Hydrogen Bonding of Carbonyl, Ether, and Ester Oxygen Atoms with Alkanol Hydroxyl Groups

JOS P. M. LOMMERSE,[1] SARAH L. PRICE,[2] ROBIN TAYLOR[1]

[1]*Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, England*
[2]*University College London, Department of Chemistry, 20 Gordon Street, London WC1H 0AJ, England*

ABSTRACT: An attractive way to study intermolecular hydrogen bonding is to combine analysis of experimental crystallographic data with ab initio–based energy calculations. Using the Cambridge Structural Database (CSD), a distributed multipole analysis (DMA)-based description of the electrostatic energy, and intermolecular perturbation theory (IMPT) calculations, hydrogen bonding between donor alkanol hydroxyl groups and oxygen acceptor atoms in ketone, ether, and ester functional groups is characterized. The presence and absence of lone pair directionality to carbonyl and ether or ester oxygens, respectively, can be explained in terms of favored electrostatic energies, the major attractive contribution in hydrogen bonding. A hydrogen bond in its optimum geometry is only slightly stronger when formed to a ketone group than to an ether group. Hydrogen bonds formed to carbonyl groups have similar properties in a ketone or ester, but the ester O^2 differs from an ether oxygen due to various environmental effects rather than a change in its intrinsic properties. For (*E*)-ester oxygens, there are few hydrogen bonds found in the CSD because of the competition with the adjacent carbonyl group, but the interaction energies are similar to an ether. Hydrogen bonds to O^2 of (*Z*)-esters are destabilized by the repulsive electrostatic interaction with the carbonyl group. The relative abundance of nonlinear hydrogen bonds found in the CSD can be explained by geometrical factors, and is also due to environmental effects producing slightly stronger intermolecular interaction energies for an off-linear geometry.   © 1997 by John Wiley & Sons, Inc.   *J Comput Chem* **18**: 757–774, 1997

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Introduction

Hydrogen bonds are one of the most important intermolecular interactions involved in biochemical processes.[1] Knowing the characteristics of the wide variety of hydrogen bonds is of utmost importance to understand these processes, such as in protein–ligand interactions. Subsequently, this will help to improve (semi-) empirical methods, in which intermolecular interactions play a main role, as in for example, docking programs. Detailed hydrogen bond analysis is therefore essential for the development of suitable parameters characterizing these protein–ligand interactions.[2]

In this article, we investigate the formation of intermolecular hydrogen bonds between the alkanol hydroxyl groups as hydrogen donor and four different types of oxygen atoms as acceptors, being present in carbonyl, ether, and ester groups. These hydrogen bonds are relevant in biological systems, as the acceptor groups are frequently part of functional groups in protein ligands, as well as incorporated in probes for drug design, whereas the hydroxyl groups of serine, threonine, or tyrosine can act as hydrogen bond donor toward these functional groups.

The most important hydrogen bond characteristics to be explored are strength, geometry, and directionality toward an acceptor molecule. The intermolecular interactions involving polar hydrogens in biomolecules can vary from only 10 kJ/mol for $C-H \cdots X$ systems[3] up to the strength of a weak covalent bond (~ 200 kJ/mol) for hydrogen bonds between ions, such as in arginine . . . aspartate amino acid side-chain interactions.[4, 5] Generally, the neutral $O-H \cdots O$ hydrogen bonds are expected to have strengths in the order of 20 kJ/mol, but this must vary considerably as ester oxygen atoms hardly accept any hydrogen bonds,[6] whereas other types of sp^3 oxygen atoms (e.g., water) are common acceptors.

Optimum hydrogen bond angles are not necessarily linear, but rather seem to depend on the asymmetry of the molecular units involved.[7] For example, in the $C \equiv O \cdots HOH$ complex the hydrogen bond angle deviates 12° from linearity.[8, 9] Such subtle differences may be reflected in optimal binding of ligands to protein binding sites.

