Studies on the Hydrogen Bonding of Organic Chemicals

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Summary

Hydrogen bonding is a very important topic in pharmacology, used in docking studies and Quantitative Structure-Activity Relationships (QSAR). While one hydrogen bond is weak, a set of hydrogen bonds provides the major force that binds a ligand and its docking site. This thesis is based on my own experiments and updates some preliminary results from my supervisor's former student Rutian Jin.

Firstly the literature is reviewed for inter- and intra-molecular hydrogen bonding and the forces between the bonded atoms. An empirical rule proposed by M. Etter is presented: intramolecular hydrogen bonds forming six-membered rings are preferred. Finally the technique used in determination of actual structure in crystals is described.

Next are the experimental results from my entire study period. Crystal structure determinations are reported for three molecules where intramolecular hydrogen bonds could create six-membered rings. Surveys of the Cambridge Structural Database (CSD) are presented. The previous general survey of the frequency of occurrence and the geometrical effects of hydrogen bonded six-membered rings has been updated. Hydrogen bonding in analogues of the new structures is analysed. The numbers of independent hydrogen bonds formed by four pharmaceutically acceptable ions are tabulated.

Finally come some conclusions about my findings. As predicted, in 2-hydroxy-4,6-dimethoxyacetophenone and most analogues in the CSD strong intramolecular O-H---O hydrogen bonds create six-membered rings, with some correlation between strength of this hydrogen bond and electronic effects of ring substituents on the OH and C=O groups. Neither *N*-hydroxymethyl- nor *N*-3-hydroxypropylphthalimide form 6-membered rings by means of intramolecular hydrogen bonds. Even with three hydrogen bond acceptor atoms instead of one, the nitrate ion tends to accept no more hydrogen bonds than chloride. The ammonium ion commonly donates one hydrogen bond per hydrogen atom. With both donor and acceptor functionality the dihydrogen phosphate ion forms a variable number of independent hydrogen bonds.

Keywords: crystal structures, hydrogen bonded ring occurrence, hydrogen bonded ring geometry, pharmaceutically important counter ions

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Chapter 1. Introduction

1.1 Chemical bonding

1.1.1 General concepts

A **chemical bond** is the physical process responsible for the attractive interactions between atoms in molecules.¹



Lewis-type Chemical bond

Fig. 1 Lewis-type chemical bond

In general, strong chemical bonding is associated with the sharing or transfer of electrons between the participating atoms. Molecules, crystals, and diatomic gases—indeed most of the physical environment around us—are held together by chemical bonds, which dictate the structure of matter. How can chemical bonding be divided into different kinds of bonds? The common types of strong bonding are:

a. ionic bonding

An ionic bond is an electrical attraction between two oppositely charged atoms or groups of atoms. Normally, atoms are neutral and have no charge. However, in order to gain stability they will sacrifice their neutrality by either losing one or more of their outermost electrons thus becoming a positive ion (cation) or gaining one or more electrons thus becoming a negative ion (anion). Elements that are described as "metallic" tend to lose electrons and elements that are described as "non-metallic" tend to gain electrons. Once this has happened then the resulting charged atoms will attract each other. That electrical attraction between two oppositely charged ions is referred to as an ionic bond. Most salts are ionic. Any metal will in principle combine chemically with any non-metal to form ionic bonds that hold the molecule together.

In an ionic bond as strictly defined, the bonding electrons have transferred to the non-metal. With total or partial transfer of electrons the bond is said to be polar. Polar bonds generate a dipole moment. A dipole moment quantifies the unequal distribution of the bonding electrons between the two bonded atoms². In the case of an ionic bond that unequal distribution is extreme. The dipole moment that is generated is quite large compared to polar forms of the covalent bond

$$Li + F \rightarrow Li^+F^-$$

 $3Na + P \rightarrow (Na^+)_3P^{3-}$

b. metallic bonding

In a metallic bond, bonding electrons are delocalized over a lattice of atoms. By contrast, in ionic compounds, the locations of the binding electrons and their charges are static.³

c. covalent bond

Covalent bonding is a form of chemical bonding that is characterized by the sharing of pairs of electrons between atoms, or between atoms and other covalent bonds. When atoms share electrons, they are attracted to each other; but if they come too close, their electron clouds repel each other. This attraction-to-repulsion stability is known as covalent bonding.

Covalent bonding includes many kinds of interactions, including σ-bonding, π -bonding, metal-metal bonding, agostic interactions, and three-center two-electron bonds. The term covalent bond dates from 1939. The prefix co- means jointly, associated in action, partnered to a lesser degree, etc.; thus a "co-valent bond", essentially, means that the atoms share "valence", such as is discussed in valence bond theory. In the molecule H_2 , the hydrogen atoms share the two electrons via covalent bonding. Covalency is greatest between atoms of similar electronegativities. Thus, covalent bonding does not necessarily require the two atoms be of the same elements, only that they be of comparable electronegativity. If the bonded atoms differ in electronegativity, their covalent bond becomes polar, and the more electronegative atom takes on the negative end of the dipole. Because covalent bonding entails sharing of electrons, it is necessarily delocalized. Furthermore, in contrast to electrostatic interactions ("ionic bonds"), the strength of a covalent bond depends on the angular relation between atoms in polyatomic molecules⁴ and the number of bonds (shared electron pairs) formed between a pair of atoms which is called bond order.

1.1.2 Hydrogen bond

A hydrogen bond is a special type of attractive interaction that exists between certain chemical groups of opposite polarity. The typical hydrogen bond is much weaker than both the ionic bond and the covalent bond, although stronger than the van der Waals forces which operate between any two atoms loosely in contact. Within macromolecules such as proteins and nucleic acids, hydrogen bonding can exist between two parts of the same molecule and figures as an important constraint on such molecules' overall shape.⁵

As the name "hydrogen bond" implies, one part of the bond involves a hydrogen atom. The hydrogen atom must be attached to a relatively electronegative element. The molecule or moiety H-X including the hydrogen atom bonded to an electronegative atom is called the hydrogen-bond donor.⁶ The most electronegative elements, such as oxygen, nitrogen, and fluorine, are most commonly involved as part of hydrogen bond donors, although carbon can also participate. The electronegative atom attracts the electron cloud from around the hydrogen nucleus and, by decentralizing the cloud, leaves the H atom with a positive partial charge. Because of the small size of hydrogen relative to other atoms and molecules, the resulting charge, though only partial, nevertheless represents a large charge density. A hydrogen bond results when this strong positive charge density attracts a lone pair of electrons on another heteroatom Y, which becomes the hydrogen-bond acceptor.⁷ Concepts needed in order to make sense of X-H---Y will be discussed later.

1.1.2.1 Donor-acceptor discussion

The hydrogen bond is often described as an electrostatic dipole-dipole interaction. However, it also has some features of covalent bonding: it is directional, relatively strong, and it produces inter-atomic distances shorter than the sum of van der Waals radii.



Fig. 2 Acceptor-donor interaction distance

Furthermore, it usually involves a limited number of interaction partners, which can be interpreted as a kind of valence. These covalent features are more significant when acceptors bind hydrogen from more electronegative donors.



Fig. 3 Acceptors bind hydrogen from more electronegative donors

The partially covalent nature of a hydrogen bond raises the questions: "To which molecule or atom does the hydrogen nucleus belong?" and "Which should be labeled 'donor' and which 'acceptor'?" Usually, this is easy to determine simply based on inter-atomic distances in the X-H...Y system: X-H distance is typically ~1.1 Å, whereas H...Y distance is ~ 1.6 to 2.0 Å.⁸

1.1.3 Geometry and energy of hydrogen bonds

Liquids that display hydrogen bonding are called associated liquids.⁹ An important aspect of weak hydrogen bond formation is that the different molecular aggregates which do form can be easily and reversibly transformed. The weaker the hydrogen bond, the shorter the lifetime of the complex it forms.

H-bonding gives rise to a specific interaction between atoms or functional groups in which: the strength is higher than that of dispersion forces alone, it is directed along a hydrogen atom, and it demonstrates some characteristic angular dependencies. Existence of the H-bond can be verified if such properties have been substantiated.⁹ Hydrogen bonds can vary in strength from very weak (1-2 kJ mol⁻¹) to extremely strong (40 kJ mol⁻¹), intermediate between the van der Waals forces and the chemical bonding. These energy values can be compared with typical values¹⁰ for covalent bonds, which include:

Table 1. Bond length (pm) and bond energy (kJ/mol) of typical covalent bonds

Bond length (pm) and bond energy (kJ/mol) Bond Length Energy Bond Length Energy H-H 74 436 H-C 109 413 C-C 154 348 H-N 101 391 H-O 96 366

The length of the H...:N or H...:O contact is related to the strength of the hydrogen

bond. The values stored in the Cambridge Structural Database (CSD) of van der Waals radii for atoms involved in simple contacts between molecules are H 1.2, N 1.55, O 1.52 Å.¹¹ As the weak attraction due to dispersion forces gains additional strength through hydrogen bonding, the H atom moves closer to the N or O acceptor atom. Thus the upper limit on the hydrogen bonded H...N or H...O distance can be taken as 2.75 or 2.72 Å respectively. The lower limit for the strongest hydrogen bonds is about half this distance. Histograms for hydrogen bond distances taken from the CSD are displayed below:



Fig. 4 Histograms for hydrogen bond distances

The X-H...Y angle also affects the strength of a hydrogen bond. At an angle of 180° repulsion between the partial negative charges on X and Y is a minimum. As bending of the hydrogen bond reduces this angle, the closer approach of X and Y increases the effectiveness of this repulsion in offsetting the attraction between H and Y. Figure 5 displays some representative hydrogen bonded systems and shows some situations where hydrogen bonding is important.



Fig. 5 Donor and acceptor groups; examples where hydrogen bonding is important¹².

1.2 Inter-and intra-molecular hydrogen bonding

1.2.1 Inter-molecular hydrogen bonding

In the case of intermolecular association one distinguishes between self-association and mixed association if the complex molecules are of the same type (water) or different type (adenine with thymine) respectively.

A perfect example of intermolecular hydrogen bonding is the association of water molecules: H₂O. Water has one oxygen and two hydrogen atoms; the hydrogen bond can be formed between two water molecules.



Fig. 6 The association of water molecules: H₂O, as an example of intermolecular

hydrogen bonding

Hydrogen bonds that exist between H₂O molecules arise principally from the electrical attractions between a positively charged hydrogen atom--which readily gives up its electron to oxygen in water becoming a donor—and a negatively charged oxygen atom--which receives these electrons as an acceptor--in a neighboring molecule.¹³ These "electrostatic interactions" can be explained perfectly by classical physics specifically by Coulomb's law, which describes the attraction and repulsion

between charged particles separated from each other by a distance.

The chemicals in which hydrogen bonding exists have different physical and chemical behavior from other similar chemicals, like the melting and boiling points, due to the difference in inter-molecular forces. Of the similar compounds shown below, the left one which forms inter-molecular hydrogen bonding increases the inter-molecular force. The right one indicates that the existence of an intra-molecular hydrogen bond is reducing the amount of inter-molecular hydrogen bonding in the crystal, along with the inter-molecular force; i.e. the melting point is much lower.



