Weak hydrogen bonding. Part 1.[1] Neutron diffraction data of amino acid C_α–H suggest lengthening of the covalent C–H bond in C–H ··· O interactions

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In C–H ··· O contacts observed in 16 high-precision neutron crystal-structure determinations of α-amino acids, there is good evidence for a correlation between the covalent bond length of C_α–H and the $H_\alpha \cdots O$ separation. For the shortest H ··· O contacts, ~2.3 Å, the lengthening of C–H is ~0.008 Å compared with the longest contacts of ~2.7 Å. This supports the view that C–H ··· O interactions have the nature of hydrogen bonds. The experimental results are in excellent agreement with calculations from the valence model of the hydrogen bond.

Introduction

The bonding character of C–H ··· O interactions has long been known to spectroscopists, who early on classified them as 'hydrogen bonds'.[2] Although the frequent occurrence of C–H ··· O hydrogen bonds in crystal structures was evident,[3] crystallographers followed this view unwillingly. Only in recent years have the structural characteristics of these interactions been investigated more closely.[4] Several groups of authors have shown that the structural properties of C–H ··· O interactions generally parallel those of the stronger O–H ··· O and N–H ··· O hydrogen bonds; this includes studies on donor and acceptor directionalities,[5] effects of donor acidity[6] and acceptor basicity[7] on mean donor–acceptor separations, the property of cooperativity,[8] the influence on molecular conformation[9] and on thermal vibrations,[10] and the roles in determining crystal-packing arrangements[11] and coordination geometries.[12]

However, some other characteristics of hydrogen bonding have not yet been shown for C–H ··· O interactions. This includes effects on the covalent bonding of the residues involved. Generally, in X–H ··· Y hydrogen bonds, the covalent X–H bond is significantly lengthened compared with free X–H.[13] This effect must occur also in C–H ··· Y hydrogen bonds, but as yet has not been proved.‡ If it can be shown, it supplies *direct* structural evidence for the bonding nature of the C–H ··· O interaction (unlike the indirect evidence derived, for example, from crystal-packing considerations).

The order of magnitude of the anticipated lengthening can be estimated from the valence model of the hydrogen bond.[14] For H ··· O separations around 2.2 Å, a lengthening of C–H by ~0.01 Å is predicted (calculation in footnote §). This is a small effect, but it is in the range observable by high resolution neutron diffraction. In the present study, this is shown with good significance in a crystal correlation study of C_α–H in neutron-diffraction crystal structures of α-amino acids.

Selection of the data sample

To determine X–H bond lengths, X-ray crystallography is unsuitable and neutron diffraction methods have to be used.¶ Since the predicted effect is weak, conclusive analysis must be restricted to data of the highest quality. To avoid effects from chemical inhomogeneity,[6] it is necessary to use only data from related structures. Only for a few substance classes, are large bodies of accurate neutron-diffraction data available. Most promising are the exceptionally well studied (in terms of neutron-diffraction) α-amino acids, for which C_α–H is known to be frequently involved in short C–H ··· O interactions.[15]

As the initial step of analysis, the Cambridge Structural Database[16] was screened for ordered and error-free neutron crystal structures of non-deuteriated α-amino acids with

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‡ An earlier analysis of carbohydrate neutron-diffraction crystal structures faintly indicated a lengthening of C–H by ~0.004 Å for contacts H ··· O < 2.4 Å, but the statistical significance was poor, giving rise to reservations in the publication and preventing any definite conclusions.[5b]