The directionality of hydrogen bonding to the lone pairs of the oxygen acceptor atoms has been a matter for discussion. On the basis of the rotational spectroscopy of small molecule complexes, rules have been proposed which state that the nonbonding electron pair is the most favored direction for the donor hydrogen.[10] Searches in crystal structure databases resulted in different directionalities between sp^3 and sp^2 hybridization state oxygen atoms.[6, 11, 12] For ether sp^3 oxygens, a directional preference for a position in the plane of the lone pairs was observed, but no preference for the lone pair direction itself, in marked contrast to carbonyl sp^2 oxygen atoms where a distinct preference for the lone pair direction was found. However, it has been argued that this latter observation might be the result of other structural factors in crystals; that is, the formation of certain hydrogen-bonded motifs, which are more favorable in an overall structure, and leading to the observed hydrogen bond geometries.[13, 14] This would suggest little intrinsic directional preference at the acceptor lone pair.

These observations show that we cannot easily generalize the characteristics of $O-H \cdots O$ hydrogen bonds, but rather have to investigate carefully the various existing types. This study of $O-H \cdots O$ hydrogen bonds considers both experimental geometrical data from crystal structures and calculated theoretical energies, and has proven to be a powerful approach.[15] The experimental data have been obtained from the Cambridge Structural Database (CSD), which presently contains the data of 146,272 crystal structures of organic and metallo-organic compounds.[16] The CSD is a very suitable source of detailed geometrical information on nonbonded interaction in the condensed phase, which can be exploited to investigate biological systems.[17, 18] Observed differences in the ability of various oxygens to accept hydrogen bonds are also investigated by theoretical methods. As hydrogen bonds are primarily the result of an electrostatic attraction,[19–21] the electrostatic interactions of model systems were studied initially, using "exp-6 + DMA" calculations, which are based on the electrostatics of a distributed multipole analysis of the monomers and empirical exp-6 repulsion–dispersion parameters.[22] These calculations provide an accurate description of the electrostatic interactions of nonoverlapping molecules and are sufficiently fast to allow the multidimensional potential energy surface to be explored thoroughly. However, more detailed and accurate data can be obtained from intermolecular perturbation theory (IMPT)[23] calculations, which are, unfortunately,

''expensive'' in terms of computer requirements. These ab initio–based calculations provide estimates of the electrostatic, exchange–repulsion, charge transfer, polarization, and dispersion contributions, giving a fairly reliable total intermolecular energy, and providing tools for a better understanding of the nature of hydrogen bonds.[2]

Alternatively, ab initio supermolecule calculations followed by energy decomposition analysis could be used to calculate the various energy contributions, but this approach is complicated by basis set superposition error (BSSE).[21, 24, 25] Ab initio calculations result in an electrostatic energy that includes both the long range electrostatic energy as well as the short range effects of interpenetration of the two charge distributions, whereas the distributed multipolar model only accounts for the long range term. The short range (penetration) term can be considerable; for example, for the N—H $\cdots$ O=C hydrogen bond about 20% of the total electrostatic energy was found to be due to penetration.[26]

In the following analysis, the experimental crystallographic data and theoretical tools have been combined to provide a detailed picture and insight into hydrogen bond characteristics of ketone, ether, and ester oxygen acceptor atoms.

Methods

EXPERIMENTAL GEOMETRIES OF HYDROGEN BONDS

Data on intermolecular hydrogen bonding in organic crystal structures were obtained from the Cambridge Structural Database (CSD,[16] version 5.10, October 1995, containing 55,226 organic compounds with atomic coordinates). The QUEST 3D software[27] was used for spatial searches of hydrogen bonds. The acquired data were graphically processed using VISTA 2.0.[28] Searches and data processing were carried out on a local Sun Sparc-Station5. Searches were restricted to better quality CSD entries by the use of secondary search criteria: (a) good quality crystallographic refinement, $R \leq 0.10$; (b) error-free coordinates; (c) no crystallographic disorder; and (d) no polymeric structures. This reduced the number of entries to be analyzed to 47,341.