Fig. 7 Melting points in °C for isomeric 4- and 2-nitrophenols

Table 2. Chemicals with different inter-molecular forces show different physical

properties

Inter-molecular hydrogen bonding affects the boiling point:

Commound	Molecular	Hydrogen	Boiling	Difference/°C
Compound	weight	bonding	point/°C	
СН3ОН	32	yes	65	153.6
CH ₃ CH ₃	30	no	-88.6	100.0
нсоон	46	yes	101	124
CH ₃ OCH ₃	46	no	-23	121
CH ₃ CH ₂ OH	46	yes	78.5	101.5
CH ₃ CHO	44	yes	21	63
CH ₃ CH ₂ CH ₃	44	no	-42	
C ₆ H ₅ OH	94	yes	181	70
C ₆ H ₅ CH ₃	92	no	111	

Inter-molecular hydrogen bonding affects the melting point:

Compound	Molecular	Hydrogen	Melting	Difference/%C
Compound	weight	bonding	point/°C	Difference/ C
CH ₃ OH	32	Yes	-97.5	85.8
CH ₃ CH ₃	30	No	-183.8	00.0

C ₆ H ₅ OH	94	Yes	41	136
C ₆ H ₅ CH ₃	92	No	-95	150
CH ₃ CHO	44	Yes	-121	68 7
CH ₃ CH ₂ CH ₃	44	No	-189.7	00.7

Hydrogen bonding effects on different compounds which are composed of two H atoms with an element from the same group of the periodic table:

Compound	Molecular weight	Melting point/°C	Boiling point/°C
H ₂ O	18	0	100
H ₂ S	34	-85	-60
H ₂ Se	81	-66	-41

Unlike H₂S and H₂Se, at ordinary temperatures hydrogen bonding keeps water in the liquid state essential for life. For the physical point of view each intermolecular H-bond forms a larger molecule, a complex, which possesses its own force constants, chemical reactions etc., because of its characteristic structure in its nuclear configuration as well as in its electronic structure. Important examples of this affect the proteins and nucleic acids and therefore life processes. The "unzipping" of DNA is a breaking of hydrogen bonds which help hold the two strands of the double helix together.



DNA: the Information Storage Unit of life

http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/D/DoubleHelix.html

Fig. 8 Intermolecular H-bond forms the DNA double helix

1.2.2 Intra-molecular hydrogen bonding

The H-bonds, which are considered as intra-molecular ones, e.g. in 2-nitrophenol or as inter-molecular ones, .e.g. in carboxylic acid dimers, are decided by whether if the atoms X and Y belong to the same molecule or not. For making this distinction the term "molecule" has to be taken in its chemical sense.



Fig. 9 Structure of 2-nitrophenol

The O—H as a donor connects with the O atom within the same molecule, and limited by the rest of the atoms in the molecule, the bond angle O—H····O can not be in a

straight line (normally 143°)¹⁴.

1.2.3 Comparison of hydrogen bonding in the solid state and in solution

The hydrogen bonding indicates different behaviour in solid state and in solutions. Hydrogen bonding in the solid state usually involves well defined infinite chains, sheets and 3D networks, some of which are shown in Figure 10. In dilute solutions, dimers are favourable since longer-range order is lost. In the concentrated solutions and melts, chains are more likely to be present. These facts complicate the definition of hydrogen bonding, and the multiple intertwined hydrogen bonding patterns in a single crystal increase the difficulty in determining preference of hydrogen bonding from crystal structures¹⁵. We know the intra-molecular bonding is not as varied as the inter-molecular bonding, which can be determined in many ways, and we still need to have a conclusive theory to find the existence and explain the behaviour.





Fig. 10 a. Hydrogen bonding in C(8) chains formed by 2-bromo-6-chloro-4-nitroaniline;

b. Diagram of beta-pleated sheet with H-bonding between protein strands;

c. A 3D network with hydrogen bonds of water molecules

Property	Intra-molecular H bond	Inter-molecular H bond	
1.Structural form	Most common in <i>ortho, cis,</i> <i>peri</i> , diequatorial, equatorial-axial positions	Most common in <i>meta</i> , <i>para</i> , <i>trans</i> -diaxial positions	
2.Molecular weight	Normal	Increased	
3.Molar volume	Lower	Lower	
4. Vapor pressure	Normal	Decreased	
5.Conductivity			
Thermal	Normal	Higher	
Acoustic	Normal	Higher	
Electrical	Normal	Can be high if H bond network forms	
6.Solvent power	Normal	Higher if H bonds to solute	
7.Melting point	Normal	Higher	
Boiling point	Normal	Higher	
8. Vibration spectra			
Location: stretch	Shifted down	Shifted down	

Table 3. Comparison of inter-and intra-molecular bonding

Location: bend	Shifted up	Shifted up	
Concentration	None	Present	
dependence			
Frequency shift	Determined by functional groups and	Determined by the functional	
	size of ring formed	groups	
Effect of phase change	Little	Much	
Correlations			
Intensity of peak	Increased	Greatly increased	
Half width of peak	Increased	Greatly increased	
9.Dielectric properties			
Solids	Normal	Higher	
Liquids	Variable according to shape of molecule	Variable according to the shape	
Dipole moment	Lower than calc. from structure	Higher	
Conc. dependence of	None	Increase with conc.	
dipole moment			
10.Reaction	Often determined by intra-molecular	Often determined by	
mechanism	H bond	inter-molecular H bond	
Reaction rate	Can make faster or slower	Can make faster or slower	
11.Linearity of bond	Usually bent	Usually straight	
12.NMR chemical	To lower field	To lower field	
shift Direction	Charles and the second second		
Concentration	Small	Large	
dependence ¹⁴			
13.Optical properties	Can be large if spiro rings formed	Usually none	
Rotation	Shifted	Shifted	
Electronic absorption Phototropy ¹⁵	Often exhibited	Seldom exhibited	
14. Surface tension	Lower	Higher	

The intra-molecular hydrogen bonding seems very obvious in some compounds: just as benzoic acid is expected to form cyclic dimers, 2-nitrophenol has an intra-molecular hydrogen bond. Just like in the definition of inter-molecular hydrogen bonding, the acidic hydrogen connects with an electronegative atom, as shown in Fig 11. By using the spectroscopic and crystallographic techniques, we confirm the finding of the intra-molecular hydrogen bonding in this molecule.



Fig. 11 Structure of 2-fluorophenol

For example, in a chemical like 2-fluorophenol (Fig. 11), how can we verify if intra-molecular hydrogen bonding exists? Experimentally, we can examine this chemical by using IR spectroscopy. The –OH functional group appears as a broad absorption peak at 3300 cm⁻¹, the inter-molecular hydrogen bonding absorption, and a small and sharp peak at 3600 cm⁻¹. From measurements on the solution at different concentrations, we can see that the small peak does not behave like the broad peak, which changes as the concentration of the solution varies. The absorption of the broad peak declined as the concentration decreased, and showed opposite signs when the concentration increased. That proves that the small peak is not inter-molecular; instead it is intra-molecular, existing between the F atom and the H atom, the acceptor and the donor. A goal in the study of hydrogen bonding is to predict the existence of the intra-molecular hydrogen bonds instead of studying them one by one.

1.2.4 Intra-molecular bonding rules ¹⁶

The empirical hydrogen bond rules¹⁶ set out below have been established by careful comparison of model systems. Subsequent experience has shown most of them to be probable rather than certain.

A. General Rules

1. All good proton donors and acceptors are used in hydrogen bonding.

2. Six-member-ring intra-molecular hydrogen bonds form in preference to inter-molecular hydrogen bonds.

3. The best proton donors and acceptors remaining after intra-molecular hydrogen bond formation create inter-molecular hydrogen bonds to one another.

B. Additional rules were set out for specific classes of functional groups, including primary nitroanilines, diarylureas, and co-crystals of carboxylic acids with 2-aminopyrimidines.

To apply the first general rule, "good proton donors" and "good proton acceptors" have to be defined. Experience shows that proton donors such as those in carboxylic acids, amides, ureas, anilines, imides, and phenols are nearly always used in hydrogen bonding in a crystal structure. Less acidic protons such as those in acetylenes, aldehydes, or activated aromatic and aliphatic compounds may be used in hydrogen bonding when there are extra proton acceptors available after all the more acidic protons have found an acceptor. Proton acceptors are typically acid and amide carbonyl groups, sulfoxides, phosphoryls, nitroxides, and amine nitrogens. Solid-state acceptor and donor properties of molecules can be ranked by creating situations where multiple donors compete for the same acceptor or multiple acceptors for the same donor.

1.2.5 Good examples

When an intra-molecular hydrogen bond exists, it is usually possible to imagine an inter-molecular alternative¹⁷. In one sense this is fair competition, since the donor and acceptor groups do not change. However, if the intra-molecular hydrogen bond closes a ring with 6 members, rule A.2 above states that this will be the preferred alternative. This rule was tested for two classes of molecules of special interest at Aston University.

1.2.5.1 Survey of special types of intra-molecular hydrogen bonds in the CSD

In previous work at Aston University by Rutian Jin intra-molecular hydrogen bonding (HB) was found to produce 6-membered rings in an oxysterol "Sterol1" (left) and a 1-alkoxy-2-triazinylbenzene derivative "WZA002" (right).



Searches⁶ for similarly hydrogen bonded structures in the Cambridge Structural Database (CSD) were performed with ConQuest 1.8 on the November 2005 release of the CSD for fragments I and II, to which Sterol1 and WZA002 respectively conform. The filters used by Bilton et al¹⁸ in an earlier study of structures most likely to form intra-molecular hydrogen bonds were applied: non-polymeric organic structures,

error-free coordinate sets, R < 10%.



Fig. 12 Structures of hydrogen bonded parts of "Sterol1" and "WZA002"

Histograms of H...O distances found in the CSD for motifs I and II are given below. Intra-molecular hydrogen bonding is not automatically imposed by the structure of these fragments: rotation about the C-O bond in I and either the C-N bond or the adjacent C-C bond in II can destroy this hydrogen bond if an alternative is preferable.



Fig. 13 H...O distances in the CSD for motif I

From the motif I:

О—Н	0C
70 hits, within the allowed H^1 O^6	55 hits; possible divisions are the
range 1.2 to 2.72Å	structures shown below
	O—alkyl (O—CH ₂)
	0aryl (⁻ 0-)
	Oester -C=O X-H-O-C

Table 4. The CSD research for O-H and O---C bonds

The mean and the standard errors have been worked out next to the histogram, but they are of limited value because there are two major concentrations in the distribution. One appears within the range of H----O hydrogen bonding and the other could be caused by the rotation of involved bonds which distanced the H atom and O atom. The same comparison is workable on the **motif II** as well.



Fig. 14 H...O distances in the CSD for motif II

The **motif IIa** can also be abstracted from the structure of WZA002 by removing the requirement for a central benzene ring. It includes the heterocyclic ring containing N atom(s), where QA = C or N. The bond type is "any" except in single NH and CO bonds.



Fig. 15 The heterocyclic ring containing N atoms

A search of the CSD for this fragment with the O^{...}H distance unrestricted, restricted to a range from 1.0Å to the sum of van der Waals radii 2.7Å and restricted to1.0 to 2.35Å is summarised below.

Potentially hydrogen bonded structures of the type shown in Figure 15

277 independent hits, of which

101 unrestricted (24 hits 1.0-2.7Å, 18 hits 1.0-2.35Å) with N⁺---H 176 unrestricted (36 hits 1.0-2.7Å, 24 hits 1.0-2.35Å) with N---H

One would expect a positively charged N to take more electron density away from its bonded H than a neutral N would, and therefore N+_H to be a stronger hydrogen bond donor. However, as shown by data above, N+_H occurs less frequently, but this is probably because fewer fragments have been studied. The numbers of hits N+_H and N_H are obviously influenced by how many structures of each type have been studied. The % of occurrences of the fragment that yield short O...H contacts may give a better indication of hydrogen bonding ability, and this is slightly greater for N+_H as donor (24% within van der Waals contact, 18% at 2.35Å or below) than for N_H (20% and 14% respectively).

