10146 J. Am. Chem. Soc. **1992**, *114*, 10146-10154

Geometry of C–H···O Hydrogen Bonds in Carbohydrate Crystal Structures. Analysis of Neutron Diffraction Data

Thomas Steiner and Wolfram Saenger*

Contribution from the Institut für Kristallographie, Freie Universität Berlin, Takustrasse 6, W-1000 Berlin 33, Germany. *Received May 30, 1992*

Abstract: Geometrical properties of C—H···O hydrogen bonds in carbohydrate crystal structures are analyzed on the basis of 30 neutron diffraction studies (395 H atoms bonded to C as potential donors, and 328 O atoms at potential acceptors). A total of 21% of the H atoms are engaged in C—H···O interactions with H···O separations of <2.5 Å (and 65% of the H's with H···O < 2.7 Å). Only 7% of the H atoms have no contact to O shorter than 3.0 Å. Correlations between hydrogen-bond distances and angles are studied in scatterplots. The shortest interactions tend to be close to linear, but the correlation between distances and angles is much less pronounced than in O—H···O hydrogen bonds. There is a continuous transition from stronger to weaker hydrogen bonds and to nonbonding arrangements; consequently, cutoffs based on van der Waals contacts should be discouraged. Intermolecular and intramolecular interactions are treated separately. Short intramolecular contacts, where H and O are separated by only four covalent bonds, occur frequently due to steric restrictions. In β-cyclodextrin inclusion complexes, host/guest C—H···O hydrogen bonds with H···O separations as short as 2.39 Å are observed; for water molecules that cannot arrange in the preferred tetrahedral O—H···O hydrogen-bond coordination, the resulting "free" acceptor potential is frequently satisfied by C—H···O interactions. C—H···O hydrogen bonds are not strong enough to significantly reduce the thermal vibrations of the engaged H atom. The lengthening of the covalent C—H bond due to the H···O interaction is at the limit of experimental accuracy: ~0.004 Å for $d_{\mathrm{H\cdots O}} < 2.4$ Å.

Introduction

The existence of C—H···X hydrogen bonds was proposed early[1] and was subsequently verified by spectroscopy.[2,3] Crystallographic evidence for C—H···O hydrogen bonds was based on numerous short C···O contacts down to, and even below, 3.0 Å in X-ray crystal structures.[4,5] After years of controversy, final evidence for the structural significance of C—H···O bonds was provided by a survey of 113 neutron diffraction structures,[6] which shows that H bonded to C has a strong tendency to form intermolecular contacts to O. It was repeatedly made clear that the C—H···O hydrogen bonds play an important role in determining the crystal packing and to some degree the molecular conformation.[7-10]

Although C—H···O interactions are present in a vast number of crystal structures, they are not commonly discussed even in neutron diffraction studies. Despite the large volume of dispersed literature, there are only a few surveys of hydrogen bonding where they are discussed in greater detail.[11]

The metrical properties of C—H···O (and in general C—H···X) hydrogen bonds are less well-known than for O—H···X or N—H···X interactions. They can be satisfactorily derived only from a relatively large set of neutron crystal diffraction data, which (unlike X-ray data) provides accurately determined H positions. To avoid complications due to chemical heterogeneity, it is preferable to restrict an analysis to a certain class of substances. The class which has been most carefully investigated for hydrogen bonding, and for which most neutron diffraction data are available, are (besides the amino acids[11]) the carbohydrates. For these, comprehensive analyses of O—H···O hydrogen bonding have been published,[11-13] and they are particularly useful for an investigation of C—H···O interactions, because they abound with CH donor and O acceptor groups. Since the C—H···O bonds are primarily electrostatic in nature and depend on the partial atomic charges, these are given in Table I. The numeric values vary considerably for different calculation methods and therefore have to be taken with reservations. Their magnitudes, however, indicate the possible significance of C—H···O interactions (though less than O—H···O) from a purely electrostatic point of view.

Table I. Magnitude of Atomic Partial Charges (in *e* units) in Carbohydrates as Estimated by ab Initio Calculations[14]

atom type	estimated charge
O (both ring and hydroxyl)	−0.46
anomeric C	0.23
all other C	−0.01
hydroxyl H	0.34
H bonded to C	0.13

Table II. Number[a] of H Atoms in CH Donor Groups and O Acceptor Atoms in the Analyzed Data Set

	total[b]	carbohydrates[c]	cyclodextrins[d]
no. of structures	30	26	4
H atoms bonded to C[e]	395 (100%)	207	188
in CH	260 (66%)	120	140
in CH$_2$	114 (29%)	66	48
in CH$_3$	21 (5%)	21	
O atoms	328 (100%)	160	168
in COH	199 (61%)	117	82
in COC	89 (27%)	33	56
in C=O, COO$^-$	5 (1.5%)	5	
in water	35 (11%)	5	30

[a] Disordered atoms are excluded and not counted. [b] For the specified chemical connectivities, the percentage of the total number is given in parentheses. [c] Mono- and disaccharides.[15] [d] Complexes of β-cyclodextrin.[17-20] [e] All C atoms are sp^3 hybridized.

In this report, we present a study of various metrical properties of C—H···O interactions in carbohydrates and show that this type of hydrogen bonds is an integral part of intra- and intermolecular interactions of this substance class.

The Data Set Analyzed

The atomic coordinates of 26 carbohydrate neutron crystal structures[15] with crystallographic quality factors $R < 0.08$ were

---

(1) Glasstone, S. *Trans. Faraday Soc.* **1937**, *33*, 200–214.

(2) Dippy, J. F. J. *Chem. Rev.* **1939**, *25*, 151–160.

(3) Green, R. D. *Hydrogen Bonding by C-H Groups*; Wiley Interscience: New York, 1974.

(4) Sutor, D. J. *Nature (London)* **1962**, *195*, 68–69.

(5) Sutor, D. J. *J. Chem. Soc.* **1963**, 1105–1110.

(6) Taylor, R.; Kennard, O. *J. Am. Chem. Soc.* **1982**, *104*, 5063–5070.

(7) Leiserowitz, L. *Acta Crystallogr. Sect. B.* **1976**, *B32*, 775–802.

(8) Berkovitch-Yellin, Z.; Leiserowitz, L. *Acta Crystallogr. Sect. B.* **1984**, *B40*, 159–165.

(9) Sarma, J. A. R. P.; Desiraju, G. R. *Acc. Chem. Res.* **1986**, *19*, 222–228.

(10) Desiraju, G. R. *Acc. Chem. Res.* **1991**, *24*, 290–296.

(11) Jeffrey, G. A.; Saenger, W. *Hydrogen Bonding in Biological Structures*; Springer-Verlag: Berlin, 1991.

(12) Ceccarelli, C.; Jeffrey, G. A.; Taylor, R. *J. Mol. Struct.* **1981**, *70*, 255–271.

(13) Steiner, Th.; Saenger, W. *Acta Crystallogr. Sect. B*, in press.

(14) Rasmussen, K. *Acta Chem. Scand. A* **1982**, *A36*, 323–327.

0002-7863/92/1514-10146$03.00/0 © 1992 American Chemical Society

Tabke III. Number of C—H⋯O Contacts with $\alpha_{CH\cdots O} > 90°$ in the Data Set[a]

	total			carbohydrates[b]	cyclodextrins[b]
H atoms bonded to C	395	intermolecular	intramolecular	207	188
no. of C—H⋯O contacts					
$d_{H\cdots O}$ <2.4 Å	21	14	7	7	14
$d_{H\cdots O}$ <2.5 Å	92	48	44	37	55
$d_{H\cdots O}$ <2.7 Å	304	139	165	150	154
no. of H atoms involved[a]					
$d_{H\cdots O}$ <2.4 Å	20 (5%)	14 (4%)	7 (2%)	6 (3%)	14 (7%)
$d_{H\cdots O}$ <2.5 Å	83 (21%)	46 (12%)	43 (11%)	34 (16%)	49 (26%)
$d_{H\cdots O}$ <2.7 Å	256 (65%)	133 (34%)	157 (40%)	125 (60%)	131 (70%)

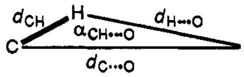
[a] For three-center and four center contacts, major *and* minor components are counted. Number and percentage of the H atoms involved. [b] See footnotes c and d of Table **II**. [c] Because for many H atoms there is more than one contact, this percentage is in most cases smaller than $n_{contacts}/n_{atom}$.

extracted from the Cambridge Structural Data Base,[16] July 1991 release (24 mono- and 2 disaccharides), and combined with those of four neutron diffraction studies of β-cyclodextrin complexes.[17-20] Most of the mono- and disaccharides, as well as two β-cyclodextrin structures, are based on room-temperature data, whereas three monosaccharides and two β-cyclodextrin structures were determined at low temperatures. Disordered H and O atoms were rigorously excluded from the analysis. The remaining data set contains 395 H atoms which are all bonded to sp^3-hybridized C, as potential C—H⋯O hydrogen-bond donors, and 328 O atoms, as potential acceptors (Table II). Of the O atoms, 61% are hydroxyl groups (COH), 27% are ether type (COC), 1.5% are of the type C═O or COO^-, and 11% are from water molecules (Table II).

Covalent C-H bond lengths are not corrected for apparent shortening by thermal vibrations; this results in a systematic reduction around or slightly above 0.01 Å compared to the "true" values. The statistical inaccuracy of the data varies from structure to structure, but generally it is around ±0.01 Å for distances and ±1° for angles.

The Parameters Analyzed

We only analyze the commonly used hydrogen-bond parameters d_{CH}, $d_{H\cdots O}$, $d_{C\cdots O}$, and $\alpha_{CH\cdots O}$.

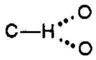


These parameters are not independent: if any three of them are given, the fourth is determined by trigonometric relations. If the covalent bond length d_{CH} is regarded as constant at ~1.10 Å, only two independent parameters remain. A more detailed analysis (considering for instance the lone-pair directionality of the hydrogen bond[6,21]) is beyond the scope of the present work.

