Role of C–H···O Hydrogen Bonds in the Coordination of Water Molecules. Analysis of Neutron Diffraction Data

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Abstract: C–H···O hydrogen bonds with water acceptors are analyzed from 101 water molecules in 46 neutron crystal structures. The shortest observed hydrogen bond distances are H···O_W ~ 2.3 Å and C···O_W ~ 3.1 Å. About 8% of the water molecules accept C–H···O_W interactions with H···O_W separations < 2.5 Å and 39% with H···O_W < 2.8 Å. CH donors may coordinate to water molecules in concert with OH and NH donors and with metal ions in many different combinations. The most frequent function of C–H···O_W hydrogen bonds is to complete a tetrahedral coordination geometry around the water. Also, there are many examples where a distorted tetrahedral O–H···O_W and N–H···O_W hydrogen bond coordination leaves "free" acceptor potential that is satisfield by additional C–H···O_W interactions. In essence, a water molecule will prefer to accept the strong hydrogen bonds from OH and NH donors (or to interact with metal ions), but if these are not available in suitable configuration, it will resort to the weaker C–H···O_W hydrogen bonds rather than leaving its multiple acceptor potential unsatisfied. This is also evident in structural biology; as shown for the enzyme actinidin, tetrahedral coordination geometries of internal water molecules may involve C–H···O_W interactions.

Introduction

C–H···O hydrogen bonds have long been known to spectroscopists[1] and crystallographers,[2] but definite evidence for their structural significance was given only few years ago.[3–5] Chloroalkyl[6] and alkynyl[7,8] CH groups have attracted greater attention due to their exceptionally strong donor potentials, and the volume of dispersed literature on other compounds is considerable. Very little is known, however, about the water molecule as an acceptor of these interactions, although hydrogen bonding in general is the major determinant of its properties.

In a recent structural study of C–H···O hydrogen bonding in carbohydrates, we found that water molecules enclosed in hydrophobic cyclodextrin cavities, which cannot arrange in the preferred tetrahedral or planar trigonal O–H···O hydrogen bond coordination, tend to satisfy "free" acceptor potentials by C–H···O_W interactions with the cavity wall.[9] For such interactions, H···O_W distances are observed as short as slightly below 2.4 Å. To generalize this observation, we extended the study to water molecules in various environments. We used only data of very good quality in order to make sure that the discussed effects are not experimental artifacts. The study was therefore restricted to neutron diffraction data (extracted from the Cambridge Database[10]) that provide H positions experimentally determined to ±0.01 Å and better.

The most serious drawback of the restriction to neutron diffraction studies is the relatively small quantity of data (total sample of 101 water molecules). This results in a discussion that is in some parts based on the presentation of selected examples. The essential finding, however, can be easily summarized: CH donors may participate in the coordination of water molecules in the same way and with the same functionality as OH and NH.

Definitions and Concepts

Since part of the terminology[11] concerning hydrogen bonds is not uniformly used in the literature, we briefly present some definitions applied in this study. As a "hydrogen bond" we regard *any* cohesive interaction X–H···Y, where H carries a positive and Y a negative (partial or full) charge, and the charge on X is more negative than on H (in CH donors, the partial charge on C may be around zero or even slightly positive). As this interaction is predominantly *electrostatic*[12] (with only smaller charge transfer and polarization contributions), it is operative also at H···Y distances exceeding the van der Waals separation and only slowly diminishes with increasing distances. Distance cutoff definitions of hydrogen bonds should therefore be avoided, as they cut a smoothly decreasing force at a distance that is arbitrary for any chosen value. As the interaction is probably not cohesive if XH points away from Y, the angle at H in our survey must be ≥90°.

In practice, however, it is difficult to completely avoid distance cutoff criteria. They may be helpful in standardized analyses of large data samples and to sort out arrangements for which it is uncertain whether they are cohesive or not (see below). In this study, the most permissive criteria are applied that seem pragmatically feasible, but it is made explicitly clear that some (hopefully weak) long-range interactions are neglected (see below).

In the geometric characterization of a hydrogen bond, the focus is on the *hydrogen bond distance* H···Y and the *hydrogen bond angle* X–H···Y. The X···Y separation (which in the literature frequently is also called "hydrogen bond distance") can be calculated from these parameters (if the X–H bond length is known[13]) and is of lesser interest. To avoid confusion between the terms "three-center" and "bifurcated" hydrogen bond, a *three-*

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[1] Green, R. D. *Hydrogen bonding by C–H groups*; Wiley Interscience: New York, 1974.

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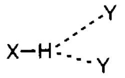
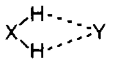
center bond is defined[11] as an interaction



where an XH donor simultaneously hydrogen bonds with two acceptor atoms (i.e., is bonded to the *three* atoms X, Y_1, Y_2). A *four-center* bond consequently is an interaction of X–H with three acceptor atoms. An arrangement



is called[11] a *bifurcated* hydrogen bond.

The Data Sample

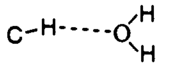
Hydrate structures that contain CH donors and have crystallographic quality factors $R < 0.08$ were extracted from the neutron diffraction subset of the Cambridge Structural Data Base[10] (July 1991 release). They were combined with the recent neutron crystal structure of β-cyclodextrin ethanol octahydrate at $T = 15$ K.[14] Water molecules with disordered O atoms or poor covalent geometry were excluded. This yielded a sample of 101 water molecules in 46 neutron crystal structures (a listing of substances and references is given in the Appendix). The substance classes in the data sample range from carbohydrates and amino acids to metallo–organic compounds and therefore supply structural data for water molecules in various different surroundings.

The structures were screened for C–H···O_W hydrogen bonds with H···O_W distances <3.2 Å and angles at H > 90°. To avoid at least the shortest C–H···H–O_W van der Waals contacts, arrangements with hydrogen–hydrogen distances H_C···H_W shorter than H_C···O_W – 0.3 Å were sorted out (see below). The accuracies of the hydrogen bond geometries vary from structure to structure, but in most cases are around (or better than) ±0.01 Å for distances and ±1° for angles.

Results

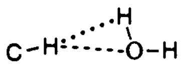
(a) C–H···H–O_W Contacts. Justification of the Distance Cutoff Limits. One of the mayor problems in data analysis was the occurrence of C–H···H–O_W contacts, for which we were unable to judge whether they are cohesive interactions or not. The problem is easiest illustrated as shown below:

(1)



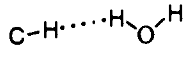
hydrogen bond

(2)



uncertain

(3)



no hydrogen bond

With only few exceptions, in short C–H···O_W contacts with H···O_W < 2.6 Å, both water OH bonds are directed more or less away from the CH donor, thereby avoiding a repulsive H_C···H_W contact (both H atoms carry positive partial charges). This arrangement (**1**) is certainly cohesive and therefore a hydrogen bond according to our definition.

