond linearity. Perhaps the C...O distances are too long for such repulsions to exert a significant effect on angle geometry. Alternatively, alkyl-oxygen repulsion (R...O), which is a possibility in alkenes (>C=C(R)—H...O) but not in alkynes (—C≡C—H...O), may result in the alkene contacts being more linear.

That the C-H...O bond is electrostatic in character is evidenced by the fact that the H atom tends to point toward the lone pairs of the O atom rather than be repelled by them, an illustration of the so-called Legon-Millen rules.²⁵ There is general agreement that, for carbonyl acceptors, the H...O=C angle ϕ is distributed around 120° and that the C-H group lies in the plane defined by the O lone pairs. For ethereal acceptors, the C-H bond tends to be in the plane of the O lone pairs, but the directional preferences within this plane, say toward the conventional lone pair directions, are far less apparent. These preferences or lack thereof have been justified theoretically.²⁶

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.²⁷ The C-H stretch in 1,3,5-trichlorobenzene is depressed by 35 cm⁻¹ in the presence of pyridine, the result of a C-H...N bond.²⁸ Sim attempted to correlate IR spectral shifts of the C(sp)-H bond between dilute solution and the solid state with the corresponding C...O length in the crystal.²⁹ However, this work was inconclusive because C-H...O bonds with more or less identical geometrical properties (*D*, θ , ϕ) were found to have significantly different spectral shifts.³⁰ For example, in propargyl 2-bromo-3-nitrobenzoate (C...O, 3.39 Å), the spectral shift between the solid state and dilute CCl₄ solution is 47 cm⁻¹, but in triethylprop-2-ynylammonium *p*-bromobenzenesulfonate (C...O, 3.36 Å), the corresponding shift is 69 cm⁻¹. However, an increase from two to nine in the number of compounds studied sufficed to reveal clear chemical information. When we

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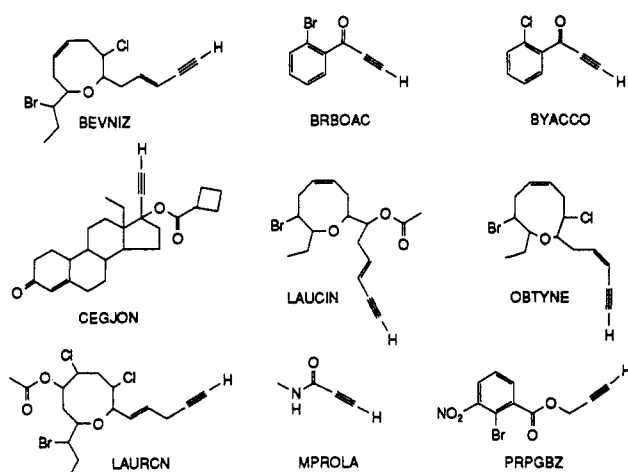
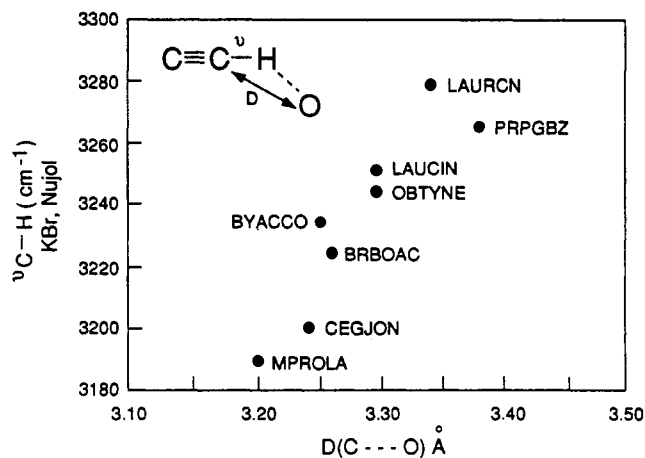


Figure 2. A correlation between crystallographic and spectroscopic (IR) properties of some C-H...O bonded terminal acetylenes. Structural formulas and Cambridge Database refcodes are given. In the compound BEVNIZ, the acetylenic H atom does not make a close approach to an intermolecular O atom and the C-H stretching frequency in the solid state and solution are identical.