Table IV. Number and Percentage of C—H⋯O Interactions with $d_{H\cdots O}$ < 2.7 Å and $\alpha_{CH\cdots O} > 90°$ Donated by the Different Types of CH Donor Groups and Accepted by the Different Types of O Atoms

	total	inter-molecular	intra-molecular
C—H⋯O donated			
total	304 (100%)	139 (100%)	165 (100%)
by CH	209 (69%)	95 (68%)	114 (69%)
by CH_2	88 (29%)	40 (29%)	48 (29%)
by CH_3	7 (2%)	4 (3%)	3 (2%)
C—H⋯O accepted			
by COH	180 (59%)	111 (80%)	69 (42%)
by COC	109 (36%)	16 (12%)	93 (56%)
by C═O, COO^-	5 (2%)	2 (1%)	3 (2%)
by water	10 (3%)	10 (7%)	

Following the terminology of O—H⋯O and N—H⋯O hydrogen bonds,[11] we define an arrangement where a donor CH simultaneously hydrogen bonds with two (three) acceptor O atoms as a three-center (four-center) hydrogen bond.



With very few exceptions, the two $d_{H\cdots O}$ distances are different. The shorter is called the "major component" and the longer the "minor component".[11] Minor components of three- and four-center bonds are included in the present analysis and considered separately, if this is required.

It is common practice in crystallography to assign X—H⋯Y contacts as "hydrogen bonds" on the basis of geometrical parameters with cutoff limits for d_{H-Y} and α_{XH-Y}. For long hydrogen bonds this is controversial, as hydrogen bonds have a major electrostatic component that diminishes only slowly with increasing distance $d_{H\cdots X}$[22] and is still significant beyond the H⋯Y van der Waals separation. If the distance cutoff selected is too restrictive (as is frequently the case), numerous long-range interactions are omitted. For C—H⋯O interactions, it was experimentally found that, even with H⋯O separations as long as 2.5–2.6 Å, they may be strong enough to force a methyl group bonded to $C(sp^3)$ into the sterically unfavorable eclipsed conformation.[23] Consequently, the cutoff limit for $d_{H\cdots O}$ in C—H⋯O must be *at least* 2.7 Å and preferably longer. The angle cutoff (usually $\alpha_{XH\cdots Y} > 90°$) demands that XH must not point away from Y and is less controversial.

To avoid bias from distance cutoffs that are too short, we analyzed the C—H⋯O contacts with $d_{H\cdots O}$ up to 3.2 Å and applied the angle cutoff $\alpha_{CH\cdots O} > 90°$. In the main part of the analysis, however, we concentrate on the "shorter" contacts with $d_{H\cdots O}$ < 2.7 Å, but always keep in mind that this limit cuts a slowly

---

(15) Entry numbers and reference codes of the 26 carbohydrate neutron structures in the Cambridge Structural Data Base are as follows:[16] 51 ABINOS01, 839 AHXGLP, 4330 CEGLCA01, 9929 FRUCTO02, 10120 GLUCIT01, 10124 GLUCSA, 12034 KDGLUM01, 12035 KDGLUM02, 12744 MALTOS11, 13348 MDRIBP02, 13489 MEMANP11, 13754 MGLUCP11, 18916 RHAMAH12, 19536 SUCROS04, 22352 XYLOBM01, 23683 LYXOSE01, 24129 ABINOR01, 24466 GLUCSA01, 24533 MBDGAL02, 24555 MGALPY01, 24709 SORBOL01, 26985 XYLOSE01, 26986 XYLOSE02, 37149 YYYYAA, 37152 YYYYAF, 51184 ABINOR04.

(16) Allen, F. H.; Bellard, S.; Brice, M. D.; Cartwright, B. A.; Doubleday, A.; Higgs, H.; Hummelink, T.; Hummelink-Peters, B. G.; Kennard, O.; Motherwell, W. D. S.; Rodgers, J. R.; Watson, D. G. *Acta Crystallogr. Sect. B* **1979**, *B35*, 2331–2339.

(17) Betzel, Ch.; Saenger, W.; Hingerty, B.; Brown, G. M. *J. Am. Chem. Soc.* **1984**, *106*, 7545–7557.

(18) Zabel, V.; Saenger, W.; Mason, S. A. *J. Am. Chem. Soc.* **1986**, *108*, 3664–3673.

(19) Steiner, Th.; Mason, S. A.; Saenger, W. *J. Am. Chem. Soc.* **1990**, *112*, 6184–6190.

(20) Steiner, Th.; Mason, S. A.; Saenger, W. *J. Am. Chem. Soc.* **1991**, *113*, 5676–5687.

(21) Murray-Rust, P.; Glusker, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 1018–1025.

(22) Umeyama, H.; Morokuma, K. *J. Am. Chem. Soc.* **1977**, *99*, 1316–1332.

(23) Seiler, P.; Weisman, G. R.; Glendening, E. D.; Weinhold, F.; Johnson, V. B.; Dunitz, J. D. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1175–1177.

(24) Brown, G. M.; Levy, H. A. *Acta Crystallogr. Sect. B* **1973**, *B29*, 790–797.

(25) Takagi, S.; Jeffrey, G. A. *Acta Crystallogr. Sect. B* **1977**, *B33*, 3033–3040.

(26) Noordik, J. H.; Jeffrey, G. A. *Acta Crystallogr. Sect. B* **1977**, *B33*, 403–408.

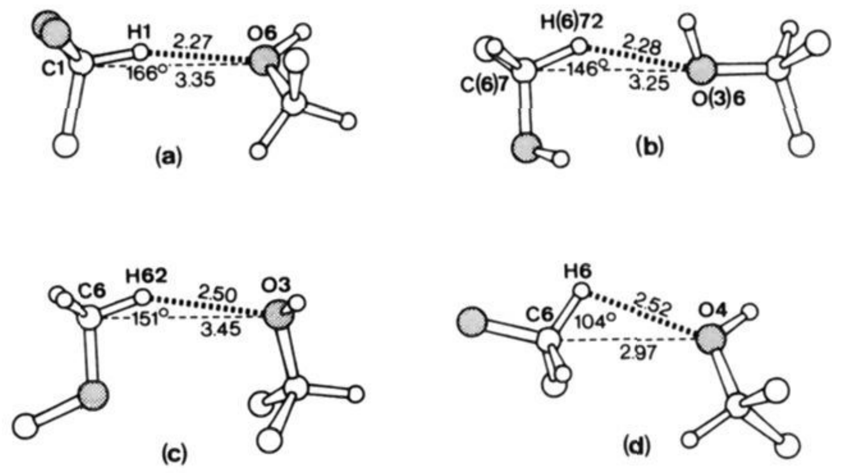


Figure 1. Examples for short C—H···O interactions in carbohydrates. For clarity, only the relevant atoms and their covalent surroundings are drawn. All contacts are intermolecular. O atoms are shaded. View is onto the C—H—O plane. (a) Shortest C—H···O hydrogen bond donated by a CH group (methine-type, only one H bonded to C) in the data set; *in sucrose.*[24] *(b) Shortest C—H···O hydrogen bond donated by a* CH_2 group (methylene-type); in β-cyclodextrin·11.6H_2O at T = 120 K.[18] (c) Shortest C—H···O hydrogen bond donated by a CH_3 group; in methyl β-D-xylopyranoside.[25] (d) Shortest intermolecular C···O contact; note the strongly bent angle $\alpha_{CH\cdots O}$. In 3-amino-1,6-anhydro-3-deoxy-β-D-glucopyranose.[26]

decreasing force as arbitrarily as any other limit would.

Results

(a) Number of C—H···O Hydrogen Bonds. In the data set, 20 H atoms (~5% of the 395) donate a total of 21 C—H···O hydrogen bonds with $d_{H\cdots O} < 2.4$ Å (Table III) (i.e., one of the H atoms donates a three-center bond with a short minor component). For $d_{H\cdots O} < 2.5$ Å, the number of H atoms increases to 83 (~21% of the total, with 92 contacts), and for $d_{H\cdots O} < 2.7$ Å, 256 H atoms are engaged in C—H···O interactions (~65% of the total, with 304 contacts). For the very long limit $d_{H\cdots O} < 3.0$ Å (not in Table III), the number of H atoms is 369 (~93% of the total, with 610 contacts). A large fraction of the C—H···O contacts is intramolecular (Table III). We associate the large number of C—H···O interactions with the high density of acceptor O atoms in carbohydrates.

(b) Different Types of Donor Groups and Acceptor Atoms. It is of interest to determine whether there is a preference for one of the types of donor groups and acceptor atoms. The CH group (methine-type, only one H bonded to the C atom) contributes 66% of the H atoms (Table II) and donates 69% of all C—H···O hydrogen bonds with $d_{H\cdots O} < 2.7$ Å (Table IV); these fractions are comparable. Similarly, CH_2 (methylene-type) contributes 29% of the H atoms and donates 29% of the hydrogen bonds. The methyl group, however, contributes ~5% to the number of H atoms, but only ~2% to the number of C—H···O interactions. This indicates that the "donor strength" of CH_3 is weaker than that of CH and CH_2. This is also supported by the observation that the shortest C—H···O bond donated by a methyl group, $d_{H\cdots O} = 2.50$ Å, is longer than the shortest bonds donated by CH, $d_{H\cdots O} = 2.27$ Å, and CH_2, $d_{H\cdots O} = 2.28$ Å (Figure 1a–c). For all three donor types, the fraction of intramolecular bonds is the same (Table IV), showing that none of them has a special preference to form inter- or intramolecular hydrogen bonds.

For the different types of acceptor O atoms, the situation is more complex: hydroxyl groups and carbonyl or carboxylate C═O accept a fraction of C—H···O bonds that is comparable to their fraction among the O atoms (Tables II and IV). Ether-type O atoms, on the other hand, contribute only 27% to the O atoms but accept 36% of the interactions, whereas water contributes 11% to the O atoms but accepts only 3% of the C—H···O bonds. For the intramolecular bonds, the preference of ether oxygens to be the acceptor, 56%, is even stronger (Table IV).

(c) Hydrogen-Bond Lengths. The shortest C—H···O hydrogen bonds in the data set have distances $d_{H\cdots O} \approx 2.27$ Å, which are somewhat longer than the shortest contacts found in other substances (e.g., 2.08 Å in 5-nitro-1-(β-D-ribosyluronic acid)uracil monohydrate[27]). If for three- and four-center bonds only the major component is considered, the distribution of H···O distances shown in Figure 2(top) is obtained. The number of contacts is relatively small for $d_{H\cdots O} < 2.4$ Å, but increases sharply from ~2.4 Å on and peaks between 2.5 and 2.6 Å. For only a few H atoms, the shortest H···O interaction is beyond 3.0 Å.