For longer H···O_W distances, an increasing number of arrangements (**2**) and (**3**) is observed. The type **3** contact is easier to interpret: one of the O_W–H bonds points rather in the direction of H_C than away from it, and the H_C···H_W separation is by several tenths of an Å shorter than H_C···O_W. The extreme case in the data set is C_3–H···H_2–O_{W2} in Li–hydrogen–phthalate monohydrate at $T = 15$ K,[15] with H_C···H_W = 2.25 Å and H_C···O_W = 2.95 Å (angle C–H···O_W = 124°). Such arrangements obviously represent H···H van der Waals contacts and not hydrogen bonds. They can be easily identified and sorted out, for example, by using the criterion H_C···H_W < (H_C···O_W – 0.3 Å).

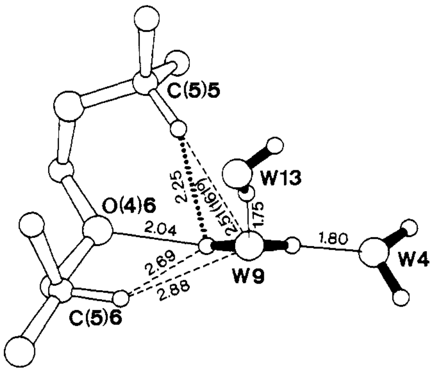


Figure 1. CH group that simultaneously forms short contacts to O and H of a water molecule; such arrangements are rare for short H···O_W distances <2.8 Å. It is not immediately evident whether the net interaction C(5)5–H···W9 is cohesive or not (in β-cyclodextrin·11.6H_2O at $T = 120$ K[16]). Water molecule W9 is included in the β-cyclodextrin cavity and forms a strong O_W–H···O hydrogen bond with an ether-type O atom of the cavity wall.

If the H_C···H_W separation is only slightly shorter than H_C···O_W, as in arrangement **2**, it often cannot be decided whether the arrangement is cohesive or not. One of the rare cases with a short H_C···O_W distance (2.51 Å) is shown in Figure 1. For H_C···O_W longer than about 2.8 Å, they rapidly become very frequent and a major fraction of the observed H···O_W contacts. As the data sample for H_C···O_W > 2.8 Å contains an unacceptably large contribution of such uncertain cases, we discuss only C–H···O_W hydrogen bonds with H···O < 2.8 Å in the main part of this study.

For O–H···O hydrogen bonds, there are similar problems,[13] suggesting a pragmatic cutoff limit of H···O < 3.0 Å, which is applied for O–H···O and N–H···O bonds in this study. As these hydrogen bonds are much stronger than C–H···O, the slightly longer cutoff can be justified.

We are aware that this procedure neglects numerous long-range interactions. The data sample obtained this way, however, contains only few dubious cases and is sufficiently complete to reveal the general trends (which is the aim of this study).

(b) C–H···O_W Hydrogen Bond Distances. The distributions of observed H···O_W and C···O_W distances are shown in Figure 2. The shortest H···O_W separations are ~2.3 Å; with increasing H···O_W, hydrogen bonds gradually become more frequent (but weaker). The pragmatic 2.8-Å cutoff used in the discussion below arbitrarily cuts the distribution (as any other cutoff would do). The observed C···O_W distances are as short as 3.1 Å, but are predominantly ≥3.3 Å, Figure 2.

Different types of CH donor groups show different hydrogen bonding properties and generally exhibit different pictures in hydrogen bond distance distributions.[8,17] The distributions shown in Figure 2 originate from an arbitrary mixture of CH donors, and a subdivision should reveal somewhat different features for different donors. Such a subdivion, however, is not feasible with the small quantity of (neutron) data available.

(c) Frequency of C–H···O_W Hydrogen Bonds. Of the 101 water molecules in neutron crystal structures that contain CH donors, only eight (~8%) are involved in short C–H···O_W interactions with H···O_W < 2.5 Å. For longer H···O_W distances, the fraction

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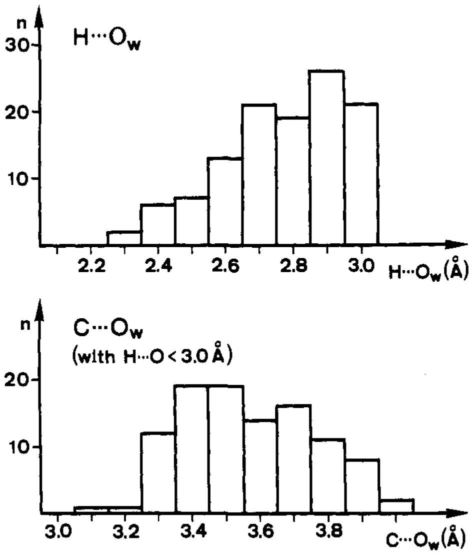

Figure 2. Histograms of H···O$_W$ (top) and C···O$_W$ (bottom) distances in C–H···O$_W$ hydrogen bonds with angles >90° at H. A bar centered at, e.g., 2.6 Å represents contacts ≥2.55 and <2.65 Å.

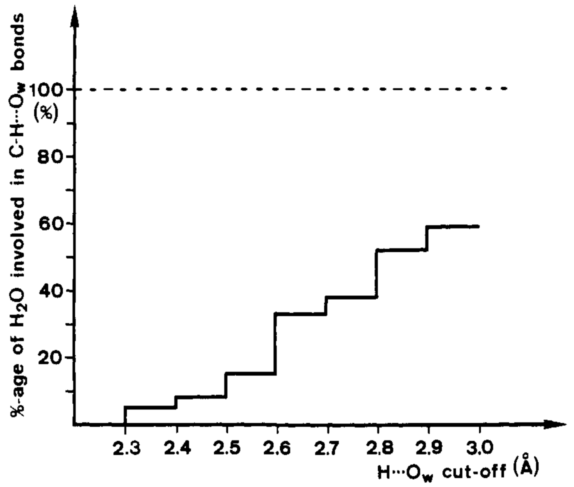

Figure 3. Percentage of the water molecules in the data sample that accept C–H···O$_W$ hydrogen bonds shorter than a given cutoff value. For example, 39% of the water molecules accept such interactions with H···O$_W$ < 2.8 Å.

of involved molecules gradually increases, Figure 3. For H···O$_W$ ≤ 2.8 Å, already 39% of the water molecules in the data set are involved, and for H···O$_W$ < 3.0 Å this fraction is even 57% (including some of the uncertain cases mentioned in part a).

