Hydrogen Bonds to Carboxylate Groups. The Question of Three-centre Interactions

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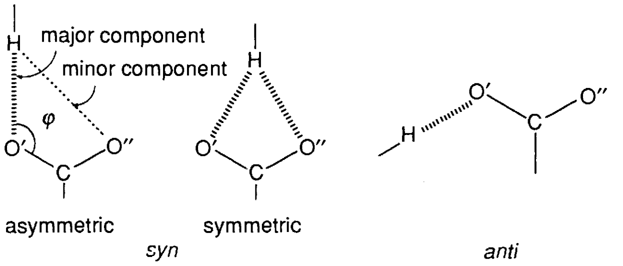
Hydrogen bond geometries as well as their stereochemical preferences have been compared for 255 small molecule carboxylate structures retrieved from the Cambridge Structural Database. A total of 974 independent hydrogen bonds were analysed. Hydrogen atoms cluster in the carboxylate lone-pair directions with no tendency to adopt a central, symmetric position between the two oxygens. The long, secondary H ··· O contacts of asymmetric *syn* hydrogen bonds do not affect either the overall geometries of the interactions or the total *syn*/*anti* distribution of accepted H-atoms, presumably due to very unfavourable C=O ··· H angles. On this basis it is suggested that *syn* hydrogen bonds to carboxylates should be regarded most frequently as two-centre rather than three-centre (bifurcated) interactions. The statistical data also show that criteria traditionally used to infer three-centre hydrogen bonds are inadequate for carboxylate acceptors.

The concept of three-centre hydrogen bonds is widely acknowledged and accepted. There is, however, a lack of consistency in the guidelines used by different authors to define a three-centre interaction. Application of dissimilar criteria have resulted in widely varying estimates of the overall proportion of three-centre hydrogen bonds, ranging from 1.3% for a survey on peptides[1] to 70% reported for amino acids.[2] In this paper we use comprehensive sets of crystallographic data to resolve some of the ambiguity concerning three-centre hydrogen bonds to carboxylate groups, one of the most abundant acceptors in organic systems (Scheme 1).



Scheme 1

We address the asymmetric and symmetric bonding modes, and assess the importance of the long secondary O ··· H contact in the asymmetric interactions. We have also critically evaluated geometric criteria previously used as evidence for claiming a hydrogen bond to be three-centred.

Terminology.—The symbol $r(A \cdots H)$ is used to denote the hydrogen bond distance between the acceptor A and H, $\alpha(A \cdots H\text{–}D)$ is used for the hydrogen bond angle $A \cdots H\text{–}D$ where D is the donor, and $\varphi(C{=}O \cdots H)$ is used for the C=O ··· H angle. A hydrogen bond to carboxylate is always taken to be accepted by atom O′; atom O″ is involved only in secondary interactions (minor H-bond components, Scheme 1). It follows that O′ and O″ labels may interchange when referring to the major + minor interactions of multiplicity H-bonded systems.

Method

The total data set consisted of 255 X-ray and neutron-diffraction structures* of small molecule carboxylates, without metal ions, which were retrieved from the Cambridge Structural Database (CSD, June 1990 release)[3] by means of the CSD program QUEST89. A maximum R-factor of 0.08 was used for primary and secondary carboxylates, while 0.10 was used for acetates and ternary carboxylates to increase the number of data points in these classes. Only contacts with $\alpha(O' \cdots H\text{–}D) > 90°$ (D = O or N) were retained in the succeeding geometry calculations with the GSTAT89 program, employing normalized H-atom positions for all X-ray structures.[4] Both 2.35 and 2.95 Å upper distance limits for $r(O' \cdots H)$ were used, giving 876 and 974 interactions, respectively. The program Cricket Graph, Version 1.3.2[5] was used to generate plots of data extracted from the CSD.