1.2.6 Descriptors of hydrogen bond geometry

For this thesis, earlier work by my supervisor's previous student Rutian Jin has been updated and extended for intra-molecular hydrogen bonds (HB) that create a 6-membered ring, reported in succession for fragments I and II defined on p. 30. The strongest HB are expected to have a linear X-H...O, but this would severely strain a 6-membered ring. Figures 16 and 17 (below) show this angle approaching 160° for the shortest (strongest) HB. Figures 18 and 19 show decreasing deviation from planarity in the 6-ring as the HB gets shorter. Figures 20 and 21 indicate that the torsion angle 2-1-6-5 about the HB is near zero for the strongest HB and increases in magnitude with either sign as the hydrogen bond weakens. The effect is similar in Figure 23, where the C3-C4 bond opposite the HB can rotate; but very little effect is seen in Figure 22, where this bond is incorporated in a cyclohexane ring.



Fig. 16 Scattergram of O-H...O angles in motif I versus the H...O distance



Fig. 17 Scattergram of N-H...O angles in motif II versus the H...O distance





in motif I versus the H...O distance


Fig. 19 Scattergram of average deviation of atoms in the 6-ring from their mean plane

TORI VIS DHO File=cq_lemp22 Test=52 Tot.Obs.=161 TORI 100.0 00 Obs.=161 80.0 Supp.=0 000 00 0 (B) 0 0 Min=1.631 60.0 0 0 0 Max.=2.717 8 000 0 Pange=1.086 Mean=2.041 Mean SE=0.021 Sample SD=0.262 0 40.0 0 RO 8 80 20.0 0 h Y-0005 Min.=-82.437 Max.=84.625 Range=167.062 Mean=-3.783 0.0 0.0 0 00 0 0 0 C -20.0 0 0 0000 Mean SE=0.001 Sample SD=0.012 80.00 d 0 0 00 200 R bar=0.804 -40.0 00 ö 00 00 0 8 00 0 -60.0 10 0 0 00 0 -80.0 0 1.8 2.0 22 2.4 2.6 2.8 DHO

in motif II versus the H...O distance



distance



Fig. 21 Scattergram of torsion angle TOR1 about the HB in motif II versus the H...O



distance

Fig. 22 Scattergram of torsion angle TOR4 across from the HB in motif I versus the



H...O distance



H...O distance

Fig. 16,18,20,22 Scattergrams that describe O-H...O angles, average deviation of atoms in the 6-membered ring from their mean plane, torsion angle TOR1(O6-H1-O2-C3, see Fig.12) about the HB and torsion angle TOR4(C3-C4-C5-O6, see Fig.12) across from the HB, versus the H...O distance in motif I.

Fig. 17,19,21,23 Scattergrams that describe N-H...O angles, average deviation of atoms in the 6-membered ring from their mean plane, torsion angle

TOR1(06-H1-N2-C3, see Fig.12) about the HB and torsion angle TOR4(C3-C4-C5-O6, also see Fig.12) across from the HB, versus the H...O distance in motif II.

1.2.7 C-H---O bonds

C-H groups can sometimes act as hydrogen bond donors, with greater likelihood if the carbon atom is bonded to an electron-withdrawing element or if it has sp hybrid orbitals¹⁹, which hold electrons somewhat more strongly than sp² or sp³ orbitals. The Infrared Absorption Spectrum²⁰ can indicate such C–H----O hydrogen bonds.

The comparison of vibrational spectra (determined e.g. by IR or Raman spectroscopy) between a 'free' R–X–H group and a R–X–H----Y hydrogen bond indicates that, the hydrogen bond formation may have several manifestations: (i) the X–H stretching frequency vs is reduced, (ii) the band-width of vs increases, (iii) the intensity of vs increases, (iv) the frequency of the R–X–H bending vibration vb increases.²¹ The spectra for free X–H can be obtained from dilute solution in non-polar solvents like CCl₄. For the system C–H----O, these effects can be clearly observed, and are suitable for probing hydrogen bonding (taking for granted that the relevant bands can be resolved and assigned, which may be a major problem). A particularly clear example²² demonstrated large shifts in wave numbers for a C=C–H⁻⁻⁻O interaction of around 130 cm⁻¹ for vs, 98 cm⁻¹ for the in-plane bending, and 114 cm⁻¹ for out-of-plane bending modes. However, unfortunately, there are also cases where not

all of the manifestations (i to iv) are present. An example is hydrogen-bonded chloroform, for which the -s band broadens and intensifies, whereas it does not shift²³. This situation was characterized²⁴ as follows: 'A spectral shift of appreciable magnitude constitutes definite evidence for hydrogen bonding, but the lack of such a shift does not necessarily indicate the absence of hydrogen bonding' (it is noted that the same is the true for 'normal' O-H---O hydrogen bonds, as discussed²⁵). This circumstance complicates the comparison between different hydrogen-bonded systems, and attempts to correlate spectral shifts with hydrogen bond enthalpies or pKa values gave poor correlations²³. An example for an affirmative correlation between spectral shifts and hydrogen bond geometry²⁴ involves us values for C-H---O contacts in crystalline terminal alkynes. These represent a good model because the alkynyl Us band is well separated from all other C-H bands. The obtained correlation plot, Fig. 24, shows a smooth decrease of Us with decreasing C---O distance. A clear example of C-H---O hydrogen bonding occurring alongside O-H---O in one of the new structures to be reported in detail later in this thesis is shown in Fig. 25.



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Fig. 24 Spectroscopic and structural indicators of C-H---O hydrogen bonding in crystals: correlation of the C-H stretching frequency with the C---O distance in some C-H---O bonded terminal alkynes. Free C=C-H groups have typical C-H stretch values slightly above 3300cm⁻¹.



Fig. 25 Diagram for C-H---O bond

Hydrogen bonds in general comprise different types of interactions, but in the medium and long-distance region, the electrostatic component is the dominant one.²⁶

1.2.8 Case study on the Cambridge Structural Database

Haynes, Jones and Motherwell²⁷ identified the 10 pharmaceutically acceptable anions and cations²⁸ that occurred most frequently in the Cambridge Structural Database. Their analysis considered frequency of occurrence as an aid to pharmaceutical formulation, but it did not report any information about the interactions of such ions. As part of the research covered in this thesis, their work has been extended in a pilot study by surveying the number of hydrogen bonds to/from representative ions.

1.3 X-ray crystallography

1.3.1 Application of X-rays in chemistry

To determine the three-dimensional structure corresponding to the molecular formula, the technology called crystallography has been applied, which grew up as a branch of mineralogy, and was involved in description and classification of naturally occurring crystals. The aim now is to obtain a picture of the nature of the crystal at the atomic level, to indicate the relative atomic positions and precisely calculate the molecular geometry, i.e. all bond lengths and the position of non-connected atoms.

X-rays are a form of electromagnetic radiation with a wavelength in the range of 10 to 0.01 nanometers, corresponding to frequencies in the range 30 to 30 000 PHz (10¹⁵ hertz). X-rays are primarily used for diagnostic radiography and crystallography. X-rays are a form of ionizing radiation and as such can be dangerous. In many languages it is called Röntgen radiation after the investigator of the radiation, (Wilhelm Röntgen.)

When light passes through a narrow slit or a very fine pinhole, and we can see that light exists in the region that we thought should be shadow, this phenomenon is named diffraction.²⁹ Because light is a wave as well as the X-ray, it has the capability to "bend around corners". The intensity of light behind the barrier is not zero in the shadow region.

It is well known that if an object can be seen in the microscope, the size of the object has to be at least half of the wavelength of the passing light. Since visible light has much longer wavelength than the size of an atom, an ordinary light microscope is useless for viewing atoms. Therefore radiation with much shorter wavelength has been introduced, which is the invisible X-ray.



Fig. 26 The wavelength of different forms of light and other electromagnetic radiation

The energy of X-rays, like all electromagnetic radiation, is inversely proportional to their wavelength as given by the Einstein equation:

$$E = h v = hc/\lambda$$

where E = energy h = Planck's constant, 6.62517 x 10^{-34} J sec v = frequency

 $c = velocity of light = 2.99793 \times 10^8 m/sec$

λ = wavelength

But the X-ray is unlike the visible light; there is no lens that can focus X-rays. This causes an X-ray microscope to be unfeasible unless someone finds a way of focusing X-rays. Until then it is necessary to use crystals to diffract x-rays and create a diffraction pattern which can be interpreted mathematically by a computer. This turns the computer into a virtual lens, so that on a monitor we can *look* at the structure of a molecule. The technology is based on the fact that X-rays penetrate the crystal, just as X-rays penetrate the human body when used in the hospital to examine the chest. Unlike the medical film, the X-rays do not leave blank areas indicating the solid tissue such as bones; when the X-rays pass the space between the electron and the nucleus, the process causes diffraction. When an X-ray beam bombards a crystalline lattice in a given orientation, the beam is scattered in a definite manner characterized by the atomic structure of the lattice.³⁰ This phenomenon, known as X-ray diffraction, occurs when the wavelength of X-rays and the inter-atomic distances in the lattice have the same order of magnitude.

The X-ray crystallography applies to the crystals because inside the crystal is composed by the repetitive identical structure called unit cells. The X-ray diffraction from one unit cell would not be significant. Fortunately, the repetition of unit cells within a crystal amplifies the diffraction enough to give results that computers can turn into a picture. And in some way it can explain why the X-ray crystallography does not work well with non-crystalline materials. In atoms the nuclei are surrounded by the electron cloud, creating an electromagnetic field which can be modified. The interaction of the X-ray photon with this field can lead to its re-emission in a different direction. Diffraction is different when the X-ray passes different part of the atom, as well as the space in the lattice between the atoms.

1.3.1.1 X-ray scattering from electrons

The scattering of x rays from electrons is called Thomson scattering. It occurs because the electron oscillates in the electric field of the incoming X-ray beam and an oscillating electric charge radiates electromagnetic waves. Thus, X-rays are radiated from the electron at the same frequency as the primary beam. However, most electrons radiate 180° out of phase with incoming beam, as shown by a mathematical model of the process. The motion of the electron is heavily damped when the X-ray frequency is close to the electron resonance frequency. This occurs near an absorption edge of the atom, changing relative phase of the radiated X-rays to 90° and giving rise to the phenomenon of anomalous scattering.³¹

1.3.1.2 X-ray scattering from atoms

When the photons pass through different part of the same atom, the diffraction is not constant. Destructive interference occurs, depending upon the scattering angle. Thus atoms diffract X-rays more weakly at higher scattering angles. Some of the electrons in the atom may additionally undergo the effect described above, and they will scatter the X-rays about 90° out of phase with the incident beam. This would happen because in the multi-electron atom, the resonance frequency of some electrons is close to the X-ray frequency, and the rest is not.

1.3.1.3 X-ray scattering from a unit cell

X-rays scattered from each atom in the unit cell contribute to the overall scattering pattern. Since each atom acts as a source of scattered X-rays, the waves will add constructively or destructively in varying degrees depending upon the direction of the diffracted beam and the atomic positions. This gives a complicated scattering pattern whose amplitude and phases vary continuously.³²

1.3.2 Measurements

1.3.2.1 Bragg's law

The unit cell is the repeat unit to compose the crystal. Stacks of planes can be imagined to cut through the unit cell, intersecting an axis 0, 1, 2, or another integral number of times. While the mathematical analysis of three-dimensional diffraction is very complicated, it is equivalent to reflection off these planes. Measurable reflection only occurs when the waves reflected from successive planes in the stack interfere constructively. This only happens when their paths differ in length by an integral number of wavelengths, as expressed by Bragg's Law.

Bragg's Law refers to the simple equation:

$n\lambda = 2d \sin\theta$

Derived by the English physicists Sir W.H. Bragg and his son Sir W.L. Bragg in 1913 to explain why the cleavage faces of crystals appear to reflect X-ray beams at certain angles of incidence (theta, θ). The variable d is the distance between atomic layers in a crystal, and the variable lambda λ is the wavelength of the incident X-ray beam; n is an integer³³.