(d) Hydrogen Bond Coordination of the Water Molecule. General. It is well-known that the preferred hydrogen bond coordination of the water molecule is tetrahedral or planar trigonal. This preference is very soft, and in crystal structures, numerous different configurations with lower and higher coordination are observed.[11,18]

In the studies of water coordination published until now, CH was not regarded as a potential hydrogen bond donor, and C–H···O$_W$ hydrogen bonds were neglected. To check whether this is a major omission, the total number of accepted interactions (hydrogen bonding and metal ion coordination) was determined for each water molecule in the data sample, Table I. If C–H···O$_W$ hydrogen bonds are neglected, the water molecules accept 0–4 interactions, with a clear preference for single (44%) and double acceptors (46%). When C–H···O$_W$ hydrogen bonds are included, these numbers change drastically: only 18% of the single acceptors remain, and the fraction of double acceptors increases to 58%. The fraction of water molecules that accept more than two interactions increases from 8% to 25%. This suggests that the hydrogen bond coordination of the water molecules should be studied in greater detail.

Table I. Number of Water Molecules in the Data Sample[a] that Accept a Specific Number of Hydrogen Bonds[b] and Contacts to Metal Ions[c]

no. of accepted interactions	no. of water molecules: CH neglected	no. of water molecules: CH included
0	3	0
1	44	18
2	46	58
3	7	21
4	1	3
5	0	1

[a] Total sample: 101 water molecules. [b] O–H···O$_W$ and N–H···O$_W$ with H···O$_W$ < 3.0 Å, C–H···O$_W$ with H···O$_W$ < 2.8 Å, angle at H > 90°. [c] M$^+$···O$_W$ < 3.0 Å.

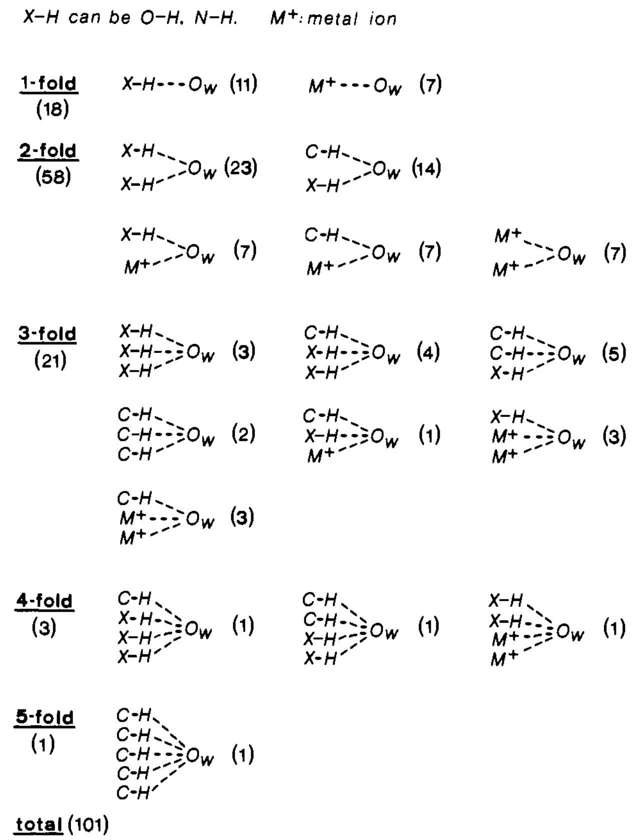

Figure 4. Acceptor functions of the 101 water molecules in the data sample. XH represents OH and NH donors, M$^+$ represents metal cations (such as Li$^+$, K$^+$, Ca^{2+}, etc.). Numbers in parentheses show the number of occurrence. Regarded are C–H···O$_W$ interactions with H···O$_W$ < 2.8 Å, X–H···O$_W$ with H···O$_W$ < 3.0 Å and M$^+$···O$_W$ < 3.0 Å.

(e) Acceptor Function of the Water Molecule. The various acceptor functions of the water molecules in the data set are shown schematically in Figure 4 (XH represents OH and NH groups), numbers in parentheses give the frequency of occurrence (2.8 Å cutoff for C–H···O$_W$).

The double-acceptor function is clearly preferred (58 out of 101). Of the total of 39 cases in Figure 4, in which C–H donors are involved, they complete such a 2-fold coordination 21 times. In the other 18 cases, CH participates in higher coordinations, with the extreme a 5-fold acceptor function of water that will be discussed below. CH, XH, and metal ions may simultaneously coordinate in virtually all combinations. Water as a triple-hydrogen bond acceptor, for example, may coordinate with three

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(18) Jeffrey, G. A.; Maluszynska, H. *Acta Crystallogr., Sect. B* **1990**, *B46*, 546–549.

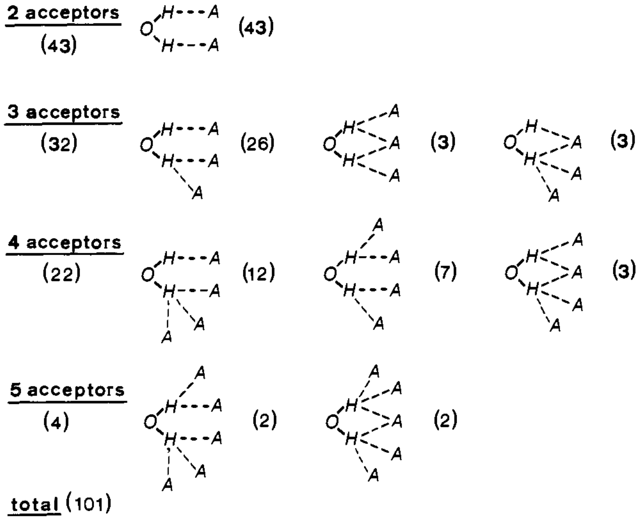

Figure 5. Donor functions of the 101 water molecules in the data sample. *A* represents any hydrogen bond acceptor atom. Numbers in parentheses show the number of occurrence. Regarded are O_W–H···A hydrogen bonds with H···A < 3.0 Å.

XH, with two XH, and one CH, with one XH and two CH, or with three CH donors (Figure 4); this indicates that XH and CH have the same principal functionality. Several features of Figure 4 will be discussed below with selected examples.

(f) Donor Function of the Water Molecule. For reasons of completeness, the donor functions of the water molecules in the data sample are shown in Figure 5. The picture for this inhomogeneous sample is very similar as for hydrates of small biological molecules.[18] Each water hydrogen atom may be involved in two-, three-, and four-center hydrogen bonds in various configurations. The total number of acceptor atoms ranges from two to five, with only the highest coordination being less frequent.

