Unrolling the hydrogen bond properties of C–H···O interactions†

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It has long been known that C–H groups may form weak hydrogen bonds. The characteristics of these interactions, however, have been explored systematically only recently. Currently, a qualitative understanding is being replaced by quantitative insight into the general properties and functions of weak hydrogen bonds like C–H···O. The current state is reviewed here, with a focus on results obtained by crystal correlation studies.

Introduction

The idea that C–H groups may be involved in attractive electrostatic interactions of appreciable strength is usually attributed to Glasstone:[1] in 1937, he explained the formation and the physical properties of liquid complexes like 1:1 chloroform–acetone by dimer association, as shown in Fig. 1.

Vibrational spectroscopists soon classified this interaction as a C–H···O 'hydrogen bond', with similar properties to O–H···O or N–H···O hydrogen bonds but lower bond energy. In the following 50 years, however, progress in the field was slow and in some periods even stagnant. Despite conclusive spectro-scopic[2] and crystallographic[3] evidence for the structural importance of C–H···O interactions, they were widely neglected or their existence even denied.[4]

Only recently, a wave of interest in weak hydrogen bonding emerged in the different fields of structural chemistry[5] and biology.[6] It is now well documented that C–H···O interactions (and other types of weak hydrogen bonds) are important as secondary interactions, and in many instances even play dominant roles in determining crystal packing[7] and molecular conformation,[8] in molecular recognition processes,[9] in the stabilisation of inclusion complexes[10] and in the stability and possibly even in the activity of biological macromolecules.[11] Most of these studies have concentrated on the *function*, not the *nature*, of weak hydrogen bonds.

The analyses of individual systems were paralleled by detailed investigations on the general characteristics of C–H···O interactions. It turned out that the 'crystal correlation' technique is particularly fruitful in this context. This statistical method is essentially based on comparative analysis of large amounts of published structural data,[12] and can reveal geometrical charac-teristics and structural preferences that cannot be shown from individual crystal structures alone. In particular, if the studied characteristics are soft, as is normally the case for effects from weak interactions, crystal correlation is often the only suitable access to the problem. The most frequently used source of structural data is the Cambridge Structural Database[13] (CSD), where currently over 160 000 organic and organometallic crystal structures are archived, which offers powerful data retrieval and analysis software. Recent statistical studies on C–H···O interactions will be briefly reviewed here. It will be necessary to point at the limitations of our models (which are

narrower than is often assumed), and *caveat* to simplified views must be stated.

Some fundamentals

In 1963, Allerhand and Schleyer[14] qualitatively concluded from vibrational spectroscopic experiments that the ability of a C–H group to donate hydrogen bonds depends on the C hybrid-isation, as $C(sp^1)$–H > $C(sp^2)$-H > $C(sp^3)$–H, and increases with the number of adjacent electron-withdrawing groups. The enhancement of the C–H donor strength by neighbouring electronegative groups is often called 'activation' of C–H. This effect can make even $C(sp^3)$–H a relatively strong hydrogen bond donor; examples are $CHCl_3$ and $CH(NO_2)_3$. Particularly strong donors are obtained if $C(sp^1)$–H is further activated by neighbouring electronegative atoms, such as in N≡C–H.

Hydrogen bonds in general are composed of different types of interactions.[6] As for all intermolecular interactions, there is a non-directional 'van der Waals' contribution, which is weakly bonding at long distances (by dispersion forces) and strongly non-bonding at short distances (by exchange repulsion). At their optimal geometry, van der Waals interactions contribute some tenths of a kcal mol^{-1} to the hydrogen bond energy. An electrostatic component (dipole–dipole, dipole–charge, *etc.*) is directional and bonding at all distances. It reduces with increasing distance and with reducing dipole moments or charges involved. For donors like O–H or N–H, the electrostatic component is the dominant one in a hydrogen bond (several kcal mol^{-1}). This is also true for strongly polarized C–H groups (up to 2 kcal mol^{-1}, see below), whereas for weakly polarized C–H groups the electrostatic component is of similar magnitude to the van der Waals contribution. Only for the strongest types of hydrogen bonds does a charge-transfer component become important;[6] it does not play a relevant role for weak C–H···O interactions. The above circumstances carry eminent implica-tions. (i) Electrostatic forces vary smoothly with varying geometry, and diminish only slowly with increasing distance; this leads to a pronounced softness of the hydrogen bond geometry. C–H···O interactions can be easily stretched, com-pressed and bent from optimal geometry. (ii) The bonding situation is strongly dependent on the donor and acceptor polarisations; therefore, weak hydrogen bonds involving polar-izable groups can be critically influenced by their surroundings. (iii) With falling C–H polarisation, the directional electrostatic component is reduced, whereas the isotropic van der Waals component is unaffected; the net interaction therefore loses directionality. (iv) Upon compression, the van der Waals contribution becomes repulsive and might even result in a positive (*i.e.* non-bonding) net energy; this will be more important the smaller the electrostatic component is.