§ The valence model of the hydrogen bond is established in inorganic chemistry,[14] but not in the context of weak hydrogen bonding effects such as C–H ··· O interactions. Nevertheless, the relevance for C–H ··· O contacts was pointed out by Brown,[14] and it is reasonable to test the concept for the present case. In this simple model, the bonds X–H and H ··· Y of an X–H ··· Y contact are given 'valences' s_1 and s_2, respectively, which are directly related to the bond distances. The sum of the valences at H, $s_1 + s_2$, must be 1. If the H ··· Y contact has a non-zero valence s_2, it reduces the valence of X–H, s_1, and this must be reflected in bond lengthening. An approximation for the relationship between valences s and bond distances r is $s = \exp[(r_0 - r)/b]$, where r_0 is the length of the relaxed bond with the valence $s(r_0) = 1$, and b is a constant which for most bonds has a value around 0.37 Å (ref. 14). Using this approximation for a C–H ··· O bond, the C–H lengthening compared with a free bond is $r - r_0 = -b \ln(1 - s_2)$. Using $b = 0.37$ Å and the approximate H ··· O valences s_2 derived from O–H ··· O bonds[13d] ($s_2 = 0.039, 0.024, 0.014, 0.009$, respectively, for H ··· O = 2.2, 2.4, 2.6, 2.8 Å, respectively; note that in this model of X–H ··· Y, s of H ··· Y is independent of the nature of X), this yields values of $r - r_0 = 0.015, 0.009, 0.005, 0.003$ Å for H ··· O separations of 2.2, 2.4, 2.6, 2.8 Å, respectively. When two C–H groups are compared which are involved in C–H ··· O interactions with different H ··· O separations k and l, their C–H bond lengths consequently differ by $\Delta r = b \ln[(1 - s_k)/(1 - s_l)]$. For example, when H ··· O is 2.4 and 2.8 Å, the C–H bond lengths should differ by 0.006 Å. The valences s_2 for general values of H ··· O can be estimated by[13d] $s_2 = \exp[(0.927 - d_{H \cdots O})/0.395]$ [similar values are given in ref. 13(*c*)].

¶ X-Rays are scattered at the atomic shells, and can therefore 'see' H-atoms only poorly. Neutrons are scattered at the atomic nuclei and 'see' H (and D) with similar accuracies as the other atoms. In response to a referee's comment, it is pointed out that one can argue whether the 'true' position of an atom is given by the nucleus or by the electron shell. Throughout the present work 'X positions' mean the centre of gravity of the vibrating nucleus of atom X. Regarding the electron shells in a short C–H ··· X contact, one must expect slight charge density distortions (at *least* at H and X) due to the H ··· X interaction. These might be detected from very accurate X-ray data. Such a study would be highly interesting, but is far beyond the scope of the present work.

Table 1 The structure data set,[a] in order of increasing H ··· O distances; distances in Å, angles in degrees

Structure	Ref.	Charge[b]	Accept.	C_α–H	H···O	C···O	$\alpha_{C-H\cdots O}$
DL-Serine	18(*a*)	±	CO_2^-	1.101(1)	2.196	3.293	174.1
L-Tyrosine	18(*b*)	±	CO_2^-	1.094(3)	2.243	3.245	151.3
L-Glutamic acid, α-form	18(*c*)	±	C=O	1.097(2)	2.287	3.351	162.9
L-Cystine dihydrochloride	18(*d*)	+	C=O	1.097(3)	2.321	3.317	150.1
L-Valine hydrochloride	18(*e*)	+	C=O	1.099(3)	2.368	3.376	151.8
Glycine, α-form	18(*f*)	±	CO_2^-	1.094(2)	2.382	3.272	137.4
Glycine, α-form	18(*g*)	±	CO_2^-	1.090(2)	2.390	3.277	137.4
L-Asparagine monohydrate	18(*h*)	±	H_2O	1.100(2)	2.402	3.352	143.6
L-Alanine	18(*i*)	±	CO_2^-	1.093(2)	2.429	3.472	159.5
4-Hydroxy-L-proline	18(*j*)	±	CO_2^-	1.084(3)	2.430	3.495	167.4
Glycine hydrochloride	18(*k*)	+	C=O	1.086(2)	2.489	3.559	168.3
DL-Aspartic acid	18(*l*)	±	C=O	1.071(6)	2.525	3.369	135.2
L-Glutamic acid, β-form	18(*m*)	±	C–OH	1.091(–)	2.538	3.326	128.3
L-Serine monohydrate	18(*n*)	±	CO_2^-	1.095(5)	2.583	3.638	161.5
L-Glutamine	18(*o*)	±	CO_2^-	1.093(4)	2.626	3.519	138.4
L-Glutamic acid hydrochloride	18(*p*)	+	C=O	1.085(10)	2.674	3.647	149.1
Glycine, α-form	18(*g*)	±	CO_2^-	1.089(2)	2.808	3.407	114.5
Glycine, α-form	18(*f*)	±	CO_2^-	1.087(2)	2.811	3.406	111.3

