

Analysis of the less common hydrogen bonds involving ester oxygen sp^3 atoms as acceptors in the crystal structures of small organic molecules

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An analysis of hydrogen bonds involving ester Osp^3 atoms as acceptors has been performed based on the data extracted from the Cambridge Structural Database [Allen (2002). *Acta Cryst. B* **58**, 380–388; version 5.25, November 2003], using the *ConQuest* package to evaluate the stereochemical and electronic properties of the acceptors. Evidence for the existence of this particular type of hydrogen bond and its structural function in crystal packing is presented. Using a cut-off limit on residual indices of $R < 0.05$ (for the structures with hydrogen bonds involving an oxygen as part of the donor group) and $R < 0.085$ (for nitrogen as part of the donor group), 230 structures out of the total CSD entries of 298 100 were found to contain hydrogen bonds with the ester Osp^3 atoms as acceptors. The hydrogen-bond donors include water molecules, hydroxyl groups, primary and secondary amines and, in a few cases, imino groups. Four modes of the participation of the ester Osp^3 atoms in hydrogen bonding are detected: as a single acceptor, as a double acceptor, as a single acceptor of a H atom involved in an intermolecular bifurcated hydrogen bond, and as a shared acceptor function with the ester Osp^2 atom in a bifurcated hydrogen bond. The role of such directed noncovalent interactions in crystal packing is demonstrated by a small gallery of selected structures.

1. Introduction

The analysis of hydrogen bonding and its role in the crystal packing of small organic molecules, along with the findings of Lommerse *et al.* (1997), motivated us to examine the potential acceptor function of the ester Osp^3 atom. Participation of the sp^2 oxygen in hydrogen bonding is well known. However, conjugation in the ester group significantly affects the C–O single bond and increases the electron density of the sp^3 oxygen, thereby increasing its capacity as a proton acceptor, leading to the formation of hydrogen bonds in sterically favourable environments.

Among the proton acceptors such as carbonyl, ether and ester O atoms, those involving ester Osp^3 atoms have been less well examined. Lommerse *et al.* (1997) studied the hydrogen-bonding capability of carbonyl, ether and ester O atoms with alkanol hydroxyl groups using *ab initio*-based energy calculations, combined with experimental crystallographic data (Cambridge Structural Database; Allen, 2002, Version 5.10, October, 1995). The theoretical approach used by Lommerse *et al.* (1997) revealed an equal potential of the Osp^3 atom in ethers and esters to serve in an acceptor role. Crystallographic data in 1995 (used in the work of Lommerse *et al.*, 1997) were not available in such great numbers as today. Therefore, we focused our analysis on hydrogen bonds involving the ester Osp^3 atom as a proton acceptor. In addition to our experience

with in-house crystal structures, we used a recent update of the Cambridge Structural Database (Allen, 2002, version 5.25, release November 2003) with significantly more data than were available for the earlier study. Thus, an extensive analysis, based on a larger number of data, has been possible.

The conventional hydrogen bonds $O-H\cdots O$, $N-H\cdots O$, $N-H\cdots N$ have been widely discussed (Jeffrey & Saenger, 1991; Jeffrey, 1997; Scheiner, 1997; Steiner, 2002). Over the last 20 years, weak $C-H\cdots A$ ($A = O, N, F, Cl, Br, I, \pi$) interactions considered to be hydrogen bonds have attracted much attention (Taylor & Kennard, 1982; Desiraju & Steiner, 1999). Hydrogen bonds that are not so common have been discussed and have generated some controversy. This is so because the classification of hydrogen bonding is closely related to its definition. Pauling (1939) recognized a hydrogen bond as an attraction between a H atom and two electronegative atoms. Pimentel & McClellan (1960) defined a hydrogen bond more generally as a bond involving an H atom already bonded to another atom. Experimental evidence on the substantial covalent character of the $O-H\cdots O$ hydrogen bond was obtained from inelastic Compton X-ray scattering on ice I_h (Isaacs *et al.*, 1999). Spectroscopic and X-ray diffraction techniques employing more sensitive detectors (CCDs) provide more accurate and reliable data and detect very fine dynamic effects (Elsaesser & Bakker, 2002), particularly recording ultrafast hydrogen transfer (time ranging from 10^{-14} to 10^{-11} s). Hydrogen bonding can thus be viewed as providing models for proton-transfer reactions (a stable hydrogen-bond $X-H\cdots Y$ is the 'frozen' state of the reaction $X-H\cdots Y^- \rightleftharpoons X^- \cdots H-Y^+$, or other such possibilities; Steiner, 2002). These new developments contribute to a new concept of the nature of hydrogen bonding. However, the analysis based on the experimental geometrical parameters and topology of hydrogen bonds extracted from crystallographic structural databases is the fundamental and most important initial step in systematic research on hydrogen bonding. Therefore, we focus our attention on this approach.

2. Methods

2.1. Cambridge Structural Database search

Experimental values for the geometrical parameters of the hydrogen bonds detected in the crystal structures of small

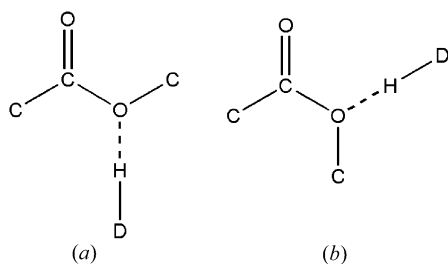


Figure 1

Fragments used for CSD searches: (a) with an *anti*-arrangement about the C—O ester bond; (b) with a *syn*-arrangement. For terminal C atoms the coordination number was set to four, corresponding to sp^3 hybridization.

organic molecules were extracted from the Cambridge Structural Database, CSD (Allen, 2002, version 5.25, release November 2003) containing *ca* 298 100 entries. *The ConQuest* software (Bruno *et al.*, 2002) was used in searches for hydrogen bonds using defined fragments with two possible spatial arrangements about the C—O ester bond, *anti*- and *syn*-arrangements (Figs. 1a and b, respectively) found in equal frequency. The search restrictions were the following: good quality refinement of crystallographic parameters, $R < 0.05$ (for structures with hydrogen bonds involving an O atom as the donor group) and $R < 0.085$ (where a nitrogen served as the donor group), error-free coordinates, no crystallographic disorder and no polymer structures.