In C–H···O bonds, the net charge on carbon may be negative; this is the classical hydrogen bonding situation ($C^{\delta-}$–$H^{\delta+}$···$O^{\delta-}$). Carbon may also carry a positive partial charge ($C^{\delta+}$–$H^{\delta+}$···$O^{\delta-}$); this also results in electrostatic attraction between donor and acceptor (with different directionality characteristics). The typical partial charges involved are roughly 0 to +0.2 *e* units on H, and depend strongly on the particular system under study.
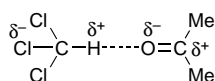

Fig. 1 Chloroform–acetone dimer

The bond energies of C–H⋯O interactions have been much debated. The energies are small and difficult to determine experimentally,[2] so that our knowledge is mainly based on computations. Earlier theoretical studies have been very inconsistent, but modern quantum chemical calculations seem to provide realistic energy estimations, at least for simple molecular systems *in vacuo* (*i.e.* isolated dimers or oligomers). Currently, there is consensus that C–H⋯O energies are typically ≤ 2 kcal mol⁻¹ and gradually fade away with increasing H⋯O separation (compare 'normal' non-ionic O–H⋯O hydrogen bonds: *ca.* 3–8 kcal mol⁻¹).[6] Gavezotti called this a 'continuum from zero to a moderately strong interaction'.[15] Only for the most acidic C–H donors, and for interactions with partly or dominant ionic character, are energies > 2 kcal mol⁻¹ reported. As examples, bond energies for some C–H⋯O bonded dimers *in vacuo* as obtained by recent *ab initio* molecular orbital calculations[16,17] are given in Table 1 (for computational details, see Table legend). According to these computations, a C≡C–H⋯OH₂ interaction can be regarded as a 'proper' hydrogen bond with an energy of *ca.* 2.2 kcal mol⁻¹.[16] For the very weakly polarized donor CH₄, on the contrary, equilibrium bond energies are calculated to be 0.5–0.6 kcal mol⁻¹, which are dominated by a two-thirds van der Waals contribution.[17] It must be stressed that the above data are valid only for the particular situation they were calculated for: hydrogen bonds are strongly influenced by their surroundings, such as by the solvent and by other hydrogen bonds, so that interaction strengths in the liquid or solid state will in the general case deviate from the values in Table 1.
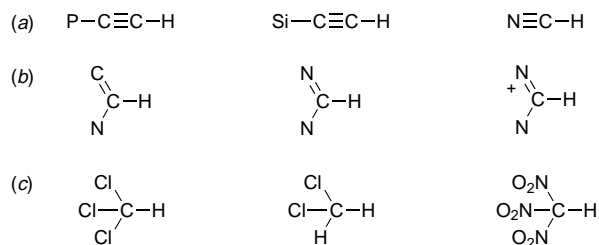
Hydrogen bond distances

The shortest bonding C–H⋯O contacts observed in crystal structures have donor–acceptor separations for C⋯O of *ca.* 3.0 Å and for H⋯O of *ca.* 2.0 Å. Such short contacts occur only with acidic C–H donors such as those shown in Fig. 2; recent examples with CH(NO₂)₃ and Si–C≡C–H are shown in Fig. 3.[18] Even for acidic C–H, however, H⋯O contacts of *ca.* 2.0 Å are not the normal case; more typical are H⋯O distances in the range 2.1–2.3 Å.

If H⋯O separations in crystals are statistically characterized, different behaviour is observed for chemically different C–H types. For the strongest C–H donors, such as C≡C–H and CHCl₃, the frequency distributions of H⋯O interactions have a well defined maximum, probably corresponding to an optimal value, and fall off for longer distances (Fig. 4). This is a characteristic that is also observed for 'conventional' hydrogen bonds like O–H⋯O.[6] For weaker donors, the maximum is shifted to longer distances and becomes less pronounced, and for the weakest C–H donor species, there is no maximum and the number of contacts increases with increasing distance. Two realistic examples of such distributions are shown in Fig. 5 (the distance cutoff of these distributions will be discussed below). The observations for weak C–H donors are not straightforward to interpret, because one might expect to see a maximum (though a weak one) for these too. One of the probable determinants of the distributions is that, in competition with other intermolecular forces, hydrogen bonds from the less acidic C–H donors will more frequently be the loosers and be pushed out of optimal geometry than those from the more acidic ones.

Crystallographers are often tempted to associate hydrogen bond distances with hydrogen bond strengths. It is stressed that this is misleading, and that the shorter contact is not necessarily the stronger hydrogen bond, nor that a given contact is 'not a hydrogen bond' just because it is beyond a certain distance

Table 1 Examples for calculated[a] hydrogen bond energies in C–H⋯O bonded dimers *in vacuo*. These values need *not* be valid for condensed state arrangements.

System	Energy/ kcal mol⁻¹	Reference
H–C≡C–H⋯O=CH₂	−1.15	16
H–C≡C–H⋯OH₂	−2.19	16
N≡C–H⋯OH₂	−3.79	16
CH₄⋯OH₂	−0.59	17(a)
CH₄⋯OH₂	−0.53	17(b)
NH₂–CH₃⋯OH₂	−0.61	17(b)
NH₃⁺–CH₃⋯OH₂	−9.3	17(b)