redid Sim's work with nine terminal acetylenes, we noted a good correlation between the solid-state C(sp)-H stretching frequencies and intermolecular C...O distances (Figure 2).³¹ The bromobenzenesulfonate studied by Sim now appears to be an outlier. We found that a closer approach of the oxygen atom progressively weakens the acetylenic C-H bond, suggesting that the C-H...O contact is a bonding interaction. Figure 2 also shows that the formation of a typical C-H...O bond with $D \sim 3.2$ Å releases an amount of energy equivalent to 100 cm⁻¹, that is, ca. 0.3 kcal/mol. Undoubtedly there is considerable scatter in C-H...O distances, and in retrospect, the early literature on C-H...O interactions appears confusing because a statistically significant number of compounds were not studied.

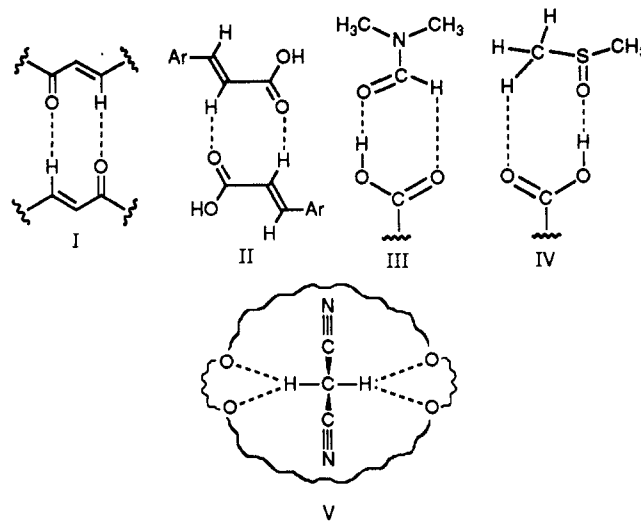
In general, a sufficiently activated C-H group seems to be required to observe consistent spectral shifts, and there exist a number of related studies involving acetylenes. The forbidden C≡C stretch in unsubstituted acetylene appears in the IR spectrum in the presence of donor solvents like acetone, indicating the removal of symmetry by intermolecular association.²⁷ Complexes of acetylene with water and other oxygen-containing bases have been isolated in inert matrices at low temperatures, and IR evidence of C-H...O bonding has

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been obtained.^{32,33} The two activated methylene H atoms in the >CH_2 group in 3,4-(methylenedioxy)- β -nitrostyrene form two C-H...O bonds (C...O, 3.15, 3.21 Å), and an IR spectral shift of 55 cm⁻¹ between the solid state and C₆H₅NO₂ solution is obtained.³⁴ Activated C-H groups in quinones have been studied by solid-state ¹³C NMR spectroscopy, and the chemical shifts of carbonyl C atoms that participate in >C=O...H-C hydrogen bonding are shifted downfield by 1-3 ppm from the corresponding solution values.³⁵ In comparison, the solid-state solution shift in a conventional >C=O...H-O hydrogen-bond situation is 8 ppm. The lack of proper spectroscopic evidence for C-H...O bonds formed by less activated C-H groups could stem from the fact that the spectral shifts are just not large enough. Alternatively, C-H...O interactions of weakly and strongly acidic C-H groups may be fundamentally different. However, not enough definitive work has been done to distinguish between these possibilities.

C-H...O Bonds and Crystal Engineering

The long-range, electrostatic and "orienting" nature of the C-H...O interaction determines its important role in crystal engineering. Common patterns such as I-V among others illustrate that the more acidic hydrogen atoms in organic molecules (alkyne > quinone > alkene > aromatic > aliphatic) tend to form C-H...O bonds more consistently and that, as far as possible, these bonds are adjusted within the framework of stronger interactions such as O-H...O and N-H...O hydrogen bonds.