The search based on these criteria revealed 230 structures with the ester Osp^3 atom as the proton acceptor and with the proton bound to oxygen or to nitrogen (structures present in the sample studied 160:70, respectively). The geometric parameters of the hydrogen bonds that were used as limits for the searches are (Fig. 2a): $D\cdots A \leq d(D-H) + r_{vW}(D) + r_{vW}(A) - 0.01 \text{ \AA}$ (van der Waals radii, r_{vW} : oxygen 1.52, hydrogen 1.20, nitrogen 1.55, carbon 1.70 \AA; Bondi, 1964) and the angle $D-H\cdots A > 90^\circ$. A pragmatic distance cut-off criteria may be used for database searches, but it is too

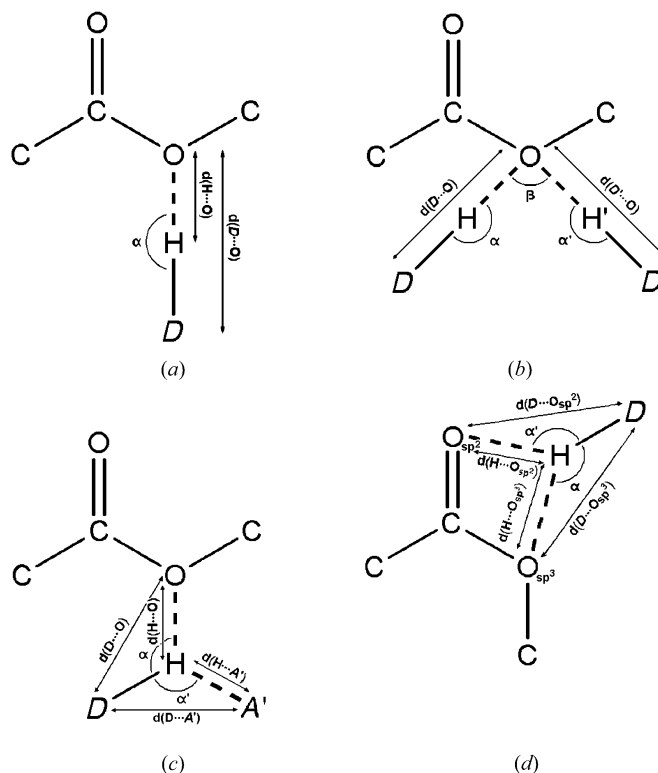


Figure 2

(a) The ester Osp^3 atom as a single acceptor; (b) as a double acceptor; (c) as an acceptor of a proton involved in an intermolecular bifurcated hydrogen bond; (d) as an acceptor of a proton involved in an intermolecular bifurcated hydrogen bond using the carbonyl oxygen atom of the same ester group as an additional acceptor. Geometric parameters are defined for the hydrogen-bond length $d \equiv O\cdots H$ and angle $\alpha \equiv O-H\cdots O$.

Table 1

Geometric parameters for intermolecular hydrogen bonds with O and N atoms as donors involving the Osp^3 atom as the acceptor.

Mean values are given with standard deviations in parentheses.

Proton donor <i>D</i>	Cluster denoted in Figs. 8 and 9	$H \cdots Osp^3$ (Å)	$D \cdots Osp^3$ (Å)	$D-H \cdots A$, α (°)	Number of structures
O	1	2.20 (17)	2.91 (6)	141 (6)	13
	2	2.56 (10)	3.07 (10)	117 (16)	76
	3	2.50 (19)	3.20 (10)	149 (26)	58
N	1'	2.31 (30)	3.03 (5)	147 (15)	12
	2'	2.63 (5)	3.19 (5)	133 (21)	35
	3'	2.53 (13)	3.31 (7)	151 (13)	22

restrictive to be used as a general criterion for hydrogen bonding (Jeffrey & Saenger, 1991; Steiner, 2002).

In hydrogen-bond networks the search revealed an approximately equal number of donors and acceptors per selected molecules; there is no prevalence of donor over acceptor sites that would be in favour of the ester Osp^3 atom as a proton acceptor. The balance of donor and acceptor sites can be slightly changed by the presence of solvent molecules in the crystal structures. In the sample selected through a search, 46 structures contain water molecules. These structures modify the donor-to-acceptor ratio and change its value from 1:1 (detected in solvent-free crystal structures) to 1:1.3 (found in structures with crystal water molecules).

3. Results and discussion

3.1. Characteristics of hydrogen bonds involving the ester Osp^3 atom

In the structures with the ester Osp^3 atoms as the acceptors, the donor groups belong to water molecules, hydroxyl groups, primary and secondary amines and, in a few cases, imino groups are involved. The CSD searches revealed four functions (Figs. 2*a–d*) of the ester Osp^3 atom in hydrogen bonding:

- (i) a single acceptor,
- (ii) a double acceptor,
- (iii) sharing a proton in an intermolecular bifurcated (three-centre) hydrogen bond or
- (iv) sharing a proton with the ester carbonyl (sp^2) oxygen in a bifurcated hydrogen bond.

In spite of the presence of the strongly electronegative ester carbonyl oxygen, a sterically favourable environment can allow access to the region of the two non-bonding electron pairs of the ester Osp^3 atom by the proton donor group(s). The studies performed by Etter & Adsmond (1990) and Etter & Reutzel (1991) revealed that hydrogen-bond accepting properties of various functional groups depend on the local intramolecular environment.

The directionality of a hydrogen bond and, in particular, the acceptor directionality should be considered. For strong hydrogen bonds the directionality of the acceptor corresponds to the geometry of the covalent product of a hypothetical proton-transfer reaction. The directionality of moderate and

weak hydrogen bonds is significantly less well expressed, but it can be anticipated from the directionality of a lone (non-bonding) electron pair defined by the pseudopolar angles θ and φ (Fig. 3); for an ester Osp^3 atom the lone pairs lie in the plane bisecting the C–O–C fragment ($\theta = 0^\circ$, $\varphi = \pm 55^\circ$). Lommerse *et al.* (1997) have already observed that the *syn*- and *anti* arrangements (Fig. 1) differ in the directionality of the proton towards the acceptor. For the *syn* arrangement the most favourable orientation of a hydrogen bond is between the two lone-electron

pairs with an inclination of 9.5° towards the C–O–C plane. However, for the *anti* arrangement a hydrogen bond is oriented towards one of the lone-electron pairs, with an inclination angle of 34.8° . For the *syn* arrangement our CSD searches revealed that hydrogen bonds bisect the angle between the two lone-electron pairs deviating from the C–O–C plane, in most cases $10 < \varphi < 30^\circ$ (Fig. 3). It was found that this class is mostly represented by lactones with both oxygen (sp^2 and sp^3) atoms acting as the acceptors in a bifurcated (three-centre) hydrogen bond (Fig. 2*d*). For the *anti* arrangement hydrogen bonds are significantly inclined ($30 < \varphi < 60^\circ$) towards the C–O–C plane, in the direction of one lone electron pair.