[a] *Ab initio* molecular orbital calculations *in vacuo*, optimised geometries, taking into account electron correlation and the basis set superposition error; ref. 16: DZP′ basis set at the MP2 level of theory; ref. 17(a): near HFL basis set at the MP2 level; ref. 17(b): D95++(d,p) basis set at the MP2 level.
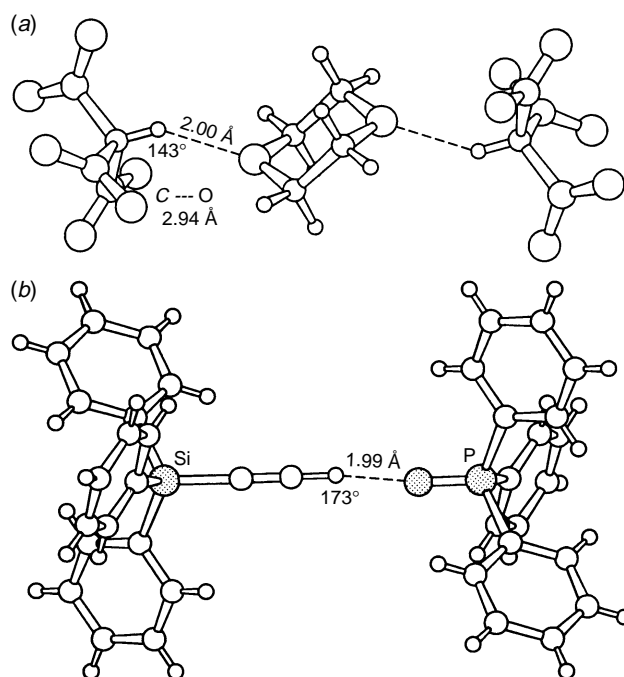

Fig. 2 C–H groups that can donate short C–H⋯O hydrogen bonds with H⋯O around and below 2.1 Å. Examples are given for (a) C(sp¹)–H, (b) C(sp²)–H and (c) C(sp³)–H. The examples given for C(sp²)–H are of particular importance for structural biology, because they occur in constituents of nucleic acids and of proteins.
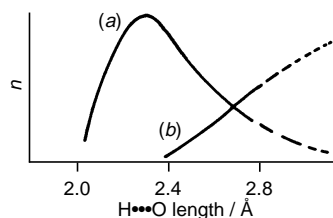
Fig. 3 The short end of C–H⋯O hydrogen bonding: the crystalline adducts (a) trinitromethane–dioxane [ref. 18(a)] and (b) triphenylsilylacetylene–triphenylphosphine oxide [ref. 18(b)]. Numerical data is given for normalised hydrogen positions (C–H = 1.09 Å).
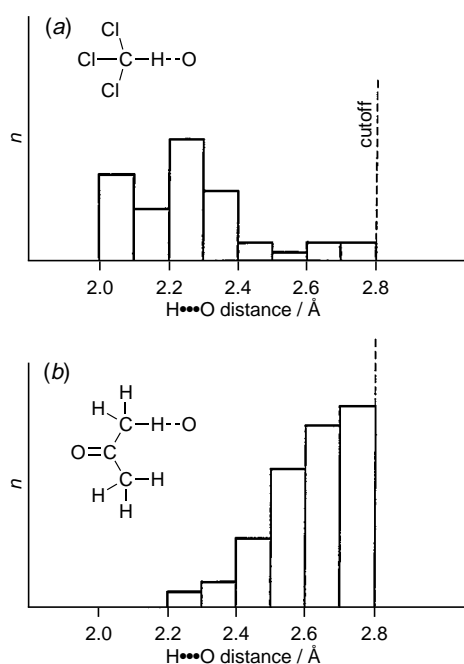

Fig. 4 H⋯O Frequency distribution for (a) strong donors and (b) weak donors

limit. Attempts to obtain reliable bond length–bond energy correlations remained unsuccessful (the same is true for conventional hydrogen bonds). Still, it will be shown below that the *mean* H···O distances of large data samples of related hydrogen bonds carry relevant chemical information on donor and acceptor nature.

Influence of donor acidity and acceptor basicity

Certain 'strong' or 'activated' C–H donors form on average shorter contacts to oxygen than the less activated species. Quantification of this effect was achieved by Desiraju in a series of crystal correlation studies.[20–22] For chloroalkyl compounds, he demonstrated that the mean donor–acceptor separation of hydrogen bonds follows the sequence Cl_3CH < Cl_2CCH < ClC_2CH < C_3CH, with mean C···O separations of 3.32, 3.40, 3.46 and 3.59 Å, respectively.[20] Similarly, alkynes form shorter

Fig. 5 Two examples for realistic H···O frequency distributions in crystals for (*a*) chloroform donors, and (*b*) acetone donors; drawn using the data analysed in ref. 19

contacts to oxygen than alkenes.[21] In an important generalisation, a direct correlation between average C···O separations and carbon acidity (in Me_2SO) could be shown (Fig. 6).[22] This correlation, however, is fairly sharp only for sterically unhindered donors, whereas for sterically hindered C–H groups, the average C···O separations are elongated compared to the values expected from Fig. 6. C–H acidity and therefore donor strengths can also be increased by steric strain on carbon, as was recently shown by Allen *et al.* for C–H in cyclopropane and related three-membered rings.[5d]

An effect of acceptor polarity on mean donor–acceptor separations was shown in a database analysis of small solvent molecules in varying crystal environments (Table 2).[19] In Table 2, the effect from donor polarisation shows up in the columns: with increasing C–H polarisation, the mean H···O separations reduce from 2.62 Å (for the Me groups of acetone) to 2.22 Å (for chloroform). This is a reduction of 0.4 Å. Note the fine gradation in the strengths of the weak methyl donors, which increase as $N≡C–Me$ > $O=S(Me)_2$ > $O=C(Me)_2$, reflecting the different degrees of 'activation'. The effect from acceptor polarity (or basicity) is weaker, but can still be clearly seen in the rows: the variation in H···O separations between the strongest acceptor, C=O, and the weakest, C–O–C, is about 0.1 Å.