[a] C_α–H ··· O contacts in α-amino acid neutron diffraction crystal structures with $R < 0.05$ determined at room temperature. [b] Charge of the amino acid: ± zwitterionic; + cationic.

crystallographic *R*-values < 0.05. Only structures for which the shortest intermolecular contact of C_α–H is to an O-atom were considered. Metal-ion complexes were excluded, whereas hydrochlorides were allowed; possible differences between zwitterionic compounds and chloride salts will be discussed later on. Because of the temperature effect on crystallographic values of X–H bond lengths,[17] mixing of room-temperature (RT) and low-temperature (LT) data must be strictly avoided. In principle, it is best to analyse LT data, which is of superior accuracy [as was done for O–H donors in ref. 13(*d*)]. In the present case, however, the quantity of the LT data is much too small, so that the RT data had to be used and the LT data excluded.

Following these steps, the original publications were inspected, and structures determined from obviously poor experimental quality were excluded. The final data set consisted of 18 C_α–H ··· O contacts in 16 crystal structures.[18]

Results and discussion

Characterisation of the data set

For each of the 18 C_α–H groups in the data set, only the shortest intramolecular contact to O was considered, and the geometric parameters of these contacts are listed in Table 1.‖ For 13 of the 18 C–H bond lengths, the standard errors are ≤0.003 Å. Possible effects from second shortest contacts ('three-centred' or 'bifurcated' arrangements[4b]) will be discussed later on, leading to the conclusion that at the present level of analysis, it is not (yet) reasonable to consider them as separate cases. Before the chemical inhomogeneities within the set are discussed, the sample is statistically characterised as a whole as shown in Fig. 1. The distribution of the H_α ··· O distances, Fig. 1(*a*), peaks around 2.4 Å, with the shortest value 2.196 Å in DL-serine[18a] (which is, notably, associated with the longest C–H bond, 1.101 Å). The distribution of the C–H ··· O angles peaks around 160°, Fig. 1(*b*). To see whether linear bonds are statistically preferred, the frequencies of C–H ··· O angles (θ) must be divided by a correction factor sin θ, in which the fact that a given angular range Δθ covers a smaller solid angle for close to linear angles than for bent angles is taken into account.[19] This correction yields a distribution which peaks at linear angles, Fig. 1(*c*), clearly showing the directional nature of the C–H ··· O interaction.

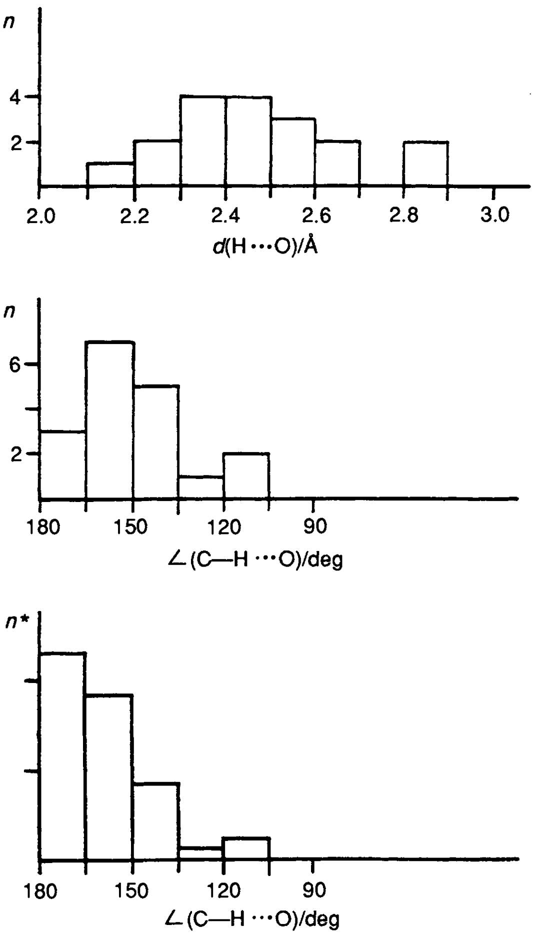

Fig. 1 Histograms describing the geometry of the C_α–H ··· O contacts in the data set: (*a*) distribution of H ··· O distances; (*b*) distribution of C–H ··· O angles; (*c*) distribution of C–H ··· O angles weighted with a correction factor 1/sin $\bar{\theta}$, where $\bar{\theta}$ is the mid-point of the angle interval (compare ref. 19).