The donors and acceptor functions shown in Figures 4 and 5 can be freely combined to yield a variety of possible water coordinations. A water molecule may, for example, coordinate with two donors and four acceptors as well as with four donors and two acceptors. Several examples for different donor functions are shown below.

(g) CH Donors Satisfying the Preferred Double-Acceptor Function of Water. The most frequent acceptor function of O_W involving C–H···O_W hydrogen bonds is the double hydrogen bond acceptor with one XH and one CH donor, Figure 4 (14 cases; of these, XH is OH eight times and NH six times). The *coordination geometry* is tetrahedral in the idealized case, but it may vary considerably; two examples are shown in Figure 6.

In picrylsulfonic acid tetrahydrate,[19] Figure 6a, water molecule W2 accepts a very short hydrogen bond from a H_3O^+ cation and a short C–H···O_W interaction with H···O_W = 2.39 Å (C···O_W = 3.41 Å) from an aromatic C atom; the coordination angles around O_W are almost ideally tetrahedral (the arrangement W2-W3$^+$ can also be regarded as a $H_5O_2^+$ cation[19]). Ignoring the C–H···O_W interaction, this would represent a trigonal-pyramidal coordination of W2.

In (*S*)-asparagine monohydrate,[20] Figure 6b, the water molecule accepts a hydrogen bond from $-NH_3^+$ and another one from C_α–H with H···O_W = 2.35 Å (C_α···O_W = 3.30 Å). The latter is directed toward the "side" of the water molecule. Neglecting the C–H···O_W interaction, the water coordination would be regarded as roughly trigonal-planar, whereas it actually is distorted tetrahedral.

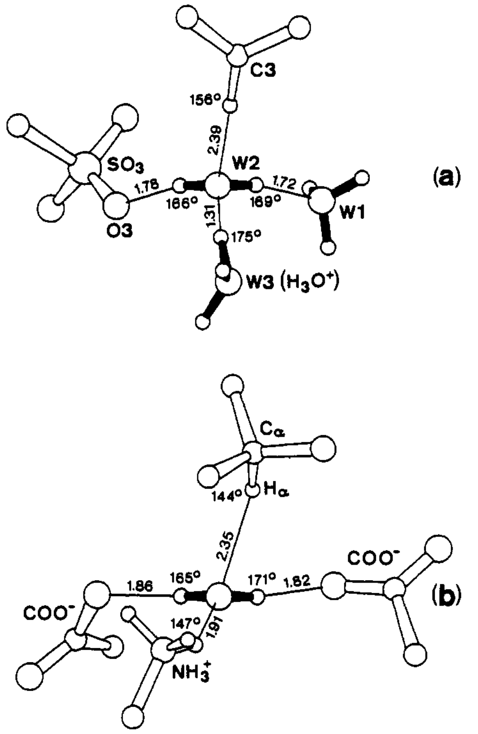

Figure 6. Examples for water molecules that accept one hydrogen bond donated by OH or NH and an additional short C–H···O_W bond (2-fold acceptor function of O_W). Projections are along the water bisector. Filled bonds: OH. (a) In picrylsulfonic acid tetrahydrate,[19] room temperature, C···O_W = 3.41 Å. The coordination angles of the accepted hydrogen bonds with respect to the water H atoms are almost ideally tetrahedral. Both H atoms of W2 are engaged in three-center hydrogen bonds; for clarity the minor components are not drawn. (b) In asparagine monohydrate at T = 15 K,[20] C_α···O_W = 3.30 Å. The coordination angles around O_W are distorted tetrahedral. In L-asparagine monohydrate[21] (at room temperature), the geometry is very similar with slightly longer hydrogen bond distances, e.g., H_α···O_W = 2.40 Å, C_α···O_W = 3.35 Å, angle C_α–H···O_W = 144°.

These observations suggest that one of the main functions of CH donors is to complete tetrahedral hydrogen bond configurations of water molecules if a sufficient number of OH and NH donors is not available.

(h) CH Donors Involved in Triple and Higher Acceptor Functions of Water. Twenty-five water molecules in the data set accept three or more hydrogen bonds or metal ion contacts, and for only seven of these, *no* C–H···O_W interaction is involved (Figure 4). All coordination geometries have a common feature: if only OH and NH donors (or M^+) are regarded, the water coordination is incomplete or heavily distorted. This results in "free" acceptor potential that is satisfied by one or more C–H···O_W hydrogen bonds. Various hydrogen bond configurations are observed, as is shown for three representative examples in Figure 7.

Water W8 in the hydrophobic cavity of β-cyclodextrinethanol octahydrate at T = 15 K,[14] Figure 7a, donates a two-center and a three-center hydrogen bond to acceptors placed outside the cavity. Within the cavity, it accepts only one hydrogen bond from another water molecule, W6. Two additional C–H···O_W interactions from the cavity wall satisfy the remaining acceptor potential (H···O_W = 2.39 and 2.56 Å, respectively, C···O_W = 3.35 and 3.40 Å, respectively).

Another example of a water molecule in a cyclodextrin cavity is W10 in β-cyclodextrin·11.6H_2O (at T = 120 K[16]), Figure 7b. W10 accepts two O–H···O_W hydrogen bonds, which are, due to steric restrictions in the cavity, rather long with H···O_W = 2.05 Å, and directed toward the "sides" of the molecule. This leaves the "backside" of the molecule accessible for another interaction, which actually is donated by a CH group of the cavity wall (H···O_W