Directionality

Donor directionality of short C–H···O contacts

Hydrogen bonds in general are directional interactions with a preference for linear geometry. For C–H···O interactions, this
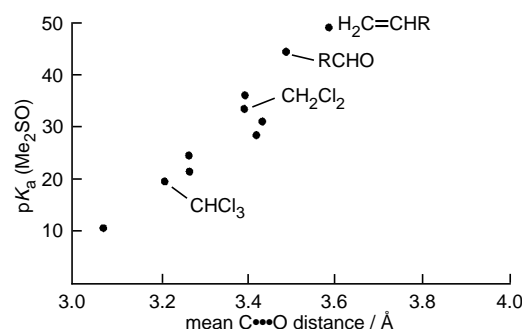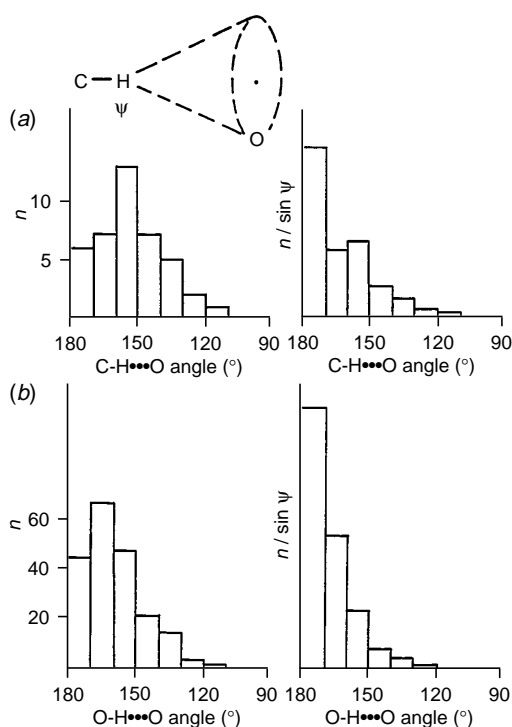

Fig. 6 Correlation of mean C···O distance with the C–H acidity. Adapted from Pedireddi and Desiraju (ref. 22). Only data for sterically unhindered donors is shown. Each of the data points represents the mean value of broad distributions such as those in Fig. 5.

Table 2 Mean C···O and H···O separations (Å) for C–H···O hydrogen bonds from small solvent molecules to various acceptor types (with H···O < 2.8 Å, for normalized H-positions)[a] (from ref. 19).

Donor	Acceptor					
	C=O	NO₂	S=O	C–OH	C–O–C	all O
Mean C···O						
CHCl₃	3.16 (3) [13]				3.26 (4) [3]	3.16 (2) [22]
CH₂Cl₂	3.21 (3) [13]	3.32 (4) [7]	3.3 (1) [3]	3.51 (5) [3]	3.43 (4) [17]	3.33 (2) [54]
C(sp³)–C≡CH[b]	3.28 (2) [15]			3.37 (4) [22]	3.38 (4) [8]	3.35 (2) [49]
MeCN	3.33 (6) [7]	3.31 (6) [13]		3.42 (9) [4]	3.37 (3) [18]	3.35 (2) [47]
Me₂SO	3.41 (2) [25]	3.45 (4) [18]	3.51 (3) [26]	3.44 (3) [11]	3.59 (6) [3]	3.46 (1) [85]
Me₂CO	3.49 (2) [32]			3.55 (5) [8]	3.61 (4) [8]	3.52 (2) [54]
Mean H···O						
CHCl₃	2.22 (5) [13]				2.31 (4) [3]	2.22 (3) [22]
CH₂Cl₂	2.27 (4) [13]	2.41 (5) [7]	2.4 (1) [3]	2.6 (1) [3]	2.50 (4) [17]	2.41 (2) [54]
C(sp³)–C≡CH[b]	2.24 (3) [15]			2.41 (5) [22]	2.44 (6) [8]	2.37 (4) [49]
MeCN	2.44 (7) [7]	2.55 (4) [13]		2.44 (7) [4]	2.46 (4) [18]	2.49 (2) [47]
Me₂SO	2.51 (2) [25]	2.57 (3) [18]	2.56 (2) [26]	2.61 (4) [11]	2.63 (6) [3]	2.56 (1) [85]
Me₂CO	2.60 (2) [32]			2.69 (2) [8]	2.69 (3) [8]	2.62 (2) [54]

[a] Standard errors of the mean values given in parentheses, number of examples (n_{CH}) given in square brackets. Data for acceptors with n_{CH} < 3 are not given individually, but included in the column for 'all O'. [b] Molecular residue.

property was first shown by Taylor and Kennard, who analysed the geometry of very short C–H···O contacts (H···O < 2.4 Å) in organic neutron crystal structures.[23] For these short contacts, the frequency distribution of C–H···O angles ψ is shown in Fig. 7(*a*): most frequent are slightly bent arrangements with angles in the interval $\psi = 150–160°$, whereas heavily bent contacts do not occur. To interpret this distribution properly, one must consider that the solid angle covered by an angular interval $\Delta\psi$ is smaller for linear than for bent angles (see inset of Fig. 7); if the distribution is weighted by $1/\sin\psi$, the more relevant figure to the right is obtained ('cone correction' as introduced by Kroon and Kanters[24]). This figure shows that linear contacts are preferred, as must be expected for electrostatic dipole interactions. For comparison, Fig. 7(*b*) also shows corresponding histograms for O–H···O hydrogen bonds in carbohydrates, which possess essentially the same characteristics, with an only slightly more pronounced preference for linearity.