Fig. 27 Bragg equation diagram

The cell dimensions can be calculated by measuring the θ values. Structure and location of each molecule in the unit cell is shown by the intensity of reflection from each stack of planes. The device used by the Braggs to measure such intensities is shown in Fig. 28.



Fig. 28 Schematic of Bragg spectrometer

However, the phase of each reflection must be supplied, and it cannot be measured. The phase of a wave determines whether a reference point is at a crest, a trough, or in between. Most frequently, as in the work reported here, the phases are determined by a computerized process called direct methods. An electron density map can be calculated from these phases and the intensity data. This shows where the atoms in the molecules are located. These positions are refined by least squares to give a final model that best fits the data. This shows the location of each atom in the molecule.

Based on the final refined model, the expected intensity I (calc) of reflection from each stack of planes can be calculated and compared with the experimentally measured value I (obs). The square root of intensity, called the structure factor F, is used in one of the most important measures of the quality of a structure determination. The conventional discrepancy index $\mathbf{R} = \Sigma ||\mathbf{F} (\mathbf{obs})| - |\mathbf{F} (\mathbf{calc})|| / \Sigma |\mathbf{F} (\mathbf{obs})|$. The sums can be taken over the reflections considered "observed", usually meaning that the intensity is at least twice its own standard deviation, or over all reflections including the weakest. Another important quality measure is the height and depth of peaks and pits on a difference electron density map. Positive peaks and negative toughs at existing atom position can indicate errors in the assignment of element type. Positive peaks in such a map may indicate sites where the model should have placed an atom but did not; and negative troughs suggest misplaced atoms in the model. Peaks and troughs could also result from an incorrect assignment of element types.

Chapter 2. Experimental

2.1 Crystal preparation and method selection. Solvent and solubility

Theory is always based on experimental fact. Based on the knowledge of the X-ray crystallography and the X-ray diffraction, the diffractometer has been used to examine crystals and collect experimental data. Good data can only be expected from good crystals.

Crystal selection and crystal mounting are the major steps in the preparation process. Selection of the crystal is crucial. Ideal crystals for diffraction studies are suitablesized single crystals with the lattices in good order. The overall quality and the size are checked under the low power magnification (up to 40X, a good depth of field, and a strong light source are required.) Good quality has some characteristics: no inclusions, no striations and no significant dislocations, smooth and flat faces, sharp edges. The crystals that are curved or are otherwise deformed, or that show re-entrant angles, are rejected.

And the most important part is that the crystal should be homogeneous, otherwise special precautions have to be taken, and the quality of the results will suffer. If possible, crystals with obvious external twinning will be rejected. A polarizing microscope is used to verify that the crystal is single (this point is as mentioned before; the boundary between different crystals would cause significant error in the data). The typical morphology is noted, along with any obvious symmetry. The specimen has to be relatively large enough to create an adequate diffraction pattern, but excessive size should be avoided to minimize the absorption of X-rays.³⁴ As the wavelength of the X-rays decreases (for instance from 1.54 Å from a copper target to 0.71 Å from molybdenum), absorption by the crystal also decreases and poses less of a problem.

For organic compounds containing no element heavier than oxygen, crystals smaller than 0.1x0.1x0.1mm³ seldom give good data with conventional laboratory instruments, although this size may be ideal for crystals of an osmium cluster compound which diffracts and also absorbs X-rays very effectively. The calculation of structure factor amplitudes assumes that the crystal is completely irradiated in the uniform beam of X-rays. Since the uniform region is about 0.4mm in diameter, this is the maximum diameter of the selected crystal. And for most cases, a minimum diameter of 0.1mm is required to produce adequate X-ray scattering. Compounds with few atoms or very heavy atoms can have all three dimensions toward the small end of this 0.1 to 0.4 mm range. The ideal crystal for compounds with many light atoms should have all three dimensions toward the high range (0.4mm). As the experimental substances in this work are composed of light atoms (C, H, N, O), a relatively large crystal is favored. Over-sized crystals can be cut with a razor blade, or solvent saw. In other cases, if the crystals are strongly absorbing, it is worthwhile to reshape the crystal to be as spherical as possible. The reshaping process can be completed by cutting, grinding or dipping the crystal in solvent.

2.1.1 Re-crystallization

The compounds studied in this work were supplied as crystalline solids, giving promise of eventual success. However, as supplied, the crystals lacked sufficient size and quality. Each specimen crystal had to be created by the process of slow evaporation of solvent from a saturated solution, using mixed solvents in some cases:

Chemical	Solvent(s) used	Ratio	Product Powders	
2-hydroxy-4,6-dimethoxyacetophenone	THF			
	EtOAc		Crystal but not single ones	
	HEXANE/THF	8:1	Good quality single crystal	
N-(3-hydroxypropyl)phthalimide	EtOAc		Thin and fine crystal but not single	
	DCM/HEXANE	8:1	Thin and fine single crystal	
N-(hydroxymethyl)phthalimide	EtOAc		Single crystal	

Table 5. Results of crystal growth experiments

2.1.1.1 Procedure

(a) Place a small amount of solvent in the test tube. (About 3-5ml)

(b) Dissolve a trace amount of crystals in the solvent, shaken until the crystals disappear; carefully add more crystals from the starting batch into the solution until they do not dissolve any further.

(c) Remove most of the solvent in the tube by volatilization. (This process takes about 2-3 days.) The re-crystallization process finishes with harvesting the crystals while some solvent remains.

2.1.2 Crystal mounting

One specimen crystal is selected for mounting on a glass fiber attached via a metal stud to a goniometer head. To reduce background scattering the glass should be thin and a minimum quantity of adhesive should be used.

2.2 Methods

X-ray data were collected on the Enraf-Nonius CAD4 diffractometer at Aston University. Data were collected with MoK α radiation to an angle of incidence and reflection θ of at least 25.2° to satisfy the requirements of *Acta Crystallographica*. Structures were solved by direct methods with SHELXS, refined by standard least-squares procedures with SHELXL, and illustrated with ORTEP. All OH and CH₃ groups of these structures were refined as idealized rotating groups. Initial positions were established from maxima in a Fourier synthesis on a cone of appropriate radius, and they were subsequently refined subject to this constraint. No preconditions about hydrogen bonding were introduced. Other H atoms were assumed to ride on their attached carbon atom.

Chapter 3. Results: Crystal structures

3.1 Structural diagrams, crystal data and structure refinement for "acpho3"

This structure was considered highly likely to form an intra-molecular hydrogen bond from the phenolic OH group to the carbonyl oxygen atom.



M.P. 80-82

2-hydroxy-4,6-dimethoxyacetophenone

Table 6. Crystal data and structure refinement for acpho3

Identification code	acpho3		
Empirical formula	C10 H12 O4		
Formula weight	196.20		
Temperature	293(2) K		
Wavelength	0.71073 A		
Crystal system	Triclinic		
Space group	P-1		

Unit cell dimensions	a = 8.0502(9) A alpha = 70.582(13) deg.
	b = 11.543(2) A beta = 77.147(9) deg.
	c = 11.6983(10) A gamma = 75.783(12) deg.
Volume	982.0(2) A^3
Z	4
Density (calculated)	1.327 Mg/m^3
Absorption coefficient	0.103 mm^-1
F(000)	416
Crystal size	0.55 x 0.40 x 0.40 mm
Theta range for data collection	2.24 to 25.22 deg.
Index ranges	-9<=h<=2, -13<=k<=13, -14<=l<=13
Reflections collected	4415
Independent reflections	3533 [R(int) = 0.0240]
Max. and min. transmission	0.9600 and 0.9456
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3533 / 0 / 261
Goodness-of-fit on F ²	1.054
Final R indices [I>2sigma(I)]	R1 = 0.0463, wR2 = 0.1325
R indices (all data)	R1 = 0.0870, wR2 = 0.1605
Largest diff. peak and hole	0.182 and -0.275 e.A^-3

x	у	Z	U(eq)		
1811	A Charles				
C(1)	2262(3)	1669(2)	4141(2)	40(1)	
C(2)	1803(3)	2484(2)	4889(2)	43(1)	
O(1)	3018(2)	2855(2)	5239(2)	59(1)	
C(3)	95(3)	2923(2)	5305(2)	50(1)	
C(4)	-1205(3)	2577(2)	4977(2)	48(1)	
O(2)	-2933(2)	2940(2)	5333(2)	66(1)	
C(5)	-838(3)	1813(2)	4213(2)	46(1)	
C(6)	866(3)	1369(2)	3806(2)	39(1)	
O(3)	1311(2)	625(1)	3058(1)	51(1)	
C(7)	4083(3)	1202(2)	3771(2)	44(1)	
O(4)	5222(2)	1563(2)	4060(2)	59(1)	
C(8)	4715(3)	270(2)	3061(2)	57(1)	
C(9)	-3445(4)	3714(3)	6129(3)	82(1)	
C(10)	-3(3)	327(2)	2641(2)	58(1)	
C(21)	5170(3)	3291(2)	800(2)	38(1)	
C(22)	5742(3)	2500(2)	18(2)	43(1)	
O(21)	7445(2)	2108(2)	-331(2)	61(1)	
C(23)	4595(3)	2091(2)	-415(2)	48(1)	
C(24)	2847(3)	2458(2)	-89(2)	45(1)	
O(22)	1587(2)	2131(2)	-453(2)	63(1)	
C(25)	2206(3)	3248(2)	656(2)	42(1)	
C(26)	3348(3)	3657(2)	1074(2)	37(1)	
O(23)	2789(2)	4450(1)	1778(1)	48(1)	

Table 7. Atomic coordinates ($x \ 10^{4}$) and equivalent isotropic displacement parameters (A² x 10³) for acpho3. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor

C(29)	2104(4)	1359(3)	-1249(3)	90(1)	
C(30)	964(3)	4888(2)	2035(2)	54(1)	
C(28)	6024(3)	4396(2)	2138(2)	52(1)	
O(24)	8029(2)	3302(2)	914(2)	61(1)	
C(27)	6468(3)	3646(2)	1253(2)	43(1)	

 Table 8. Bond lengths [A] and angles [deg] for acpho3.

C(1)-C(6)	1.418(3)	
C(1)-C(2)	1.422(3)	
C(1)-C(7)	1.453(3)	
C(2)-O(1)	1.344(2)	
C(2)-C(3)	1.381(3)	
O(1)-H(1)	0.8200	
C(3)-C(4)	1.374(3)	
C(3)-H(3)	0.9300	
C(4)-O(2)	1.363(3)	
C(4)-C(5)	1.394(3)	
O(2)-C(9)	1.427(3)	
C(5)-C(6)	1.378(3)	
C(5)-H(5)	0.9300	
C(6)-O(3)	1.357(2)	
O(3)-C(10)	1.412(3)	
C(7)-O(4)	1.243(3)	
C(7)-C(8)	1.498(3)	
C(8)-H(8A)	0.9600	
C(8)-H(8B)	0.9600	
C(8)-H(8C)	0.9600	
C(9)-H(9A)	0.9600	
C(9)-H(9B)	0.9600	

C(9)-H(9C)	0.9600
С(10)-Н(10А)	0.9600
C(10)-H(10B)	0.9600
С(10)-Н(10С)	0.9600
C(21)-C(26)	1.417(3)
C(21)-C(22)	1.429(3)
C(21)-C(27)	1.464(3)
C(22)-O(21)	1.349(2)
C(22)-C(23)	1.384(3)
O(21)-H(21)	0.8200
C(23)-C(24)	1.372(3)
C(23)-H(23)	0.9300
C(24)-O(22)	1.357(3)
C(24)-C(25)	1.398(3)
O(22)-C(29)	1.425(3)
C(25)-C(26)	1.369(3)
C(25)-H(25)	0.9300
C(26)-O(23)	1.361(2)
O(23)-C(30)	1.430(3)
C(27)-O(24)	1.238(3)
C(27)-C(28)	1.492(3)
C(28)-H(28A)	0.9600
C(28)-H(28B)	0.9600
C(28)-H(28C)	0.9600
C(30)-H(30A)	0.9600
C(30)-H(30B)	0.9600
C(30)-H(30C)	0.9600
C(29)-H(29A)	0.9600
C(29)-H(29B)	0.9600
C(29)-H(29C)	0.9600