Fragments for the searches were defined as shown in Figure 1. The coordination number for peripheral carbon atoms was set to four, thus representing an sp^3 hybridization state. As the posi-
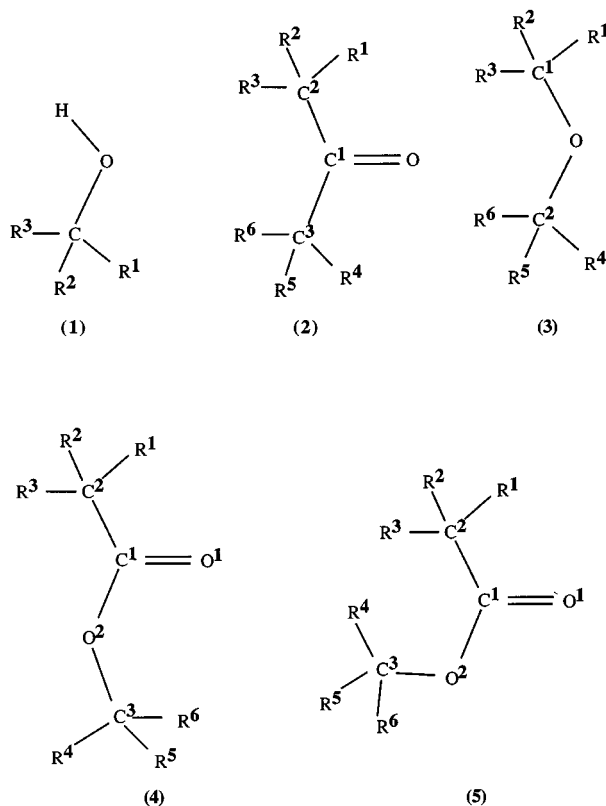
FIGURE 1. Hydrogen bond donor (**1**) and oxygen acceptors (in **2**, **3**, **4**, and **5**). In the case of describing the fragments for the searches in the CSD: R = any atom. In the case of the model systems used for theoretical calculations: R = H.

tions of H atoms for X-ray crystallographic data are usually poorly determined, the length of the O—H bond was set to a fixed value of 0.983 Å along the O—H vector, which is the average of the well-determined H—O bond lengths from neutron crystallographic data. Hits were defined by intermolecular contact of the hydroxyl hydrogen (of **1**) with the acceptor oxygen (of **2**, **3** and **4**, **5**; with separation $d \leq 2.61$ Å, this limit being based on the van der Waals radii of oxygen [1.52 Å[29]] and hydrogen [1.09 Å, when bonded to carbon[30]]). However, a hit was rejected if the O—H $\cdots$ O angle was less than 90°, as it becomes likely that another intermolecular interaction or packing phenomenon is responsible for the observed geometry.

Hydrogen bond lengths (d) and bond angles (α) and parameters determining the lone pair directionality (θ and φ) of each hit were stored (defined in Fig. 2a and b). Instead of using the ''chicken wire'' contours,[6] we represented the distributions of hydrogen atoms around the acceptor

(a)

(b)
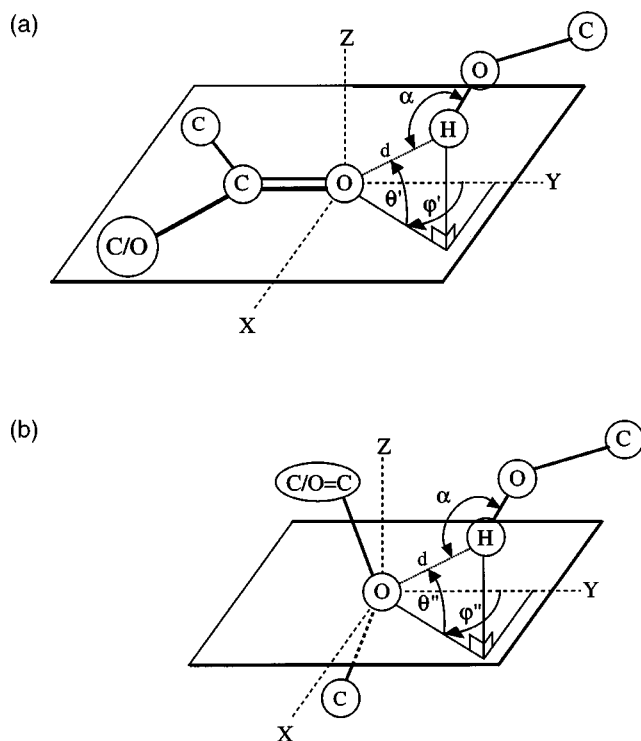
FIGURE 2. Definition of parameters describing the geometry of hydrogen bonding for (a) sp^2 oxygens in C=O and (b) sp^3 oxygens in C—O—C. d is the hydrogen bond length O$\cdots$H; α the hydrogen bond angle O—H$\cdots$O; θ and φ are the pseudopolar angles describing the position of H with respect to acceptor O.