Among various definitions that characterize the properties of hydrogen bonds, the interaction geometries found in crystal structures are in common use (Jeffrey & Saenger, 1991; Steiner, 2002). The hydrogen-bond lengths observed for a particular donor/acceptor combination in the same class of compounds are in the range $\pm 10\%$ of the class mean value. According to experimental evidence hydrogen bonds occur with a continuum of strengths. For practical reasons classification according to energy criteria is informative; hydrogen bonds associated with energies in the range *ca* 17–63 kJ mol⁻¹ can be classified as of moderate strength (mainly electrostatic), whereas those above and below these limits can be treated as strong (quasi-covalent nature) and weak (electrostatic/dispersion), respectively. Jeffrey's (1997) classification of

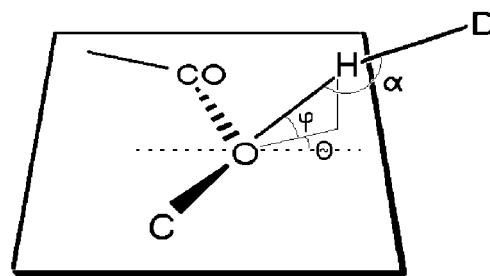


Figure 3

Pseudopolar angles: θ defines the inclination of the hydrogen-bond direction towards the bisecting line of the C–O–C angle, and φ defines the inclination of the hydrogen bond towards the C–O–C plane (adapted from Lommerse *et al.*, 1997).

Table 2Geometric parameters for intermolecular bifurcated hydrogen bonds involving the ester O_{sp^3} atom as the acceptor.

Mean values are given with the standard deviations in parentheses and are classified according to the different donor groups.

Proton donor D	$H \cdots O_{sp^3}$ (Å)	$D \cdots O_{sp^3}$ (Å)	$H \cdots A'$	$D \cdots A'$ (Å)	$D-H \cdots O_{sp^3}$, α ($^\circ$)	$D-H \cdots A'$, α' ($^\circ$)	Number of structures
O	2.56 (3)	3.10 (12)	2.10 (6)	2.89 (22)	123 (18)	150 (20)	42
N	2.44 (10)	3.16 (16)	2.31 (6)	3.09 (21)	138 (20)	143 (16)	22

hydrogen bonds is based on both the geometrical and energy criteria, and is of practical value. However, to understand this noncovalent interaction, various influences should be considered. To summarize such an approach, the description given by Jeffrey & Saenger (1991, page 26) can be quoted as 'the properties of hydrogen bonds are group properties, depending not only upon the first neighbour atoms D and A , but also upon the sequential nature of the total pattern of bonding'.

Our analysis (Tables 1 and 2, Figs. 4 and 5) shows that hydrogen bonds involving the ester O_{sp^3} atom are characterized by $D \cdots O_{sp^3}$ distances mostly in the range 2.8–3.3 Å and in some cases larger than 3.3 Å (mostly for N–H donors, Fig. 5). The $D-H \cdots O_{sp^3}$ (α) angles for nitrogen donors are larger than 130° (Table 1). To obtain better insight into angular preferences, a cone correction (weighted by $1/\sin \alpha$; Kroon & Kanters, 1974; Steiner, 2002) has been applied. The analysis (Figs. 6 and 7) revealed that the directionality of N–H \cdots O hydrogen bonds is more pronounced than for O–H \cdots O hydrogen bonds.

Although the borders between particular classes of hydrogen bonds are diffuse, the clustering of geometric parameters can be used to recognize a class. The large range of both $O \cdots A$ and $N \cdots A$ distances (Figs. 4 and 5, respectively) reveals clustering of the data in three groups for a particular

donor type (Fig. 8, clusters 1–3, and Fig. 9, clusters 1'–3'). Each cluster follows roughly a Gaussian distribution. The geometric characteristics of moderate-strength hydrogen bonds (clusters 1 and 1' in Figs. 8 and 9, respectively; $O \cdots O_{sp^3} < 3.0$ Å, $N \cdots O_{sp^3} < 3.1$ Å and α angles larger than 140°) and weak hydrogen bonds (clusters 3 and 3', $O \cdots O_{sp^3} > 3.0$ Å, $N \cdots O_{sp^3} > 3.1$ Å; Tables 1 and 2) are in agreement with Jeffrey's criteria (Jeffrey, 1997). The theoretical data of Lommerse *et al.* (1997) strongly support the experimental evidence for the medium-strength hydrogen bonds observed in this analysis. The $O \cdots O_{sp^3}$ values for medium-strength bonds (Table 1, cluster 1, Fig. 8) correspond fairly well with the values for $O_w-H \cdots O$ hydrogen bonds ($O_w = O$ atom of a water molecule) as found for the ether fragment C–O–C [($H \cdots O_{sp^3}$) 1.978 (9) Å (range 1.78–2.33 Å) ($O_w \cdots O_{sp^3}$) 2.910 (7) Å (range 2.74–3.17 Å), $N = 254$; Steiner, 2002] and theoretical values for the *anti*-methylacetate/methanol dimer ($H \cdots O_{sp^3}$ 1.95–1.98 Å, $O \cdots O_{sp^3}$ 2.82–2.85 Å). The structure of 4-nor-18-homo-*ent*-kauran-4-(18)-en-15- β ,16- β ,17-triol-19,3- β -olide 16-*O*- β -D-glucopyranoside (tricalysioside A; Dong-Hui *et al.*, 2002; Table 1, cluster 1, Fig. 8) reveals hydrogen bonding using the O_{sp^3} of a lactone group. According to the geometric parameters it lies on the borderline between strong- and medium-strength hydrogen bonds