A number of quinones and quinone complexes form C-H...O mediated layered crystal structures,¹⁰ acetic acid forms a C-H...O stabilized catemer rather than a dimer; and the syn-anti conformational preference of crystalline α,β -unsaturated acids is strongly dependent on C-H...O bonding.³⁶ In general, a full understanding of the packing arrangement in an oxygen-containing organic crystal structure is possible only when the C-H...O bonds are considered. However, it is not easy to predict any arbitrary oxygenated crystal structure just

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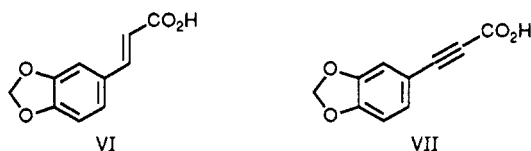
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on the basis of C-H...O interactions.

Progress has been made in designing crystal structures of planar oxygenated aromatics that are determined by an interplay of herringbone-steering C...H interactions^{37,38} and lateral C-H...O bonds which steer to stacked (or β) structures with short axes of 3.8–4.2 Å.^{12,13} The inclined herringbone pattern may be stabilized by C(δ^-)...H(δ^+) interactions whereas the C...C stabilized stack structures are characterized by parallel, overlapped molecules. Planar aromatic hydrocarbons generally adopt the herringbone structure (or its variants) because C...H interactions predominate. Their oxygenated derivatives show a pronounced tendency to adopt the stack structure because the lateral nature of the C-H...O contacts, which arise from the O atoms, assists in the formation of two-dimensional motifs such as sheets or ribbons. The numbers of O and H atoms seem to determine if a herringbone or stack structure will be formed for a particular molecule. To summarize, the stack structure is favored by higher C:H ratios, and these ratios are effectively raised by an increasing number of O atoms.

These ideas have been applied in the design of crystal structures that permit an intermolecular solid-state Diels-Alder reaction.³⁹ The strategy involved identification of substances that may act as either diene or dienophile and will crystallize in a structure that permits a topochemical 4 + 2 conversion. Accordingly, substituted phenylpropionic acids were considered; not only are they used in self-Diels-Alder reactions in lignan synthesis but the crystallographically related *trans*-cinnamic acids have been extensively investigated. The starting point in this crystal engineering exercise, the 4-Å stack structure of 3,4-(methylenedioxy)cinnamic acid (VI), was therefore 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 VI, C₁₀H₈O₄, that of [3,4-(methylenedioxy)phenyl]propionic acid (VII), C₁₀H₆O₄. Both VI and VII are planar molecules with similar volumes, shapes, and functionalities. The smaller number of H atoms in VII was expected therefore to enhance the tendency for stack structure adoption.

This prediction was confirmed; acids VI and VII are isomorphous, and Figure 3 shows that VII molecules form a compact sheet characterized by O-H...O (O...O, 2.63 Å) and C-H...O (C...O, 3.36, 3.39 Å) bonds. These bonds stabilize the sheet motif and with it the stacked β -structure. Analogously, (3,4-dimethoxyphenyl)- and (3,4,5-trimethoxyphenyl)propionic acids, both of which are efficiently C-H...O bonded, also form layered 4-Å structures.⁴⁰ Almost predictably, phenylpropionic acid

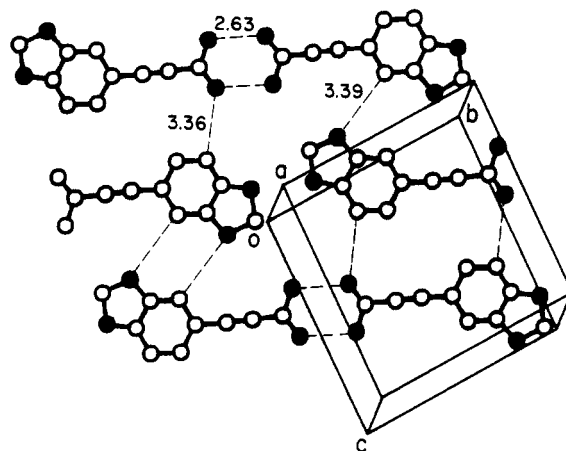


Figure 3. View of the crystal structure of [3,4-(methylenedioxy)phenyl]propionic acid (VII) down the 4-Å short axis. Oxygen atoms are shaded. C-H...O and O-H...O bonds are shown.