Results and Discussion

Distributions for various H-bond parameters are given in Fig. 1. A stereo plot of 974 locations for H-atoms accepted by carboxylate groups in small molecule crystal structures is shown in Fig. 2. It is evident that H-atoms cluster in the lone-pair directions. More specifically, there are very few data points in the central region between the two oxygen atoms. Accordingly, most *syn* H-bonds have distinctly asymmetric geometries (Scheme 1). This raises the question as to whether the minor component has any general significance for the overall stabilization of the interaction. If it has, the *syn* H-bond to carboxylate should be regarded as three-centred. Otherwise, the *syn* H-bond is better represented as a simple two-centre interaction.

An additional stabilization resulting from proximity to a second *syn* lone orbital could manifest itself in two different ways: (*a*) Extra interaction energy from the second lone-pair should make *syn* H-bonds energetically more favourable than *anti* H-bonds, in the absence of other perturbing effects, and (*b*) The presence of the minor component should affect the observed geometry of the major component of the interaction.

Interaction Energy.—Even though it has been demonstrated that statistical analysis of structural parameters in crystals cannot be used to derive quantitative energy relationships,[6] one could reasonably assume that a significant energy difference between *syn* and *anti* hydrogen bonds would result in *syn*

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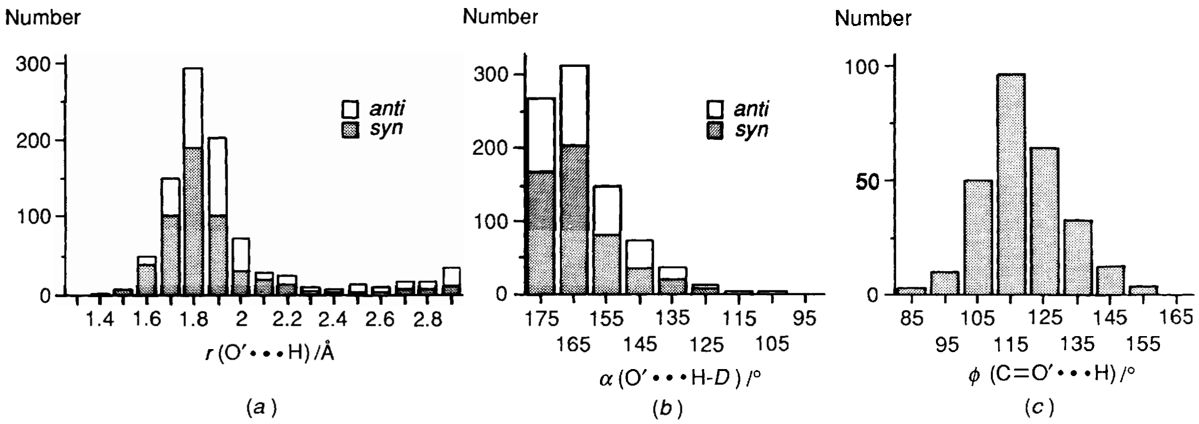


Fig. 1 (*a*) Distribution of $r(O' \cdots H)$ for complete sample of 974 H-bonds < 2.95 Å. (*b*) Distribution of $\alpha(O' \cdots H\text{-}D)$ for 876 H-bonds < 2.35 Å. (*c*) Distribution of $\varphi(C{=}O' \cdots H)$ for 527 *syn* H-bonds < 2.35 Å [*anti* H-bonds are not included since their $\varphi(C{=}O' \cdots H)$ values are sensitive to steric hindrance].

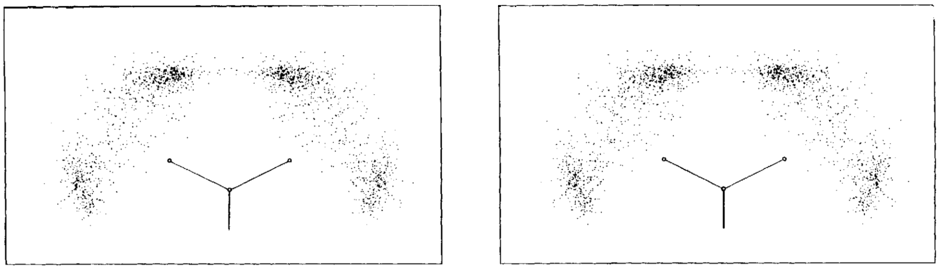


Fig. 2 Stereo plot of 974 superimposed positions of H-atoms with $r(O' \cdots H) < 2.95$ Å accepted by one carboxylate oxygen atom. Mirror symmetry was used to generate 974 additional H-atoms around the other oxygen.