The data sample contains 14 C_α–H donors from zwitterionic

‖ There are some cases of discrepancies of 0.001 or 0.002 Å between the bond lengths given in the publications and in the database, which are apparently rounding effects. In these cases, the originally published values were preferred.

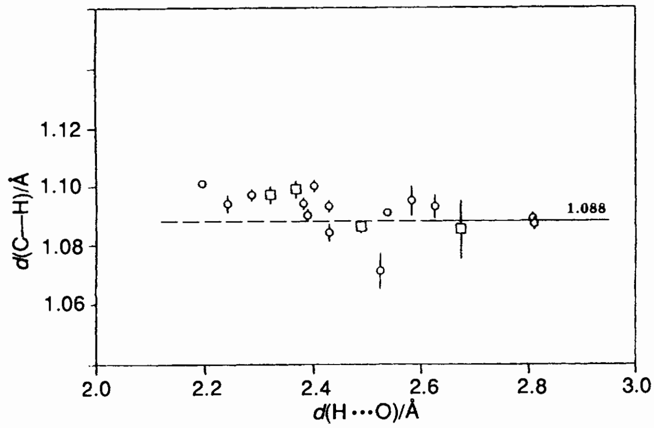

Fig. 2 Covalent bond length C_α–H plotted against the H···O separation in C_α–H···O contacts. The horizontal line shows the mean C–H bond distance for the longest H···O separations, 1.088 Å (Table 3). Circles show C_α–H donors from zwitterionic amino acids and squares show cations donors of hydrochloride salts. Vertical lines show the standard errors of C_α–H given in the original publications.

α-amino acids (NH_3^+–C_αR–CO_2^-), and four from cations of chloride salts (NH_3^+–C_αR–CO_2H). Furthermore, there are four acceptor types: CO_2^- (10), C=O (6), C–OH (1) and H_2O (1), Table 1, resulting in five different donor–acceptor combinations with slightly different donor acidities and acceptor basicities. To check whether this causes differences in the mean C–H and H···O distances, these values are individually listed in Table 2 for the different donors and acceptors. All variations are within the standard errors, so that the 18 data can be analysed in the following in a common set. The occurrence of chemical variations, however, is still a *caveat* and must be kept in mind.

Correlation of the C–H bond length with the H···O distance

A plot of C_α–H bond length against hydrogen bond distance H···O is shown in Fig. 2. Vertical bars indicate the standard errors of C_α–H given in the original publications. The sample contains one obvious outlier, C_α–H = 1.071(6) Å in DL-aspartic acid, which will be excluded from all following calculations.** For the remaining 17 data, short H···O distances apparently correlate with longer C–H bond lengths. Standard methods of analytical statistics[20] infer, with a reliability better than 99%, that a correlation between C–H and H···O actually exists (see footnote ††). This means that the data show the anticipated lengthening of C_α–H due to the H···O bond with good significance.

Table 2 Mean C_α–H and H_α···O distances for some subsets of the data sample; standard uncertainties[a] are given in parentheses

Sample	n	mean C–H[b] (Å)	mean H···O (Å)
all data	18	1.093(1)	2.47(4)
C_α–H from zwitterions	14	1.093(1)	2.48(5)
C_α–H from cations	4	1.092(2)	2.46(8)
with CO_2^- acceptors	10	1.092(2)	2.49(6)
with C=O acceptors	6	1.093(3)	2.44(6)

[a] Standard uncertainties (standard errors) su (x) of the mean values $\bar{x}$ are calculated as: su ($\bar{x}$) = $[\Sigma_i(x_i - \bar{x})^2/n(n-1)]^{0.5}$. [b] Calculated without the single outlier 1.071 Å in DL-aspartic acid.