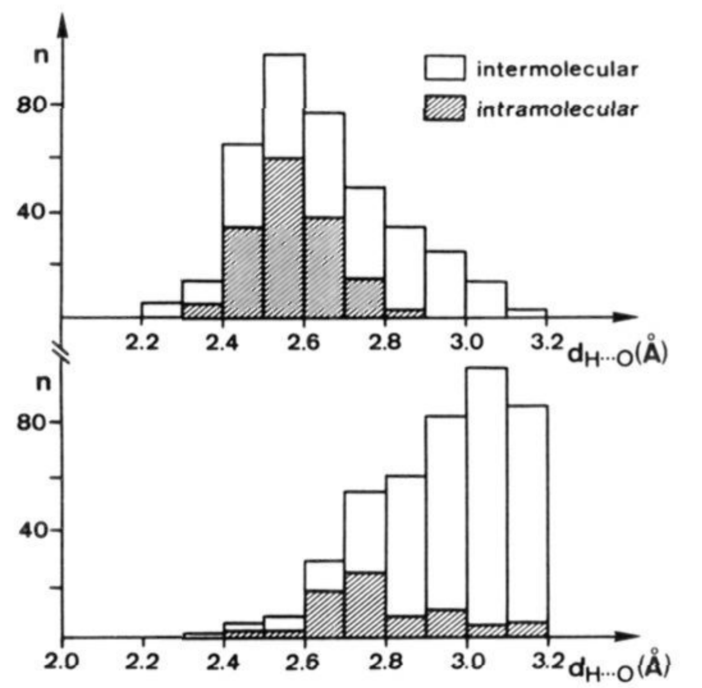


Figure 2. Distribution of H···O distances for C—H···O contacts with $\alpha_{CH\cdots O} > 90°$. Top: Two-center interactions and major components of three-center and four-center contacts. Bottom: Minor components of three-center and four-center contacts. The fraction of intramolecular contacts is shaded.

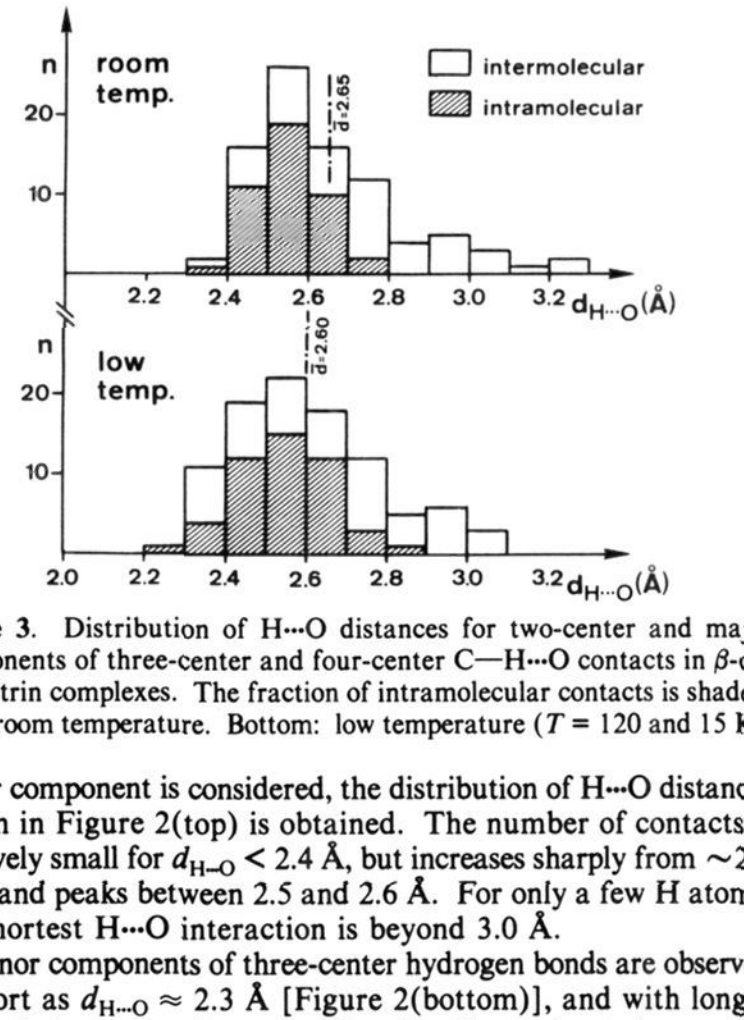


Figure 3. Distribution of H···O distances for two-center and major components of three-center and four-center C—H···O contacts in β-cyclodextrin complexes. The fraction of intramolecular contacts is shaded. Top: room temperature. Bottom: low temperature (T = 120 and 15 K).

Minor components of three-center hydrogen bonds are observed as short as $d_{H\cdots O} \approx 2.3$ Å [Figure 2(bottom)], and with longer $d_{H\cdots O}$, their number increases sharply. From about $d_{H\cdots O} \approx 2.7$ Å on, they make up the larger part of C—H···O contacts. From about $d_{H\cdots O} \approx 2.9$ Å on, an increasing number of arrangements is observed, for which it is difficult to decide whether they are repulsive C—H···H—O contacts rather than attractive C—H···O interactions (see section j). Note that any cutoff limit for the identification of hydrogen bonds, such as $d_{H\cdots O} < 2.7$ Å, would arbitrarily cut both distributions shown in Figure 2.

The data set contains four crystallographically isomorphous crystal structures of β-cyclodextrin; two were determined at room temperature[17,20] and two at low temperatures, T = 120 K[18] and T = 15 K.[19] Because the reduction in temperature is accompanied with reduction in unit cell volume, these data permit one to investigate whether the mutual approach of the molecules shortens the C—H···O bonds on average. Figure 3 shows the $d_{H\cdots O}$ dis-

---

(27) Takusagawa, F.; Koetzle, T. F.; Srikrishnan, T.; Parthasarathy, R. *Acta Crystallogr. Sect. B* **1979**, *B35*, 1388–1394.

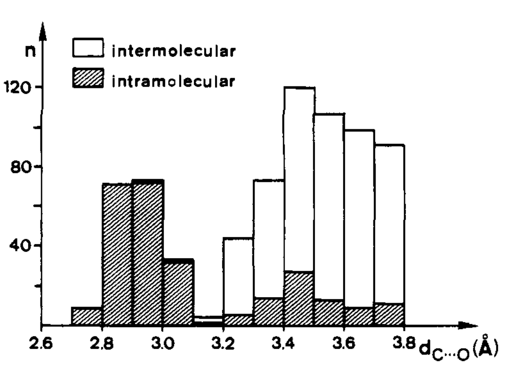


Figure 4. Distribution of C···O distances for all C—H···O hydrogen bonds with $\alpha_{CH\cdots O} > 90°$. For three-center hydrogen bonds, major and minor components are included. The fraction of intramolecular contacts is shaded.

tribution of the major C—H···O components at room temperature (top) and at low temperature (bottom). Actually, a shift of the distribution toward shorter $d_{H\cdots O}$ is observed, as the average value reduces by 0.05 Å from $\langle d_{H\cdots O}\rangle = 2.65$ to 2.60 Å. As expected, this is mainly due to shortening of the intermolecular contacts, which reduce by 0.09 Å, whereas the intramolecular bonds on the average reduce by only 0.01 Å. This parallels the behavior of O—H···O hydrogen-bond lengths upon cooling.[20]

The distribution of C···O distances (Figure 4) shows completely different behavior for inter- and intramolecular interactions. *Inter*molecular distances are found down to 2.97 Å, but they occur predominantly beyond 3.2 Å. *Intra*molecular contacts start at 2.7 Å, their number sharply peaks at ~2.9 Å, almost falls to zero at ~3.1 Å, and peaks again between 3.4 and 3.5 Å. This suggests that inter- and intramolecular interactions should be treated separately throughout this work and that the intramolecular C—H···O bonds should be divided into different types (see below).

We note that the distributions shown in Figures 2 and 4 are a structural property of crystalline carbohydrates and will be different for other compound classes (as was shown for alkynes and alkenes[28]).

(d) Correlations between Hydrogen-Bond Distances and Angles. In X—H···Y hydrogen bonds, the distances $d_{H\cdots Y}$ and $d_{X\cdots Y}$ are correlated with the angle $\alpha_{XH\cdots Y}$. In general, short hydrogen bonds tend to be close to linear, whereas the longer hydrogen bonds may be strongly bent. These correlations are "soft" and are best studied in scatterplots of $\alpha_{XH\cdots Y}$ against $d_{H\cdots Y}$ and $d_{X\cdots Y}$, as was repeatedly shown for O—H···O.[13,29,30] In the present study, these scatterplots are shown in Figures 5 and 6 (also note the legend to Figure 6). Inter- and intramolecular interactions are drawn with dots and circles, respectively. Note the error bars of the top right point in Figure 5, which represent the typical experimental accuracy, ±0.01 Å and ±1°.

We have already noted that the H···O van der Waals separation is not a useful criterion to characterize a hydrogen bond. This statement is put on more solid grounds if we look at the data point distribution in Figure 5. The "classical" H···O van der Waals separation (based on the sum of radii of spherical atoms[31]) would be a vertical line at roughly $d_{H\cdots O} = 2.6$ or 2.7 Å in Figure 5. As the van der Waals shape of the bonded H atom (as of many atoms) is actually nonspherical ("polar flattened"[32]) with a head-on radius $r_h \approx 1.0$ Å (in the direction of the covalent bond) and a side-on radius $r_s \approx 1.25$ Å[33] (for H bonded to C(sp^3)), the H···O van der Waals separation becomes orientation dependent as indicated by a dashed line in Figure 5. All data points left of the line correspond to C—H···O contacts shorter than the van der Waals distance, i.e., hydrogen bonds in "classical" terms. This line (as well as a vertical at 2.6 or 2.7 Å) can be taken as an indication for the irrelevance of the van der Waals distance in this context. If some properties of C—H···O contacts dramatically changed at the van der Waals separation, e.g., the interaction became significantly stronger within a narrow decrease of $d_{H\cdots O}$, one would expect a singular behavior of the data scatter at or close to this line. Such discontinuous behavior, however, is not observed at any $d_{H\cdots O}$.