oxygens in statistically corrected two-dimensional plots, which can be directly used for comparison between the different systems investigated by transforming the pseudopolar angle, θ, into its sine value. The rationale for this correction is that a random hydrogen contact is more likely to be found at smaller θ values, correlating with a sine distribution.[10, 11] A similar correction was applied for the polar hydrogen bond angle, α, which correlates with a cosine distribution.[31]

COMPUTATIONAL DETAILS

The energy calculations were carried out on a Silicon Graphics Indigo[2] workstation. The ab initio package, CADPAC 4.2,[32] was used to calculate the wave functions of the individual monomers at the 6-31G* basis set level throughout. The geometries of the model compounds (Fig. 1) were optimized at the SCF level, starting with geometries obtained from average bond lengths and bond angles of the fragments used for the hydrogen bond searches in

the CSD. Electron correlation was included in the wave function by second-order Møller−Plesset theory (MP2),[33] and a distributed multipole analysis (DMA)[34] was performed to calculate atomic multipoles up to hexadecapole.

The orientational preference of the interacting hydrogen bond donor toward the acceptor was explored by minimizing the intermolecular energy of the methanol and each model acceptor molecule, using the ORIENT 3.0 program.[34] The model intermolecular potential *exp-6 + DMA* was comprised of the ab initio−based DMA electrostatic model plus an empirical atom−atom *exp-6* repulsion−dispersion term. The electrostatic energies were calculated using all terms in the multipole expansion up to and including r^{-5}, were r is the intermolecular separation of the pair of atomic sites. It has been shown previously that this truncation is adequate for an accurate description of interactions involving hydrogen bonds.[20] A distinction between polar and aliphatic hydrogen atoms was made in the empirical repulsion and dispersion parameters. The *6-exp* repulsion−dispersion parameters have been derived and tested on a wide range of crystal structure data in conjunction with a DMA electrostatic model (FIT parameters).[35] A large number of starting orientations for the dimers were generated, in which different parts of the surface of the hydrogen bond donor molecule (methanol) faced the various parts of the surface of the acceptor molecule. The two nearest atomic sites were separated by 3 to 4 Å for the approximately 100, 100, and 400, 400 different starting orientations for the methanol $\cdots$ propanone, methanol $\cdots$ methoxymethane, methanol $\cdots$ (Z)-methylacetate, and methanol $\cdots$ (E)-methylacetate systems, respectively. The surface around the acceptor oxygen atom was probed particularly thoroughly.

Partial ab initio potential energy surfaces around the acceptor oxygen atoms were scanned in the regions of minima in the *exp-6 + DMA* model interaction energy, using the intermolecular perturbation theory (IMPT)[23] method within the CADPAC 4.2 package. It provides estimates of each of the significant contributions to the intermolecular interaction energy. At first order, the electrostatic energy (E_{es}) term describes the classical Coulombic interaction of charge distributions between the molecules. This can be an attractive or a repulsive interaction. The exchange−repulsion (E_{er}) term is the sum of: (i) an energy lowering due to exchange of electrons of parallel spin be-

tween the molecules; and (ii) a repulsive part, based on the prohibition of electrons with parallel spin from occupying the same region in space (the Pauli exclusion principle). The first order energy term, E_{er}, is positive (repulsive), and increases exponentially with decreasing separation as the wave functions penetrate.