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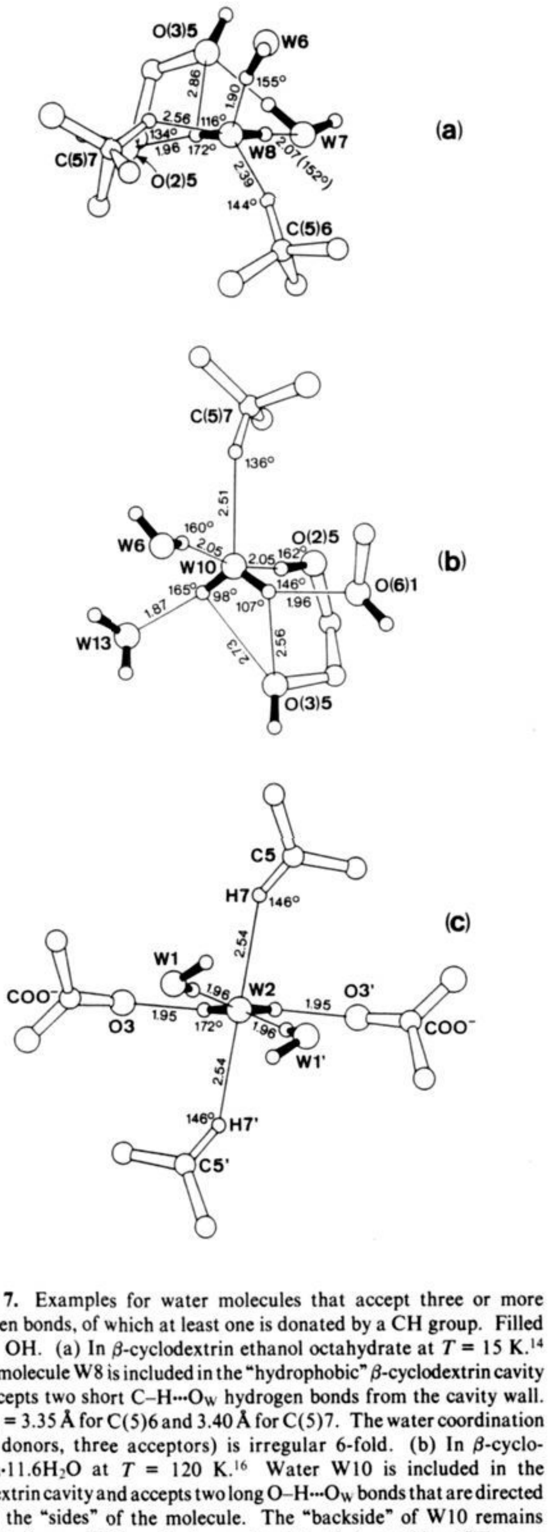

Figure 7. Examples for water molecules that accept three or more hydrogen bonds, of which at least one is donated by a CH group. Filled bonds: OH. (a) In β-cyclodextrin ethanol octahydrate at $T = 15$ K.[14] Water molecule W8 is included in the "hydrophobic" β-cyclodextrin cavity and accepts two short C–H···O_W hydrogen bonds from the cavity wall. C···O_W = 3.35 Å for C(5)6 and 3.40 Å for C(5)7. The water coordination (three donors, three acceptors) is irregular 6-fold. (b) In β-cyclodextrin·11.6H_2O at $T = 120$ K.[16] Water W10 is included in the cyclodextrin cavity and accepts two long O–H···O_W bonds that are directed toward the "sides" of the molecule. The "backside" of W10 remains accessible for an additional hydrogen bond that is donated by a CH group of the cavity wall (C···O_W = 3.38 Å). Note that the water coordination would be roughly 4-fold planar if the long-range interactions were neglected. Including the C–H···O_W contact and the bifurcated O_W–H···O hydrogen bond donated to O(3)5 (O_{W10}···O(3)5 = 2.98 Å), the water coordination is roughly octahedral. (c) In aqua(*N*-salicylideneglycinato)copper(II) hemihydrate at $T = 130$ K.[22] W2 is placed on a 2-fold axis. The O–H···O_W hydrogen bonds donated by the symmetry-equivalent water molecules W1 and W1′ are associated with a short H_{W1}···$H_{W1'}$ contact of 2.19 Å.[22] The symmetry-equivalent C–H···O_W bonds directed toward the "sides" of W2 have C···O_W separations of 3.50 Å. W2 donates three-center O–H···O hydrogen bonds; for clarity, the minor components are not drawn.

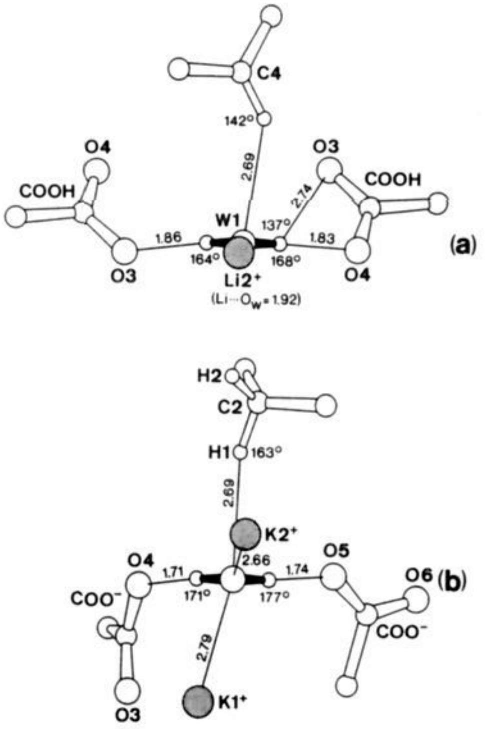

Figure 8. Examples for water molecules that simultaneously interact with metal cations and CH hydrogen bond donors. Filled bonds: OH. Shaded spheres: metal cations. Projections are along the water bisector. (a) In lithium hydrogen phthalate monohydrate at $T = 15$ K.[15] The Li^+ ion coordinates along the water bisector, and an additional long C–H···O_W hydrogen bond is directed toward the "side" of the water molecule (C···O_W = 3.61 Å). (b) In tripotassium citrate monohydrate[23] at room temperature. The water molecule interacts with two K^+ ions, and one "side" remains accessible for an additional long C–H···O_W interaction (C···O_W = 3.76 Å).

= 2.51 Å, C···O_W = 3.38 Å). Also note the remarkable bifurcated O–H···O hydrogen bond donated by W10 to the hydroxyl group O(3)5.

An arrangement that is "complementary" to the one given above is found in aqua(*N*-salicylideneglycinato)copper(II) hemihydrate at $T = 130$ K,[22] Figure 7c (this is the only example of the present study where the C–H···O_W interaction was recognized in the original paper). Water molecule W2, which is placed on a 2-fold axis, accepts two O_W–H···O_W hydrogen bonds that are directed towards the "backside" of O_{W2}. If alone, they would represent a very peculiarly distorted hydrogen bond configuration of W2. The free "sides" of the water molecule, however, accept two additional C–H···O_W hydrogen bonds from aromatic C atoms. The resulting 4-fold acceptor function of water is one of the rarer coordinations observed in Figure 4.

(i) CH Donors Coordinating Together with Metal Ions. In the data set, there are 11 water molecules which simultaneously *coordinate to a CH hydrogen bond donor and one or two metal* ions (Figure 4). These, however, originate from only few substances and several of them seem dubious. Therefore, a larger quantity of accurate data is required for a conclusive analysis.

For the well-defined crystal structures, the water coordination geometries are generally dominated by the ion–water interactions. They are less affected from the additional C–H···O_W hydrogen bonds and have longer H···O_W distances than in the configurations discussed above. Two typical examples are shown in Figure 8.