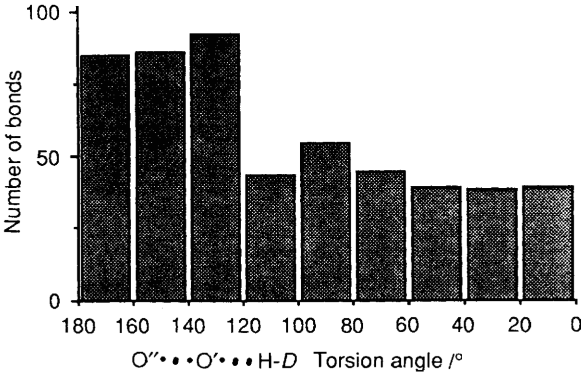


Fig. 3 Distribution of the $O'' \cdots O' \cdots H\text{-}D$ torsion angle for *syn* H-bonds (symmetry permits use of the absolute value). In this and all remaining figures 2.35 Å has been used as a distance limit for $r(O' \cdots N$.

geometry being observed more frequently. We have previously shown that, in the absence of steric hindrance, a 1:1 *syn*/*anti* distribution occurs in crystal structures of carboxylates.[7] Accordingly, there is no indication from our statistical data that *syn* geometry for H-bonds is energetically more favourable than *anti*. This conclusion is basically in agreement with *ab initio* calculations which indicated small energy differences between *syn* and *anti* H-bonds for formate-planar ammonia (*syn* 1.2 kJ mol^{-1} < *anti*)[8] and formate–water (*anti* 1.2 kJ mol^{-1} < *syn*)[9] complexes.

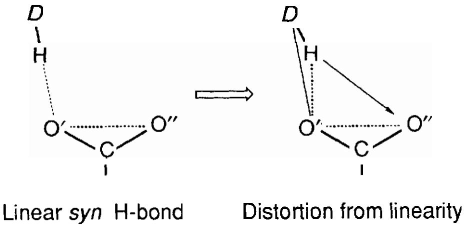
Geometric Effects.—In the past,[2,10,11] three-centred interactions have been invoked from geometrical observations of asymmetric H-bonds. The following three statements can be made.

(1) For $\alpha(A_1 \cdots H\text{-}D)$ the displacement of the H-atom from linearity is always such as to imply an attractive force from the more distant acceptor atom A_2.

(2) The sum of $\alpha(A_1 \cdots H\text{-}D)$, $\alpha(A_2 \cdots H\text{-}D)$ and the $A_1 \cdots H \cdots A_2$ angle $\approx 360°$.

(3) The H-atom is close to the plane defined by A_1, A_2 and D (complementary to 2).

Statement (1). The proposed distortion of the hydrogen bond geometry is illustrated schematically for a carboxylate acceptor in Scheme 2.



Scheme 2

To study this effect in our statistical material, we have chosen to monitor the torsion angle $O'' \cdots O' \cdots H\text{-}D$. A distortion of a H-bond from linearity to bring H closer to O″ would give $O'' \cdots O' \cdots H\text{-}D$ torsion angles in the $< -180°, -90° >$ or $< 90°, 180° >$ intervals, while torsion angles in $< -90°, 90° >$ would indicate displacements away from O″. The actual distribution is given in Fig. 3, where for convenience the absolute values of the torsion angles have been used. If Statement 1 were true for H-bonds to carboxylates, we would expect to see all $O'' \cdots O' \cdots H\text{-}D$ torsion angles $> 90°$ in such a diagram, and mostly values close to 180°. It can be seen from Fig. 3 that the majority of the interactions do indeed have