Table 3 Mean C_α–H bond lengths for given ranges of H···O; standard uncertainties[a] are given in parentheses

H_α···O range	n	mean H_α···O (Å)	mean C_α–H (Å)
<2.4	7	2.31(3)	1.096(1)
2.4–2.6	6	2.48(3)	1.091(2)
>2.6	4	2.73(5)	1.088(2)

[a] Standard uncertainties (standard errors) su (x) of the mean values $\bar{x}$ are calculated as: su ($\bar{x}$) = $[\Sigma_i(x_i - \bar{x})^2/n(n-1)]^{0.5}$.

To quantify the lengthening of C_α–H, the data are divided into three subsets with increasing H···O distance. The corresponding mean C_α–H bond lengths actually increase with decreasing H···O, Table 3. The mean value for the longest H···O distances, 1.088(2) Å, is included as a horizontal line in Fig. 2. For the set of shortest H···O distances, <2.4 Å, *all* data points are scattered above this line, showing nicely the lengthening of C_α–H.

One might suspect that the bond lengthening described is only an artifact due to thermal vibration effects. Closer investigation of the published displacement parameters, however, shows that this is not the case, as is described in detail in footnote ‡‡.

** Note in response to a referee's comment: defining and treating outliers is non-trivial and to a large degree subjective. The C–H bond mentioned is by far the shortest in the data set, 1.071(6) Å (associated with a H···O contact of 2.53 Å), to be compared with the second shortest C–H bond, 1.084(3) Å. The other C–H bonds in the same H···O range (2.4–2.6 Å) have a mean length of 1.091(2) Å, Table 3, with an rms-deviation σ = 0.006 Å. The mentioned C–H bond length is outside the 3σ region of this value and should be omitted to avoid bias.

†† The correlation (if significant) must be non-linear. This is because it must have a negative slope for short H···O distances (as for O–H···O bonds[13]), and at the same time extrapolate to a constant ('relaxed') value for long H···O. Therefore, the commonly used linear correlation coefficient is unsuitable in this context. An appropriate test quantity for the present correlation is the Spearman-rank-correlation coefficient r_s, which is calculated to be r_s = 0.71 (for 17 data). This value excludes the null hypothesis (H_0 = zero correlation) at the 1% significance level, so that the factual existence of a correlation between C–H and H···O is inferred with more than 99% reliability (for the computational method, see ref. 20, or any other advanced textbook on applied statistics).

‡‡ In crystallography, observed X–H bond lengths are systematically shortened by an artifact caused by thermal vibrations, and this apparent shortening becomes more pronounced with increasing vibration amplitudes.[17] In O–H···O hydrogen bonds, the vibration amplitude of the H-atom reduces with reducing hydrogen bond length,[21] and a similar effect was found for the highly acidic –C≡C–H donors.[10] Therefore, one could also assume that in the present case, the H atoms involved in the shortest contacts vibrate with the smallest amplitudes and the corresponding C–H bonds are shortened to the least extent; this might be exactly the effect shown in Fig. 2. On the other hand, the amino acid C_α–H bond has a rigidly confined orientation and cannot rotate as O–H in H_2O or C–OH, or participate in large amplitude librations of a whole residue as in –C≡C–H. For the comparably confined C(sp^3)–H bonds in carbohydrates, *no* effect of C–H···O interactions on the thermal H-vibrations was detectable,[5b] so that similarly plain vibration behaviour might also be expected in the present case. To clear this point, it was checked in a similar way as in the earlier study reported in ref. 10, whether the H_α vibrations correlated with the H···O separations. Since the *absolute* displacement parameters of H, U_H, cannot reasonably be compared between different structures, the ratio of the isotropic U_{eq}-values of H_α and C_α, U_H/C_H, was analysed instead, which is a relative quantity that can be compared between different structures.[10] If the H_α vibration decreases significantly in a C–H···O bond, a *positive correlation* between U_H/U_C and H···O must be observed (*i.e.*, U_H/U_C must decrease with decreasing H···O). Consequently, the relevant U-values were picked from the original publications,[18] and correlated with H···O from Table 1. The linear correlation coefficient obtained, r = −0.37 for 17 data, is (*a*) *not* non-zero at the 95% significance level,[20] *i.e.*, statistically compatible with the null-hypothesis 'no correlation', and (*b*) is *negative*, *i.e.* if truly non-zero, the effect would operate in the reverse direction from that originally expected; this is physically unreasonable. In other words, a systematic reduction of the H-vibrations in C_α–H···O interactions does *not* show up in the data, and a systematic effect on the C–H bond length as a consequence of such a reduction cannot be inferred.