The water molecule W1 in lithium hydrogen–phthalate monohydrate (at $T = 15$ K[15]) interacts with one Li^+ ion, Figure 8a, which is placed on the water bisector (as is expected for a

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Table II. Hydrogen Bond Parameters[a] for Tetrakis(pyridine)platinum(II) Chloride Trihydrate[24] (Distances in Å, Angles in deg)

hydrogen bond	X–H	H···A	X···A	X–H···A
O_W–H···Cl^-				
O(A)–H1···Cl(1)	0.97	2.17	3.14	177
O(A)–H2···Cl(2)	0.97	2.16	3.13	170
O(B)–H1···Cl(1)	0.95	2.38	3.33	178
O(B)–H2···Cl(2)	0.91	2.30	3.20	177
O(C)–H1···Cl(1)	0.93	2.27	3.18	168
O(C)–H2···Cl(2)	0.94	2.19	3.12	175
C–H···O_W				
C(1)–H···O(A)	1.08	2.44	3.42	152
C(2)–H···O(B)	1.07	2.77	3.32	111
C(2)–H···O(C)	1.07	2.49	3.53	163
C(7)–H···O(B)	1.03	2.58	3.53	153
C(9)–H···O(C)	1.07	2.43	3.43	154
C(10)–H···O(A)	1.07	2.47	3.47	156
C(13)–H···O(A)	1.08	2.37	3.34	149
C(15)–H···O(A)	1.06	2.69	3.54	137
C(15)–H···O(C)	1.06	2.64	3.31	121
C(16)–H···O(A)	1.06	2.58	3.57	154
C(17)–H···O(B)	1.06	2.64	3.49	137
C–H···Cl^-				
C(3)–H···Cl(1)	1.07	3.01	3.70	122
C(4)–H···Cl(1)	1.09	2.93	3.66	125
C(6)–H···Cl(1)	1.07	2.78	3.77	153
C(11)–H···Cl(1)	1.10	2.61	3.55	143
C(12)–H···Cl(2)	1.05	2.66	3.68	164
C(19)–H···Cl(2)	1.09	2.72	3.79	165
C(20)–H···Cl(1)	1.09	2.56	3.59	158

[a] O_W–H···Cl^- with H···O_W < 3.0 Å; C–H···O_W with H···O_W < 2.8 Å; C–H···Cl^- with H···O_W < 3.1 Å; angle at H > 90°.

single ion). An additional long C–H···O_W hydrogen bond is directed toward the "side" of the water molecule, with H···O_W = 2.69 Å (C···O_W = 3.61 Å).

In tripotassium citrate monohydrate,[23] Figure 8b, the water molecule interacts with two K^+ ions that are arranged such that one side of the water molecule remains accessible for an additional long hydrogen bond (donated by an ethylene-type C atom, H···O_W = 2.69 Å, C···O_W = 3.76 Å).

(j) Chelation of a Water Molecule by C–H···O_W Hydrogen Bonds. The metallo–organic compound tetrakis(pyridine)platinum(II) chloride trihydrate[24] exhibits an exceptional wealth of C–H···O_W (and C–H···Cl^-) hydrogen bonds and deserves a detailed discussion. The three symmetry-independent water molecules in the complex use all their donor potential for O_W–H···Cl^- hydrogen bonds, Table II. As there are no other OH or NH donors, and no metal ions available, they have to satisfy all their acceptor potentials with C–H···O_W interactions from the $[Pt(C_5H_5N)_4]^{2+}$ cation. Consequently, one of these water molecules accepts five and the other two three C–H···O_W hydrogen bonds each, Table II (also see Figure 4).

Most remarkable is water molecule W(A): it is chelated in one bay of the $[Pt(C_5H_5N)_4]^{2+}$ cation and accepts four short concentric C–H···O_W hydrogen bonds from the four pyridine moieties, Figure 9, with the shortest H···O_W distance at 2.44 Å (Table II). A fifth C–H···O_W interaction is donated from a symmetry-related cation and directed toward the "side" of W(A) with H···O_W = 2.37 Å. The opposite bay of the $[Pt(C_5H_5N)_4]^{2+}$ cation chelates Cl^- anion Cl(1) less regularly, Figure 9 and Table II. The other two water molecules, W(B) and W(C), and the anion Cl(2) interact only with the peripheral CH groups of the cation.

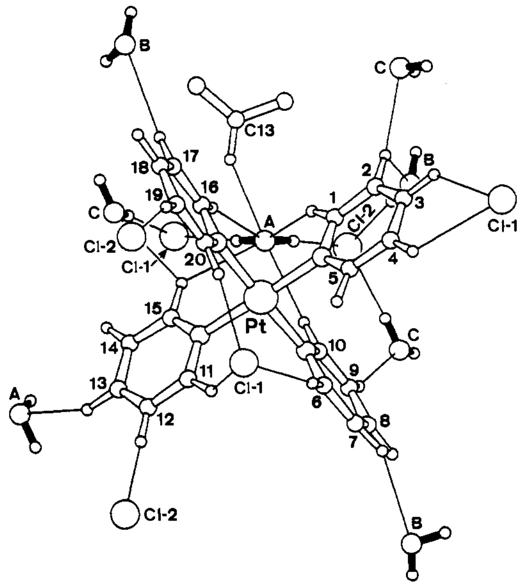

Figure 9. Hydrogen bond surrounding of the cation in the metallo–organic compound tetrakis(pyridine)platinum(II) chloride trihydrate[24] (room temperature). Hydrogen bond parameters are listed in Table II. Note that the $[Pt(C_5H_5N)_4]^{2+}$ cation chelates a water molecule in one of its bays and a Cl^- anion in the other one. Filled bonds: OH. Projection is along the bisector of water molecule W(A).

Of the 20 CH groups of the four pyridine moieties, 16 donate C–H···O_W and C–H···Cl^- hydrogen bonds, with the shortest H···O_W and H···Cl^- distances at 2.37 and 2.56 Å, respectively. Apart from the "normal" hydrogen bonds, two types of hydrogen bond patterns should be mentioned: C(2)–H and C(15)–H donate *three-center* C–H···O_W hydrogen bonds, Figure 9. Whereas three-center C–H···O interactions are not unusual,[3,9] they are very rare with both acceptor atoms being water molecules. C(3)–H and C(4)–H donate a *bifurcated*-type C–H···Cl^- bond (both components, however, are long with H···Cl^- = 3.01 and 2.93 Å, respectively).