At second order, the IMPT gives the polarization or induction (E_{pol}) and the charge transfer (E_{ct}) energy terms. The polarization of molecule A is an intramolecular change of its wave function, due to the presence of undistorted charge distribution B, whereas the charge transfer to A is an actual transfer of electron density from molecule B to A, thus changing the wave functions of both A and B. Both second order terms describe distortions of the charge distribution within molecules A and B, which occur only because they are energetically favorable, thus lowering the total energy of A and B. Finally, the attractive dispersion energy (E_{disp}) term is given by the second order double-excitation IMPT term. E_{disp} will certainly be underestimated at the 6-31G* basis set level of the calculations.[36] Using the IMPT as currently implemented in CADPAC, the calculation of the polarization and charge transfer energy terms is free of basis set superposition error (BSSE), although the division between these terms is not completely basis set independent.[37] BSSE is a major problem for calculation of interaction energies using the supermolecule approach.[39–41]

## Results and Discussion

CRYSTALLOGRAPHIC GEOMETRICAL PROPERTIES

In Figure 2, the parameters that describe location of the conventionally viewed lone pairs are given. For planar hybridized (sp^2) oxygen atoms the lone pairs are in the C—C=O plane at $\theta' = 0°$ (sin $\theta' = 0$) and at $\varphi' = \pm60°$. For tetrahedral hybridized (sp^3) oxygen atoms they are in the plane which bisects the covalent bonds of the C—O—C fragment, at $\theta'' = 0°$ (sin $\theta'' = 0$), with $\varphi'' = \pm55°$. The CSD distributions of the hydroxyl hydrogen atoms of the donor molecular around that of the acceptor oxygen atoms are given in Figures 3a–c. Furthermore, the geometrically corrected O ⋯ H—O hydrogen bond angles are shown in Figure 4a–c and the distribution of O ⋯ H hydrogen bond lengths in Figure 5a–c. The resulting

geometrical features are briefly discussed in what follows.

LONE PAIR DIRECTIONALITY

In the case of alkanol ⋯ ketone hydrogen bonding (Fig. 3a) it can be seen that the preferred hydrogen bond orientation is near or in the plane of the oxygen lone pairs (sin $\theta' = 0$) and almost pointing to one of the acceptor oxygen lone pairs ($\varphi' = 50°$). The alkanol ⋯ ether hydrogen bond shows a different geometrical pattern (Fig. 3b). The preferred hydrogen orientation is still near or in the plane of the lone pairs, which is also to be expected because this plane is sterically the best accessible position for the donor molecule. However, the clustering of data points between $\varphi'' = -45°$ and $\varphi'' = +45°$ points to a more favorable hydrogen position between both lone pairs, rather than in the lone pair directions. For the alkanol ⋯ ester carbonyl O^1 hydrogen bond the asymmetrical geometry with respect to the C=O axis in the plane of the lone pairs must be considered, as well as a distinction between (Z)-esters (4) and (E)-esters (5), where the (E)-ester is usually found in lactone ring systems. In Figure 3c, no distinction has been made between (Z)- and (E)-esters, but we note that about 56% of the total hydrogen bonds are found at the ''cis side'' of the carbonyl group (defined by $\varphi > 0°$, see Fig. 2) for the (E)-esters, in contrast to only 27% for (Z)-esters. The lower percentage of the (Z)-ester is obviously due to steric hindrance of C^3 and groups attached to this carbon and, by consequence, this also produces smaller average $|\varphi|$ values at the cis-side of the (Z)-esters. The preferred position of the hydrogen is in the lone pairs plane ($\theta' = 0°$) and approximately in the lone pair directions ($|\varphi'| = 60°$) at both sides of the carbonyl group of the (Z, E)-esters. This lone pair directionality is very similar to that of the ketone acceptor (Fig. 3a). It corroborates the results from CSD searches of hydrogen bonding to C=O groups in different molecular environments,[38] where hydrogen bonds to carboxylates, carboxylic acids, and terminal amides were also found to be preferably in the lone pair direction of the sp^2 oxygens.