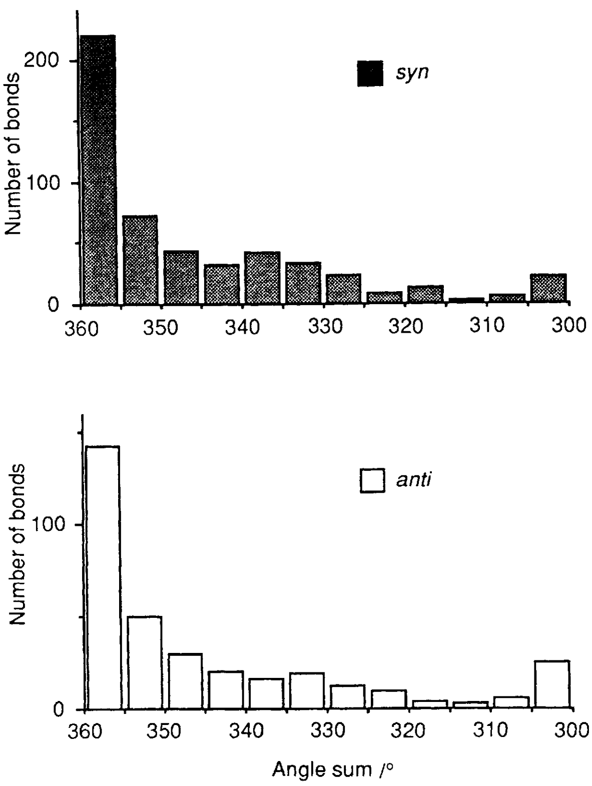
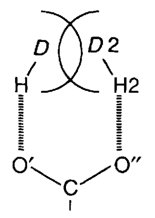


Fig. 4 Distribution of the angle sums of $\alpha_1,\alpha_2,\alpha_3$ from 527 *syn* H-bonds (top), and $\alpha_4,\alpha_5,\alpha_6$ from 349 *anti* H-bonds (bottom). The rightmost column in each distribution represents all sums < 305°.

O″ ··· O′ ··· H–*D* > 90°, but the presence of numerous torsion angles < 90° shows that Statement 1 is in general not valid for H-bonds to carboxylates.

It has been shown in Fig. 2 that almost all *syn* H-bonds are very asymmetric. We also find that most carboxylates accept two H-atoms in *syn* positions, one on each lone pair. If O ··· O ··· H–*D* torsion angles are simultaneously < 90° for both these hydrogen bonds, steric conflict occurs due to close proximity of the two donor atoms *D* and *D2* (Scheme 3).



Scheme 3

We attribute the dominance of O″ ··· O′ ··· H–*D* torsion angles > 90° to this steric effect, rather than to electronic attraction from O″. It would have been interesting to obtain a O″ ··· O′ ··· H–*D* distribution for carboxylates that accept only one *syn* H-atom, in which case we would expect no preference for torsion angles > 90°. Unfortunately, the number of such structures is too small (~ 10) to give reasonable statistics.

Statement (2). We tested this observation by calculating the angle sum for *syn* interactions ($\alpha_1 + \alpha_2 + \alpha_3$), and for comparison also a corresponding sum for *anti* interactions ($\alpha_4 + \alpha_5 + \alpha_6$), using the angles defined by H, O′, C$^\alpha$, and *D* (Scheme 4).

The resulting distributions are given in Fig. 4. The *syn* curve has the expected peak close to 360°, apparently in good agreement with Statement 2, but the *anti* curve is almost identical and does not represent a three-centre hydrogen bond. This means that other geometrical factors are involved which promote a large number of angle sums close to 360°, and the *syn* curve in Fig. 4 does not provide sufficient evidence to infer the existence of three-centre H-bonds.