(k) Internal Water Molecules in Proteins. The observations presented above must also have implications for structural biology. The idea that C–H···O hydrogen bonds play a role in protein stabilization is old,[5] but unproven. The possible occurrence of C–H···O_W hydrogen bonds in biological systems is best examined for internal water molecules of proteins, which in crystal structures usually are better ordered (and refined) than external water molecules. In a survey of such internal water molecules, 29 out of 60 (~48%) were found to be 3-fold and 22 (~37%) 4-fold coordinated.[25] It is reasonable to assume that internal water molecules in proteins might have higher coordinations, if C–H is considered as a hydrogen bond donor.

As an example, the exceptionally well-refined internal water cluster in the X-ray structure of actinidin[26,27] was analyzed. The resolution of 1.7 Å and the positional accuracy ~0.15 Å[27] for non-hydrogen atoms are a serious caveat to such an analysis; H atoms were calculated to idealized positions. Figure 10 shows a section of this cluster, with the hydrogen bonding scheme of four water molecules that were earlier designated as "three-fold" coordinated.[25,26] Actually, two of them exhibit short C···O_W contacts that complete a tetrahedral coordination: W14 presumably accepts a hydrogen bond from C_ϵ–H of Lys181, with C···O_W = 3.36 Å (H_{calcd}···O_W = 2.29 Å, C–H_{calcd}···O_W = 169°). Notably, the hydrogen bond donor potential of C_ϵ must be relatively strong due to the attached $-NH_3^+$ group. W26 accepts a short contact from $C_{\gamma 2}$ of Val165, C···O_W = 3.13 Å (H_{calcd}···O_W = 2.25 Å, C–H_{calcd}···O_W = 136°, see footnote of Figure 10). The

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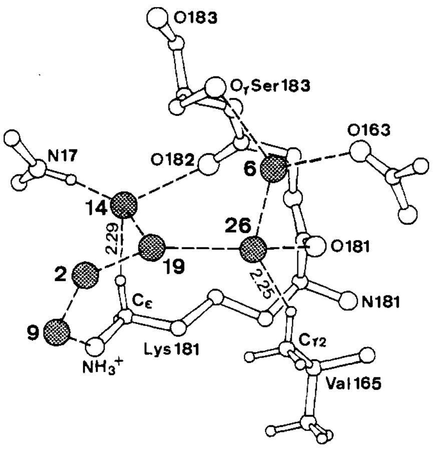

Figure 10. Hydrogen bond coordination for four internal water molecules of the enzyme actinidin.[26] Two water molecules (W14 and W26) presumably accept C–H···O_W hydrogen bonds, resulting in a tetrahedral coordination. C_ϵLys 181···O_{W14} = 3.36 Å and $C_{\gamma2}$ Val 165···O_{W26} = 3.13 Å. H positions are calculated; this is not unambiguous for Val 165, as the methyl groups may rotate, the calculated distance H_{Val165}···O_{W26} therefore has to be taken with reservation.

other two water molecules, W6 and W19, actually have a 3-fold hydrogen bond coordination.

The related protein papain exhibits an internal water cluster of very similar geometry:[28] there, both C–H···O_W interactions seem conserved with somewhat different hydrogen bond distances (C_ϵ Lys 174–H···O_{W1}, C···O_W = 3.16 Å, and $C_{\gamma2}$ Val 32–H···O_{W23}, C···O_W = 3.45 Å).

The analysis of protein X-ray structures certainly is of much lesser accuracy and reliability compared to small molecule neutron diffraction data. On the basis of the results presented in the preceding sections, however, these observations indicate that C–H···O_W hydrogen bonds play a similar role in water coordination in macromolecular structures as in smaller systems.

Summary and Discussion

(1) Neutron diffraction structures that contain CH groups as donors and water molecules as acceptors were analyzed for C–H···O_W hydrogen bonds (101 water molecules in 46 crystal structures). The substances in the sample range from carbohydrates and amino acids (and a protein) to metallo–organic compounds and provide data for water molecules in many different surroundings. The restriction to high-quality neutron diffraction studies yields a very accurate but relatively small data sample. This minimizes the serious danger to produce an analysis based on experimental artifacts, but it also reduces the significance of statistical considerations.

(2) C–H···O_W contacts were extracted to H···O_W distances <3.2 Å, but in the main part of the analysis, only interactions H···O_W < 2.8 Å were discussed. This is to pragmatically exclude dubious arrangements that are a considerable fraction of the longer contacts H···O_W > 2.8 Å. This way, numerous cohesive long-range interactions are neglected. The data sample, however, is still sufficiently complete to reveal the general trends.

(3) Of the water molecules in the data sample, ~8% accept C–H···O_W hydrogen bonds with H···O_W distances <2.5 Å and 39% with H···O_W < 2.8 Å (Figure 3). The shortest observed C–H···O_W hydrogen bonds have H···O distances ~2.3 Å.

(4) If C–H···O_W interactions are neglected (as is frequently done in the literature), the water molecules in the data sample accept 0–4 hydrogen bonds or contacts with metal ions, with a preference for single (44%) and double acceptors (46%). After inclusion of the C–H···O_W hydrogen bonds, they accept 1–5 such interactions, only 18% of the single acceptors remains, and the fraction of double acceptors increases to 58% (Table I).

(5) CH, OH, and NH hydrogen bond donors, and metal ions, may coordinate to a water molecule in many different combinations (Figure 4). The most frequent function of C–H···O_W hydrogen bonds is to complete a tetrahedral coordination geometry (Figure 6). Furthermore, there are many examples where a distorted tetrahedral O–H···O_W and N–H···O_W hydrogen bond coordination leaves "free" acceptor potential that is satisfield by additional C–H···O_W interactions (Figure 7). In extreme cases, water molecules may accept no other cohesive near-neighbor interactions than C–H···O_W hydrogen bonds (Figure 9).

(6) These results were derived from accurately determined hydrogen positions in neutron crystal structures of small hydrated molecules. They justify the analyzation of C–H···O_W hydrogen bonds (on a lower level of accuracy) also from X-ray structures, for which a much larger body of data is available. Also, we see no reason why the general trends should not be similar in larger systems, in particular for biological macromolecules for which hydration plays a most essential role. As an example, the internal water cluster in the X-ray structure of the enzyme actinidin was analyzed for short C···O_W contacts that are suggestive for C–H···O_W hydrogen bonds. Actually, two such contacts were found that neatly complete a tetrahedral coordination of the involved water molecules (Figure 10).

(7) We note that in computer simulation studies, to save computer time, H atoms bonded to C are often not regarded as separate atoms, but fused with C to "united atoms" with an averaged partial charge. This inevitably must neglect all C–H···O hydrogen bonding effects. The consequences are uncertain, but may be disquieting for systems in which C–H···O hydrogen bonds actually play a significant role (as for water molecules in a partly "hydrophobic" surrounding).