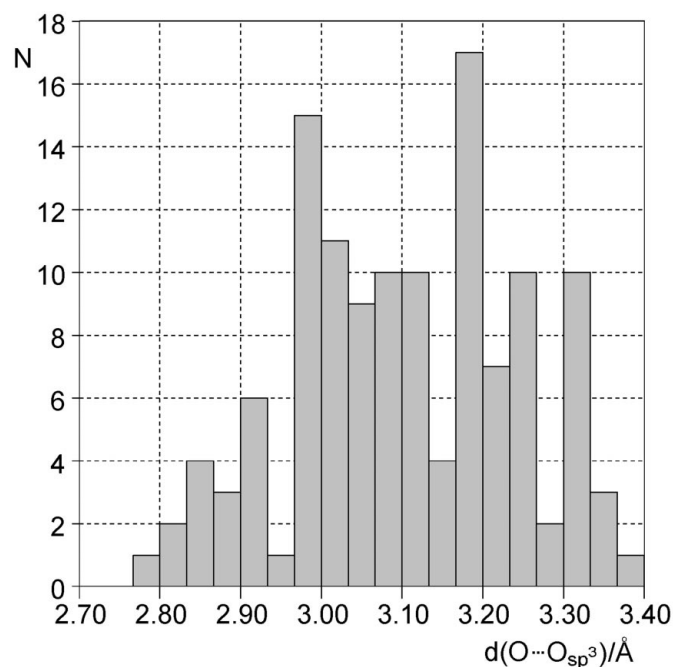


Figure 4
Distribution of $O \cdots O_{sp^3}$ distances in hydrogen bonds O–H \cdots O.

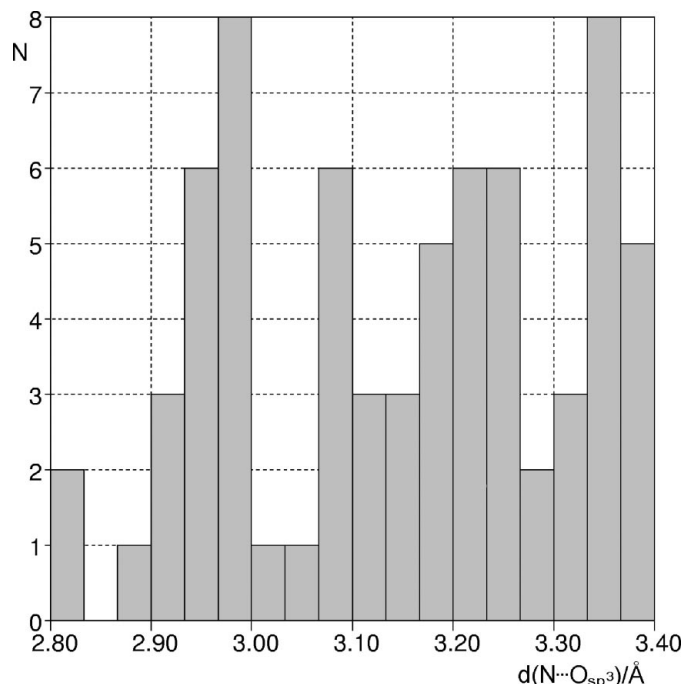


Figure 5
Distribution of $N \cdots O_{sp^3}$ distances in hydrogen bonds N–H \cdots O.

($\text{H}\cdots\text{O}_{\text{sp}^3}$ 1.918 Å, $\text{O}\cdots\text{O}_{\text{sp}^3}$ 2.864 Å, $\text{O}-\text{H}\cdots\text{O}_{\text{sp}^3}$ 148°). To test the acceptor ability of various functional groups containing O atoms, Böhm *et al.* (1996) performed *ab initio*

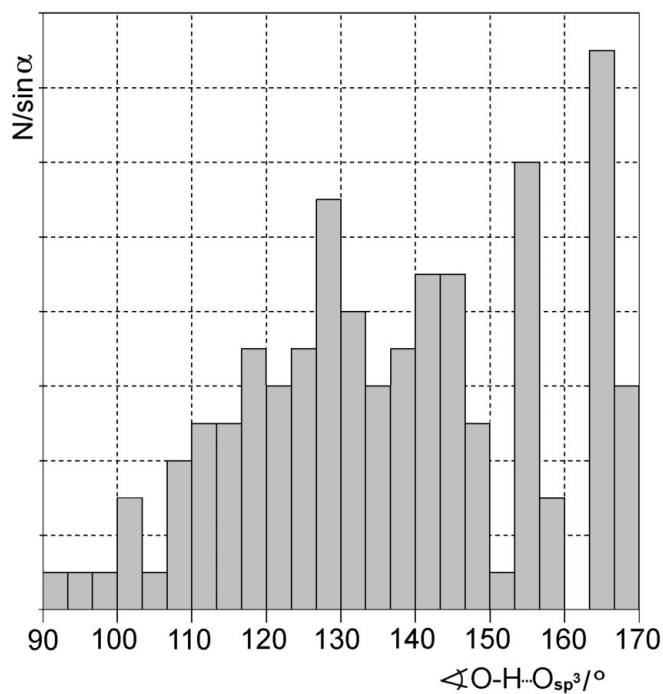


Figure 6
Distribution of the $\text{O}-\text{H}\cdots\text{O}$ angles using a cone correction (weighting with $1/\sin \alpha$).

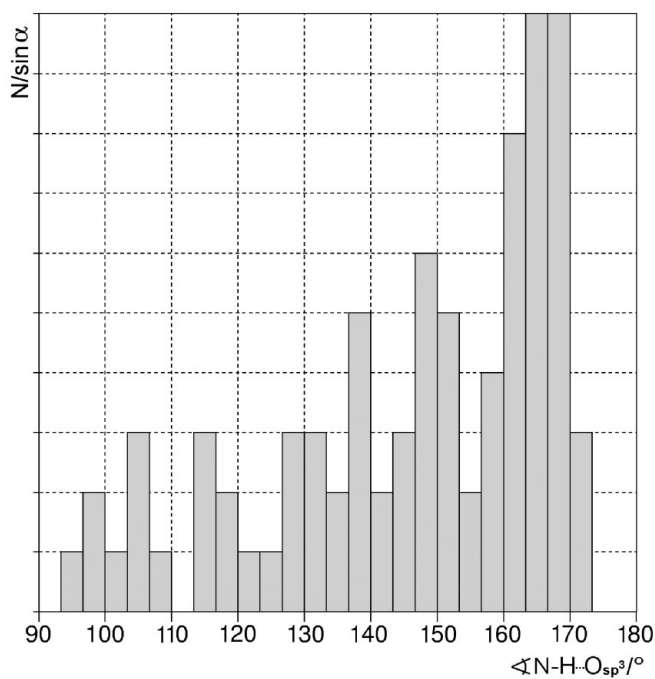


Figure 7
Distribution of the $\text{N}-\text{H}\cdots\text{O}$ angles using a cone correction (weighting with $1/\sin \alpha$).