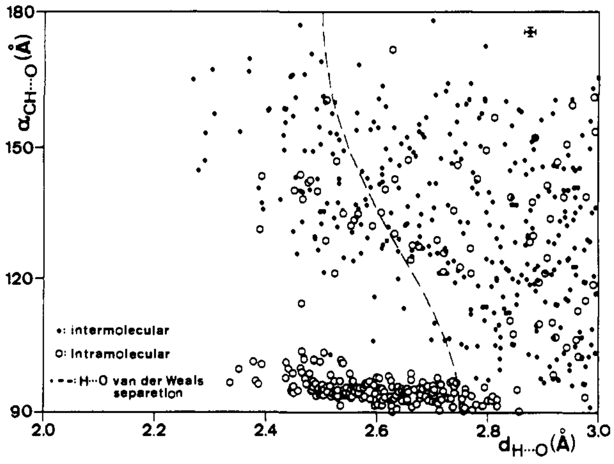


Figure 5. Scatterplot of $\alpha_{CH\cdots O}$ against $d_{H\cdots O}$: (●) intermolecular contacts; (○) intramolecular contacts; (- - -) H···O van der Waals separation based on a spherical O atom with $r \approx 1.50$ Å and a spheroidal H atom with a side-on radius $r_s \approx 1.25$ Å and a head-on radius $r_h \approx 1.0$ Å.[33] The "classical" van der Waals separation would be a vertical line at $d_{H\cdots O} \approx 2.6$ Å. The error bars of the top right point represent the typical experimental uncertainty ±0.01 Å and ±1°.

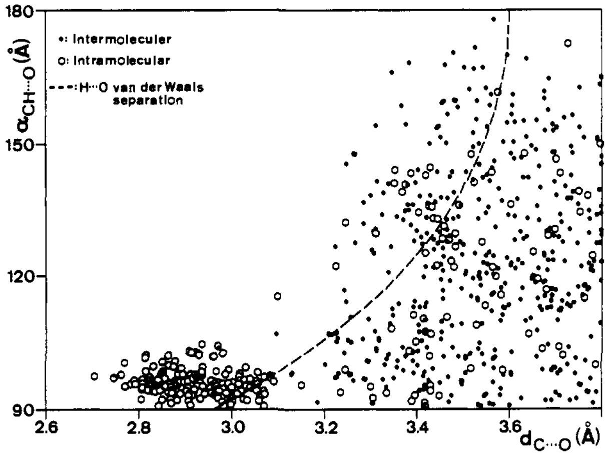


Figure 6. Scatterplot of $\alpha_{CH\cdots O}$ against $d_{C\cdots O}$. Symbols are the same as in Figure 5. Figures 5 and 6 are not independent, as $d_{C\cdots O}$ is trigonometrically determined by d_{CH}, $d_{H\cdots O}$, and $\alpha_{CH\cdots O}$. d_{CH} varies in a much narrower range than $d_{H\cdots O}$ and $d_{C\cdots O}$. If, consequently, d_{CH} is regarded as constant at ~1.10 Å, the position of any data point in Figure 6 can be almost precisely calculated from the corresponding point in Figure 5 (we have discussed this matter elsewhere in greater detail[13]). The two shortest *inter*molecular C···O distances are from 3-amino-1,6-anhydro-3-deoxy-β-D-glucopyranose[25] (shown in Figure 1d; $d_{C\cdots O} = 2.97$ Å, $d_{H\cdots O} = 2.52$ Å, $\alpha_{CH\cdots O} = 104°$) and C4–H4···O6 in methyl β-D-galactopyranoside[34] ($d_{C\cdots O} = 3.09$ Å, $d_{H\cdots O} = 2.60$ Å, $\alpha_{CH\cdots O} = 106°$).

In Figure 5, two clearly distinct regions of scattered points are observed. The first region extends from $d_{H\cdots O} \approx 2.25$ Å to the limit of the plot, $d_{H\cdots O} = 3.0$ Å. For the shorter interactions $d_{H\cdots O} < 2.4$ Å, only angles $\alpha_{CH\cdots O} > 130°$ are observed, whereas from about $d_{H\cdots O} \approx 2.5$ Å on, contacts are found for all angles $\alpha_{CH\cdots O}$. Short contacts are not as sharply correlated with close to linear angles as in equivalent plots for O—H···O,[13,29,30] but a certain preference for the more linear contacts is obvious. Inter- and

---

(28) Desiraju, G. R. *J. Chem. Soc., Chem. Commun.* **1990**, 454–455.

(29) Olovsson, I.; Jönsson, P.-G. In *The Hydrogen Bond, Recent Developments in Theory and Experiments*; Schuster, P., Zundel, G., Sandorfy, C., Eds.; North-Holland: Amsterdam, 1976; pp 393–455.

(30) Savage, H. F. J.; Finney, J. L. *Nature (London)* **1986**, *322*, 717–720.

(31) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441–451.

(32) Nyburg, S. C. *Acta Crystallogr. Sect. A* **1979**, *A35*, 641–645.

(33) Nyburg, S. C.; Faerman, C. H.; Prasad, L. *Acta Crystallogr. Sect. B* **1987**, *B43*, 106–110.

(34) Takagi, S.; Jeffrey, G. A. *Acta Crystallogr. Sect. B* **1979**, *B35*, 902–906.

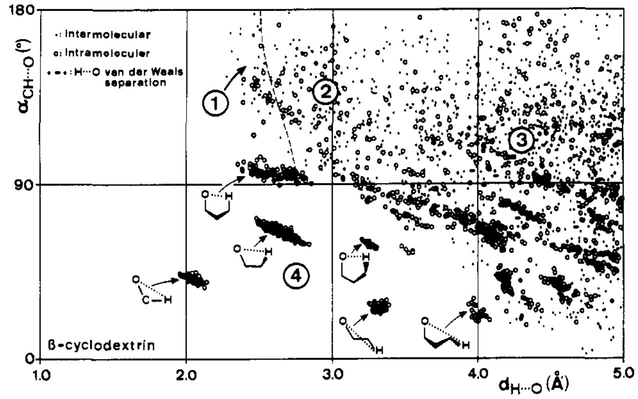


Figure 7. Extended scatterplot of $d_{H\cdots O}$ against $\alpha_{CH\cdots O}$ for *all* arrangements C—H···O, no matter whether they represent hydrogen bonds or not. Symbols are the same as in Figure 5. Circled numbers indicate regions of (1) C—H···O hydrogen bonds, (2) transition between hydrogen bonds and nonbonding arrangements, (3) long-distance arrangements with no direct interaction between CH and O, and (4) special types of nonbonding intramolecular H···O contacts. Schematic representations of the contacts are indicated. Note the continuous transition between regions 1, 2, and 3.

intramolecular contacts are similarly scattered in this region, except for the shortest distances $d_{H\cdots O} < 2.35$ Å where only intermolecular interactions are observed. With increasing $d_{H\cdots O}$, an increasing fraction of the data points represents minor components of three- and four-center hydrogen bonds (compare with Figure 2).

The second region of data points in Figure 5 is a very densely populated elongated cluster of intramolecular contacts at angles $\alpha_{CH\cdots O}$ between about 90° and 105°. They correspond to contacts where H and O are separated by only four covalent bonds (see below).

In the plot of $\alpha_{CH\cdots O}$ against $d_{C\cdots O}$ (Figure 6), the regions that are equivalent to those in Figure 5 can be immediately recognized. For the first region, it is surprising that, for the shortest intermolecular C···O contacts, there is a certain preference for the bent rather than for the linear angles $\alpha_{CH\cdots O}$; the five intermolecular interactions in the data set with $d_{C\cdots O} < 3.2$ Å all have angles $\alpha_{CH\cdots O} < 110°$ (Figure 1d and legend of Figure 6). This behavior is different for O—H···O, where more linear angles are preferred for short O···O contacts.[13,29,30]

(e) Extended Scatterplot of $\alpha_{CH\cdots O}$ against $d_{H\cdots O}$. If general properties of the data scattered in plots like Figures 5 and 6 are to be studied, it can be helpful to extend the limits of these plots far beyond the hydrogen-bond region.[13] In Figure 7, the plot of $\alpha_{CH\cdots O}$ against $d_{H\cdots O}$ is shown for *all* H···O contacts with $d_{H\cdots O} < 5.0$ Å and $\alpha_{CH\cdots O} > 0°$, no matter whether they represent hydrogen-bonding or nonbonding arrangements (to avoid data overflow, only data for the β-cyclodextrin structures are shown). Symbols are as in Figure 5. Several distinct regions are observed: (1) region of C—H···O hydrogen bonds, also containing a cluster of short intramolecular contacts with restricted geometry. With increasing $d_{H\cdots O}$, it continuously merges with the transition region 2. (2) Transition region between hydrogen bonds and nonbonding arrangements. In this region, long C—H···O hydrogen bonds as well as nonbonding C—H···H—O contacts are found. From about $d_{H\cdots O} = 2.8$–2.9 Å on, an increasing number of contacts to hydroxyl groups and water molecules is observed, where the H···H separations are shorter than the corresponding H···O distances (see below). Frequently, it is difficult (or impossible) to decide whether such a contact represents an attractive or repulsive arrangement, i.e., whether it should be regarded as a long C—H···O—H hydrogen bond or as a C—H···H—O repulsion. (3) Region with long non-hydrogen-bonding H···O separations. There is no nearest-neighbor interaction between CH and O, which consequently may adopt any mutual orientation. This results in a random scatter of data points. (4) Special types of non-hydrogen-bonding intramolecular H···O contacts that are characteristic for carbohydrates; schematic representations of the contacts are shown in Figure 7. Further clusters of long non-hydrogen-bonding intramolecular H···O distances are found embedded in region 3.