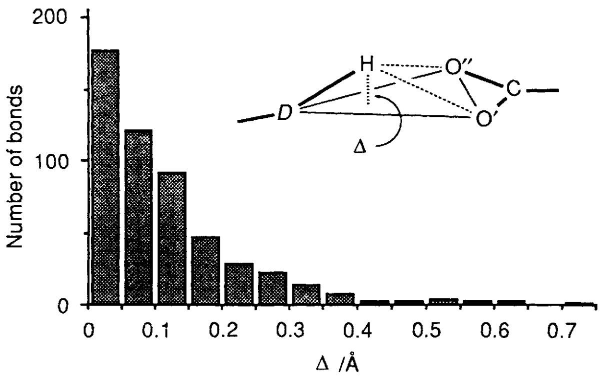
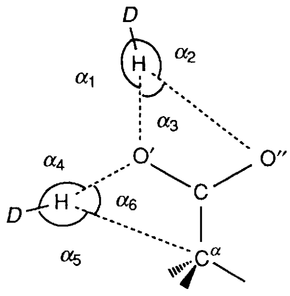


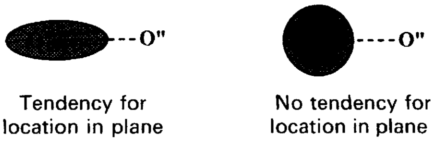
Fig. 5 Distribution of Δ for *syn* H-bonds



Scheme 4

Statement (3). For this observation to be of any interest, it must imply that in three-centre hydrogen bonds H-atoms are not only reasonably close to but display a significant preference for the O′–O″–*D* plane. The subtle difference between closeness and preference was studied by calculating the deviation (Δ) of the H-atom from the plane. The distribution given in Fig. 5 looks very similar to one presented for N–H ··· O=C H-bonds.[10] A traditional utilization of Statement (3), with *e.g.* a 0.30 Å limit on Δ, would result in most interactions being classified as three-centred. However, the plot is in fact deceiving, as an actual preference for the heavy atom plane should have produced even more observations close to 0.0 Å than seen in Fig. 5.

Support for this argument comes from consideration of H-atom distributions, as viewed along the O′ ··· *D* axis for *syn* interaction, Fig. 6. The projected cluster must be off-centred, shifted slightly towards O″ (see Scheme 2) as the average C=O′ ··· *D* angle is 120.1° *vs.* 118.9° for C=O′ ··· H, but here we are concerned more with the actual shape of the H-atom distribution. If there were a significant force attracting H-atoms to positions near the plane defined by the three heavy atoms, it should be observed as an elliptical distribution. A spherical symmetric distribution might be expected without such an attractive force.



It can be seen from Fig. 6*a* that the latter distribution is observed in crystal structures. A similar plot for observations along the O′ ··· *D* axis for *anti* H-bonds is included for comparison (Fig. 6*b*), and it exhibits exactly the same properties relative to the O′–C$^\alpha$–*D* plane. Accordingly, there is no indication from our analyses that the H-atom prefers a position

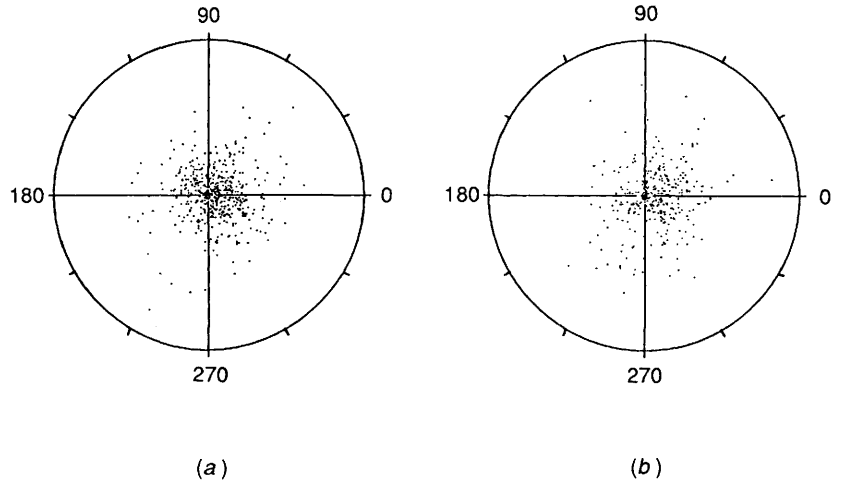


Fig. 6 Polar projection of H-atoms viewed along the $\mathrm{O'\cdots}D$ axis for (*a*) 527 *syn* H-bonds and (*b*) 349 *anti* H-bonds. The radius of each circle is 1.0 Å.