calculations on hydrogen-bonded complexes of water with molecules containing different functional groups. For a comparison with data from our analysis two examples are of interest. A water molecule hydrogen-bonded to the O_{sp^2} atom of the ester group revealed an interaction energy of $-29.0 \text{ kJ mol}^{-1}$ and an $\text{H}\cdots\text{O}_{\text{sp}^2}$ distance of 1.99 Å. On the

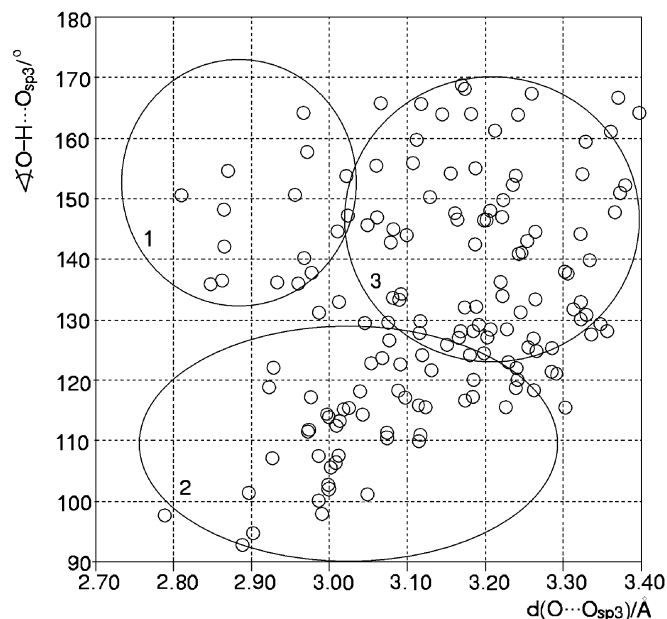


Figure 8
Plot of the $\alpha = \text{O}-\text{H}\cdots\text{O}$ versus donor \cdots acceptor distance $\text{O}\cdots\text{O}_{\text{sp}^3}$. Clusters of medium strength (cluster 1) and weak hydrogen bonds (cluster 3), and bifurcated hydrogen bonds (cluster 2) are shown.

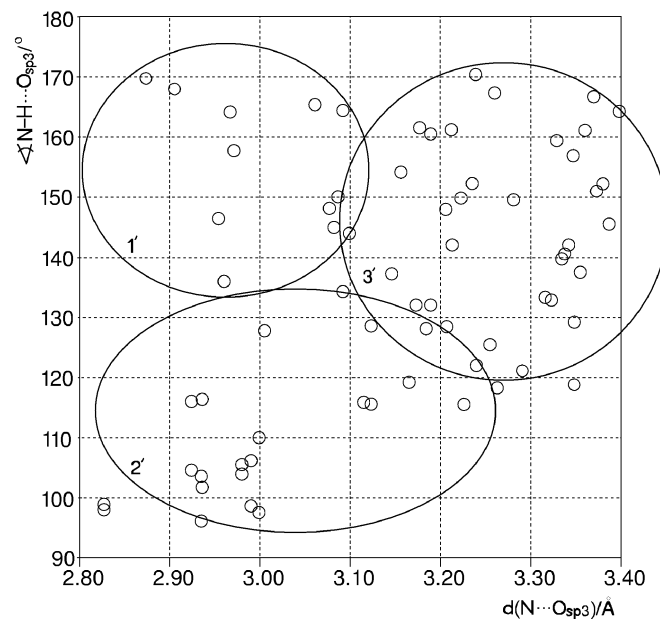


Figure 9
Plot of $\alpha = \text{N}-\text{H}\cdots\text{O}$ versus $\text{N}\cdots\text{O}_{\text{sp}^3}$ distance. Clusters of medium strength (cluster 1') and weak hydrogen bonds (cluster 3') and bifurcated hydrogen bonds (cluster 2') are shown.

other hand, the values for the analogous complex involving the Osp^3 atom revealed an energy of $-20.9 \text{ kJ mol}^{-1}$ and an $H \cdots Osp^3$ distance of 2.08 \AA (Böhm *et al.*, 1996). Obviously, the energy difference between these two different acceptors in the formation of hydrogen bonds can be compensated for by the steric and electronic properties of the neighbouring atoms.

In spite of the paucity of the data (12 medium strength and 35 weak bonds) for the $N-H \cdots Osp^3$ system, statistical analysis shows that the distribution of $N \cdots Osp^3$ distances is symmetric and Gaussian. The values for cluster 1' representing medium-strength hydrogen bonds (Fig. 9, Table 1) correspond fairly well to the range for $N-H \cdots Ow$ bonds ($H \cdots Osp^3$ 1.71 – 2.16 , $N \cdots Osp^3$ 2.7 – 3.1 \AA ; Steiner, 2002). As an illustrative example, the structure of cluster 1' (*R*)-(1-naphthyl)-glycyl-(*R*)-phenylglycine (*S*)-methylacetate clathrate (Akazome *et al.*, 1999) exhibits a hydrogen bond using the ester Osp^3 atom as the acceptor with the geometric parameters: $H \cdots Osp^3$ 2.033 , $N^+ \cdots Osp^3$ 2.967 \AA , $N^+-H \cdots Osp^3$ 164° .

Just as the distinction between strong- and moderate-strength hydrogen bonds is blurred, it is even more so for medium-strength and weak hydrogen bonds. The nature of the interactions represents a continuum from electrostatic to dispersive (long-range) interactions. Using the $H \cdots O$ distance to distinguish the nature of these interactions, it is known that for a distance of 3.50 \AA the electrostatic component of the bond energy is reduced by 50% compared with the value at equilibrium separation (interaction diminished by r^{-1}). However, the dispersion component is dependent on r^{-6} . According to Jeffrey & Saenger (1991, pages 19–20), the hydrogen bonds detected in our analysis (Table 1, cluster 3 in Fig. 8 and cluster 3' in Fig. 9) are good representatives of weak-strength hydrogen bonds.