Table V. Types of Short *Intra*molecular C—H···O Contacts with $d_{H\cdots O} < 3.0$ Å and $\alpha_{CH\cdots O} > 90°$ in the Four Structures of β-Cyclodextrin[17–20] (Distances in Å)

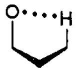
contact	pattern[a]	% H[b]	$d_{H\cdots O}$ range	$\langle d_{H\cdots O}\rangle$[c]
C(1)—H···O(6)′[d]	*S*(7)	40	2.72–3.00[e]	2.89 (3)
C(2)—H none[f]				
C(3)—H···O(4)′[d]	*S*(5)	100	2.49–2.86	2.60 (2)
C(4)—H···O(6)	*S*(5)	80	2.44–2.82	2.57 (2)
C(5)—H···O(4)′[d]	*S*(5)	100	2.35–2.60	2.48 (1)
C(6)—H···O(4)	*S*(5)	100	2.66–2.88	2.75 (1)
C(6)—H···O(5)″[d]	*S*(7)	100	2.39–2.91	2.59 (3)
C(6)—H···O(6)″[d]	*S*(10)	15	2.80–3.00[e]	2.89 (5)

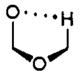
[a] According to the graph-set analysis of hydrogen-bond patterns.[35] For *S*(5), H and O are separated by four, for *S*(7) by six, and for *S*(10) by nine covalent bonds. [b] Percentage of the CH atoms which donate such a contact. [c] Arithmetic mean of the contacts with $d_{H\cdots O} < 3.0$ Å. The standard deviation given in parentheses is estimated according to $\mathrm{esd} = [\sum_i(\langle d_{H\cdots O}\rangle - d_{H\cdots O,i})^2/n(n-1)]^{1/2}$. [d] Primed atoms (′) belong to the neighboring D-glucose residue with the next higher number. Double-primed atoms (″) belong to the one with the next lower number. [e] Very long contacts with $d_{H\cdots O} > 3.0$ Å are also found but not included here. [f] The C(2)–H groups are engaged only in intermolecular C—H···O interactions.

The merging of regions 1, 2, and 3 shows that there is a completely continuous transition from stronger to weaker C—H···O hydrogen bonds and finally to nonbonding arrangements.

(f) Intermolecular C—H···O Hydrogen Bonds. On the average, over 34% of all H atoms bonded to C are involved in intramolecular H···O interactions with $d_{H\cdots O} < 2.7$ Å (Table III). The large proportion of these interactions shows that they must contribute significantly to crystal packing forces and suggests that one analyze them in a similar way as the simultaneously present and stronger O—H···O hydrogen bonds. The effect of these forces, however, has to be studied in each crystal structure separately; this is not the object of the present work.

(g) Intramolecular C—H···O Hydrogen Bonds. (1) H and O Separated by Four Covalent Bonds. Of the prominent clusters of short intramolecular H···O separations in Figure 7, only one is placed in the hydrogen bond region with $\alpha_{CH\cdots O} > 90°$. It corresponds to C—H···O contacts of the types





i.e., of 5-membered "circular" arrangements. In the formalism of the graph-set analysis of hydrogen-bond patterns,[35] such an arrangement is characterized as *S*(5), where *S* (standing for "self") denotes an intramolecular contact and 5 is the number of atoms in the "ring" (in this case, atoms in the shortest covalent path from H to O). These contacts are a structural characteristic of the carbohydrates; they are inherent for contacts between axial H and O atoms in pyranoses, but they are also found for other intramolecular arrangements (see Figure 8a,b and Table V). As their geometry is basically different from that of the other intramolecular C—H···O interactions, they have to be treated separately. They underlie strong stereochemical constraints, but due to conformational flexibility, the geometric parameters may vary in considerable ranges (Figures 5 and 6); the mean values are $\langle d_{H\cdots O}\rangle = 2.60$ Å, $\langle d_{C\cdots O}\rangle = 2.92$ Å, and $\langle\alpha_{CH\cdots O}\rangle = 96°$. Even in the contacts between chemically identical axial H and O atoms in the D-glucose residues of β-cyclodextrin, $d_{H\cdots O}$ varies by almost 0.4 Å from residue to residue (see below). In monosaccharides, they are the only intramolecular C—H···O interactions observed.

The characteristic geometry of these C—H···O contacts is only rarely observed, but not forbidden, for intermolecular interactions. One of the intermolecular C—H···O hydrogen bonds with a sim-

---

(35) Etter, M. C.; MacDonald, J. C.; Bernstein, J. *Acta Crystallogr. Sect. B* **1990**, *B46*, 256–262.

(36) Brown, G. M.; Levy, H. A. *Acta Crystallogr. Sect. B* **1979**, *B35*, 656–659.

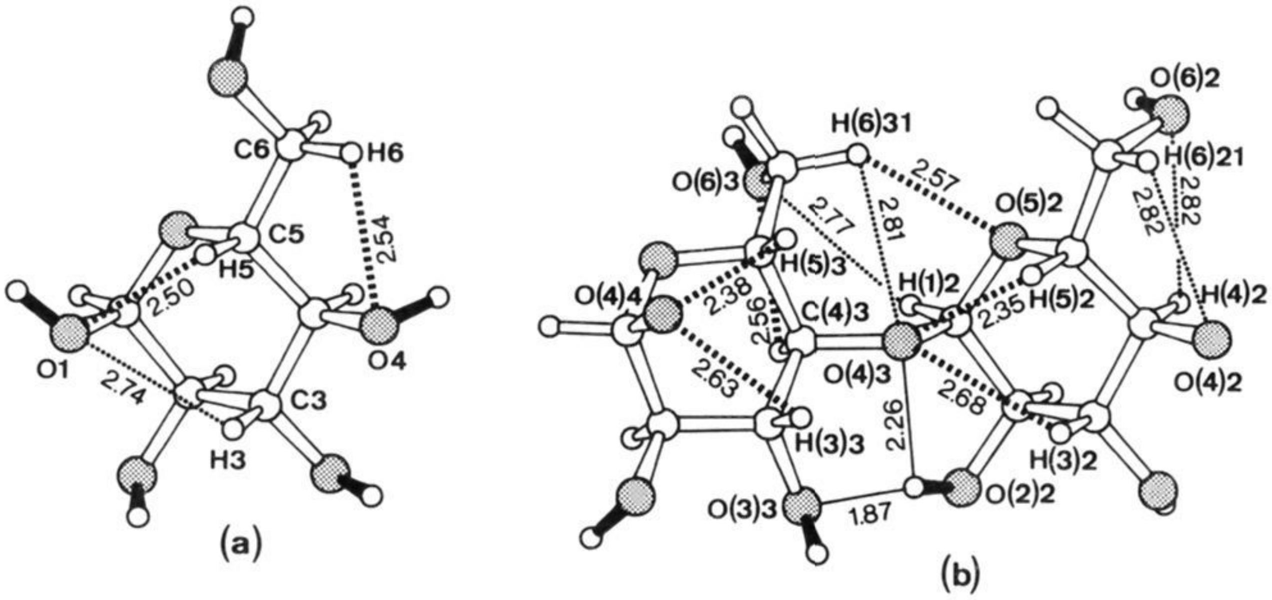


Figure 8. Examples for short intramolecular C—H···O contacts with $\alpha_{\mathrm{CH\cdots O}} > 90°$. O atoms are shaded. Distances are in angstroms. Filled covalent bonds represent O—H; darkened broken lines are C—H···O hydrogen bonds with $d_{\mathrm{H\cdots O}} < 2.7$ Å. Dotted lines are C—H···O hydrogen bonds with $2.7 \leq d_{\mathrm{H\cdots O}} < 3.0$ Å, and thin lines are O—H···O hydrogen bonds. (a) In α-D-glucose,[36] all contacts are of the type *S*(5) (H and O separated by four covalent bonds). C3—H3···O1 and C5—H5···O1 are inherent due to the axial conformation of H3, H5, and O1; C6—H6···O4 is always formed if the O5—C5—C6—O6 torsion angle is rotated into one of the sterically favorable orientations. (b) Two α-D-glucose fragments of β-cyclodextrin (from β-cyclodextrin ethanol octahydrate at *T* = 15 K[19]). The interglucose contact C(6)3—H···O(5)2 is of the type *S*(7) (H and O separated by six covalent bonds). Note the short intramolecular three-center O—H···O bond donated by O(2)2.

ilarly bent $\alpha_{\mathrm{CH\cdots O}}$ and short $d_{\mathrm{H\cdots O}}$ is shown in Figure 1d. This justifies regarding C—H···O contacts of this type as bonding arrangements, even if their geometry is primarily determined by steric restraints.

(2) H and O Separated by More Than Four Covalent Bonds. In interresidue intramolecular contacts of oligosaccharides (in the analyzed data set were sucrose,[24] β-maltose,[37] and β-cyclodextrin[17-20]), C—H···O interactions with H and O separated by more than four covalent bonds are observed between *all* neighboring residues. In Figures 5 and 6, these correspond to the data points for intramolecular interactions scattered off the cluster of *S*(5) contacts. In these interactions, stereochemical restrictions are weaker, and data points in Figures 5 and 6 are scattered over a wide region with geometries similar to intermolecular hydrogen bonds; $d_{\mathrm{H\cdots O}}$ separations are observed down to slightly below 2.4 Å. In β-maltose and β-cyclodextrin, numerous *S*(7) (Figure 8b) and some *S*(10) contacts are found; crystalline sucrose exhibits the intersaccharide *S*(11) hydrogen bond C6—H′6···O6′ ($d_{\mathrm{H\cdots O}}$ = 2.51 Å).

(3) Intramolecular C—H···O Contacts in β-Cyclodextrin. For the four β-cyclodextrin structures, which supply a total of 28 chemically identical D-glucose moieties, the observed intramolecular C—H···O contacts were systematically analyzed (Table V and Figure 8b). The contact geometries vary considerably from glucose to glucose, reflecting the different individual distortions and the varying mutual orientations of the D-glucose moieties (undistorted D-glucoses cannot form a closed macrocycle). Several of the contacts occur in *all* glucoses (with varying $d_{\mathrm{H\cdots O}}$), while others are found only for certain orientations of the $CH_2O(6)$ group, which may rotate around the C(5)—C(6) bond.

For the contacts between axial H and O atoms, it is characteristic that H(5)···O(4)′ is systematically shorter than H(3)···O(4)′ (Table V). This is due to the shorter covalent bonds in H(5)–C(5)–O(5)–C(1)–O(4)′ compared with H(3)–C(3)–C(2)–C(1)–O(4)′ (Figure 8a,b).