Numerical values and comparison with the valence model of the hydrogen bond

Numerically, the observed lengthening compared with the set of the longest contacts [$\langle H \cdots O \rangle = 2.73$ Å] is 0.008(3) Å for the shortest bonds [$\langle H \cdots O \rangle = 2.31$ Å], and 0.003(3) Å for the set with $\langle H \cdots O \rangle = 2.48$ Å, Table 3. The standard uncertainties given in parentheses show that these values have to be taken with reservations: whereas the mere *existence* of a correlation is derived quite reliably, the numerical results remain semi-quantitative at best. Note also that these data do *not* describe the lengthening compared with 'free' C_α–H, for which no crystallographic data are available, but compared with C_α–H which forms weaker intermolecular interactions than the average.

The valence model mentioned above§ yields numerical values for C–H lengthening compared with a long C–H $\cdots$ O bond ($H \cdots O = 2.73$ Å) of 0.007 Å for $H \cdots O = 2.31$ Å, and of 0.003 Å for $H \cdots O = 2.48$ Å. These values agree excellently with the experimental results (considering the uncertainty of the data, the agreement is better than might be expected).

Possible effect from second shortest H $\cdots$ O contacts

In response to a referee's comments: in the above analysis, second-shortest H $\cdots$ X contacts were neglected. This is not without problems, because it must be expected that 'minor components' of three-centre[4b,5b] ('bifurcated') C–H $\cdots$ X interactions cause slight C–H bond lengthening *in addition* to the lengthening by the shortest contact. Actually, for five of the 17 C–H $\cdots$ O interactions analysed, there is a second contact with $H \cdots X < 2.8$ Å, the shortest in glycine with $H \cdots O = 2.45$ Å. In a rigorous analysis, these additional contacts must be considered as was done for the stronger O–H $\cdots$ O bonds.[13c,d] However, this is not very promising with only 5 data and the statistical limitations discussed above; therefore, the 5 data were tentatively *omitted* as a whole to see if this changed the results, which became as follows. For $H \cdots O < 2.4$ Å: $n = 4$, mean C_α–H = 1.098(1) Å; for H $\cdots$ O 2.4–2.6 Å: $n = 4$, mean C_α–H = 1.093(3) Å; for $H \cdots O > 2.6$ Å: $n = 4$, mean C_α–H = 1.088(2) Å. This is the same result as in Table 3, suggesting that such delicacies can be only analysed from much larger sets of accurate data.

Conclusions

In this study, the C_α–H bond length of α-amino acids which form C_α–H $\cdots$ O interactions is analysed from high precision neutron diffraction data. The data infer the *existence* of a correlation of the C_α–H and the $H_\alpha \cdots O$ distances with a statistical reliability better than 99%. This is good evidence for the effect *per se*.§§ Owing to the small number of data, the derived *numerical values* are only semi-quantitative. However, the results are in favour of the view that C–H $\cdots$ O interactions are in nature 'hydrogen bonds', and extend the number of parallel properties of C–H $\cdots$ O, O–H $\cdots$ O and N–H $\cdots$ O interactions.

The valence model of the hydrogen bond[14] is not well established for the treatment of weak hydrogen bonding effects. The excellent agreement of the experimental data and the prediction derived from this model suggests that it is also applicable in these subtle situations.

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§§ There is a residual 1% risk of error. Since this error, if true, is fatal to the study, it is desirable to repeat the analysis from independent data (which presently is not available).

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