Donor directionality: the general case

Fig. 7 demonstrates that C–H···O interactions are in principle directional. Due to the weakness of the interaction, however, the C–H···O hydrogen bond can be easily bent, so that directionality is blurred if steric hindrance or competition with other hydrogen bonding groups comes into play. This can be clearly observed for C–H···O contacts in carbohydrates, where O–H···O hydrogen bonds are the dominant intermolecular interaction forming a frame in which the weaker interactions have to adjust. Fig. 8 shows a scatterplot of ψ against H···O bond lengths for intermolecular C–H···O contacts in carbohydrate neutron crystal structures.[25] Most of the donors are of the type shown in Fig. 9, *i.e.* 'activated' C(sp³)–H groups. Despite the competitive situation, numerous C–H···O interactions with H···O separations down to about 2.25 Å are formed. The shortest of the contacts

show the same preference for approximate linearity as those in Fig. 7, but with increasing distance the directionality rapidly becomes softer. From about H···O = 2.7 Å on, all angles ψ occur. The quasi-isotropic behaviour at longer distances should not be regarded as a sign of a lack of directionality; it is merely a consequence of competition with stronger forces.

Not every near-neighbour arrangement involving C–H and O is necessarily a hydrogen bond, and in a plot like Fig. 8 it is not generally possible to spot which of the data represent significant bonding interactions, which do not, and which are borderline cases. One of the circumstances causing this uncertainty is the occurrence of simultaneous contacts to atoms other than oxygen, in particular the ubiquitous repulsive H···H contacts. This problem can be illustrated[27] as shown for water acceptors in Fig. 10. A realistic example with a clearly repulsive and an 'uncertain' arrangement is shown in Fig. 11. The real problem is the uncertain cases, which are very difficult to interpret in individual crystal structures, and to filter them out from a given statistical data sample.

A problem that has as yet not been tackled seriously is the directionality behaviour of the weakest C–H donor types such as methyl groups. For these, contributions from dispersion forces are similar or even larger than the electrostatic contribution,[17] so that C–H···O interactions might become almost isotropic.
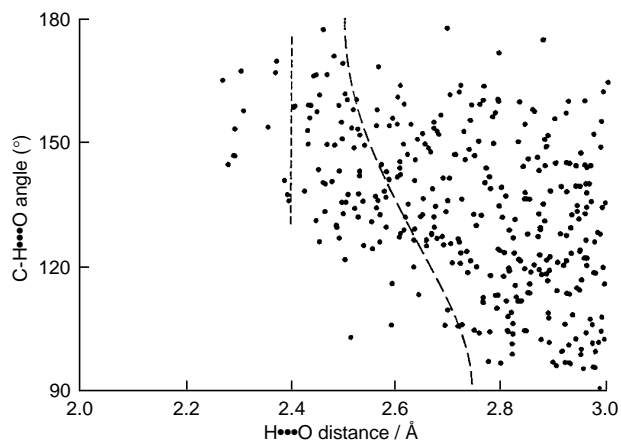
Fig. 8 Scatterplot of the C–H···O angle against the H···O distance in intermolecular C–H···O contacts in carbohydrate neutron crystal structures. Drawn using data analysed in ref. 25. The straight dashed line at H···O = 2.4 Å shows the arbitrary distance cutoff used in ref. 23 (compare Fig. 7). The curved dashed line represents the H···O van der Waals separation based on a spherical oxygen atom and a non-spherical hydrogen atom (ref. 26). The conventional assumption of the van der Waals separation would be a vertical line at H···O = 2.6 or 2.7 Å.
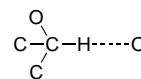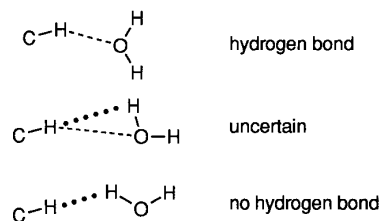
Fig. 7 Frequency distribution of X–H···O angles (ψ) in crystal structures: (*a*) 41 intermolecular C–H···O contacts with H···O < 2.4 Å in organic neutron crystal structures (ref. 23); (*b*) 196 O–H···O hydrogen bonds in carbohydrate X-ray crystal structures (ref. 24). The inset illustrates the 'cone correction' (ref. 24) (weighting by $1/\sin\psi$) that relates the left and the right histograms. The idea to show C–H···O and O–H···O histograms in one figure was adapted from a lecture of J. Kroon (Utrecht, Sept. 5, 1995).

Fig. 9 Typical C–H donor in carbohydrates

Fig. 10 Possible geometries of C–H to water contacts

Acceptor directionality

The acceptors of hydrogen bonds exhibit complex but weak directionality behaviour that depends on their chemical nature. For carbonyl acceptors, X–H vectors tend to point at the oxygen 'lone-pair lobes' which are in the carbonyl plane, in theory forming angles of 120° with the C=O bond.[29] For ether, hydroxy and water acceptors, hydrogen bonds are weakly clustered in the bisecting plane of R^1–O–R^2.[30]

In the context of C–H···O hydrogen bonding, acceptor directionality has as yet only been discussed for C=O acceptors. Following initial indications,[23,31] the subject was studied in more detail in a crystal correlation study of acidic and sterically unhindered C–H donors which are not in competitive situations (CHCl$_3$, CH$_2$Cl$_2$, C≡C–H).[32] If the approach of C–H to O=C is characterized by the angle α (H···O=C) and the torsion angle ω (H···O=C–Y), the polar scatterplot shown in Fig. 12 is obtained. The histogram shows the distribution of angles ω and indicates a preference for in-plane contacts (ω ≈ 0). The acceptor directionality that becomes apparent from Fig. 12 is very soft, but significant.

