204. *Evidence for the Existence of* C–H · · · O *Hydrogen Bonds in Crystals.*

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Since an activated C–H group may take part in hydrogen bonding, the angles involved in the " short " interaction have been calculated for various compounds of known crystal structure containing activated C–H groups and " short " C · · · O distances. In these compounds, the conditions for hydrogen bonding are satisfied by the methylidyne group and probably by the methylene and the methyl group. This type of hydrogen bond occurs rather widely and may be of importance in the structures of biological molecules.

An investigation of " short " intermolecular and intramolecular C · · · O contacts has shown that many of these are due to C–H · · · O hydrogen bonds. Here the term " short " implies that the distance between the carbon and the oxygen atom is less than the sum of their van der Waals radii plus some allowance for the hydrogen atom or atoms attached to the carbon. Thus C · · · O distances in the region of 3·1 Å are considered.*

The present work was prompted by the discovery of an intermolecular distance of 3·00 Å between a methyl group and an oxygen atom in the crystal structure of 1,3,7,9-tetramethyluric acid.[1] This value, obtained originally from a two-dimensional analysis of

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* This is necessary because of the range of values found for hydrogen bonds. The O · · · O distance in an O–H · · · O hydrogen bond is usually less than the van der Waals distance. However the less electronegative nitrogen atom forms N–H · · · O and N–H · · · N bonds in which the N · · · O and N · · · N distances are frequently greater than the van der Waals distance. Carbon which is less electronegative and has to be activated in order to participate in a hydrogen bond should behave similarly to nitrogen, forming even longer bonds.

[1] Sutor, *Acta Cryst.*, in the press.

the compound, is so much shorter than the accepted distance (the sum of the van der Waals radii of a methyl group and an oxygen atom is 3·40 Å) that it was at first felt that the structure might represent a homometric one.[2] However, three-dimensional analysis established the structure beyond doubt and with good accuracy, so that an explanation was needed for this " short " distance, which was not altered by three-dimensional refinement of the atomic co-ordinates. At the same time the literature was searched for similar contacts.

The considerable shortening of the van der Waals separation indicates bond formation. It is known the C–H group can participate in hydrogen bonds under favourable conditions, but the tendency to do so is weak. The number of known examples is few, and the author could find no value for the distance corresponding to such an interaction; nor could she find many crystallographic papers where the possibility of such an interaction was considered, although " short " C · · · O contacts had been observed in cases where the carbon atom was attached to at least one hydrogen atom. I therefore here present a summary of occurrences of " short " intermolecular C · · · O distances and briefly examine their nature.

Hydrogen bonding[3] involves a shortening of the van der Waals distance between the atoms concerned. The hydrogen atom lies between two electronegative atoms, and it is assumed that the donor, hydrogen, and acceptor atoms are aligned linearly. The donor and the acceptor atom are usually the most electronegative of the elements—fluorine, oxygen, nitrogen, and chlorine—but a C–H group that is activated by groups promoting ionisation or partial ionisation can also take part in hydrogen-bond formation. Thus chloroform, where the hydrogen is activated by chlorine, forms hydrogen bonds with acetone and strong bases such as pyridine and triethylamine. Similarly, hydrogen-bond formation by halogenated alkanes, by acetylenes, and by aldehydes has been observed. Here the evidence comes from infrared and nuclear magnetic resonance spectroscopy and from measurements of the vapour pressure, etc. There was, however, no quantitative evidence as to the length of the contact and the position of the hydrogen atom.

In 1951, Dulmage and Lipscomb[4] showed that at —120° and —80° the molecules of hydrogen cyanide are arranged in infinite chains with " short " carbon–nitrogen distances (3·18 Å) along the C–H · · · N direction. Activation of the C–H group occurs, and the interaction is of the hydrogen-bond type. In 1953, Dougill and Jeffrey[5] suggested weak association or polarisation bonding between the carbonyl and methyl groups in dimethyl oxalate. The methyl group has three carbonyl-oxygen atoms at distances of 3·35, 3·54, and 3·57 Å and approximately in the direction of the C–H bonds. The exact positions of the hydrogen atoms were not determined. They considered that " polarisation bonding would appear to be a more appropriate description than C–H · · · O hydrogen bonding."