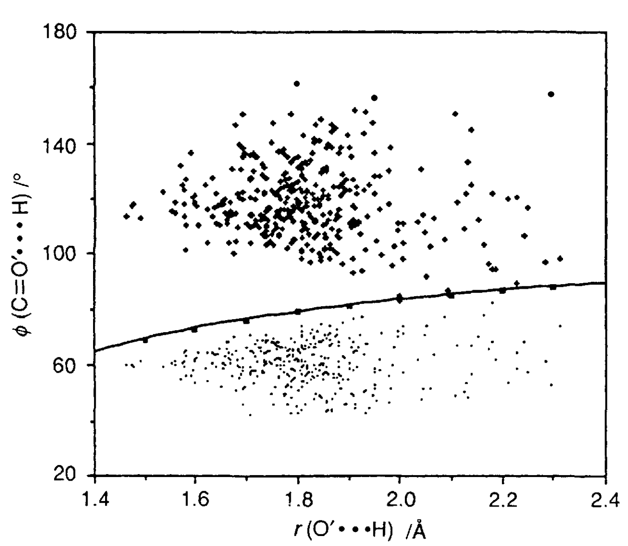
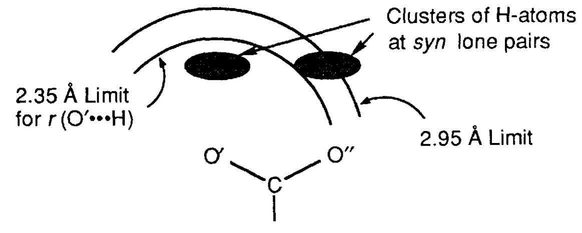


Fig. 7 Scatter plot of $r(\mathrm{O'\cdots H})$ *vs.* $\varphi(\mathrm{C{=}O'\cdots H})$ (+) and $\varphi(\mathrm{C{=}O''\cdots H})$ (·) for *syn* H-bonds. The curved line shows $\varphi(\mathrm{C{=}O\cdots H})$ values for symmetric H-atom positions.

close to the O′–O″–*D* plane. This means that the Δ distribution in Fig. 5 merely reflects the fact that a large fraction of the H-bonds studied are close to linear, giving by default small values for Δ.

The Lone-pair Approach.—The crystallographic data suggest that the minor component is irrelevant in almost all *syn* H-bonds to carboxylates. This result seems to contradict purely electrostatic considerations, since the H-bond interaction attenuates as r^{-1}, indicating that even the fairly long minor components (average 3.00 Å) need to be considered. However, due to stereoelectronic factors, distance criteria cannot be used alone as evidence for a hydrogen bond. An interesting way of examining this question is shown in Fig. 7, where values for both $\varphi(\mathrm{C{=}O'\cdots H})$ and $\varphi(\mathrm{C{=}O''\cdots H})$ are plotted against the shorter of the two $\mathrm{O\cdots H}$ distances, $r(\mathrm{O'\cdots H})$. For the shortest H-bonds, $\varphi(\mathrm{C{=}O'\cdots H})$ is close to the lone-pair angle, 120°. As $r(\mathrm{O'\cdots H})$ increases, the distribution curve flares out so that $\varphi(\mathrm{C{=}O'\cdots H})$ is in the 100–150° range when $r(\mathrm{O'\cdots H})$ is around the 1.8 Å average value. This observed distribution provides qualitative information about the shape of the low-energy region of the potential surface,[6] and illustrates a very important feature of hydrogen bonds, namely the tendency to approach the acceptor in the classical lone-pair directions. In previous surveys similar results have been obtained for N–H and O–H hydrogen bonds to several common acceptors[12,13] including Asp and Glu side-chain carboxylates in protein structures,[13] as well as for $\mathrm{C{-}H\cdots O}$ interactions.[14] If we now consider the location of the H-atom relative to the distant O-atom O″, it can be seen from Fig. 7 that the secondary contacts of typical *syn* H-bonds [again with $r(\mathrm{O'\cdots H})$ around 1.8 Å] have observed values for $\varphi(\mathrm{C{=}O''\cdots H})$ in the interval 40–75°. This is so far from the preferred range for $\varphi(\mathrm{C{=}O'\cdots H})$ that most minor components cannot be regarded as hydrogen bonds. It is therefore necessary to impose some limit on $\varphi(\mathrm{C{=}O\cdots H})$ values to ensure that only contacts with H-atoms in acceptor lone-pair directions are recognized as hydrogen bonds. This conclusion would not result from a simple model of a H-bond as an isotropic electrostatic attraction between point charges.