Notes on cutoff criteria

Formerly, it was common practice among crystallographers to define hydrogen bonds as X–H···Y contacts shorter than the H···Y or the X···Y van der Waals separation. It has been repeatedly pointed out that this concept is faulty:[6] there is no experimental or theoretical evidence that at a certain critical distance, the interaction is switched from 'hydrogen bond' to 'van der Waals' type. The electrostatic component of the hydrogen bond also operates beyond van der Waals separation. This is reflected in the appearance of Fig. 8, which lacks any discontinuities. The straight dashed line shows the conservative
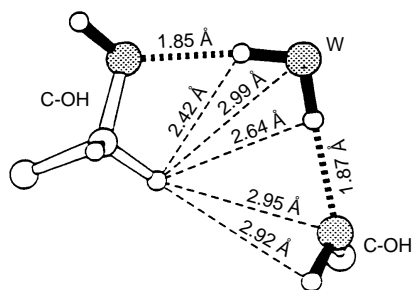
Fig. 11 An example of long C–H···O contacts associated with repulsive H···H contacts. The C–H··· water contact is presumably repulsive, and the net interaction of the C–H···OH contact is uncertain. In other geometries, such long C–H···O contacts can be assessed as weakly bonding in nature [adapted from ref. 25, using neutron diffraction data of β-cyclodextrin–11.6 H$_2$O at 120 K (ref. 28)].
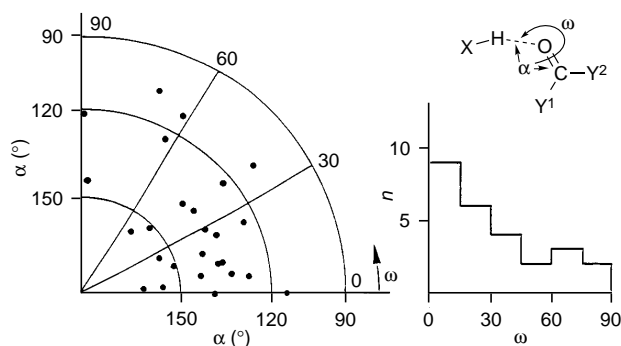
Fig. 12 Approach of acidic and sterically unhindered C–H donors to C=O acceptors (26 data points) (ref. 32). Geometrical definitions are shown in the inset. The data are indicative of soft but significant acceptor directionality.

2.4 Å van der Waals cutoff used by Taylor and Kennard,[23] and the curved dashed line represents an alternative van der Waals cutoff[25] based on a possibly non-spherical H-atom.[27] Both divide the distribution as arbitrarily as any other cutoff would do.

In many instances, computational practice requires the use of cutoff definitions. A compromise must then be found between the desire not to omit too many attractive long-distance interactions, and not to include too many dubious (Fig. 10) or insignificant 'hydrogen bonds'. The first desire calls for a distance cutoff so long that maxima in distance distributions (if existing, Fig. 4) are included; this requires values > 2.6 Å. Since dubious arrangements, such as those shown in Fig. 10, occur mainly with long H···O separations > 2.8 Å,[27] the author has repeatedly used this value as a pragmatic cutoff distance in crystal correlation studies. In samples containing fewer dubious arrangements, longer cutoff values, such as 3.0 or 3.2 Å, can be justified. In any case, cutoff criteria are coarse instruments and should be avoided whenever possible.

Effect on covalent geometries

Hydrogen bonding has consequences for the covalent bonding of the involved groups. In an interaction R^1–X–H···Y–R^2, the X–H and Y–R^2 bonds are weakened, resulting in bond lengthening and lowering of the stretching frequencies, and the R^1–X bond is strengthened and thereby shortened. These effects are very pronounced for O–H···O hydrogen bonds.[33] For the C–H···O interactions, analogous effects should be expected to occur on a smaller scale. In infrared absorption spectra, weakening of C–H and Y–R can in many instances be clearly observed,[2,34] but the extent to which the weakening reflects in the covalent geometry has been only poorly investigated. As a first such effect, slight lengthening of the C–H bond was shown from neutron diffraction data of amino acid C$_\alpha$–H bonds.[35a] The reported lengthening, of *ca.* 0.01 Å for contacts with H···O of *ca.* 2.3 Å, corresponds to a weakening of the C–H bond by roughly 0.03 valence units (for bond length–bond valence relations in general, see ref. 36).

In an individual neutron crystal structure, slight lengthening of an acetylenic C–H bond in a short C≡C–H···O interaction (H···O = 2.07 Å) was reported only recently.[35b]

Cooperativity

Hydrogen bonds possess the important property of *cooperativity*; in arrays of *n* interconnected hydrogen bonds, the total bond energy is larger than the sum of *n* isolated hydrogen bonds ('*non-additivity*'). There are two different mechanisms that can produce this effect: functional groups which may act as hydrogen bond donor and acceptor simultaneously often form chains of the type $O^{\delta-}$–$H^{\delta+}$···$O^{\delta-}$–$H^{\delta+}$···$O^{\delta-}$. In these chains, due to mutual polarisation of the involved groups, the individual hydrogen bonds enhance each other's strengths by around 20%.[6] A different mechanism is charge flow in suitably polarizable π-bond systems ('*resonance assisted hydrogen bonds*'.[37])