In the last ten years, many examples of " short " intermolecular and intramolecular C · · · O distances have appeared but have rarely been discussed as to their significance. Tables 1 and 2 list some of these compounds with *d*(C · · · O) less than 3·3 Å. Although the search of the literature was not exhaustive, the Tables show that " short " C · · · O distances are not uncommon; they occur mainly in heterocyclic molecules and sometimes in compounds containing atoms of varying electronegativity with, frequently, a conjugated double-bond system or a series of double bonds. In all cases, except deoxyribonucleic acid which is hardly comparable, the carbon atom of the CH group is directly attached to the heteroatom or more electronegative atom or group, or is part of a conjugated double-bond system containing a heteroatom. Activation of the CH group is highly probable, and thus the right conditions exist for the formation of hydrogen bonds, but it remains to be shown whether or not the hydrogen toms are involved in the interaction.

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[2] Patterson, *Phys. Rev.*, 1944, **65**, 195.

[3] For details see Pimentel and McClellan, " The Hydrogen Bond," W. H. Freeman and Co., San Francisco, 1960, and references cited there.

[4] Dulmage and Lipscomb, *Acta Cryst.*, 1951, **4**, 330.

[5] Dougill and Jeffrey, *Acta Cryst.*, 1953, **6**, 831.

TABLE 1.

Intermolecular distances with $d(C \cdots O) < 3{\cdot}3$ Å (distances in parentheses do not denote hydrogen bonds).

Compound	$d(C \cdots O)$ (Å)	Groups	Atoms	Ref.
Ethylene carbonate	3·11	$CH_2 \cdots O$(keto)	C_1, C_2, O_3	*a*
Glycyl-L-tyrosine hydrochloride	3·07	$CH_2 \cdots O$(water)	C_{11}, H_2O	*b*
	(3·23, 3·25)	$CH_2 \cdots O$(water)	C_{10}, C_{11}, H_2O	
Hydroxy-L-proline	3·22	$CH_2 \cdots O$(hydroxyl)	C_5, O_3	*c*
	3·29, 3·30	$CH_2 \cdots O$(carboxyl)	C_5, O_2	
1,3,7,9-Tetramethyluric acid	3·00	$CH_3 \cdots O$(keto)	C_{12}, O_{11}	1
Uracil	3·19, (3·18)	$CH \cdots O$(keto)	C_2, O_8	*d*
	3·28	$CH \cdots O$(keto)	C_5, O_8	
Theophylline	3·22, (3·33)	$CH \cdots O$(keto)	C_8, O_{11}	*e*
	3·24	$CH_3 \cdots O$(water)	C_{10}, O_{15}	
Caffeine	3·18, (3·30)	$CH \cdots O$(keto)	C_8, O_{11}	*f*
	3·24	$CH_3 \cdots O$(keto)	C_{14}, O_{13}	
Di-(*p*-chlorophenyl) sulphone	3·21, 3·27	$CH \cdots O$(sulphonyl)	C_6, O	*g*
	3·24	$CH \cdots O$(sulphonyl)	C_5, O	
Furoic acid	3·14	$CH \cdots O$(ring)	C_5, O (ring)	*h*
Phenazine *N*-oxide	3·16	$CH \cdots O$(oxy)	C_5, O	*i*
	3·11	$CH \cdots O$(oxy)	C_3, O	
Tetramethylene tetranitramine	3·01	$CH_2 \cdots O$(nitro)	C_1, O_3	*j*
	3·12	$CH_2 \cdots O$(nitro)	C_2, O_3	
N-Ethyl-2,2′-dimethylsulphonylvinylideneamine	3·27	$CH_2 \cdots O$(sulphonyl)	C_5, O_4	*k*
NN′-Diglycyl-L-cystine dihydrate	2·92	$CH_2 \cdots O$(keto)	C_4, O_3	*l*
	3·24	$CH \cdots O$(carboxyl)	C_2, O_2	
Acetylcholine bromide	3·00	$CH_3 \cdots O$(acetyl)	C_5, O_1	*m*
	3·00	$CH_3 \cdots O$(ester)	C_6, O_2	
Nicotinamide	3·24	$CH \cdots O$(water)	C_1, H_2O	*n*
N-Benzyl-1,4-dihydronicotinamide	3·22	$CH_2 \cdots O$(amide)	C_7, O	*o*