The analysis of bifurcated hydrogen bonds was performed using great caution; the competition between the two acceptors was carefully analysed. Two types of intermolecular bifurcated hydrogen bonds with the participation of the sp^3 ester oxygen as the acceptor were recognized: (*c*) the second acceptor A' (Fig. 2*c*) is oxygen (mostly OH, ether, $C=O$ of a neighbouring molecule or water) or nitrogen (primary or secondary amines), and (*d*) the second acceptor was the Osp^2 carbonyl O atom of the same *R* or the lactone group (Fig. 2*d*). In category (*c*) approximately 42 structures were identified by applying the previously noted geometric criteria. The analysis revealed that in *ca* 20% of these structures the ester Osp^3 atom acts as a more favourable acceptor than the second acceptor A' in the bifurcated hydrogen bonds. In this category there are also *ca* 25% of the structures in which both acceptors are equally favoured. The remaining structures found in category (*c*) show a more favourable interaction based upon geometric parameters for the A' acceptor. However, geometric parameters of hydrogen bonds involving the ester Osp^3 atom acceptors correspond generally to accepted geometric criteria (Jeffrey & Saenger, 1991). Category (*d*) is the most sensitive one; the acceptor abilities of the Osp^3 and Osp^2 atoms belonging to the same ester or lactone group can be verified using steric, electronic and geometric parameters. Out of 63 structures found in category (*d*), *ca* 13% of them

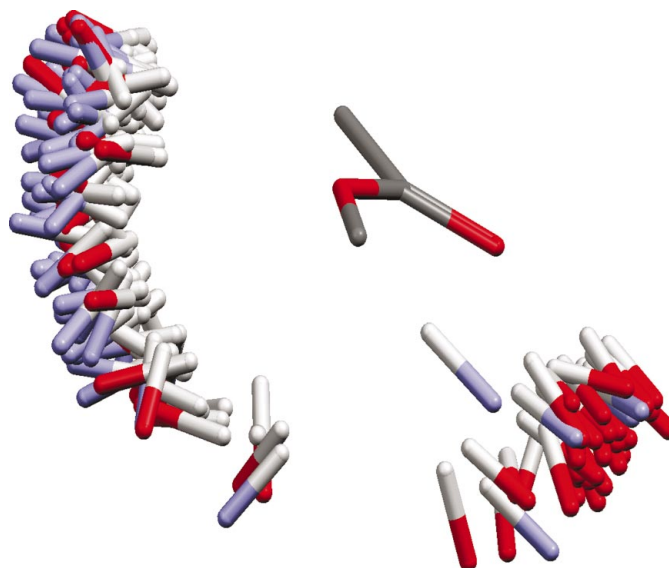


Figure 10

Scatterplot illustrating the grouping of proton donors oriented towards the lone-electron pairs of the ester Osp^3 atom and carbonyl O atom (the latter participating in bifurcated hydrogen bonds as A').

showed the ester Osp^3 atom as the favoured acceptor, whereas in the remaining structures there are bifurcated hydrogen bonds that indicate a preference for the Osp^2 atom acceptor. It is rather common that in bifurcated hydrogen bonds two acceptors exhibit different interaction strengths or geometries.

The geometric parameters of bifurcated hydrogen bonds with the ester Osp^3 atom as the acceptor (Figs. 2*c* and *d*) are presented in Table 2. The $O \cdots Osp^3$ distances are clustered about 3.0 \AA (Fig. 8, cluster 2), whereas the distances involving the second acceptor $O \cdots A'$ are somewhat shorter (Table 2). Values of the $O-H \cdots Osp^3$ angles (with cone corrections) are scattered over the whole range (90 – 180°). Values of the angles $O-H \cdots A'$ tend to cluster around 180° if the second acceptor is a strong one; in bifurcated hydrogen bonds two acceptors are often of different polarity (one being a better acceptor than the other).

Structural databases (Allen & Motherwell, 2002) and the application of suitable software (*e.g.* *IsoStar*; Bruno *et al.*, 1997) reveal that hydrogen bonds exhibit a wide range of geometric preferences, from a strong lone-pair directionality to a hardly detectable directionality. To visualize the directionality of hydrogen bonds involving the ester Osp^3 atom a CSD scatterplot (*IsoStar*; Bruno *et al.*, 1997) was prepared (Fig. 10). Inspection of the scatterplot shows the clustering of the proton donors around the ester Osp^3 atom, but also around Osp^2 , representing the interaction with the second acceptor A' in bifurcated hydrogen bonds.

3.2. Hydrogen-bonding patterns involving the ester Osp^3 atom in the crystal structures

As an illustration of the ester Osp^3 -atom acceptor function in hydrogen bonding, a small gallery of structures has been selected and is presented below.

A search for the fragments illustrated in Fig. 1 revealed crystal structures with a high prevalence of noncentrosymmetric over centrosymmetric space groups (3:1); in the sample studied chiral molecules prevailed (4:1). Among the noncentrosymmetric crystal structures, the space groups $P2_12_12_1$ and $P2_1$ were found to be most common, whereas the space group $P2_1/c$ was dominant within the centrosymmetric examples (along with its alternative settings $P2_1/a$ and $P2_1/n$). Triclinic $P1$ and $P\bar{1}$ space groups were next in the order of frequency. The space-group frequency statistics for our sample are in agreement with the statistical analysis of a small sample made by Kitaigorodsky (1955), as well as the more recent analysis of a larger sample by Allen, made using the CSD (Allen, 2002).

It would be interesting to analyse the crystal packing with respect to the symmetry and dimensionality of hydrogen-bond networks. One-dimensional hydrogen-bonded chains and three-dimensional networks are the most common, whereas two-dimensional hydrogen-bonded patterns and hydrogen-bonded dimers are less frequent. Each type of hydrogen-bonded pattern is illustrated below by selected crystal structures (Figs. 11–16). The structures have also been chosen to clarify the preference of the ester Osp^3 atom as the acceptor (Figs. 11, 12 and 14) or to illustrate its competition with the carbonyl Osp^2 atom in bifurcated hydrogen bonds (Figs. 13 and 15).