(8) The essential finding can be briefly summarized: CH donors can (and often do) participate in the coordination of water molecules similar to OH and NH. Certainly, a water molecule will prefer to accept the stronger hydrogen bonds from OH and NH donors or to coordinate to cations. If these are not available in sufficient numbers and in suitable configuration in a given local environment, however, a water molecule will resort to the formation of weaker C–H···O_W interactions rather than leaving its multiple hydrogen bond acceptor potential unsatisfied. In the resulting water coordination, OH, NH, and CH donors have the same principal functionality, with differences only in the hydrogen bond distances (and strengths).

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Appendix

Substance and reference listing of the 46 neutron crystal structures in the data sample. Reference codes and entry numbers in the Cambridge Structural Database (CSD) are given in parentheses. If no temperature is given, crystal structures were determined at room temperature. We thank a reviewer for giving the well-founded[29] advice to produce such a listing.

(1) Crystal Structures with Short C–H···O_W Hydrogen Bonds, H···O < 2.5 Å (n = 7). The short C–H···O_W hydrogen bonds in all these compounds are discussed in the main text, except for NACTMO02 (the latter is based on data of somewhat lesser accuracy, crystallographic resolution 1.09 Å).

Picrylsulfonic acid tetrahydrate[19] (PICSUL01, 17550). L-Asparagine monohydrate[21] (ASPARM02, 1619). (*S*)-Asparagine monohydrate at T = 15 K[20] (ASPARM06, 71808). Disodium di-μ-oxo-bis([cysteinato(2–)]oxomolybdate) (Mo–Mo)

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pentahydrate[30] (NACTMO02, 34729). Tetrakis(pyridine)platinum(II) chloride trihydrate[24] (CIWKEY01, 72040). β-Cyclodextrin·11.6D$_2$O at T = 120 K[16] (CUXCON01, 60579). β-Cyclodextrinethanol octahydrate at T = 15 K[14] (not in the 1991 release of the CSD).

(2) Crystal Structures with Longer C–H···O$_W$ Hydrogen Bonds, 2.5 < H···O < 2.8 Å (*n* = 19). Only few of these crystal structures are discussed in the main text.

Bis(2-amino-2-methyl-3-butanone oximato)nickel(II) chloride monohydrate[31] (AMBONC01, 1040). Bis(2-amino-2-methyl-3-butanone oximato)platinum(II) chloride 3.5-hydrate[32] (AMBXPT10, 1049). L-Arginine dihydrate[33] (ARGIND11, 1568). *trans*-Dichlorobis(ethylenediamine)cobalt(III) chloride hydrochloride dihydrate[34] (EDTCOH11, 9324). L-Histidine hydrochloride monohydrate[35] (HISTCM12, 10710). L-Lysine monohydrochloride dihydrate, study I[36] (LYSCLH02, 12571). L-Lysine monohydrochloride dihydrate, study II[37] (LYSCLH11, 12572). Lithium thallium tartrate monohydrate[38] (LITLTA10, 25294). 2-Nitro-1,3-indandione oxonium dihydrate[39] (NINDOD01, 31541). Manganese acetate tetrahydrate[40] (AMNACT01, 36122). Sodium 1-pyrrolidinecarbodithioate dihydrate[41] (NAPYCT03, 41289). Lithium hydrogen phthalate monohydrate[15] at T = 15 K (LIHPAL01, 57227), at T = 100 K (LIHPAL02, 57228), and at room temperature (LIHPAL03, 57229). Telluric acid–glycine ($^1/_2$) monohydrate[42] (BINFAF02, 65722). Aqua(*N*-salicylideneglycinato)copper(II) hemihydrate at T = 130 K[22] (SGLACU01, 82579). Tripotassium citrate monohydrate[23] (ZZZHVI02, 84238). Cyclosporin A monohydrate[43] (KEPNAU, 89733). Rubidium trihydrogen-1-hydroxyethane-1,1-diphosphonate dihydrate[44] (SATHIE01, 90311).

(3) Crystal Structures Containing No C–H···O$_W$ Hydrogen Bonds with H···O Shorter than 2.8 Å (*n* = 20). Eleven of these 20 crystal structures contain C–H···O$_W$ contacts with H···O$_W$ distances between 2.8 and 3.0 Å (CYSTAC01, 6707; KDGLUM01, 12034; KDGLUM02, 12035; MALTOS11, 12744; MGBGUH01, 13727; ODACCE01, 16118; RHAMAH12, 18916; MGALPY01, 24555; CUFOHY04, 32411; NAHMAL01, 49120; NSMEDT, 51123). For the reasons outlined above (Results, section a), these contacts are disregarded by the distance cutoff limit used in this study and are not included in Figure 4.

Barium methacrylate monohydrate[45] (BAMACR, 1973). L-Cysteic acid monohydrate[46] (CYSTAC01, 6707). Glycylglycine hydrochloride monohydrate[47] (GLCICH01, 10072). Potassium trichloroethylene platinate monohydrate[48] (Zeise's salt) (KCLEPT03, 12016). Potassium D-gluconate monohydrate,[49] form A (KDGLUM01, 12034) and form B (KDGLUM02, 12035). Lithium formate monohydrate[50] (LIFORM02, 12439). L-Serine monohydrate[51] (LSERMH10, 12507). β-Maltose monohydrate[52] (MALTOS11, 12744). Methylglyoxal bisguanylhydrazone dihydrochloride monohydrate[53] (MGBGUH01, 13727). Trisodium tris(oxydiacetato)cerate(III) nonahydrate[54] (ODACCE01, 16118). α-L-Rhamnose monohydrate[55] (RHAMAH12, 18916). Calcium malonate dihydrate[56] (CAMALD03, 22629). Methyl α-D-galactopyranoside monohydrate[57] (MGALPY01, 24555). 5-Nitro-1-(β-D-ribosyluronic acid)uracil monohydrate at T = 80 K[58] (NRURAM11, 26607). Guanidine tetramolybdatodimethylarsinate monohydrate[59] (GUMOAS02, 30087). Copper(II) formate tetrahydrate[60] at T = −196 °C (CUFOHY04, 32411). Sodium hydrogen maleate trihydrate at T = 120 K[61] (NAHMAL01, 49120). Sodium triaqua(ethylenediamine tetraacetato)samarate(III) pentahydrate at T = 37 K[62] (NSMEDT02, 51123). 6-Nitro-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide sodium (6-nitrosaccharin) tetrahydrate at T = 123 K[63] (JAPKOA, 79466).

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