Based on structural and electrostatic analogies, such effects can be postulated to occur also with weak hydrogen bond types. Of particular interest is the C≡C–H residue, which can donate C–H···Y and accept X–H···π hydrogen bonds simultaneously.[38–40] Three patterns that are topologically equivalent are shown in Fig. 13, and one may expect that they also have analogous cooperativity properties (of course, of different strengths).
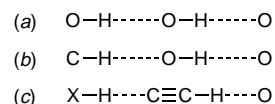
Fig. 13 Three topologically equivalent hydrogen bond patterns

Unfortunately, direct experimental evidence for energy enhancement is difficult to obtain. For arrangements like the one in Fig. 13(c), however, spectroscopic evidence for cooperativity has been supplied.[38a] The crystalline sex steroid mestranol contains cooperative and non-cooperative C≡C–H···O hydrogen bonds, which can be directly compared spectroscopically.[38b] More complex patterns have also been observed, such as the cycles shown in Fig. 14, for which non-additivity has been claimed.[40]

A well known example for conventional 'resonance assisted hydrogen bonding' is the carboxylic acid dimer shown in Fig. 15(a), and an analogous C–H···O pattern is shown in Fig. 15(b). It is supposed that this pattern is stronger than just the sum of two C–H···O=C hydrogen bonds. However, the mere structural analogy is not a proof for significant cooperativity effects in Fig. 15(b), so that further investigations are required.

A pattern with C–H···N bonding that is immediately suggestive of cooperativity is the infinite chains in crystalline HCN[41] (Fig. 16). Liquid HCN is composed of finite chains of this kind. In a recent *ab initio* quantum chemical study of $(HCN)_n$ chains, it was in fact calculated that the H···N distances and the C–H stretching frequencies reduce with increasing system size, whereas the C–H bond lengths increase. Even at the octamer stage, saturation of the effect had not yet completely been reached.[42]

Quantum chemical calculations have also been performed on the infinite molecular chains in crystalline *N,N*-dimethyl-nitroamine (Fig. 17). For these, using semiempirical molecular orbital calculations, Sharma and Desiraju estimated an energy enhancement of around 20%; the effect reaches saturation at about the pentamer stage.[43]

Thermal vibrations

Hydrogen bonding reduces the thermal vibrations of the engaged residues. For C–H···O interactions, this effect was first shown for terminal alkynes.[44] The acetylenes are good probes in this context, because they are among the most acidic C–H donors and, at the same time, they enjoy pronounced vibrational freedom. The situation is sketched in Fig. 18.
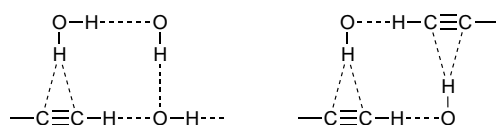

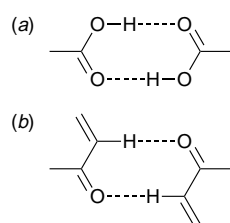**Fig. 14** Two cooperative hydrogen bond cycles involving C–H···O interactions

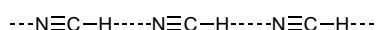**Fig. 15** Resonance assisted hydrogen bonding

Fig. 16 The infinite hydrogen bonded chains in crystalline HCN
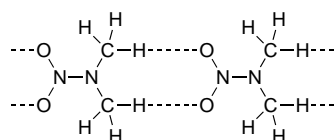

Fig. 17 The infinite molecular chains of crystalline *N,N*-dimethylnit-roamine

A free C≡C–H moiety can vibrate strongly, normally with the vibration amplitude largest for the terminal C-atom [Fig. 18(a)]. In a C≡C–H···X hydrogen bond, the alkynyl orientation is more restricted [Fig. 18(b)]. The vibration behaviour can be described semi-quantitatively by the ratio of isotropic displacement parameters $U(C2)/U(C1)$, which is significantly larger than 1 for the situation in Fig. 18(a), and close to 1.0 for that in Fig. 18(b). This ratio was correlated with the H···X separation for 51 C≡C–H groups in 42 crystal structures (X = O, N, π-acceptors), and the obtained correlation clearly shows the anticipated effect (Fig. 19):[44] on average, the U ratio continuously reduces with shortening H···X distance, indicating a reduction of the thermal vibration. It is of relevance that this effect is not only observed for the shortest hydrogen bonds, but also for relatively long contacts with H···X in the range 2.6–2.8 Å, reflecting the long-range nature of the interaction.

The complementary effect on the acceptor side was shown by Braga *et al.* for an organometallic compound[31] (Fig. 20). For metal-coordinated carbonyl groups, the ratio $U(O)/U(C)$ was reported to be larger for free M–CO [Fig. 20(a)] than for CO accepting M–CO···H–C interactions [Fig. 20(b)], indicating reduction of the acceptor vibration due to C–H···O hydrogen bonding.

C–H···O replacing stronger hydrogen bonds

In many crystal structures, C–H···O interactions are observed as bystanders or subalterns to more dominant systems of stronger interactions. This can easily lead to the view that C–H···O interactions, although in principle of hydrogen bond type, are too weak to have similar functions in structure formation and
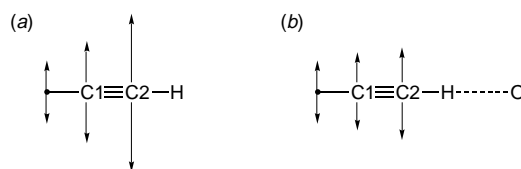

Fig. 18 Thermal vibrations of the (a) unbonded and (b) C–H···O bonded C≡C–H moiety