References: (*a*) Brown, *Acta Cryst.*, 1954, **7**, 92. (*b*) Smits and Wiebenga, *Acta Cryst.*, 1953, **6**, 531. (*c*) Donohue and Trueblood, *Acta Cryst.*, 1952, **5**, 419. (*d*) Parry, *Acta Cryst.*, 1954, **7**, 313. (*e*) Sutor, *Acta Cryst.*, 1958, **11**, 83. (*f*) Sutor, *Acta Cryst.*, 1958, **11**, 453. (*g*) Sime and Abrahams, *Acta Cryst.*, 1960, **13**, 1; Bacon and Curry, *ibid.*, p. 10. (*h*) Goodwin and Thompson, *Acta Cryst.*, 1954, **7**, 166. (*i*) Curti, Riganti, and Locchi, *Acta Cryst.*, 1961, **14**, 133. (*j*) Eiland and Pepinsky, *Z. Krist.*, 1954, **106**, 273. (*k*) Daly, *J.*, 1961, 2801. (*l*) Yakel and Hughes, *Acta Cryst.*, 1954, **7**, 291. (*m*) Sörum, *Acta Chem. Scand.*, 1959, **13**, 345. (*n*) Wright and King, *Acta Cryst.*, 1954, **7**, 283. (*o*) Karle, *Acta Cryst.*, 1961, **14**, 497.

TABLE 2.

Intramolecular distances with $d(C \cdots O) < 3{\cdot}3$ Å.

Compound	$d(C \cdots O)$ (Å)	Groups	Atoms	Ref.
Dimethyl oxalate	2·70	$CH_3 \cdots O$(keto)	C_2, O_1	5
Indirubin	3·01	$CH \cdots O$(keto)	C_4', O	*p*
Muscarine iodide	2·87	$CH_3 \cdots O$(ring)	C_9, O_1	*q*
Angelic acid	2·8	$CH_3 \cdots O$(carboxyl)		*r*
9-Anthraldehyde (and many similar compounds)	3·06	$CH \cdots O$(aldehyde)	C(F), O	*s*
Caffeine	3·28	$CH_3 \cdots O$(keto)	C_{14}, O_{13}	*f*
	2·71, 2·66, 2·76	Adjacent CH_3 & O Subst. in rings		
Theophylline	2·71, 2·67, 2·71	Adjacent CH_3 & O Subst. in rings		*e*
1,3,7,9-Tetramethyluric acid	3·12	$CH_3 \cdots O$(keto)	C_{14}, O_{13}	1
	2·75, 2·65, 2·70 2·87 ,2·93	Adjacent CH_3 & O Subst. in ring		
Calcium thymidylate	2·90	Adjacent CH_3 & O Subst. in ring		*t*
Cytidine	3·24	$CH \cdots O$(hydroxyl)	C_4, O_5'	*u*
Acetylcholine bromide (ring form)	3·00	$CH_3 \cdots O$(ester)	C_5, O_2	*m*
Deoxyribonucleic acid	2·88	$CH \cdots O$(phosphate)	C_3', O_4	*v*