Proportion of Three-centre Hydrogen Bonds.—When combined with a distance limit (DL) for $r(\mathrm{O\cdots H})$, the introduction of a $\varphi(\mathrm{C{=}O\cdots H})$ limit has a profound effect on the estimated proportion of three-centre hydrogen bonds, Table 1. If no limit is used, the proportion increases from 1.3% with DL = 2.35 to 43.5% with DL = 2.95 Å. The latter value is clearly unreasonable, as it results from counting H-atoms which are in fact interacting with only one *syn* lone pair (Scheme 5).



Scheme 5

With an 80° limit for $\varphi(\mathrm{C{=}O\cdots H})$, the proportion goes from 0.9% (DL = 2.35 Å) to 1.1% (DL = 2.95 Å). It is evident that for a consistent estimate of the importance of three-centre hydrogen bonds, application of limiting $\varphi(\mathrm{C{=}O\cdots H})$ values is essential.

Based on Fig. 1 and additional considerations of the crystallographic material, we suggest the following working definitions for a hydrogen bond to carboxylates in crystal structures:

(1) $r(\mathrm{O\cdots H}) < 2.8$ Å
(2) $\alpha(\mathrm{O\cdots H{-}}D) > 90°$
(3) $80° < \varphi(\mathrm{C{=}O\cdots H}) < 160°$

Table 1 Proportion of three-centre hydrogen bonds to carboxylate groups depending on the limits used for $r(\mathrm{O}\cdots\mathrm{H})$ and $\varphi(\mathrm{C{=}O}\cdots\mathrm{H})$

	$r(\mathrm{O}\cdots\mathrm{H})$ limit Å						
$\varphi(\mathrm{C{=}O}\cdots\mathrm{H})$ limit	2.35, 527[a]	2.40, 530	2.50, 532	2.60, 533	2.70, 534	2.80, 541	2.95, 557
None	7,[b] 1.3%	13, 2.4%	26, 4.9%	51, 9.5%	99, 18.4%	165, 30.4%	243, 43.5%
>70°	7, 1.3%	13, 2.4%	23, 4.3%	31, 5.8%	39, 7.3%	44, 8.1%	49, 8.8%
>75°	7, 1.3%	8, 1.5%	10, 1.9%	11, 2.1%	11, 2.1%	12, 2.2%	14, 2.5%
>80°	5, 0.9%	5, 0.9%	6, 1.1%	6, 1.1%	6, 1.1%	6, 1.1%	6, 1.1%

[a] Total number of *syn* interactions with $r(\mathrm{O'}\cdots\mathrm{H})$ within the limit, used for calculation of percentages. [b] Number of interactions where both O ··· H contacts satisfy the limits for distance and angle.

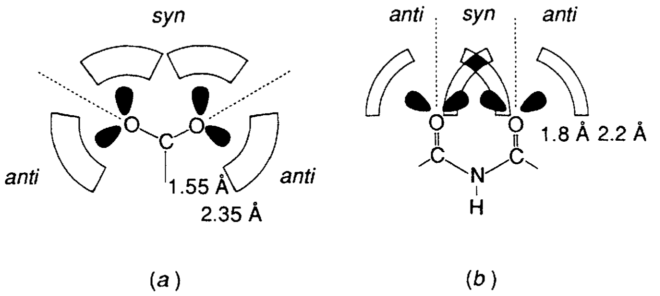


Fig. 8 Most favourable regions [$\varphi(\mathrm{C{=}O}\cdots\mathrm{H})$ in the interval <90°, 150°>] for H-atoms accepted by (*a*) carboxylate groups and (*b*) imides. There is no overlap in the central position in (*a*), while in (*b*) a doubly favourable region, marked in black, occurs due to the fortuitous spatial arrangement of oxygen lone pairs.