The alkanol ⋯ ester O^2 hydrogen bond turns out to occur only incidentally (if at all, as all O ⋯ H intermolecular distances are longer than 2.0 Å). Indeed, most of the oxygens near O^2 of the (E)-esters are actually hydrogen bonded to the carbonyl group. No conclusions on geometrical
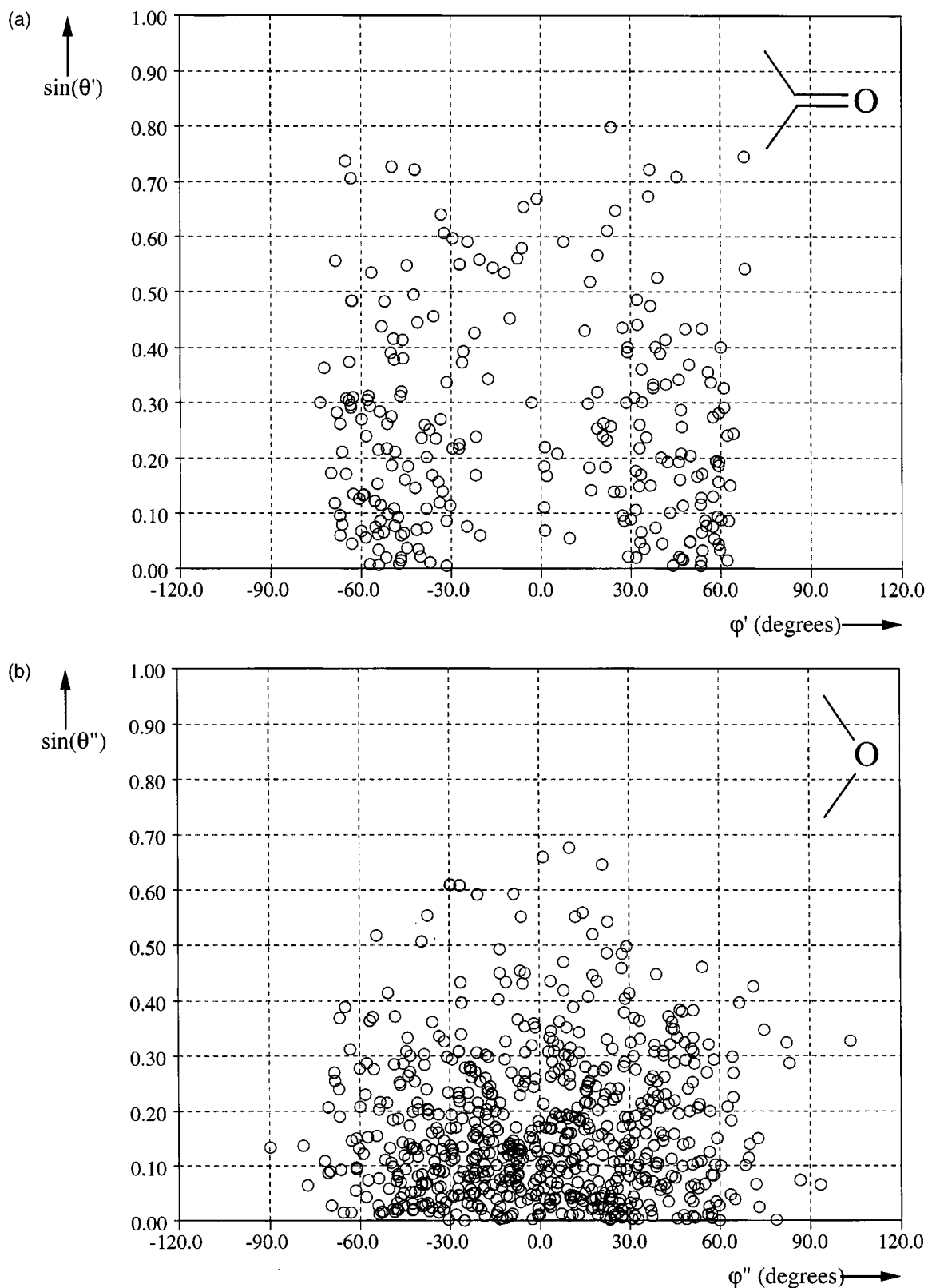
FIGURE 3. Statistically corrected distribution of the hydrogen bond H atoms around acceptor O atoms, as found in the crystal structures in the CSD, represented by φ, θ angles (see text and Fig. 2), for the following systems: (a) alkanol $\cdots$ ketone; (b) alkanol $\cdots$ ether, and (c) alkanol $\cdots$ (Z / E)-ester carbonyl.
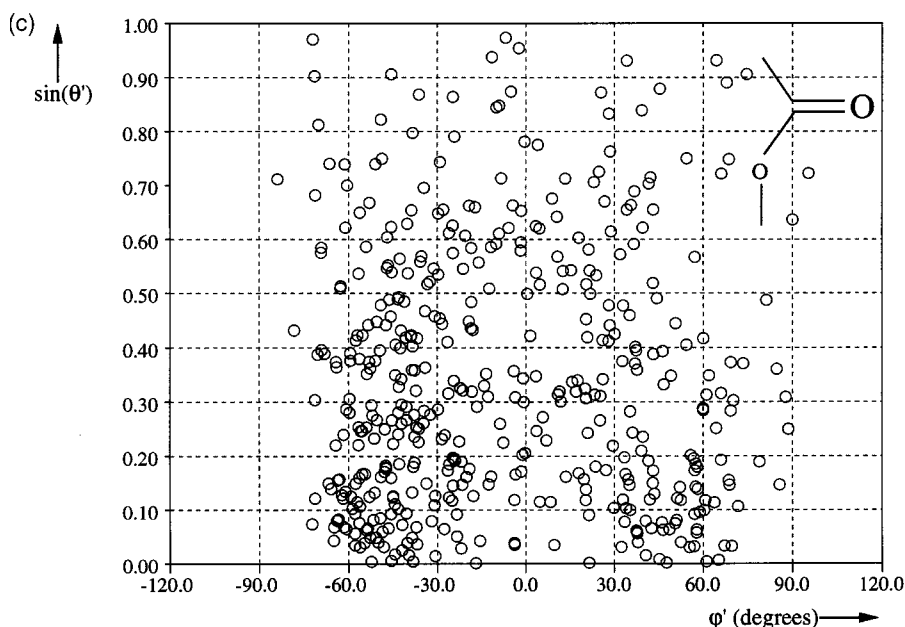
FIGURE 3. (Continued)