References: (*e, f, m*) See Table 1. (*p*) Pandraud, *Acta Cryst.*, 1961, **14**, 901. (*q*) Jellinek, *Acta Cryst.*, 1957, **10**, 277. (*r*) Porte and Robertson, *J.*, 1959, 825. (*s*) Trotter, *Acta Cryst.*, 1959, **12**, 922. (*t*) Trueblood, Horn, and Luzzati, *Acta Cryst.*, 1961, **14**, 965. (*u*) Furberg, *Acta Cryst.*, 1950, **3**, 325. (*v*) Langridge, Marvin, Seeds, Wilson, Hooper, and Wilkins, *J. Mol. Biol.*, 1960, **2**, 38.

Although the hydrogen bond is assumed to be linear or nearly so, the position of the hydrogen atom has rarely been accurately determined. It is generally agreed that the deviation from linearity (the angle between the direction of the hydrogen atom A–H, and the direction A · · · A′) is not greater than about 15°. Hamilton,[6] in a neutron-diffraction study of dimethylglyoxime, has however shown this angle to be as much as 24°. The angle O–H · · · N is 140° ± 3°, a value significantly different from 180°. He suggests that this may be due to " factors such as the tendency of the covalent bond angles to remain undistorted and steric repulsion between hydrogen atoms " and to the need for the hydrogen atom to be directed towards the lone pair orbital of the nitrogen atom. Some other data are summarised in Table 3. It seems that the deviation from the ideal linear arrangement may be as much as 24° (or possibly more).

TABLE 3.

Angles showing deviation from linearity in the hydrogen bond.

Compound	Type of bond	Angle	Ref.
Na sesquicarbonate	O–H···O	3·5°	*A*
α-Resorcinol	O–H···O	10°	*B*
Cuprous chloride dihydrate	O–H···Cl	15° 37′	*C*
Urea	N–H···O	16°, 13°	*D*
Dimethylglyoxime	N–H···O	24°	*E*

References: (*A*) Bacon and Curry, *Acta Cryst.*, 1956, **9**, 82. (*B*) Bacon and Curry, *Proc. Roy. Soc.*, 1956, **235***A*, 552. (*C*) Peterson and Levy, *J. Chem. Phys.*, 1957, **26**, 220. (*D*) Worsham, Levy, and Peterson, *Acta Cryst.*, 1957, **10**, 319. (*E*) Hamilton, *Acta Cryst.*, 1961, **14**, 95.

There is no accurate determination of the hydrogen atom positions in any of the compounds listed in Tables 1 and 2, but in some cases approximate co-ordinates are given and in others values for the parameters have been calculated here. From these, angles involving the hydrogen atoms were evaluated and they are listed in Table 4 [thymine[7] is included because of an error in the paper which states that d(C · · · O) = 3·04 Å; this corresponds to the hydrogen–oxygen separation]. Most of these angles do not appear in the original papers. Although there may be rather large errors arising from inaccuracies in the atomic positions, certain trends are evident. In particular, there is a striking similarity among like angles in each part of Table 4, and these will now be considered.

Methylidyne (CH) *Groups*.—In part 1(a) of Table 4, d(C · · · O) is about 3·22 and d(H · · · O) is 2·18 Å; the latter is less than 2·6 Å, the sum of the van der Waals radii for an oxygen and a hydrogen atom. Although d(H · · · O) is longer than in an O–H · · · O hydrogen bond, it follows the expected trend with decreasing electronegativity of the donor atom. The increase in length is a consequence of increased separation of C · · · O compared with the O · · · O, since d(O–H) and d(C–H) are approximately the same. The angles C–H · · · O and H–C · · · O are well within the accepted limits for a hydrogen bond. Thus theophylline, caffeine, uracil, and, probably, thymine [though d(C · · · O) is somewhat " long " in the last compound] satisfy the accepted conditions for hydrogen-bond formation. The hydrogen-atom positions in di-(*p*-chlorophenyl) sulphone, furoic acid, phenazine *N*-oxide, nicotinamide, and *NN*′-diglycyl-L-cystine dihydrate are not known and have not been calculated, but by analogy it is reasonable to assume that C–H · · · O hydrogen bonding is present. In part 1(b), the set of angles and distances for the molecule directly below that containing the acceptor atom of the compounds in part 1(a) are included for comparison; these are not hydrogen bonds.