When $\varphi(\mathrm{C{=}O}\cdots\mathrm{H})$ values are kept > 80°, there are so few observations between 2.35 and 2.95 Å [none at all for hydrogen bonds with $\alpha(\mathrm{O'}\cdots\mathrm{H}\text{–}D) > 150°$] that calculated values for various geometric H-bond parameters remain largely unchanged for any choice of DL in the interval. For carboxylates this renders much of the previous discussion concerning the proper upper limit for $r(\mathrm{O}\cdots\mathrm{H})$ in hydrogen bonds obsolete, and we can afford to make the rather arbitrary choice of 2.8 Å. It can be seen from Fig. 1(*a*) that very little information is lost by applying a significantly smaller value, *e.g.* 2.35 Å. A strict DL cutoff has the practical advantage that using limits on $\varphi(\mathrm{C{=}O}\cdots\mathrm{H})$ values is not so critical (Table 1).

It is important to note that in an isolated system, the stabilizing energy of a reasonably linear $D\text{–}\mathrm{H}\cdots\mathrm{O}_{\mathrm{carboxylate}}$ contact with $r(\mathrm{O}\cdots\mathrm{H}) > 2.8$ Å may be significant. For most purposes, however, it is unnecessary to consider these longer contacts in crystals, since H-atoms in such long interactions are always much closer to another nearby carboxylate (or other) acceptor. The main hydrogen bond patterns in the crystals are determined by these short interactions, the long contacts being generally unfavourable with $\alpha(\mathrm{O}\cdots\mathrm{H}\text{–}D)$ typically < 120° and almost random values for $\varphi(\mathrm{C{=}O}\cdots\mathrm{H})$.

With the limits given above, only *ca.* 1% of *syn* H-bonds to carboxylate groups are classified as three-centred (Table 1), a surprisingly low figure indicating a very poor ability of carboxylates to participate in three-centre hydrogen bonds. This is also reflected by the observation that out of 527 interactions with a major component < 2.40 Å, only 8 have $r(\mathrm{O''}\cdots\mathrm{H}) - r(\mathrm{O'}\cdots\mathrm{H}) < 0.4$ Å and 4 have $r(\mathrm{O''}\cdots\mathrm{H}) - r(\mathrm{O'}\cdots\mathrm{H}) < 0.2$ Å. In the survey on N–H ··· O=C H-bonds[10] 83 out of 1509 interactions had $r(\mathrm{O}\cdots\mathrm{H}) - r(\mathrm{X}\cdots\mathrm{H}) < 0.2$ Å (X = O, N, S, halogen).

The parallel orientation of the carboxylate *syn* lone pairs prevents symmetric H-atom positions, but truly three-centred interactions can exist in functional groups like imides where the orientation of their carbonyl lone pairs leads to substantial regions of overlap of their respective favourable H-bond regions, Fig. 8. For five acyclic imide crystal structures[15] only *syn* H-bonds have been observed. All H-atoms have favourable positions relative to both oxygen atoms, and four of them have fully symmetric interactions.

Conclusions

A statistical analysis of hydrogen bonds to carboxylate groups show very few *syn* interactions with close to symmetric H-atom locations. The exceptions are only outliers from a general distribution clustered in the classical lone-pair directions. Statistical and geometrical observations suggest that the minor component is without relevance in the vast majority of the asymmetric *syn* hydrogen bonds studied. The criteria suggested for recognizing a contact as a hydrogen bond result in only *ca.* 1% of *syn* interactions being classified as three-centred. The results mean that some high estimates of the proportion of three-centre hydrogen bonds presented in the past need to be reconsidered.

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