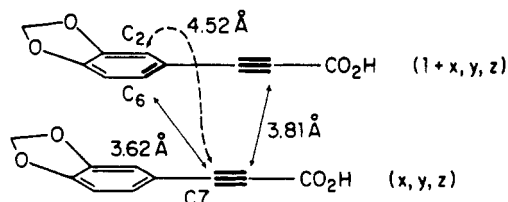


Figure 4. Schematic view of a topochemical Diels-Alder reaction for acid VII.

(C₆H₅C≡CCO₂H) forms O-H...O hydrogen-bonded dimers which pack in a herringbone fashion since a paucity of O atoms results in a dovetailing of terminal phenyl groups so as to optimize C...H interactions. The theme conveyed is that a *critical number of oxygen atoms will permit a planar aromatic molecule to cross the structural threshold from a C...H stabilized herringbone structure to a C-H...O stabilized layer structure.*

Our model for a solid-state intermolecular Diels-Alder reaction draws from the early work of Haworth,⁴¹ who found that when phenylpropionic acids (such as VII) are refluxed with acetic anhydride, the symmetrical anhydrides (ArC≡CCO)₂O so formed are converted quantitatively into anhydrides of the corresponding 1-phenylanthracene-2,3-dicarboxylic acids. The chemical expedient of forming the symmetrical anhydride in situ brings diene and dienophile components together for a Diels-Alder reaction. By construction of a 4-Å short axis, the identical 4 + 2 cycloaddition is achieved in the solid at temperatures below 80 °C and the molecular arrangement in the crystal parallels Haworth's original lignan synthesis very closely (Figure 4). In contrast, the unsubstituted acid which does not have a 4-Å stack structure is heat stable below its melting point.

C-H...O Bonds as Crystal Structure Directors

Typically, the directional preferences of C-H...O bonds are satisfied within the geometrical constraints 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 need not be passive

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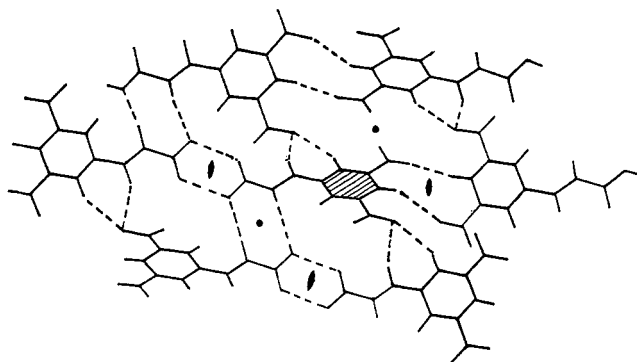


Figure 5. Crystal structure of 3,5-dinitrocinnamic acid (VIII) to show O-H...O and C-H...O hydrogen bonds. The reference molecule is shaded and linked to one of its 2-fold related neighbors by O-H...O bonds.

bystanders in a crystal; in fact they may be able to discriminate between alternative O-H...O (or other) networks which, though geometrically reasonable, are structurally quite distinct. In such cases, C-H...O bonds may be termed "steering" or "tugboat" interactions which, though small in energy, are sufficient to select a particular crystallization pathway from among several possibilities. The energy of an individual C-H...O interaction may be small, but if their number crosses a critical threshold, the structure may focus into an unconventional packing.

An arresting example is provided by 3,5-dinitrocinnamic acid (VIII), a molecule that contains several activated H and acceptor O atoms. Acid VIII crystallizes as an O-H...O dimer wherein the hydrogen-bonded molecules are related, not by an inversion center, as is usual, but by a 2-fold rotation axis.⁴² Both inversion and 2-fold dimers are equienergetic, and in principle, both are reasonable possibilities. However, Figure 5 shows an extensive C-H...O bond network (seven contacts with C...O < 3.75 Å) in the crystal. These C-H...O bonds dominate the structure, and their combined directional requirements appear to be incompatible with an O-H...O inversion dimer.