Methylene (CH_2) *and Methyl* (CH_3) *Groups*.—There is apparently no tendency for these groups to form more than one " short " contact. This is in contrast to the NH_3^+ group which can form three hydrogen bonds. The distances and angles in these two parts (2 and

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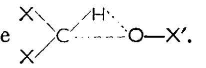
[6] Hamilton, *Acta Cryst.*, 1961, **14**, 95.

[7] Gerdil, *Acta Cryst.*, 1961, **14**, 333.

TABLE 4.

Angles in the structure



X = C unless otherwise stated in parentheses after the angle.

Compound and H atom	$d(H \cdots O)$ (Å)	$d(C \cdots O)$ (Å)	∠C–H···O	∠H–C···O	∠H···O···C	∠X–C–H	∠H···O–X′	∠X–C···O	∠C···O–X′	Deviation* (Å)
					CH···O *distances*					
Part 1(*a*).										
Theophylline (H_1)	2·25	3·22	173·3°	4·7°	2·0°	120·9°(N), 124·8°(N)	165·9°	125·3°(N), 120·3°(N)	164·7°	0·37
Caffeine (H_1)	2·07	3·18	166·7	8·6	4·7	122·5(N), 134·8(N)	164·9	107·1(N), 140·0(N)	168·5	0·36
Thymine (H_3)	2·64	3·46	158·4	16·3	5·3	110·7(N), 127·5	150·1	97·8(N), 139·4	147·1	0·40
Uracil (H_9)	2·22	3·28	159·2	14·0	6·9	120·9, 122·6	121·3	108·9, 133·6	115·7	0·29
(H_{10})	2·17	3·19	153·5	17·7	8·8	117·5, 120·8(N)	148·5	129·2, 108·0(N)	145·9	0·76
Part 1(*b*).										
Theophylline (H_1)	3·39	3·33	78·2	85·1	16·6	120·9(N), 124·8(N)	85·3	92·0(N), 94·4(N)	101·2	
Caffeine (H_1)	3·07	3·30	91·2	68·6	20·2	112·5(N), 134·8(N)	85·7	98·9(N), 102·5(N)	105·7	
Thymine (H_3)	3·04	3·37	104·7	60·9	14·4	110·7(N), 127·3	111·4	85·9(N), 119·5	120·9	
Uracil (H_{10})	2·79	3·18	100·9	59·5	19·7	117·5, 120·8(N)	110·3	115·2, 92·4(N)	123·5	
					CH_2···O *distances*					
Part 2(*a*).										
Ethylene carbonate ...	2·73	3·11	102·6	59·4	18·3	107·7(O), 40·9	163·1	76·8, 166·0(O)	116·9	
Tetramethylene tetranitramine (H_2).........	2·41	3·01	114·5	46·8	18·7	106·9(N), 123·9(N)	92·4(N)	78·2(N), 169·4(N)	110·6(N)	
Hydroxy-L-proline (H_6)	2·25	3·22	147·0	22·4	10·6	114·5, 106·7(N)	135·8	95·9, 126·2(N)	145·1	
NN′-Diglycyl-L-cystine dihydrate (H_5).........	2·42	2·92	115·6	48·4	16·0	107·0, 114·6(N)	142·7	106·9, 143·8(N)	157·1	
Part 2(*b*).										
Ethylene carbonate ...	3·01	3·11	86·3	74·9	8·8	107·5(O), 40·0	172·8	76·8, 166·0(O)	116·9	
NN′-Diglycyl-L-cystine dihydrate (H_6)	2·74	2·92	92·3	69·6	18·1	115·8, 98·4(N)	158·4	106·9, 143·8(N)	157·1	
					CH_3···O *distances*					
Part 3.										
Theophylline (H_4)	2·77	3·24	114·4	51·0	15·0	152·6(N)	128·2(O) 73·0(O) 111·9(N)	156·3(N)	139·6(O) 78·7(O) 97·4(N)	
Caffeine (H_2)	2·76	3·24	109·1	53·9	17·1	121·5(N)	137·5	171·2(N)	149·1	0·08
1,3,7,9-Tetramethyluric acid (H_1)	2·26	3·00	120·8	40·0	19·0	113·0(N)	164·0	148·0(N)	154·0	0·09