The interglucose interaction C(6)—H···O(5)″ (Figure 8b) is found between all residues (i.e., for each observed orientation of C(6)—O(6), one of the two H(6) atoms contacts O(5)′), but $d_{\mathrm{H\cdots O}}$ varies by more than 0.5 Å between short (2.39 Å) and long (2.91 Å) distances; the mean distance is 2.59 Å. This suggests that C(6)—H···O(5)″ interactions play a role in determining (and stabilizing) the overall conformation of the macrocycle.

The intraglucose contact C(4)—H···O(6) can only be formed if the O(5)—C(5)—C(6)—O(6) torsion angle is in the (−)gauche range. The long *S*(10) contacts C(6)—H···O(6)″ can only be formed if that torsion angle is (−)gauche for C(6)—O(6) and (+)gauche for C(6)″—O(6)″; these contacts are found no shorter than 2.80 Å, and consequently they are of lesser importance for structure stabilization.

(h) Host/Guest Interactions in β-Cyclodextrin Inclusion Complexes. In cyclodextrins, the inner surface of the molecular cavity is formed by H atoms bonded to C(3) and C(5) and by the glycosidic O(4) atoms. The latter are somewhat "hidden" and not easily accessible as hydrogen-bond acceptors; consequently only few (or none) of these atoms accept O—H···O bonds from guest molecules. The cyclodextrin cavity is therefore commonly regarded as "hydrophobic". In some instances, one or two $CH_2(6)O(6)H$ groups that are located on the rim of the molecule are oriented such that an O—H···O hydrogen bond with a guest molecule can be formed. In the β-cyclodextrin inclusion complexes, there are very few (or no) host/guest O—H···O bonds, and O—H···O hydrogen-bond potentials of included hydrophilic molecules (such as H_2O or alcohols) are frequently only partially satisfied. The occurrence of C—H···O hydrogen bonds has so far not been taken into account as a significant contribution to the host/guest interactions.

Only in two[18,19] of the four β-cyclodextrin crystal structures in the data set are the guest molecules ordered and determined sufficiently well for accurate analysis of short host/guest C—H···O contacts. In β-cyclodextrin ethanol octahydrate[19] (*T* = 15 K, Figure 9), one ethanol and three water molecules are included in the molecular cavity. The cluster of guest molecules forms no O—H···O hydrogen bonds with the host, but only with neighboring molecules outside the cavity. The ethanol and two water molecules (W6 and W8) accept only one O—H···O hydrogen bond (due to overlap in the projection, not all relevant atoms are drawn; see the legend to Figure 9), i.e., they have unsatisfied acceptor potential. As a compensation, there are several short host/guest C—H···O interactions: two C(5)H groups of the inner cavity lining donate hydrogen bonds ($d_{\mathrm{H\cdots O}}$ = 2.39 and 2.56 Å) to water molecule W8, and the ethanol molecule accepts a C—H···O bond from another C(5)H group ($d_{\mathrm{H\cdots O}}$ = 2.66 Å) and donates one to an O(4) atom of the cavity wall ($d_{\mathrm{H\cdots O}}$ = 2.63 Å). Water molecule W6, which also has "free" acceptor potential, accepts only a very long C—H···O contact, with $d_{\mathrm{H\cdots O}}$ = 2.98 Å.

In β-cyclodextrin·11.6H_2O[18] (*T* = 120 K), 6.6 water molecules are included by the macrocycle. They form three O—H···O hydrogen bonds with the host. Three of these water molecules accept only one O—H···O bond, and *all three* satisfy the free acceptor potential by at least one additional C—H···O interaction with $d_{\mathrm{H\cdots O}} < 2.7$ Å. A further short C—H···O contact ($d_{\mathrm{H\cdots O}}$ = 2.51 Å) is donated to a water molecule (W10) that accepts two

---

(37) Gress, M. E.; Jeffrey, G. A. *Acta Crystallogr. Sect. B* **1977**, *B33*, 2490–2495.

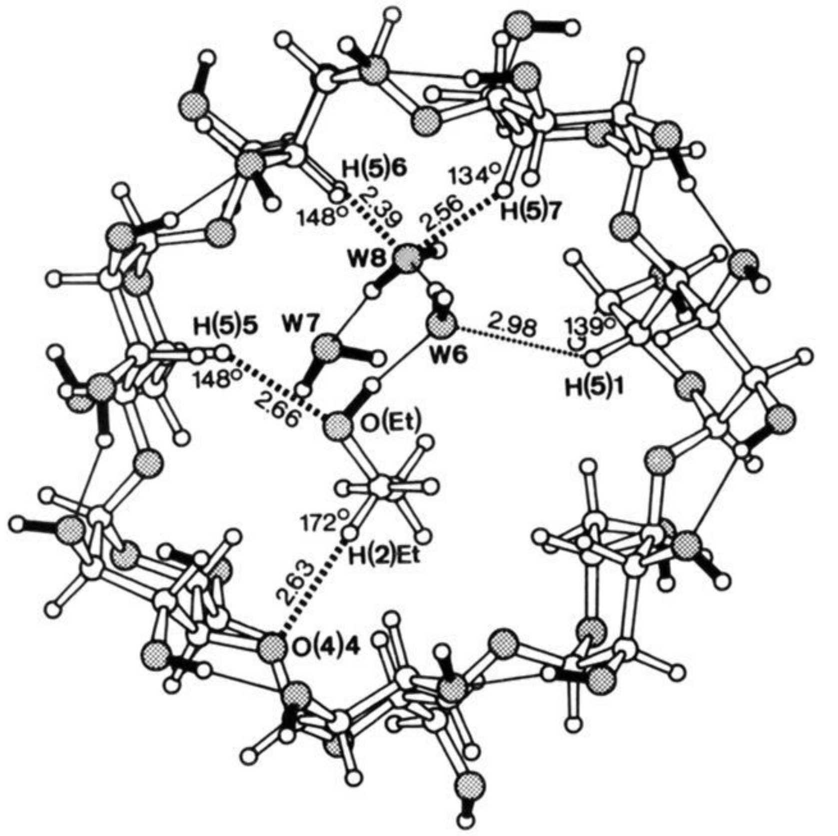


Figure 9. Host/guest C—H···O interactions in a cyclodextrin inclusion complex: crystal structure of β-cyclodextrin ethanol octahydrate at $T = 15$ K;[19] view is onto the equatorial plane of the macrocycle. One water molecule in the cavity (W4) is not drawn, as it covers the ethanol in this view and is not engaged in C—H···O interactions. W7 is already placed slightly outside the cavity, "below" the rim of the β-cyclodextrin molecule; the other water molecules outside the cavity are not drawn. EtOH accepts an O—H···O bond from, and W6, W7, and W8 donate O—H···O bonds to, molecules that are not drawn. *Filled covalent bonds represent* O—H; thin lines are O—H···O hydrogen bonds with $d_{H\cdots O} < 2.2$ Å. Darkened broken lines are C—H···O hydrogen bonds with $d_{H\cdots O} < 2.7$ Å, while the dotted lines are C—H···O hydrogen bonds with $2.7 < d_{H\cdots O} < 3.0$ Å.

long O—H···O hydrogen bonds, both with $d_{H\cdots O}$ 2.05 Å.

These observations clearly show that, numerous C—H···O hydrogen bonds are formed, if hydrophilic molecules are included in a cyclodextrin cavity. The resulting host/guest interactions therefore comprise a third significant component besides the O—H···O hydrogen bonds and the van der Waals contacts. This is most important for water molecules that cannot arrange in the preferred tetrahedral (or trigonal) O—H···O hydrogen-bond coordination with $d_{H\cdots O} \approx 1.7$–$1.9$ Å in at least fairly ideal geometry: the resulting "free" acceptor potential is often satisfied by C—H···O interactions. In addition, the glycosidic O(4) atoms of the cavity wall may accept weak C—H···O hydrogen bonds from guest molecules.

(i) Three-Center C—H···O Hydrogen Bonds. The data set contains 43 three-center and 2 four-center C—H···O hydrogen bonds with all components having $d_{H\cdots O} < 2.7$ Å, i.e., 11% of all CH hydrogen atoms are involved in such interactions (9 three-center and no four-center with $d_{H\cdots O} < 2.5$ Å). In about 80% of the total, at least one component is intramolecular and of the *S*(5) type (Figure 10a). This is because the *S*(5) intramolecular contacts are strongly bent with angles $\alpha_{CH\cdots O} \approx 95°$ (Figure 5) and permit spatially an additional short "head-on" contact. In only eight three-center bonds with $d_{H\cdots O} < 2.7$ Å are both components intermolecular (Figure 10b).

(j) Nonbonding C—H···H—O Contacts. If CH donates a short hydrogen bond to a hydroxyl group or a water molecule, the H atom(s) of the acceptor is (are) in most instances turned away from the donor, thereby avoiding a C—H···H—O van der Waals contact. There are, however, exceptional cases where CH forms very short contacts with both atoms of an OH group, as shown in Figure 10b ($d_{H\cdots O} = 2.35$ Å, $d_{H\cdots H} = 2.17$ Å). With increasing $d_{H\cdots O}$, such arrangements occur more frequently, and from $d_{H\cdots O} = 2.8$–2.9 Å on, it becomes increasingly difficult to judge for certain long contacts whether they are of a bonding or nonbonding nature. This is illustrated in Figure 11: the contact C(6)5—H···O(6)4, $d_{H\cdots O} = 2.95$ Å, may be regarded as a very long (and weak) hydrogen-bonding interaction, as the corresponding repulsive H···H separation is not significantly shorter. The contact C(6)5—H···OW5, $d_{H\cdots O} = 2.99$ Å, on the other hand, is probably more than compensated by the two H···H repulsions, $d_{H\cdots H} = 2.42$ and 2.64 Å, respectively, resulting in a nonbonding net interaction. In the transition region 3 of Figure 7, numerous related contacts with various geometries are found.