The first example is a dimer generated by hydrogen bonds between O–H (donor) and the ester Osp^3 atom (acceptor) of two centrosymmetrically related molecules in the structure of trimethyl-5-acetylmethyl-4-oxo-5-hydroxy-4,5-dihydro-1*H*-pyrrolo-[2,3-*f*]quinoline-2,7,9-tricarboxylate (Fig. 11; Itoh *et al.*

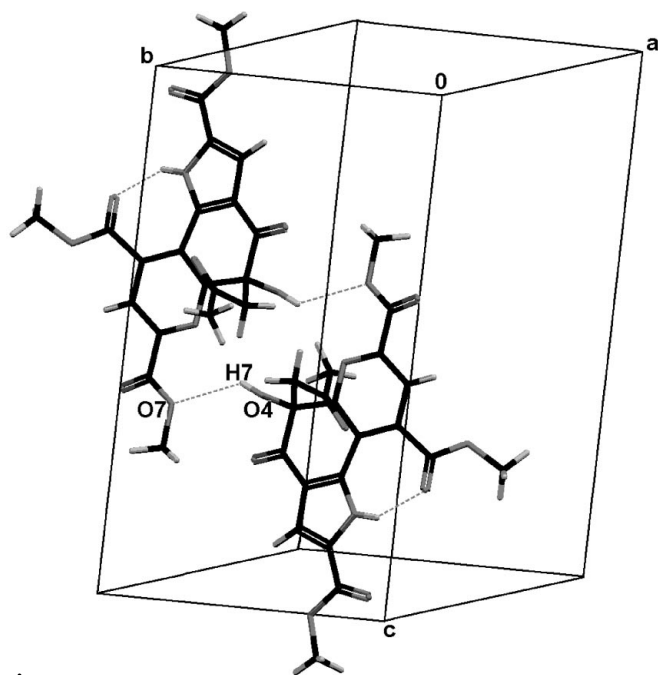


Figure 11
The hydrogen-bonded dimer in the crystal structure of trimethyl-5-acetylmethyl-4-oxo-5-hydroxy-4,5-dihydro-1*H*-pyrrolo[2,3-*f*]quinoline-2,7,9-tricarboxylate (Itoh *et al.*, 1993; CSD code HAWWAD). The geometric parameters ($O4 \cdots O7$ 3.012, $H7 \cdots O7$ 2.411 Å, $O4-H7 \cdots O7$ 132.9°) are within the accepted range defined for a hydrogen bond.

et al., 1993; CSD code HAWWAD). In the structures shown in Figs. 11 and 12 the Osp^3 acceptor function is sterically favoured in the intermolecular hydrogen bond, whereas the Osp^2 atom is only the acceptor in an intramolecular hydrogen bond. The crystal structures of di-*tert*-butyl-2,4,9-trihydroxy-2-methyl-6-oxo-1,7-dioxaspiro[4.4]nonane-8,9-dicarboxylate (Fig. 12; Calter *et al.*, 2002; CSD code AFERUY) and nepetalic acid (Fig. 13; Eisenbraun *et al.*, 1981; CSD code

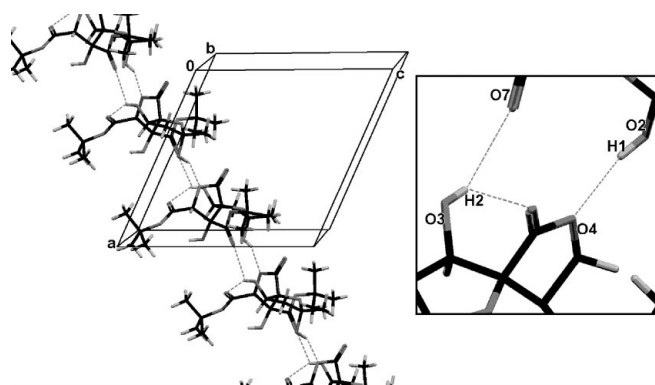


Figure 12
A chain created by hydrogen-bonded molecules *via* O–H \cdots Osp^3 in the crystal structure of di-*tert*-butyl-2,4,9-trihydroxy-2-methyl-6-oxo-1,7-dioxaspiro[4.4]nonane-8,9-dicarboxylate (Calter *et al.*, 2002; CSD code AFERUY). The hydrogen bond is characterized by geometric parameters [$O2 \cdots O4sp^3$ 2.809, $H1 \cdots O4$ 2.046 Å, and angle $O2-H1 \cdots O4$ of 150.7°]. An additional hydrogen bond is part of a bifurcated hydrogen bond ($O3 \cdots O7$ 2.977, $H2-O7$ 2.478 Å, $O3-H2 \cdots O7$, 119.0°; O7 is a carbonyl oxygen that does not belong to an ester group). This additional intermolecular O–H \cdots O=C hydrogen bond is part of the intramolecular interaction, exhibiting a less favourable geometry.

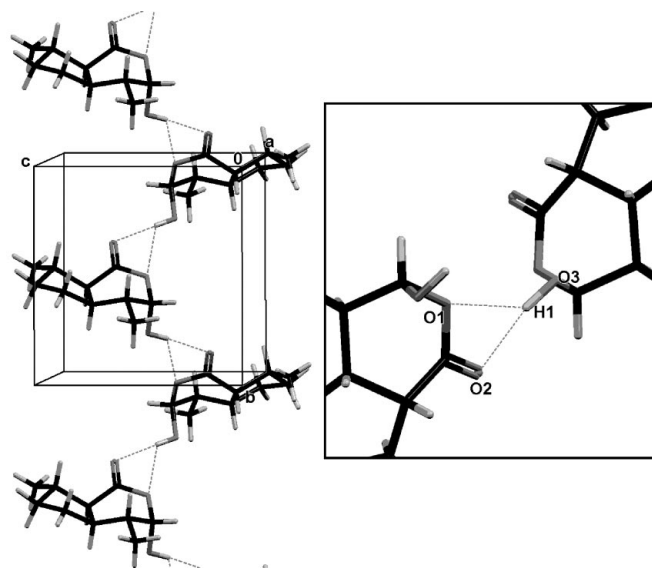


Figure 13
A chain realised through a bifurcated hydrogen bond that connects molecules using Osp^3 and Osp^2 of a lactone group in the structure of nepetalic acid as the acceptors (Eisenbraun *et al.*, 1981; CSD code BAKZUI). The hydrogen-bond lengths are: $O3 \cdots O1sp^3$ 3.228, $H1 \cdots O1$ 2.591, $O3-H1 \cdots O2sp^2$ 2.817, $H1 \cdots O2$ 1.931 Å, and angles $O3-H1 \cdots O1$ 128.4, $O3-H1 \cdots O2$ 168.3°.