C(6)-C(1)-C(2)	116.26(19)
C(6)-C(1)-C(7)	124.48(19)
C(2)-C(1)-C(7)	119.26(19)
O(1)-C(2)-C(3)	116.7(2)
O(1)-C(2)-C(1)	121.4(2)
C(3)-C(2)-C(1)	121.90(19)
C(2)-O(1)-H(1)	109.5
C(4)-C(3)-C(2)	119.3(2)
C(4)-C(3)-H(3)	120.3
C(2)-C(3)-H(3)	120.3
O(2)-C(4)-C(3)	124.9(2)
O(2)-C(4)-C(5)	113.7(2)
C(3)-C(4)-C(5)	121.4(2)
C(4)-O(2)-C(9)	118.0(2)
C(6)-C(5)-C(4)	119.2(2)
C(6)-C(5)-H(5)	120.4
C(4)-C(5)-H(5)	120.4
O(3)-C(6)-C(5)	122.09(19)
O(3)-C(6)-C(1)	116.05(18)
C(5)-C(6)-C(1)	121.85(19)
C(6)-O(3)-C(10)	119.48(18)
O(4)-C(7)-C(1)	120.0(2)
O(4)-C(7)-C(8)	116.1(2)
C(1)-C(7)-C(8)	123.9(2)
C(7)-C(8)-H(8A)	109.5
C(7)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5
C(7)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5

O(2)-C(9)-H(9A)	109.5
O(2)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
O(2)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
O(3)-C(10)-H(10A)	109.5
O(3)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
O(3)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
C(26)-C(21)-C(22)	115.53(19)
C(26)-C(21)-C(27)	125.63(18)
C(22)-C(21)-C(27)	118.84(18)
O(21)-C(22)-C(23)	116.43(19)
O(21)-C(22)-C(21)	121.3(2)
C(23)-C(22)-C(21)	122.3(2)
C(22)-O(21)-H(21)	109.5
C(24)-C(23)-C(22)	119.0(2)
С(24)-С(23)-Н(23)	120.5
С(22)-С(23)-Н(23)	120.5
O(22)-C(24)-C(23)	125.1(2)
O(22)-C(24)-C(25)	113.5(2)
C(23)-C(24)-C(25)	121.4(2)
C(24)-O(22)-C(29)	118.0(2)
C(26)-C(25)-C(24)	119.23(19)
С(26)-С(25)-Н(25)	120.4
С(24)-С(25)-Н(25)	120.4
O(23)-C(26)-C(25)	121.46(18)

O(23)-C(26)-C(21)	116.07(18)	
C(25)-C(26)-C(21)	122.47(18)	
C(26)-O(23)-C(30)	118.13(16)	
O(24)-C(27)-C(21)	119.6(2)	
O(24)-C(27)-C(28)	116.8(2)	
C(21)-C(27)-C(28)	123.57(19)	
C(27)-C(28)-H(28A)	109.5	
C(27)-C(28)-H(28B)	109.5	
H(28A)-C(28)-H(28B)	109.5	
C(27)-C(28)-H(28C)	109.5	
H(28A)-C(28)-H(28C)	109.5	
H(28B)-C(28)-H(28C)	109.5	
O(23)-C(30)-H(30A)	109.5	
O(23)-C(30)-H(30B)	109.5	
H(30A)-C(30)-H(30B)	109.5	
O(23)-C(30)-H(30C)	109.5	
H(30A)-C(30)-H(30C)	109.5	
H(30B)-C(30)-H(30C)	109.5	
O(22)-C(29)-H(29A)	109.5	
O(22)-C(29)-H(29B)	109.5	
H(29A)-C(29)-H(29B)	109.5	
O(22)-C(29)-H(29C)	109.5	
H(29A)-C(29)-H(29C)	109.5	
H(29B)-C(29)-H(29C)	109.5	

2.7			12.20		A standard		
U11	U22	U33	U	U23		U12	
	and the					999	
C(1)	43(1)	40(1)	40(1)	-12(1)	-5(1)	-13(1)	
C(2)	47(1)	44(1)	45(1)	-16(1)	-7(1)	-15(1)	
O(1)	55(1)	69(1)	72(1)	-39(1)	-10(1)	-19(1)	
C(3)	56(1)	50(1)	50(1)	-26(1)	-2(1)	-11(1)	
C(4)	42(1)	51(1)	50(1)	-19(1)	-2(1)	-10(1)	
O(2)	45(1)	82(1)	82(1)	-50(1)	2(1)	-5(1)	
C(5)	44(1)	51(1)	51(1)	-21(1)	-6(1)	-13(1)	
C(6)	44(1)	37(1)	40(1)	-14(1)	-4(1)	-12(1)	
O(3)	48(1)	57(1)	61(1)	-35(1)	-5(1)	-13(1)	
C(7)	44(1)	45(1)	42(1)	-11(1)	-4(1)	-14(1)	
O(4)	43(1)	71(1)	72(1)	-30(1)	-7(1)	-18(1)	
C(8)	45(1)	65(2)	64(2)	-32(1)	-2(1)	-5(1)	
C(9)	61(2)	99(2)	98(2)	-66(2)	7(2)	-2(2)	
C(10)	64(2)	59(2)	65(2)	-30(1)	-16(1)	-18(1)	
C(21)	38(1)	36(1)	40(1)	-10(1)	-4(1)	-7(1)	
C(22)	39(1)	39(1)	47(1)	-13(1)	0(1)	-4(1)	
O(21)	40(1)	68(1)	79(1)	-41(1)	1(1)	-1(1)	
C(23)	54(1)	44(1)	50(1)	-24(1)	-3(1)	-5(1)	
C(24)	48(1)	44(1)	50(1)	-19(1)	-8(1)	-11(1)	
O(22)	53(1)	77(1)	82(1)	-53(1)	-10(1)	-12(1)	
C(25)	36(1)	45(1)	46(1)	-20(1)	-1(1)	-7(1)	
C(26)	38(1)	37(1)	37(1)	-13(1)	-3(1)	-8(1)	
O(23)	38(1)	58(1)	60(1)	-36(1)	-3(1)	-6(1)	

Table 9. Anisotropic displacement parameters (A^2 x 10^3) for acpho3. Theanisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ...+ 2 h k a* b* U12]

C(27)	37(1)	39(1)	47(1)	-7(1)	-7(1)	-7(1)	
O(24)	34(1)	71(1)	81(1)	-31(1)	-7(1)	-8(1)	
C(28)	49(1)	57(1)	59(1)	-23(1)	-13(1)	-15(1)	
C(30)	39(1)	64(2)	65(2)	-36(1)	0(1)	-4(1)	
C(29)	86(2)	106(3)	117(3)	-84(2)	-16(2)	-18(2)	

Table 10. Hydrogen coordinates ($x \ 10^{4}$) and isotropic displacement parameters (A² x 10³) for acpho3.

x	у	z	U(eq)		
Part an	State of				
H(1)	3984	2539	4958	88	
H(3)	-172	3447	5802	60	
H(5)	-1733	1605	3981	55	
H(8A)	5957	52	2973	85	
H(8B)	4366	628	2264	85	
H(8C)	4227	-466	3490	85	
H(9A)	-2909	3311	6853	123	
H(9B)	-4683	3848	6355	123	
H(9C)	-3087	4503	5714	123	
H(10A)	-718	-133	3329	87	
H(10B)	517	-171	2095	87	
H(10C)	-702	1084	2214	87	
H(21)	8020	2377	-13	91	
H(23)	5003	1574	-920	58	
H(25)	1017	3492	866	50	
H(28A)	7067	4441	2377	78	
H(28B)	5274	4005	2850	78	
H(28C)	5445	5225	1756	78	

H(30A)	509	5296	1279	82	
H(30B)	754	5469	2501	82	
H(30C)	403	4193	2499	82	
H(29A)	2867	1738	-1959	135	
H(29B)	1098	1268	-1499	135	
H(29C)	2696	552	-825	135	

3.2 Structural diagrams, crystal data and structure refinement for "hwang3".

This molecule could form a 6-membered intra-molecular hydrogen bond from the hydroxypropyl group to the nitrogen atom, but this N atom was not expected to be a good acceptor. The carbonyl O atoms should be stronger acceptors, but an intramolecular hydrogen bond would form a less favoured 8-membered ring.



N-(3-Hydroxypropyl phthalimide)

Table 11. Crystal data and structure refinement for hwang3.

Identification code

hwang3

Empirical formula	C11 H11 N O3
Formula weight	205.21
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system	monoclinic
Space group	P21/c
Unit cell dimensions	a = 12.2439(17) A alpha = 90 deg.
	b = 7.4543(8) A beta = 94.282(10) deg.
	c = 21.973(2) A gamma = 90 deg.
Volume	1999.9(4) A^3
Z	8
Density (calculated)	1.363 Mg/m^3
Absorption coefficient	0.100 mm^-1
F(000)	864
Crystal size	0.43 x 0.42 x 0.40 mm
Theta range for data collection	2.40 to 25.25 deg.
Index ranges	-14<=h<=14, -8<=k<=2, -26<=l<=0
Reflections collected	4424
Independent reflections	3583 [R(int) = 0.0520]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3583 / 0 / 273
Goodness-of-fit on F^2	0.973

Final R indices [I>2sigma(I)]	R1 = 0.0426, wR2 = 0.0975
R indices (all data)	R1 = 0.1414, wR2 = 0.1240
Largest diff. peak and hole	0.148 and -0.173 e.A^-3

Table 12. Atomic coordinates ($x \ 10^{4}$) and equivalent isotropic isplacement parameters (A² x 10³) for hwang3. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor

x	у	Z	U(eq)		
				11.5	
C(1)	6790(2)	1925(4)	926(1)	62(1)	
C(2)	5936(2)	1847(4)	1294(2)	72(1)	
C(3)	6090(2)	1324(5)	1895(2)	74(1)	
C(4)	7115(2)	822(4)	2146(1)	63(1)	
C(4A)	7973(2)	891(4)	1774(1)	48(1)	
C(5)	9143(2)	403(4)	1892(1)	50(1)	
N(6)	9631(2)	749(3)	1356(1)	51(1)	
C(7)	8885(2)	1357(4)	900(1)	53(1)	
C(1A)	7812(2)	1443(3)	1174(1)	47(1)	
C(8)	10787(2)	381(4)	1283(1)	60(1)	
C(9)	11525(2)	1912(4)	1517(1)	58(1)	
C(10)	12723(2)	1459(4)	1508(1)	62(1)	
O(11)	13021(2)	-74(3)	1869(1)	68(1)	
O(12)	9609(2)	-227(3)	2349(1)	70(1)	
O(13)	9094(2)	1723(3)	387(1)	77(1)	
C(21)	8603(2)	5859(4)	1602(1)	50(1)	
C(22)	9555(2)	5897(4)	1298(1)	56(1)	
C(23)	9551(2)	6459(4)	705(1)	61(1)	

C(24)	8595(2)	7014(4)	381(1)	54(1)
C(24A)	7649(2)	6991(3)	684(1)	43(1)
C(25)	6517(2)	7526(4)	476(1)	48(1)
N(26)	5897(2)	7259(3)	977(1)	46(1)
C(27)	6527(2)	6600(4)	1476(1)	45(1)
C(21A)	7657(2)	6419(3)	1283(1)	41(1)
C(28)	4728(2)	7655(4)	974(1)	51(1)
C(29)	4024(2)	6092(4)	754(1)	57(1)
C(30)	2817(2)	6459(5)	782(1)	63(1)
O(31)	2492(2)	6489(3)	1383(1)	68(1)
O(32)	6154(2)	8093(3)	-12(1)	67(1)
O(33)	6180(1)	6272(3)	1967(1)	59(1)

Table 13.	Bond	lengths	[A]	and angles	[deg]	for	hwang3.