The examples in Parts 1(*b*) and 2(*b*) are not hydrogen bonds. In 1(*b*) the angles and distances for the molecule directly below that containing the acceptor atom in 1(*a*) are given. In 2(*b*), values for the second hydrogen atom of the methylene group are included for comparison.

* This is the distance of H from the plane of the molecule OX′.

3 of Table 4) are very similar, but they differ considerably from those in part 1. In some cases, *d*(C · · · O) is much shorter, *e.g.*, 2·92 Å in *NN′*-diglycyl-L-cystine dihydrate, 3·00 Å in 1,3,7,9-tetramethyluric acid. Sometimes *d*(H · · · O) is longer than 2·6 Å. The hydrogen atoms are no longer directed towards the acceptor atoms, as angles H–C · · · O and C–H · · · O range from 22° to 59° and from 102° to 147°, respectively. On the other hand, steric hindrance from the other hydrogen atoms of the methylene or methyl groups, and the arrangement of this group which is forming only one " short " contact, may prevent this one hydrogen atom from occupying a more or less linear position with respect to the carbon and oxygen atoms. de Santis *et al.*[8] suggested that dipole–dipole interaction is responsible for the pairing of the molecules in parallel planes in caffeine, theophylline, and 1,3,7,9-tetramethyluric acid. Until the limits in the angles representing the departure from linearity of the hydrogen atom are known, it cannot be definitely stated whether these " short " C · · · O interactions, where the carbon atom belongs to a methylene or methyl group, are true hydrogen bonds. Nevertheless, it is felt that these contacts and those in Table 1 correspond to hydrogen bonds typical of these groups. Part 2(b) of Table 4 contains the angles for the second hydrogen atom of the CH_2 group; these contacts are probably not hydrogen bonds.

No angles are available for the intramolecular contacts in Table 2, which also contains values for the separation between adjacent methyl and oxygen substituents of rings. As in many other intramolecular hydrogen bonds, the angle C–H · · · O is not expected to be 180°, and the hydrogen atom is probably directed towards the lone-pair orbital of the acceptor atom. The intramolecular distances are considerably shorter than the intermolecular ones.

There are many compounds with C · · · O distances in the range 3·3—3·4 Å, *e.g.*, 3·38 Å in 1,3,7,9-tetramethyluric acid. This represents a similar though weaker contact. There are also many examples of " short " C · · · O contacts where there is no hydrogen atom attached to the carbon, *e.g.*, 2·83 Å in alloxantin,[9] and 2·82 Å in chloranil.[10] These must be electrostatic interactions.

It is tempting to speculate as to whether the C–H · · · O hydrogen bond plays as important a part in the structure of biological molecules as the other kinds of hydrogen bonds do, especially since many of the heterocyclic examples contain a purine or pyrimidine skeleton. Particularly of interest is the structure of deoxyribonucleic acid which has had to be constructed with " short " C · · · O contacts. Also of interest is the ability of 1,3,7,9-tetramethyluric acid to form crystalline complexes with organic solvents; these could well be linked together by hydrogen bonds of this type.

Brief details of this paper have been published in *Nature*.[11]

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