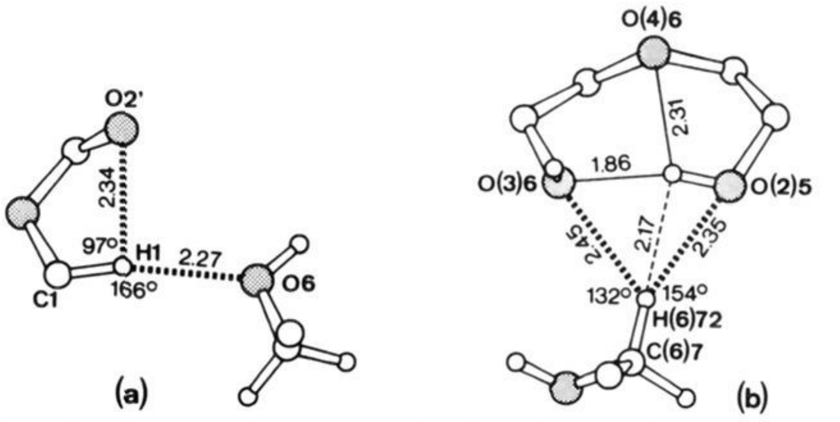


Figure 10. Examples of three-center C—H···O hydrogen bonds. O atoms are shaded. (a) A "side-on" intramolecular component of the *S*(5) type and a "head-on" intermolecular component (in sucrose;[24] the major component is already shown in Figure 1a). This is the most frequent arrangement for three-center bonds. (b) Two intermolecular components; this is a less common arrangement. Note the short C—H···H—O van der Waals contact. In β-cyclodextrinethanol octahydrate,[19] the intramolecular three-center O—H···O bond is similar to that shown in Figure 8b.

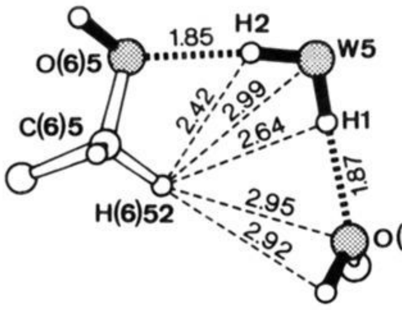


Figure 11. Example of long C—H···O contacts associated with repulsive H···H contacts; *all H···O and H···H separations beyond van der Waals* distance (in β-cyclodextrin·11.6H_2O; $T = 120$ K[18]). O atoms are shaded. Darkened broken lines are O—H···O hydrogen bonds, while the dashed lines represent C—H···O and C—H···H contacts. The contact of C(6)5H to the hydroxyl group O(6)4H is assumed to be weakly bonding, whereas the interaction with the water molecule C(6)5—H···W5 should not be bonding due to the two short H···H contacts.

(k) Thermal Vibrations of the Hydrogen-Bonding H Atoms. In the hydrogen-bonding water molecule, there is a strong correlation between hydrogen-bond length $d_{H\cdots O}$ and H vibration behavior: in long hydrogen bonds, the H atom on the average vibrates more vigorously than in short ones, with the mean square amplitude perpendicular to the O—H bond for $d_{H\cdots O} = 2.0$ Å roughly twice as high as for $d_{H\cdots O} = 1.7$ Å.[38] To check for a similar effect in C—H···O hydrogen bonds, we only used the data from cyclodextrins, as for most mono- and disaccharides the thermal parameters are not easily available. For a first (and crude) analysis, the equivalent isotropic temperature factors (U_{eq}) of H are plotted against $d_{H\cdots O}$ of two-center and major components of three-center C—H···O interactions (Figure 12). As expected, the U_{eq} values are smaller for the low-temperature than for the room-temperature structures, but there is no obvious systematic dependence of U_{eq} on $d_{H\cdots O}$. The C—H···O interaction is not strong enough to significantly reduce the vibration of the engaged H atom; this, however, can also be due to the more rigid orientation of a C(sp^3)—H bond compared with H_2O or COH groups that have rotational freedom around the C—O bond. Also note that the H···O distances are on the average shorter at low temperature than at room temperature (compare with Figure 3).

(l) Lengthening of the Covalent C—H Bond by the C—H···O Interaction. It is well-known that in X—H···Y hydrogen bonds

---

(38) Eriksson, A.; Hermansson, K. *Acta Crystallogr. Sect. B* **1983**, *B39*, 703–711.

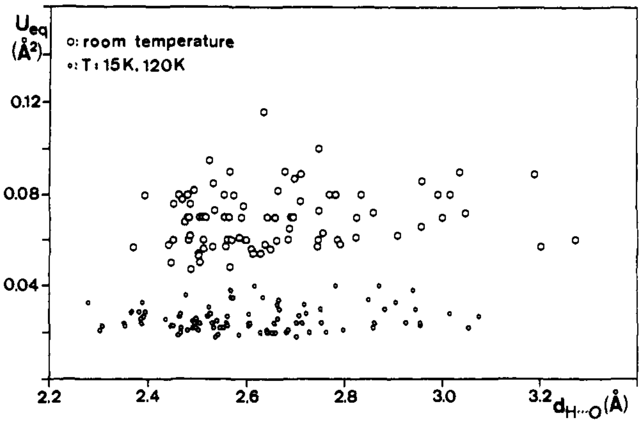


Figure 12. Equivalent isotropic temperature factor U_{eq} (Å²) plotted against $d_{H\cdots O}$ for H in two-center C—H···O hydrogen bonds and major components of three-center bonds in β-cyclodextrin complexes at room temperature[17,20] (large circles) and low temperature (T = 120[18] and 15 K;[19] small circles). Thermal vibrations are not significantly reduced by the formation of short H···O interactions.

Table VI. Mean C-H Bond Lengths $\langle d_{CH}\rangle$ for Given Ranges of $d_{H\cdots O}$ in Two Low-Temperature β-Cyclodextrin Structures[a,b] (T = 120[18] and 15 K[19])

$d_{H\cdots O}$ range	n	$\langle d_{CH}\rangle$	$\langle d_{H\cdots O}\rangle$
<2.4	12	1.1065 (23)	2.36 (1)
2.4–2.6	41	1.1041 (19)	2.51 (1)
2.6–2.8	30	1.1030 (22)	2.68 (1)
≥2.8	15	1.1021 (22)	2.98 (2)

[a] Distances in angstroms. Standard deviations given in parentheses estimated as in footnote c of Table V. [b] For three-center hydrogen bonds, only the major component is considered.

the X—H bond is lengthened due to the H···Y interaction. The lengthening increases with shortening hydrogen-bond distance $d_{H\cdots Y}$. The dependence of d_{XH} on $d_{H\cdots Y}$ has been repeatedly described for O—H···O[29,39,40] and also for N—H···O.[29,41] In O—H···O and N—H···O, an asymptotic value for relaxed O—H or N—H is not reached even for the longest hydrogen bonds, $d_{H\cdots O}$ ≈ 2.1 Å, showing that the lengthening, and consequently the strength of the interaction, is significant also for longer distances.[40] This suggests the need to check for weak covalent bond lengthening in C—H···O hydrogen bonds.

The present data set mainly consists of room-temperature structures where the experimental uncertainty, as well as the systematic bond shortening by thermal vibrations, is around 0.01 Å and exceeds the anticipated effect. The two β-cyclodextrin low-temperature structures,[18,19] however, supply a considerable number of very well determined CH groups and C—H···O hydrogen bonds. Of the 98 H atoms bonded to C, 97 are engaged in C—H···O contacts with $d_{H\cdots O}$ < 3.2 Å. For these, d_{CH} is plotted against $d_{H\cdots O}$ in Figure 13 (two-center and major components of three- and four-center contacts). The horizontal line at d_{CH} = 1.102 Å represents the mean d_{CH} value for the longest contacts $d_{H\cdots O}$ ≳ 2.8 Å. There is no dramatic lengthening of d_{CH} for the shortest interactions, but a close look at the figure shows that, for the distances $d_{H\cdots O}$ < 2.5 Å, the data points are scattered more above than below the horizontal line.

To quantify this observation, the C—H bonds are divided into four sets with increasing $d_{H\cdots O}$. The observed mean bond lengths actually continuously decrease with increasing $d_{H\cdots O}$ (Table VI). The difference, however, even between the shortest and longest contacts is at the limit of experimental accuracy: $\langle d_{CH}\rangle$ = 1.106 (2) Å for $d_{H\cdots O}$ < 2.4 Å, and $\langle d_{CH}\rangle$ = 1.102 (2) Å for $d_{H\cdots O}$ ≥ 2.8 Å. This corresponds to a lengthening of d_{CH} by ~0.004 Å in the shortest C—H···O hydrogen bonds with $d_{H\cdots O}$ < 2.4 Å. This result has to be taken with reservations and needs to be verified from a larger quantity of accurate data.

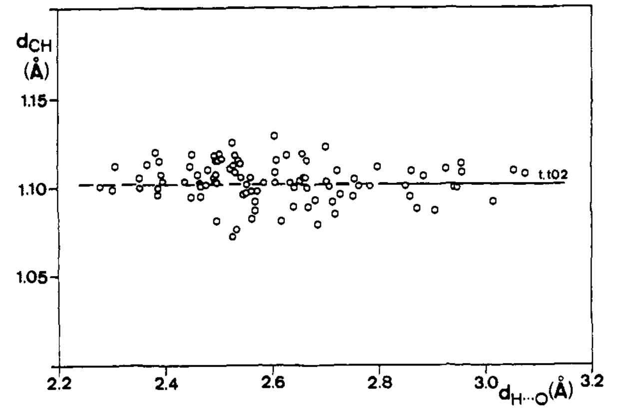


Figure 13. Covalent bond length d_{CH} plotted against $d_{H\cdots O}$ in two-center C—H···O hydrogen bonds and major components of three-center bonds in β-cyclodextrin low-temperature structures. The horizontal line represents the mean value $\langle d_{CH}\rangle$ for $d_{H\cdots O}$ > 2.8 Å. Even at the shortest $d_{H\cdots O}$ distances, the data are scattered only very slightly above this line: the lengthening of d_{CH} by short C—H···O interactions is only marginal, if detectable at all.

Summary and Discussion

(1) The data set analyzed consists of 30 carbohydrate neutron diffraction crystal structures; 4 of these are from β-cyclodextrin complexes. It contains 395 H atoms as potential C—H···O hydrogen-bond donors and 328 O atoms as potential acceptors. This large quantity of data ensures good statistical significance of the results.