In other carboxylic acids such as *trans*-cinnamic acid (II), a smaller number of C-H...O bonds stabilize the inversion dimer. In the extreme, there are cases such as (4-chlorophenyl)propionic acid (IX) where the complete absence of C-H...O interactions leads to an unexpected hydrogen-bonded catemer motif rather than the dimer (Figure 6).⁴³ The O-H...O catemer is intrinsically more stable than the dimer. Therefore, if the dimer is to be formed, it must be stabilized 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 favored. Failure of IX, C₉H₅ClO₂, 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, with higher relative O stoichiometries, contain C-H...O bonds and the molecules crystallize as dimers.

Such studies show that C-H...O bonds, which are probably far more ubiquitous than has been generally recognized, need to be considered as important contributors in the formation of hydrogen-bond patterns

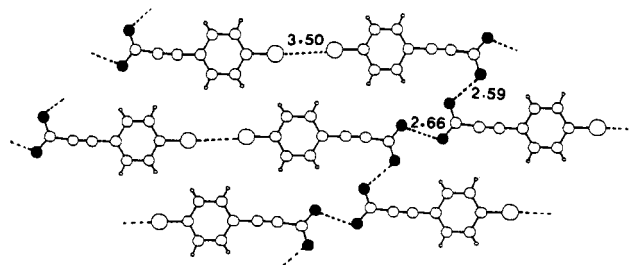


Figure 6. Crystal structure of (4-chlorophenyl)propionic acid (IX) down the short axis to show O-H...O and Cl...Cl interactions. Oxygen atoms are shaded. Molecular layers such as shown here are stacked along the short axis. Notice the catemer O-H...O network and the absence of C-H...O interactions.

in organic crystals and that their presence or absence could well determine the manner of networking of stronger O-H...O hydrogen bonds. Consequently, an ability to predict hydrogen-bond patterns could be improved by a better understanding of C-H...O interactions.

The C-H...O Hydrogen Bond in Crystals: What Is It?

The evidence in hand suggests that the C-H...O bond is, like the O-H...O and N-H...O hydrogen bonds, a largely electrostatic, attractive interaction with a long-range distance character. The length of the bond is variable but depends on C-H acidity. The angular approaches of the C-H and O-C groups which form the bond are largely predictable. Considering also the spectroscopic data on C-H...O bonds, especially of the more acidic C-H groups, it seems that the terminology C-H...O *hydrogen bond* is fully justified.

The attractive and non van der Waals character of the C-H...O interaction is also indicated since the addition of specific hydrogen-bonding terms of the $-D \exp(-Fr)$ or the Morse type^{44,45} improves the optimization of oxohydrocarbon crystals with (exp-6-1) or (12-6-1) potentials. A heavier theoretical treatment is difficult, among other reasons, because of basis set superposition errors. However, ab initio calculations show that while H₂O...CH₃NO₂ does not form a hydrogen bond, H₂O...CH₂(CN)₂ forms a hydrogen bond of ca. 5 kcal/mol energy.⁴⁶ Other calculations indicate that an activated C-H group is polarized C(δ⁻)-H(δ⁺) and can hence form an electrostatic interaction with an O atom. A less activated C-H bond dipole, however, has the sense C(δ⁺)-H(δ⁻) that is reversed by O atom polarization in a C-H...O bond.⁴⁷ These results corroborate our own findings that strongly acidic groups form better C-H...O bonds, but more needs to be done before we can determine if C-H...O interactions of weakly and strongly acidic C-H groups are similar or fundamentally different. All these studies show that the C-H...O bond is an attractive interaction, but it must be emphasized that neither a geometrical-statistical nor a theoretical approach reveals the degree of covalent bonding between the C-H and O moieties. Spectroscopy is probably a better tool to resolve this question.

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"What is a C-H...O hydrogen bond?" In the same vein one might well ask, "What is an O-H...O or an N-H...O hydrogen bond?" At a practical level, structural chemists have not been used to thinking in terms of C-H...O bonds, and it is in order to reexamine older ideas about crystal packing in this new light. For example, there is every indication that phenomena such as three-center bonding (bifurcation) and cooperative and resonance-assisted hydrogen bonding exist for C-H...O networks, and hence 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, in general. References to C-H...O bonds in the physical organic literature are even more sparse, but here again, these forces have been invoked to explain some surprising observations.^{47,48} In con-

clusion, it seems appropriate to state (with due apologies to Donohue) that a better answer to the question in the title of this Account and this section is: "It certainly is."