C(1)-C(2)	1.369(4)
C(1)-C(1A)	1.374(4)
C(1)-H(1)	0.9300
C(2)-C(3)	1.376(4)
C(2)-H(2)	0.9300
C(3)-C(4)	1.385(4)
C(3)-H(3)	0.9300
C(4)-C(4A)	1.380(4)
C(4)-H(4)	0.9300
C(4A)-C(1A)	1.380(3)
C(4A)-C(5)	1.481(4)
C(5)-O(12)	1.211(3)
C(5)-N(6)	1.385(3)
N(6)-C(7)	1.381(3)
N(6)-C(8)	1.462(3)

C(7)-O(13)	1.206(3)
C(7)-C(1A)	1.487(4)
C(8)-C(9)	1.521(4)
C(8)-H(8A)	0.9700
C(8)-H(8B)	0.9700
C(9)-C(10)	1.507(4)
C(9)-H(9A)	0.9700
C(9)-H(9B)	0.9700
C(10)-O(11)	1.423(3)
С(10)-Н(10А)	0.9700
C(10)-H(10B)	0.9700
O(11)-H(11)	0.8200
C(21)-C(21A)	1.373(3)
C(21)-C(22)	1.386(4)
C(21)-H(21)	0.9300
C(22)-C(23)	1.369(4)
С(22)-Н(22)	0.9300
C(23)-C(24)	1.387(4)
C(23)-H(23)	0.9300
C(24)-C(24A)	1.379(3)
C(24)-H(24)	0.9300
C(24A)-C(21A)	1.384(3)
C(24A)-C(25)	1.481(3)
C(25)-O(32)	1.205(3)
C(25)-N(26)	1.398(3)
N(26)-C(27)	1.382(3)
N(26)-C(28)	1.461(3)
C(27)-O(33)	1.214(3)
C(27)-C(21A)	1.483(3)
C(28)-C(29)	1.508(4)

C(28)-H(28A)	0.9700
C(28)-H(28B)	0.9700
C(29)-C(30)	1.508(3)
С(29)-Н(29А)	0.9700
С(29)-Н(29В)	0.9700
C(30)-O(31)	1.409(3)
С(30)-Н(30А)	0.9700
С(30)-Н(30В)	0.9700
O(31)-H(31)	0.8200
C(2)-C(1)-C(1A)	117.9(3)
C(2)-C(1)-H(1)	121.0
C(1A)-C(1)-H(1)	121.0
C(1)-C(2)-C(3)	121.4(3)
C(1)-C(2)-H(2)	119.3
C(3)-C(2)-H(2)	119.3
C(2)-C(3)-C(4)	121.0(3)
C(2)-C(3)-H(3)	119.5
C(4)-C(3)-H(3)	119.5
C(4A)-C(4)-C(3)	117.5(3)
C(4A)-C(4)-H(4)	121.3
C(3)-C(4)-H(4)	121.3
C(1A)-C(4A)-C(4)	121.1(3)
C(1A)-C(4A)-C(5)	108.0(2)
C(4)-C(4A)-C(5)	130.9(3)
O(12)-C(5)-N(6)	124.8(2)
O(12)-C(5)-C(4A)	129.1(3)
N(6)-C(5)-C(4A)	106.1(2)
C(7)-N(6)-C(5)	111.9(2)
C(7)-N(6)-C(8)	125.2(2)
C(5)-N(6)-C(8)	122.8(2)

O(13)-C(7)-N(6)	125.3(2)
O(13)-C(7)-C(1A)	128.6(3)
N(6)-C(7)-C(1A)	106.1(2)
C(1)-C(1A)-C(4A)	121.1(3)
C(1)-C(1A)-C(7)	131.0(3)
C(4A)-C(1A)-C(7)	107.8(2)
N(6)-C(8)-C(9)	112.2(2)
N(6)-C(8)-H(8A)	109.2
C(9)-C(8)-H(8A)	109.2
N(6)-C(8)-H(8B)	109.2
C(9)-C(8)-H(8B)	109.2
H(8A)-C(8)-H(8B)	107.9
C(10)-C(9)-C(8)	112.5(2)
С(10)-С(9)-Н(9А)	109.1
C(8)-C(9)-H(9A)	109.1
С(10)-С(9)-Н(9В)	109.1
C(8)-C(9)-H(9B)	109.1
H(9A)-C(9)-H(9B)	107.8
O(11)-C(10)-C(9)	112.5(2)
O(11)-C(10)-H(10A)	109.1
С(9)-С(10)-Н(10А)	109.1
O(11)-C(10)-H(10B)	109.1
C(9)-C(10)-H(10B)	109.1
H(10A)-C(10)-H(10B)	107.8
С(10)-О(11)-Н(11)	109.5
C(21A)-C(21)-C(22)	117.2(3)
С(21А)-С(21)-Н(21)	121.4
С(22)-С(21)-Н(21)	121.4
C(23)-C(22)-C(21)	121.4(3)
С(23)-С(22)-Н(22)	119.3

C(21)-C(22)-H(22)	119.3
C(22)-C(23)-C(24)	121.5(3)
С(22)-С(23)-Н(23)	119.2
С(24)-С(23)-Н(23)	119.2
C(24A)-C(24)-C(23)	117.1(3)
C(24A)-C(24)-H(24)	121.4
C(23)-C(24)-H(24)	121.4
C(24)-C(24A)-C(21A)	121.1(2)
C(24)-C(24A)-C(25)	130.4(2)
C(21A)-C(24A)-C(25)	108.5(2)
O(32)-C(25)-N(26)	124.4(2)
O(32)-C(25)-C(24A)	130.0(2)
N(26)-C(25)-C(24A)	105.6(2)
C(27)-N(26)-C(25)	111.8(2)
C(27)-N(26)-C(28)	124.3(2)
C(25)-N(26)-C(28)	123.9(2)
O(33)-C(27)-N(26)	124.3(2)
O(33)-C(27)-C(21A)	129.2(2)
N(26)-C(27)-C(21A)	106.5(2)
C(21)-C(21A)-C(24A)	121.7(2)
C(21)-C(21A)-C(27)	130.7(2)
C(24A)-C(21A)-C(27)	107.6(2)
N(26)-C(28)-C(29)	112.4(2)
N(26)-C(28)-H(28A)	109.1
C(29)-C(28)-H(28A)	109.1
N(26)-C(28)-H(28B)	109.1
C(29)-C(28)-H(28B)	109.1
H(28A)-C(28)-H(28B)	107.9
C(28)-C(29)-C(30)	112.6(2)
C(28)-C(29)-H(29A)	109.1

C(30)-C(29)-H(29A)	109.1
С(28)-С(29)-Н(29В)	109.1
C(30)-C(29)-H(29B)	109.1
H(29A)-C(29)-H(29B)	107.8
O(31)-C(30)-C(29)	112.9(2)
O(31)-C(30)-H(30A)	109.0
C(29)-C(30)-H(30A)	109.0
O(31)-C(30)-H(30B)	109.0
C(29)-C(30)-H(30B)	109.0
H(30A)-C(30)-H(30B)	107.8
С(30)-О(31)-Н(31)	109.5

Table 14. Anisotropic displacement parameters (A² x 10³) for hwang3. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h² a^{*} U11 + ... + 2 h k a^{*} b^{*} U12]

U11	1122	1133	1123		U13	1112
			025			012
C(1)	61(2)	51(2)	72(2)	5(2)	-6(2)	9(2)
C(2)	52(2)	58(2)	104(3)	-8(2)	-1(2)	4(2)
C(3)	52(2)	74(2)	98(3)	-22(2)	23(2)	-5(2)
C(4)	64(2)	69(2)	58(2)	-11(2)	14(1)	-11(2)
C(4A)	52(2)	43(2)	48(2)	-8(1)	3(1)	-6(1)
C(5)	54(2)	48(2)	48(2)	-2(1)	-2(1)	-7(1)
N(6)	44(1)	57(2)	54(1)	1(1)	7(1)	3(1)
C(7)	58(2)	47(2)	54(2)	3(1)	6(1)	-3(1)
C(1A)	50(2)	36(2)	55(2)	-5(1)	2(1)	-1(1)
C(8)	48(2)	61(2)	72(2)	-8(2)	7(1)	0(2)
C(9)	55(2)	49(2)	69(2)	0(2)	13(1)	0(1)
--------	-------	-------	-------	--------	--------	-------
C(10)	58(2)	64(2)	66(2)	-2(2)	13(1)	-6(2)
O(11)	72(1)	70(2)	61(1)	-13(1)	-6(1)	12(1)
O(12)	67(1)	83(2)	57(1)	7(1)	-10(1)	-4(1)
O(13)	83(1)	90(2)	59(1)	18(1)	16(1)	4(1)
C(21)	51(2)	46(2)	53(2)	-4(1)	-1(1)	2(1)
C(22)	44(2)	57(2)	68(2)	-10(2)	-3(1)	6(1)
C(23)	46(2)	68(2)	69(2)	-16(2)	10(1)	-1(2)
C(24)	56(2)	62(2)	46(2)	-9(1)	10(1)	-4(2)
C(24A)	43(1)	42(2)	46(2)	-6(1)	1(1)	3(1)
C(25)	54(2)	47(2)	43(2)	-4(1)	3(1)	2(1)
N(26)	39(1)	51(1)	47(1)	2(1)	0(1)	5(1)
C(27)	47(2)	42(2)	47(2)	-5(1)	3(1)	-2(1)
C(21A)	39(1)	39(2)	44(1)	-4(1)	2(1)	1(1)
C(28)	39(1)	51(2)	62(2)	-3(2)	2(1)	7(1)
C(29)	48(2)	60(2)	64(2)	-13(2)	2(1)	2(1)
C(30)	47(2)	79(2)	62(2)	-14(2)	2(1)	-7(2)
O(31)	66(1)	73(2)	67(1)	-2(1)	18(1)	-8(1)
O(32)	67(1)	84(2)	48(1)	5(1)	-5(1)	9(1)
O(33)	56(1)	72(1)	51(1)	9(1)	11(1)	2(1)

Table 15. Hydrogen coordinates ($x \ 10^{4}$) and isotropic displacement parameters (A² x 10³) for hwang3.

			The second second		
x	у	Z	U(eq)		
H(1)	6682	2292	522	74	
H(2)	5236	2155	1134	86	

H(3)	5497	1309	2136	88
H(4)	7221	451	2550	76
H(8A)	10887	180	855	72
H(8B)	10999	-707	1503	72
H(9A)	11367	2965	1266	69
H(9B)	11364	2202	1931	69
H(10A)	12893	1239	1091	75
H(10B)	13155	2478	1660	75
H(11)	13201	241	2220	102
H(21)	8604	5470	2004	60
H(22)	10211	5533	1502	68
H(23)	10205	6470	515	73
H(24)	8593	7385	-24	65
H(28A)	4559	8681	713	61
H(28B)	4555	7971	1384	61
H(29A)	4222	5047	1001	68
H(29B)	4169	5817	336	68
H(30A)	2644	7606	590	75
H(30B)	2403	5543	552	75
H(31)	2683	7438	1547	102

3.3 Structural diagrams, crystal data and structure refinement for "hwetac3".

This structure was examined to find out whether an intra-molecular hydrogen bond formed between the hydroxymethyl group and either carbonyl oxygen atom.



N-(Hydroxymethyl) phthalimide

 Table 16.
 Crystal data and structure refinement for hwetac3.