BAKZUI) illustrate one-dimensional hydrogen-bonded patterns with different participations of the lactone Osp^3 and Osp^2 atoms in hydrogen bonding. In the structure of nepetalic acid (Fig. 13) both O atoms of the lactone group compete for the acceptor role in the bifurcated hydrogen bond (see also Fig. 15 for a two-dimensional hydrogen-bonding pattern). The two-dimensional pattern (Figs. 14 and 15) is represented by two different modes of hydrogen bonding. The first mode is observed in the structure of *endo*-methyl-1(*R*), 2(*S*), 3(*R*), 4(*S*)-2-benzamido-3-(1,2-dihydroxyethyl)bicyclo[2.2.1]-heptane-2-carboxylate (Fig. 14; Buñuel *et al.*, 2000; CSD code KONQUZ); the ester Osp^3 is sterically and electronically favoured as the acceptor in the hydrogen bond $O-H\cdots O$,

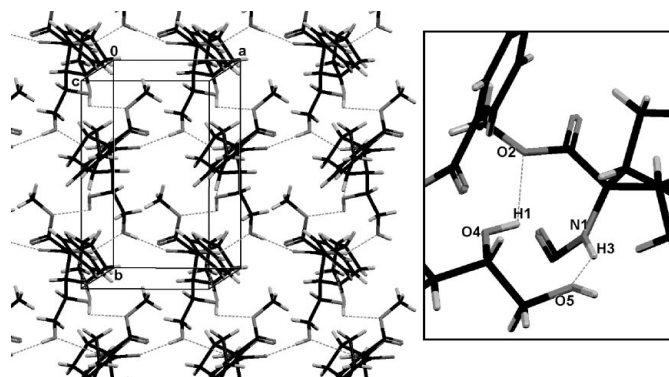


Figure 14

A two-dimensional hydrogen-bonded network realised by $N-H\cdots O$ and $O-H\cdots Osp^3$ interactions in the crystal structure of *endo*-methyl-1(*R*), 2(*S*), 3(*R*), 4(*S*)-2-benzamido-3-(1,2-dihydroxyethyl)bicyclo[2.2.1]-heptane-2-carboxylate (Buñuel *et al.*, 2000; CSD code KONQUZ) with geometric parameters $O4\cdots O2sp^3$ 3.025, $H1\cdots O2$ 2.546 Å; angle $O4-H1\cdots O2$ 115.4°, $N1\cdots O5$ 2.917 Å; $H3\cdots O5$ 2.169 Å; angle $N1-H3\cdots O5$ 145.5°.

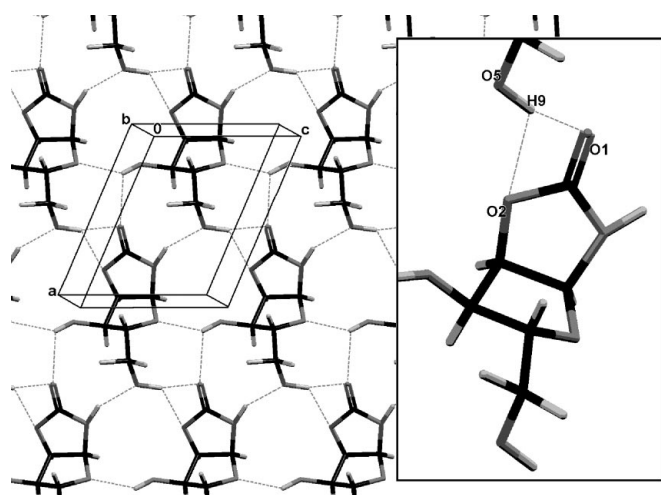


Figure 15

A two-dimensional network realised by a bifurcated hydrogen bond using both O atoms (Osp^3 and Osp^2) of a lactone group as the acceptors in the crystal structure of α -D-ribofuro(1',2',4,5)-oxazolidone (Singh & Hodgston, 1976; CSD code RFOXAZ) with geometric parameters $O5\cdots O2sp^3$ 3.318, $H9\cdots O2$ 2.568 Å, $O5-H9\cdots O2$ 128.3°, $O5\cdots O1sp^2$ 1.825 Å, $O5-H9\cdots O2$ 166.1°.

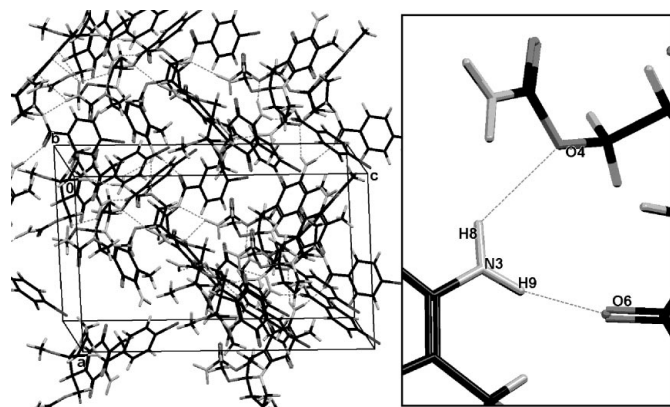


Figure 16

A three-dimensional hydrogen-bonded network with the participation of $N-H\cdots Osp^3$ in the crystal structure of 1-*N*-(*p*-bromobenzoyl)-mitomicyn C (Shirahata & Hirayama, 1983; CSD code CEGNIL) with geometric parameters $N3\cdots O4sp^3$ 3.143, $H8\cdots O4$ 2.416 Å, $N3-H8\cdots O4$ 130.9°; $N3\cdots O6sp^2$ 2.896, $H9\cdots O6$ 1.996 Å, $N3-H9\cdots O6$ 160.9° and $N4\cdots N16$ 3.317, $H16\cdots N1$ 2.341 Å, $N4-H16\cdots N1$ 167.2° (this hydrogen bond is shown in the packing diagram but not in the insert).

whereas the interaction $N-H\cdots OH$ completes the two-dimensional hydrogen-bonding pattern. However, the Osp^2 atom is located in a hydrophobic region and does not participate in hydrogen bonding. The second mode is represented by the participation of a lactone group in a bifurcated hydrogen bond (Figs. 13 and 15). An example is α -D-ribofuro(1',2',4,5)-oxazolidone (Fig. 15; Singh & Hodgston, 1976; the CSD code RFOXAZ). A three-dimensional network of hydrogen bonds is illustrated by the crystal packing of 1-*N*-(*p*-bromobenzoyl)-mitomicyn C (Fig. 16; Shirahata & Hirayama, 1983; CSD code CEGNIL), where each molecule exhibits three donor and three acceptor functions.

Among the various modes of the acceptor function of the ester Osp^3 atom already shown and discussed, the most predictable hydrogen-bonding pattern is observed with the lactone group as the proton acceptor(s). Through the introduction of a reduced number of donors carefully positioned in the molecule to meet the sterically favoured environment for lactone O atoms, an engineered hydrogen-bonding pattern may be generated.

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