(2) We should emphasize that, due to the abundance of CH donors and O acceptors, carbohydrates are particularly useful to the study of both intra- and intermolecular C—H···O interactions. These will not occur as frequently in other classes of compounds, but the general principles will be identical.

(3) Hydrogen bonds are long-range interactions comprising an electrostatic component that only slowly diminishes with increasing H···O separation. We consequently avoided restrictive applications of distance cutoff limits. C—H···O contacts were analyzed to $d_{H\cdots O}$ > 3.0 Å, but frequently only the shorter interactions $d_{H\cdots O}$ < 2.7 Å are discussed.

(4) For reasons outlined in conclusion 2, there is a large number of C—H···O hydrogen bonds: about 22% of all H atoms bonded to C have $d_{H\cdots O}$ separations <2.5 Å (with $\alpha_{CH\cdots O}$ > 90°), 66% have $d_{H\cdots O}$ separations < 2.7 Å, and only 7% have no contact to O < 3.0 Å (Table II).

(5) A total of 45 H atoms donate three-center C—H···O hydrogen bonds with both components shorter than 2.7 Å.

(6) The donor groups CH (methine-type with only one H bonded to C) and CH_2 (methylene-type) have similar "donor strengths", with the shortest interactions donated having $d_{H\cdots O}$ = 2.27 and 2.28 Å, respectively. The methyl group donates proportionally fewer C—H···O hydrogen bonds, and the shortest interaction is longer: $d_{H\cdots O}$ = 2.50 Å.

(7) For the shortest H···O separations, more or less linear angles $\alpha_{CH\cdots O}$ are preferred (Figure 5), but the correlation between hydrogen-bond lengths and angles is much less pronounced compared to O—H···O hydrogen bonds. Scatterplots of $d_{H\cdots O}$ (and $d_{C\cdots O}$) against $\alpha_{CH\cdots O}$ (Figures 5–7) show a completely continuous transition from stronger to weaker interactions and finally to nonbonding arrangements. At the H···O distance corresponding to van der Waals separation, no discontinuous behavior whatsoever is observed, i.e., there is no justification to use cutoff criteria based on the van der Waals radii to characterize C—H···O interactions.

(8) *Intra*molecular C—H···O contacts with H and O separated by only four covalent bonds are (due to steric restrictions) special with bent angles $\alpha_{CH\cdots O}$. These contacts are a consequence of the stereochemistry of carbohydrates and occur systematically. Only

---

(39) Chiari, G.; Ferraris, G. *Acta Crystallogr. Sect. B* **1982**, *B38*, 2331–2341.

(40) Steiner, Th.; Saenger, W. *J. Am. Chem. Soc.* **1992**, *114*, 7123–7126.

(41) Koetzle, T. F.; Lehmann, M. S. In *The Hydrogen Bond, Recent Developments in Theory and Experiments*; Schuster, P., Zundel, G., Sandorfy, C., Eds.; North-Holland: Amsterdam, 1976; pp 457–469.

very few examples of *inter*molecular C—H···O hydrogen bonds with similar geometry are observed.

(9) In β-cyclodextrin (β-CD) inclusion complexes, numerous host/guest C—H···O hydrogen bonds with $d_{\mathrm{H \cdots O}}$ as short as 2.39 Å are observed. These can be donated not only by CH groups of the inner cavity lining of β-CD to hydrophilic guest molecules but also from a guest to a glycosidic O atom of the cavity wall. Although they are weak, we consider the C—H···O bonds as a third, direct cohesive host/guest interaction besides van der Waals contacts and O—H···O hydrogen bonds; in concert, they will contribute to the overall stability and structure of the inclusion complexes of the cyclodextrins.

(10) If water molecules in a "hydrophobic" surrounding cannot arrange in the preferred tetrahedral or trigonal O—H···O hydrogen-bond coordination geometry, the "free" acceptor potential is often partially satisfied by C—H···O hydrogen bonds.

(11) C—H···O hydrogen bonds are not strong enough to significantly reduce the thermal vibrations of the engaged H atom.

(12) Any lengthening of the covalent C—H bond in the C—H···O hydrogen bond would supply *direct* experimental evidence for the strength of the interaction. The observed lengthening of d_{CH} by ~0.004 Å for the shortest distances $d_{\mathrm{H \cdots O}} < 2.4$ Å, however, is at the very limit of experimental accuracy. It is desirable to verify this observation by other means or by an extended data set.

Acknowledgment. This study was supported by the Bundesministerium für Forschung und Technologie (FKZ 03 SA3 FUB) and by Fonds der Chemischen Industrie.

Registry No. Sucrose, 57-50-1; β-cyclodextrin, 7585-39-9; methyl β-D-xylopyranoside, 612-05-5; 3-amino-1,6-anhydro-3-deoxy-δ-D-glucopyranose, 57649-09-9; β-cyclodextrin ethanol octahydate, 138858-69-2.

Versatile Nitronium Chemistry for C_{60} Fullerene Functionalization

Long Y. Chiang,* Ravi B. Upasani, and John W. Swirczewski

Contribution from the Corporate Research Laboratory, Exxon Research and Engineering Company, Annandale, New Jersey 08801. *Received June 10, 1992*

Abstract: We have demonstrated the high reactivity of fullerene molecules toward the electrophilic attack of the nitronium ion in the presence of nucleophilic reagents, such as aromatic carboxylic acids, under mild reaction conditions. The observed nucleophilicity of fullerenes in terms of their vulnerability to electrophilic additions in solution compensates for difficulties that have been encountered in achieving the electronic oxidation of C_{60} molecules for further functionalization. It also represents a versatile synthetic methodology for introducing multiple polar functionalities, especially hydroxyl and functionalized carboxylic ester groups, onto fullerene molecules, leading to an enormous variation of novel fullerene derivatives. The structure of these new fullerene derivatives was characterized as consisting of a chemical composition of an average of 13–15 hydroxyl substituents and 4–5 *p*-bromobenzoate moieties per C_{60} molecule. Hydrolysis of these derivatives in alkaline aqueous solution affords the corresponding water-soluble fullerols consisting of 18–20 hydroxyl groups per C_{60} molecule on average.

Introduction

The electron affinity of C_{60} fullerene molecules has been investigated extensively by cyclic voltammetry.[1,2] Six reversible consecutive electronic reductions can be achieved in solution to generate a stable hexaanionic fullerene (C_{60}^{-6}).[2] Nevertheless, no reversible oxidation waves were detected in the cyclic voltammetry study, indicating its inherent inactivity to the multiple electronic oxidations. The observed high electron affinity of C_{60} fullerene over its electron-donating ability leads to the prediction that this class of materials is more susceptible to nucleophilic additions[3] than to electrophilic additions. In fact, certain nucleophiles, such as organoamines[4] and organolithium or Grignard reagents,[3,5] were found to be effective for nucleophilic addition reactions on fullerenes. Recently, we have demonstrated that the reactivity of electrophilic additions on fullerenes can be significantly enhanced using aqueous acid chemistry.[6] The acid chemistry transforms the instability of cationic fullerenes into highly reactive intermediates suitable for derivatization. In the presence of water molecules, these intermediates can be converted directly into polyhydroxylated fullerene derivatives (fullerols) with a high solubility in acidic water. Here we describe the synthesis and characterization of new polyhydroxyorganocarboxylated fullerene derivatives through the electrophilic addition of nitronium tetrafluoroborate onto fullerenes in the presence of arenecarboxylic acid in a nonaqueous medium. Hydrolysis of the ester moieties of polyhydroxyorganocarboxylated fullerene derivatives provides an alternative efficient route for the preparation of water-soluble fullerols.

Experimental Section

Nitronium tetrafluoroborate was purchased from Aldrich Chemicals and used as received. Methylene chloride was distilled over CaH_2 prior to use. ^{1}H NMR and ^{13}C NMR spectra were measured with either a Brucker 360 spectrometer or a JEOL FX-100 Fourier transform spectrometer. The infrared spectra were recorded on a Perkin-Elmer 680 series spectrometer as KBr pellets. Mass spectroscopic studies of all

---

(1) Haufler, R. E.; Conceicao, J.; Chibante, L. P. F.; Chai, Y.; Byrne, N. E.; Flanagan, S.; Haley, M. M.; O'Brien, S. C.; Pan, C.; Xiao, Z.; Billups, W. E.; Ciufolini, M. A.; Hauge, R. H.; Margrave, J. L.; Wilson, L. J.; Curl, R. F.; Smalley, R. E. *J. Phys. Chem.* **1990**, *94*, 8634. Allemand, P. M.; Koch, A.; Wudl, F.; Rubin, Y.; Diederich, F.; Alvarez, M. M.; Anz, S. J.; Whetten, R. L. *J. Am. Chem. Soc.* **1991**, *113*, 1050. Cox, D. M.; Bahal, S.; Disko, M.; Gorun, S. M.; Greaney, M.; Hsu, C. S.; Kollin, E. B.; Millar, J.; Robbins, J.; Sherwood, R. D.; Tindall, P. *J. Am. Chem. Soc.* **1991**, *113*, 2940. Jehoulet, C.; Bard, A. J.; Wudl, F. *J. Am. Chem. Soc.* **1991**, *113*, 5456. Dubois, D.; Kadish, K. M.; Flanagan, S.; Haufler, R. E.; Chibante, L. P.; Wilson, L. J. *J. Am. Chem. Soc.* **1991**, *113*, 4364. Dubois, D.; Kadish, K. M.; Flanagan, S.; Wilson, L. J. *J. Am. Chem. Soc.* **1991**, *113*, 7773.

(2) Xie, Q.; Perez-Cordero, E.; Echegoyen, L. *J. Am. Chem. Soc.* **1992**, *114*, 3978.

(3) Wudl, F.; Hirsch, A.; Khemani, K.; Suzuki, T.; Allemand, P. M.; Koch, A.; Eckert, H.; Srdanov, G.; Webb, H. *ACS Symp. Ser.* **1992**, *481*, 161.

(4) Hirsch, A.; Li, Q.; Wudl, F. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1309.

(5) Hirsch, A.; Soi, A.; Karfunkel, H. R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 766.

(6) Chiang, L. Y.; Upasani, R.; Swirczewski, J. W. *Mater. Res. Soc. Symp. Proc.* **1992**, *247*, 285.