Identification code	hwetac3	
Empirical formula	C9 H7 N O3	
Formula weight	177.16	
Temperature	296(2) K	
Wavelength	0.71073 A	
Crystal system	Monoclinic	
Space group	P21/c	
Unit cell dimensions	a = 11.3115(13) A	alpha = 90 deg.
	b = 6.5996(10) A	beta = 117.020(10) deg.
	c = 11.8452(15) A	gamma = 90 deg.
Volume	787.74(18) A^3	
Z	4	
Density (calculated)	1.494 Mg/m^3	

Absorption coefficient	0.114 mm^-1
F(000)	368
Crystal size	0.43 x 0.42 x 0.40 mm
Theta range for data collection	2.02 to 27.03 deg.
Index ranges	-14<=h<=14, -8<=k<=5, -15<=l<=15
Reflections collected	5769
Independent reflections	1726 [R(int) = 0.0253]
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	1726 / 0 / 119
Goodness-of-fit on F ²	1.067
Final R indices [I>2sigma(I)]	R1 = 0.0324, wR2 = 0.0886
R indices (all data)	R1 = 0.0366, wR2 = 0.0934
Largest diff. peak and hole	0.220 and -0.194 e.A^-3

Table 17. Atomic coordinates ($x \ 10^{4}$) and equivalent isotropic displacement parameters (A² x 10³) for hwetac3. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor

x	у	Z	U(eq)	
O(9)	5678(1)	3021(1)	-114(1)	42(1)
O(10)	8064(1)	2783(2)	4184(1)	49(1)
O(11)	4874(1)	1230(1)	2273(1)	41(1)
C(1)	8941(1)	6798(2)	3342(1)	38(1)
C(2)	9090(1)	8389(2)	2655(1)	43(1)

C(3)	8361(1)	8471(2)	1342(1)	45(1)
C(4)	7463(1)	6951(2)	670(1)	40(1)
C(4A)	7329(1)	5366(2)	1360(1)	31(1)
C(5)	6459(1)	3547(2)	944(1)	31(1)
N(6)	6707(1)	2478(1)	2037(1)	33(1)
C(7)	7658(1)	3431(2)	3119(1)	33(1)
C(1A)	8046(1)	5296(2)	2669(1)	31(1)
C(8)	5961(1)	706(2)	2077(1)	36(1)

Table 18. Bond lengths [A] and angles [deg] for hwetac3.

O(9)-C(5)	1.2111(13)	
O(10)-C(7)	1.2070(14)	
O(11)-C(8)	1.3945(14)	
O(11)-H(11)	0.8200	
C(1)-C(1A)	1.3823(15)	
C(1)-C(2)	1.3851(18)	
C(1)-H(1)	0.9300	
C(2)-C(3)	1.3911(19)	
C(2)-H(2)	0.9300	
C(3)-C(4)	1.3921(17)	
C(3)-H(3A)	0.9300	
C(4)-C(4A)	1.3782(16)	
C(4)-H(4)	0.9300	
C(4A)-C(1A)	1.3864(15)	
C(4A)-C(5)	1.4873(14)	
C(5)-N(6)	1.3858(14)	
N(6)-C(7)	1.3946(13)	
N(6)-C(8)	1.4551(14)	
C(7)-C(1A)	1.4842(16)	

C(8)-H(8A)	0.9700
C(8)-H(8B)	0.9700
C(8)-O(11)-H(11)	109.5
C(1A)-C(1)-C(2)	117.23(11)
C(1A)-C(1)-H(1)	121.4
C(2)-C(1)-H(1)	121.4
C(1)-C(2)-C(3)	121.18(11)
C(1)-C(2)-H(2)	119.4
C(3)-C(2)-H(2)	119.4
C(2)-C(3)-C(4)	121.32(11)
C(2)-C(3)-H(3A)	119.3
C(4)-C(3)-H(3A)	119.3
C(4A)-C(4)-C(3)	117.11(11)
C(4A)-C(4)-H(4)	121.4
C(3)-C(4)-H(4)	121.4
C(4)-C(4A)-C(1A)	121.53(10)
C(4)-C(4A)-C(5)	130.61(10)
C(1A)-C(4A)-C(5)	107.84(9)
O(9)-C(5)-N(6)	124.36(10)
O(9)-C(5)-C(4A)	129.45(10)
N(6)-C(5)-C(4A)	106.19(9)
C(5)-N(6)-C(7)	111.92(9)
C(5)-N(6)-C(8)	124.42(9)
C(7)-N(6)-C(8)	123.29(9)
O(10)-C(7)-N(6)	124.68(11)
O(10)-C(7)-C(1A)	129.39(10)
N(6)-C(7)-C(1A)	105.92(9)
C(1)-C(1A)-C(4A)	121.62(11)
C(1)-C(1A)-C(7)	130.26(10)
C(4A)-C(1A)-C(7)	108.13(9)

O(11)-C(8)-N(6)	112.01(9)	
O(11)-C(8)-H(8A)	109.2	
N(6)-C(8)-H(8A)	109.2	
O(11)-C(8)-H(8B)	109.2	
N(6)-C(8)-H(8B)	109.2	
H(8A)-C(8)-H(8B)	107.9	

Table 19. Anisotropic displacement parameters (A^2 x 10^3) for hwetac3. Theanisotropic displacement factor exponent takes the form: $-2 pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$

U11	U22	U33	U23		U13	U12
				1		
O(9)	44(1)	49(1)	27(1)	-8(1)	10(1)	-10(1)
O(10)	53(1)	51(1)	29(1)	5(1)	8(1)	-7(1)
O(11)	39(1)	45(1)	38(1)	-2(1)	17(1)	-6(1)
C(1)	29(1)	42(1)	36(1)	-7(1)	10(1)	-5(1)
C(2)	36(1)	40(1)	53(1)	-9(1)	21(1)	-11(1)
C(3)	45(1)	41(1)	54(1)	4(1)	27(1)	-7(1)
C(4)	39(1)	45(1)	35(1)	3(1)	17(1)	-3(1)
C(4A)	27(1)	35(1)	30(1)	-2(1)	12(1)	-2(1)
C(5)	30(1)	35(1)	28(1)	-4(1)	13(1)	-1(1)
N(6)	36(1)	31(1)	29(1)	-3(1)	11(1)	-5(1)
C(7)	31(1)	35(1)	28(1)	-2(1)	9(1)	-1(1)
C(1A)	26(1)	34(1)	31(1)	-2(1)	11(1)	-1(1)
C(8)	43(1)	29(1)	36(1)	-4(1)	18(1)	-6(1)

Table 20. Hydrogen coordinates (x 10⁴) and isotropic displacement parameters (A²

x 10^3) for hwetac3.

x	у	Z	U(eq)		
H(11)	5126	1479	3026	62	
H(1)	9424	6743	4220	45	
H(2)	9689	9420	3078	52	
H(3A)	8475	9563	906	54	
H(4)	6974	7003	-208	48	
H(8A)	5653	-30	1285	43	
H(8B)	6541	-183	2755	43	

3.4 Similar compounds researched in the CSD and subsequent independent structure determinations

For 2-hydroxy-4,6-dimethoxyacetophenone (Acpho3) a search in the November 2006 edition of the CSD confirmed that this structure had not been previously determined. However, independent structure determinations appeared in the literature late in 2006 for two of the three already completed structures reported in the previous chapter: 2-hydroxy-4,6-dimethoxyacetophenone³⁵ and N-(hydroxymethyl)phthalimide³⁶. Given that the differences in unit cell dimensions between the pairs of structure determinations in the table below are <0.01 Å and <0.02 Å respectively, it can be concluded that in each case these represent identical structures rather than polymorphs (more than one crystal form for the same compound).

	R-FAC/%	SPGN	ZUAL	A CEL/ Å	B CEL/ Å	C CEL/ Å
acpho3	4.630	2	4	8.050	11.543	11.698
acpho3(reported)	4.860	2	4	8.055	11.551	11.707
hwetac3	4.260	14	4	11.312	6.600	11.845
hwetac3 (reported)	3.400	14	4	11.324	6.604	11.862

R-FAC = the conventional R factor

SPGN = the space group number, in order of occurrence in the International Table for X-ray Crystallography

ZUAL = number of molecules in the unit cell

ACEL, BCEL, CCEL = a, b, c unit cell axis lengths

Five comparison structures were picked, all containing the structural unit:



Where one of B,C is COMe and the other is OH, and one of A, A' could be H

The five chemicals and their CSD recodes are listed below:



1.DACGIY



5.WAKHEW

	R-FAC/%	SPGN	COOR	ZUAL	A CEL/ Å	B CEL/ Å	C CEL/ Å
1	6.000	2	108	12	13.401	13.706	14.928
2	6.010	2	22	2	7.246	8.145	8.414
3	4.540	14	22	4	6.724	8.792	14.689
4	4.900	2	48	4	7.431	7.604	16.007

5	4.130	2	38	4	7.646	8.325	12.803
Acpho3	4.630	2		4	8.0502	11.5432	11.6983

R-FAC = the conventional R factor

SPGN = the space group number, in order of occurrence in the International Table for X-ray Crystallography

COOR = number of atoms with coordinates in the asymmetric unit

ZUAL = number of molecules in the unit cell

ACEL, BCEL, CCEL = a, b, c unit cell axis lengths

Although each of these structures has adjacent OH and acetyl groups, this structural

similarity does not produce any obvious similarity in the unit cell dimensions a, b, c.

For N-(3-Hydroxypropyl) phthalimide & N-(hydroxymethyl)phthalimide a search based on the general structure, result in two reports of the same structure:



	R-FAC/%	SPGN	COOR	ZUAL	A CEL/ Å	B CEL/ Å	C CEL/ Å
VUNZAF	6.400	2	0	4.000	7.336	10.950	14.693
VUNZAF10	6.400	2	54	4.000	7.336	10.950	14.693

Chapter 4. Discussion of structural properties

4.1 General features

According to the second empirical rule of hydrogen bonding proposed by Margaret Etter¹⁵, "Six-member-ring intra-molecular hydrogen bonds form in preference to intermolecular hydrogen bonds". All three compounds reported here have the formal capability to satisfy this rule, and they will be discussed in decreasing order of likelihood. Acpho3 (A) features three electron-donating substituents, *o*-OH, *o*-OMe, and *p*-OMe capable of feeding electron density into the ring and thence to the carbonyl O atom, making it an ideal hydrogen bond acceptor. Hwetac (B) can transfer some electron density from the imide nitrogen atom to be divided between the carbonyl O atoms, one of which must be the acceptor if the CH₂OH group is to form a 6-membered hydrogen bonded ring. In Hwang3 (C) a 6-membered ring with the hydroxypropyl group as hydrogen bond donor must have the imide nitrogen atom as the (weakened) acceptor.













B





C Fig. 29 The molecular and packing diagrams of "acpho3"(A), "hwetac3"(B) and "hwang3"(C)

While A and C have two independent molecules in the asymmetric unit, B has only one. Excluding hydrogen atoms, A is nearly planar: the r.m.s. deviation of ring carbon atoms from their least-squares planes is <0.01 Å in both rings, and the angle between these planes is $0.8(2)^{\circ}$. All torsion angles representing the orientation of C=O and OMe groups with respect to the ring are 0° or $180^{\circ} \pm 3.5^{\circ}$, but torsion angles controlling one OMe group (O2-C9, O22-C29) are of the same sign in both independent molecules while the others (O3-C10, O23-C30) are of opposite sign. The angles of CH₃C(=O) groups to their aromatic ring plane are $4.8(2)^{\circ}$ and $4.3(3)^{\circ}$.



The diagram shows that the two independent molecules and their counterparts related by inversion lie approximately parallel to the 0 1 -1 plane. The left and right boundary surfaces of the drawing are drawn parallel to this plane.