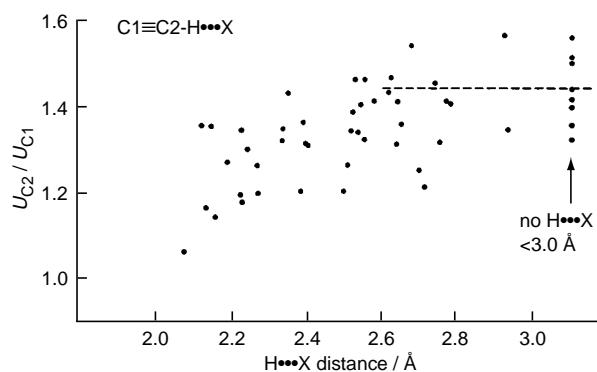**Fig. 19** Correlation of the quantity $U(C2)/U(C1)$ with the H···X distance in C1≡C2–H···X hydrogen bonds (X = O, N, π-bonds), for normalized hydrogen positions. The horizontal line shows the mean value for C≡C–H groups with no H···X contact shorter than 2.8 Å (adapted from ref. 44).
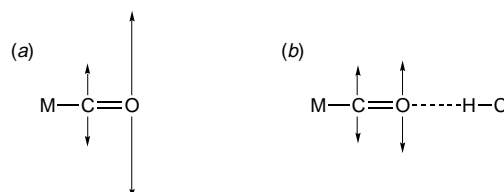

Fig. 20 Thermal vibrations for the (a) unbonded and (b) M–C=O···H bonded M–CO moiety

stabilisation as the stronger O/N–H···O hydrogen bonds. However, this is not true in all cases (in many, though, it is), and opposite observations have also been made. The author first encountered this problem when studying the coordination of water molecules in various environments,[27,45,46] mainly from highly accurate neutron diffraction data. It became apparent that water molecules frequently accept C–H···O_W interaction, which have the major function of 'filling up' the preferred two-fold acceptor functionality, if stronger O–H or N–H donors are not suitably available (Fig. 21). The coordination geometries of the arrangements shown are completely analogous. There is no doubt that these C–H···O_W interactions are formed only as a last resort if stronger hydrogen bonds are lacking, but if they form, C–H donors actually take the role and function of O–H or N–H.

Several examples have been published where, in isomorphous crystal structures, an N/O–H···O hydrogen bond in one structure is isofunctionally replaced by a C–H···O interaction in the other. The classical examples are the isomorphous complexes urea–barbital and acetamide–barbital[47] (Fig. 22). Other examples are the isomorphous inclusion complexes of β-cyclodextrin with diethanolamine and with pentane-1,5-diol, where a clearly structure-stabilizing N–H···O bond is substituted by a C–H···O interaction of the same function,[48] and the replacement of an N–H···Cl⁻ by a C–H···Cl⁻ interaction in isomorphous adenosine derivatives.[49] In all these cases, both interactions have the same function in structure stabilisation, *i.e.* in these instances, the C–H···O interactions do in fact play the role of a stronger hydrogen bond.

Outlook

The process of characterizing the hydrogen bond properties of C–H···O interactions is slow and troublesome, and far from being finished. Some of these properties are already well documented, whereas others appear vague and indistinct (making parts of the review unsatisfactory to write). Important points that are as yet only poorly understood are the long-distance properties of weak hydrogen bonds, cooperativity effects, non-additivity properties in general, the competition properties with other intermolecular forces, the roles of very weakly polarized groups like Me, the C–H groups of organic ions (N⁺–C–H of various types, P⁺Ph₄ *etc.*), the behaviour upon compression by other crystal forces or by intramolecular strain ('*forced contacts*') and the gradual transition from directional to isotropic interactions.

Relevant effects that cannot be studied by crystallographic methods are (for example) bond energies, thermodynamic properties in general and the influence of solvent. A large volume of quantum chemical calculations is required to obtain a broad picture of interaction energies under various conditions. This should include studies on non-additivity phenomena.
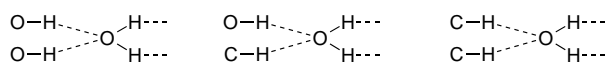
Fig. 21 Analogous coordination geometries for two different forms of hydrogen bond
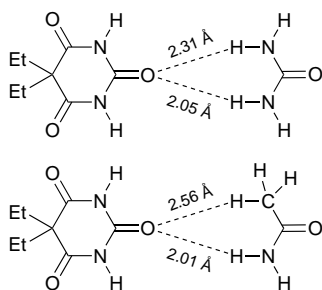
Fig. 22 Isomorphous complexes of (*a*) urea–barbital and (*b*) acetamide–barbital

This review has concentrated on the special case of the weak hydrogen bonds formed between C–H donors and oxygen acceptors. Related directional interactions between other weak donor–acceptor combinations are also studied extensively, in particular with the important π-acceptors (see ref. 50 and literature cited therein). Also these interactions play important roles in structural chemistry and biology, and deserve further investigation.

Footnote

† This ChemComm is also available *via* the World Wide Web: http://chemistry.rsc.org/rsc/cccenha.htm

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Thomas Steiner was born in 1961 near Reutte (Tirol), Austria. He studied physics at the Technische Universität Graz, Austria, and obtained his PhD at the Freie Universität Berlin, Germany, in the field of neutron scattering (1990). Currently, he is a research scientist at the crystallography institute of the Freie Universität, Berlin. His active interests cover conventional and weak hydrogen bonding, isotropic intermolecular interactions, disorder phenomena, structure correlation, organic and bio-organic X-ray and neutron crystallography (acetylenes, peptides, carbohydrates, inclusion compounds, hydrates) and IR-spectroscopy.

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