Warm thanks are due to the following students, past and present, who have worked with me on the topic of C-H...O hydrogen bonding in organic crystals: J. A. R. P. Sarma, K. V. Radha Kishan, V. R. Pedireddi, C. V. K. M. Sharma, and B. N. Murty. I thank J. P. Glusker and A. Gavezzotti for their valuable comments on this manuscript. It is impossible to list all the colleagues with whom I have had spirited discussions on this controversial subject, but I must mention C. Ramakrishnan and R. Parthasarathy, who filled me in on the early days of C-H...O bonds, especially in the G. N. Ramachandran group in Madras.

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Acyclic Stereochemical Control in Free-Radical Reactions

NED A. PORTER,*[†] BERND GIESE,*[‡] and DENNIS P. CURRAN*[§]

Department of Chemistry, Duke University, Durham, North Carolina 27706, Institute of Organic Chemistry, University of Basel, CH-4056 Basel, Switzerland, and Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received June 17, 1991 (Revised Manuscript Received September 5, 1991)

Since Gomberg's discovery of the persistent triphenylmethyl radical over 90 years ago,¹ there has been a steady increase in interest in free radicals. Recent years have seen the emergence of new free-radical synthetic methods that are efficient and convenient,^{2,3} and new chain-propagation schemes have been reported that are based on tin hydride-alkyl halide or borohydride-mercurial reductions, halogen atom transfer reactions,³ thiohydroxamate⁴ or allylstannane addition-fragmentation processes,^{5,6} and manganese(III) oxidations.⁷

Ring construction by free-radical cyclization has proved to be particularly useful, and five-membered rings are readily produced by this approach. The fundamental work of Walling, Beckwith, and Ingold⁸ provided information about the regiochemistry, absolute rate, and stereochemistry of cyclizations. Synthetic

efforts have benefited tremendously from this body of mechanistic work, and the cyclization reaction has been put to good synthetic use.^{9,10} Intermolecular free-radical addition reactions have also received renewed interest. Systematic studies have shown that polar and steric effects are most important in controlling the rate of addition of radicals to carbon-carbon double bonds, and there are many examples of the useful incorporation of intermolecular radical additions into synthetic sequences.^{2,3}

Despite major advances in the past 10 years, a significant barrier for the application of free-radical methodology in organic synthesis remains: there is no general approach to the control of acyclic stereochem-

[†]Duke University.

[‡]University of Basel.

[§]University of Pittsburgh.

Ned Porter graduated from Princeton in 1965 with a B.S. in chemical engineering and accepted a position as Assistant Professor at Duke University in 1969, after receiving his Ph.D. with Paul D. Bartlett at Harvard. He is now a James B. Duke Professor of Chemistry at Duke. His major research interests have involved studies of free radicals and radical pairs, lipids and bilayer membranes, and more recently, radical macrocyclization, hydrophobic stereo-enforcement, and enzyme photoactivation.

Bernd Giese studied in Heidelberg, Hamburg, and Munich, where he received his Dr. Rer. Nat. (1969) working in the group of Rolf Huisgen. After two years at BASF/Ludwigshafen, he carried out his habilitation in Münster and Freiburg (1976). He has been Professor at TH Darmstadt (1978-1988) and has held the chair of organic chemistry at the University of Basel since 1989. His primary research interests are the structure, selectivity, synthetic applications, and biochemical importance of radicals.

Dennis P. Curran received his B.S. from Boston College in 1975 and his Ph.D. from the University of Rochester in 1979, where he worked under Professor Andrew S. Kende. After a postdoctoral stay with Professor Barry M. Trost at the University of Wisconsin as a National Institutes of Health Postdoctoral Fellow, he joined the faculty of the Chemistry Department at the University of Pittsburgh in September 1981. He was promoted to the rank of Associate Professor in 1986 and Professor in 1988. His research interests lie in the area of natural products synthesis and the development of new synthetic methods.

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