The dihedral angles between the benzene ring and the 5-membered heterocyclic ring in both structures are 0.73° in B, 1.20° and 2.14° in C respectively, which indicates that the bicyclic ring system in B and C remain nearly planar as well as A. The torsion angle of C7-N6-C8-O11 in B is 82.62° rather than 90°, the C8 atom lies out of the plane of the bicyclic ring system and breaks the planarity of the molecule; the main difference between the independent molecules of C is at the terminus of the hydroxypropyl chain with C-C-C-O torsion angles of -59.0(3)° and -71.6(3)°.

4.1.1 Molecular geometry

The C=O distances of 1.243(3) and 1.238(3) Å in A are longer than the 1.211(1), 1.207(1) Å in B and the 1.211(3), 1.208(3) Å and 1.205(3), 1.214(3) Å in C, suggesting that the input of electron density is greater in A and this carbonyl oxygen atom should be a better hydrogen bond acceptor.



4.2 Analysis of hydrogen bonding

Compound A indeed forms a 6-membered ring, designated by graph set symbol S(6), via an intra-molecular O-H...O hydrogen bond (HB) from the phenolic OH to the carbonyl O in both independent molecules (Table 21), well within the limit for significant HB (H...O distance ≤ 2.3 Å). These same carbonyl O atoms use their other lone pair to accept additional C-H...O HB at H...O distances of 2.44 and 2.45 Å and H...O...H angles 107 and 110°. In B the O-H...O HB infinite chain repeating every 6 atoms, graph set C(6), is supplemented by a dimeric R₂²(10) ring formed by

C-H...O HB(see diagram below):



Again the same O atom is the acceptor for both types of HB; this time the H...O...H angle is 73°. The other carbonyl O atom only makes van der Waals contacts. Neither independent molecule of C uses its N atom in any intermolecular contacts. Each OH group acts as HB donor forming chains, although the acceptor is the other OH in one case and a carbonyl O in the other; when the molecular diagram is observed from other angle (below), it appears that the extended chains of C might constitute a helix.



Parameters are tabulated below for all O-H...O HB and the C-H...O HB for which the H...O distance < 2.50 Å.

Cpd.	Atoms	Graph	d(XO)/Å	d(HO)/Å	X-H0/ °
A (mol. 1)	01-H104	S(6)	2.500(2)	1.77	147
A (mol. 2)	O21-H21O24	S(6)	2.490(2)	1.76	147
A (mol. 1)	C5-H5O4 ⁱ	C(6)	3.304(3)	2.44	154
A (mol. 2)	C25-H25O24 ⁱ	C(6)	3.295(3)	2.45	150
В	O11-H11O9 ⁱⁱ	C(6)	2.844(1)	2.03	177
В	C8-H8AO9 ⁱⁱⁱ	$R_2^2(10)$	3.313(1)	2.49	143
С	O11-H11O33 ^{iv}	C(10)	2.851(3)	2.04	171
С	O31-H31O11 ^v	C(10)	2.832(3)	2.02	173
С	C4-H4O31 ^{vi}	C(9)	3.269(3)	2.47	144

Table 21. HB parameters for different HB donors in the crystal structures investigated

Symmetry codes: (i) -1+x,y,z; (ii) x,0.5-y,0.5+z; (iii) 1-x,-y,-z; (iv) 2-x,-0.5+y,0.5-z; (v) -1+x,1+y,z; (vi) 1-x,-0.5+y,0.5-z

4.2.1 Related structures in the CSD

In a CSD search for similar structures the O-H bond distances were normalized to average values obtained from neutron diffraction. This avoids the effect on HB distances of random errors due to weak interaction of hydrogen atoms with X-rays and systematic errors due to sharing of the only electrons around hydrogen with another atom. Of 1154 structures in the CSD with adjacent hydroxyl and carbonyl substituents on a benzene ring, 1028 form intra-molecular HB with d (H...O) within the sum of van der Waals radii, and 1020 of these are classified³¹ as "strong" with $d(O-H) \le 2.3$ Å. Only 16 of 91 2-hydroxymethylcyclopentanones and their 2-aza analogues in the CSD form S(6) rings, 10 with strong HB. In 23 structures from the CSD similar to molecule C no HB to the imide N can be verified.

Refcode	o- to MeCO	<i>p</i> - to MeCO	o- to OH	<i>p</i> - to OH	Normalized HO / Å
Mol. A	OMe	OMe	Н	Н	1.62,1.64
ADCPME	Н	Н	CH ₂ R	Cl	1.61,1.81
BAGPAA	Н	Н	COMe	Me	1.66
DACGIY	Н	Н	Cl	Cl	1.62 to 1.73
DACGOE	Н	Н	Н	Cl	1.66,1.68
DOTRUZ	Н	OH	OH	Н	1.61,1.64
FERYEH	OH	OH	Н	Н	1.62
GADBAP01	Н	Н	Н	NO ₂	1.68
GAVJUJ	Н	Н	Н	N=NR	1.70
HAMLEM	Н	OMe	Н	Н	1.65
ILIQEZ	Н	OH	Me	Me	1.68
JASTUT	Н	Н	NO ₂	CH ₂ R	1.72
JEDZOI	OMe	Н	Н	Н	1.58
JEFBUS	OMe	OH	Me	CH ₂ R	1.60,1.63
JIFVEZ	Н	Н	t-Bu	Me	1.63
JIVVIT	Н	Н	Н	Н	1.67
KASREB	Н	OR	Pr	Н	1.65
LAMNAP01	H	OMe	Н	Н	1.63
LARVEG	OH	OH	R	Н	1.62
LIZBUR	Me	Me	Н	Н	1.60,1.62
NARBAJ	OMe	OMe	Н	COMe	1.58
NAWZUH	Н	Me	Н	Br	1.73
PARLIE	OH	OH	COMe/H	H/COMe	1.50,1.57/1.55,1.56
PARLOK	OMe/OH	OH/OMe	COMe/H	H/COMe	1.55,1.58/1.52,1.52
QAMNUN	OH	OR	Me	Н	1.61
QQQGTD01	OMe/OH	ОН	CHR ₂	CH ₂ R	1.56/1.55
SAYYAT	Н	Н	Н	N=NR	1.69
SEGFIU	Н	Н	NO ₂	Cl	1.60
SEGFUG	Н	Н	NO ₂	C1	1.61
VOXPED	Н	OH	Н	COMe	1.60,1.63
WAKHEW	OH	Н	Н	Н	1.60,1.66
WAWFAC	Н	Н	Н	N=NR	1.68
XEGXOW	OH	OR	Me	Н	1.63

Table 22. Acetophenone derivatives with S(6) ring

Note: SEGFIU and SEGFUG have the same chemical structure; the only difference between them is that the latter one is composed of a co-crystal with another molecule.

In the table of H...O distances within S(6) rings in the acetophenones the shortest distances (<1.6 Å) are highlighted in gold. Electron-donating substituents *ortho/para* to C=O are expected to feed electron density into the carbonyl oxygen atom, making it a better acceptor. Additionally, electron-withdrawing substituents *ortho/para* to the phenolic OH group should increase its strength as a donor. Suitably positioned substituents of the right character are highlighted in green, dark if strong and light if weak. Substituents of the wrong type for their position are highlighted in red if strong and pink if weak. It can be seen that when the H...O distance is very short, dark green substituents dominate.

The vast majority of strong HB¹⁸ donors and acceptors in the acetophenone series obey Etter's Rule and make intra-molecular HB, but the weaker ones in the phthalimide series generally do not.

4.3 Hydrogen bonding in pharmaceutically acceptable ions

Of the 10 most popular pharmaceutically acceptable anions and cations²⁵, 4 were chosen to compare their role as acceptors or donors in different organic salts. On grounds of steric accessibility it was expected that chloride, being a single atom, would accept fewer hydrogen bonds than a multi-atom ion like nitrate. Ammonium ion was chosen as a cationic hydrogen bond donor. Finally, the dihydrogen phosphate anion was chosen because, as an anion, it should be a good hydrogen bond

acceptor, but it also has two OH groups which can donate hydrogen bonds.



Structure 1 Chloride (most hits in the CSD^{25})

According to the Cambridge Database research, the amount of chemicals which have a similar group as structure 1 is 2983 and 2960 of them form hydrogen bonds with other groups or molecules in the same crystalline salt. The numbers are larger than those in ref. 29 because a later (November 2005) version of the CSD has been surveyed. The following tables are set out in terms of the numbers of unique hydrogen bonds to these ions. It must be noted that a large number of unique hydrogen bonds could result either from many hydrogen bonds to one ion or a large number of unique ions in the unit cell. With the methodology employed it was not possible to distinguish between these cases, but since the majority of structures have one unique formula unit in the unit cell, information is still accessible about the preferred number of hydrogen bonds per ion.

Table 23. Number of unique H-	bonds formed in c	crystalline organic salts	of chloride
	ions		

Number of H bonds formed	Crystalline salts with the same number of		
Number of H-bonds formed	H-bonds		
1	360		
2	354		
3	596		
4	357		
5	400		
6	269		
7	155		
8	135		
9	58		
10	60		
11	53		
12	31		
13	24		
14	19		
15	15		
Over 15	74		

From the data above, the numbers of H-bonds formed were mostly lower than 6, but a great deal higher than the chemical structure shown in Fig. 30.



Fig.30 Chloride as hydrogen bond acceptor

Here each chloride theoretically has 2 hydrogen bonds. The fact that most crystals formed more than this basic structure shows that the chloride is a good acceptor.

The number of crystal structures which have a similar group to structure 2 is 2418; 373 of them do not form HB with other groups or molecules in the same crystalline salt.

Number of H-bonds formed	Crystalline salts with the same number of H-bonds		
1	221		
2	433		
3	372		
4	311		
5	160		
6	129		
7	101		
8	91		
9	44		
10	35		
11	27		
12	33		
13	16		
14	8		
15	4		
Over 15	60		

Table 24. Number of unique H-bonds formed in crystalline organic salts of nitrate ions

D



Fig. 31 Nitrate as hydrogen bond acceptor

The nitrate as shown would form 3 hydrogen bonds in the unit, but according to the table, it often does not form as many bonds as theoretically expected even though access should be easy. So it is a good acceptor but not as good as Cl⁻, probably because the -1 charge is spread over three oxygen atoms.

The number of crystal structures which have a similar group to structure 3 is 478; 7 of them do not form HB with other groups or molecules in the same crystalline salt, and the number of crystal structures which have a similar group to structure 4 is 265; 116 of them do not form HB with other groups or molecules in the same crystalline salt.

Am	monium	Dihydrogen Phosphate		
Number of H-bonds formed	Crystalline salts with the same number of H-bonds	Number of H-bonds formed	Crystalline salts with the same number of H-bonds	
1	4	1	13	
2	11	2	6	
3	25	3	1	
4	135	4	3	
5	95	5	2	
6	57	6	1	

 Table 25. Number of unique H-bonds formed in crystalline organic salts of Ammonium ions and Dihydrogen Phosphate ions

7	25	7	5
8	41	8	6
9	16	9	5
10	21	10	3
11	12	11	6
12	9	12	5
13	5	13	4
14	0	14	8
15	2	15	2
Over 15	13	16	2
		17	3
		18	4
		19	2
		20	6
		21	6
		22	1
		23	6
		25	3
		27	4
		28	2
		29	4
		Over 30(including	26
		30)	30

The Ammonium and the Dihydrogen Phosphate can be discussed together, as they are generally both forming small numbers of hydrogen bonds, but different from each other. The theoretical model of one HB per ammonium proton is indeed most commonly observed. Relatively few ammonium ions leave one or more protons unsatisfied. More ions find greater than one acceptor per proton. The Dihydrogen Phosphate ion offers numerous possibilities for hydrogen bonding, and in some cases each ion forms very many HB. However, there is a frequency maximum for just one HB per ion. Thus the last structure is not very favorable to the formation of hydrogen bonding.

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