O—H ⋯ O LINEARITY

The most common O—H ⋯ O angle, α, is $165° \pm 5°$ for the data set. However, when the geometric cosine correction for space surface is applied, then most hydrogen bonds occur in the region $0.975 < -\cos\alpha < 1.000$ ($167° < \alpha < 180°$), showing that the preferred direction is approximately linear (Fig. 4a−c). Kroon et al. found similar data for O—H ⋯ O—H hydrogen bonds in crystal structures, which were explained as a combination of the geometrical cosine factor and a slightly off-linear optimum hydrogen bond in a shallow energy well.[31]

H ⋯ O DISTANCE

The H ⋯ O distances are remarkably similar for the different hydrogen bond acceptors, as most fall in the range of 1.8 to 2.0 Å for all systems. This suggests no great differences in hydrogen bond strengths between these systems. The ethers tend to form relatively more hydrogen bonds at longer distances, which suggests that the hydrogen bond is more readily elongated by competing interactions.

This analysis, based on the most recent CSD crystal structure database, confirms previous ob-servations when much fewer database entries were available.[10, 11, 31] The crystallographic data raise several questions. Why is there a lone pair preference for hydrogen bonding to a carbonyl type of oxygen atom and not to an ether type of oxygen? Why does the ester O^2 oxygen hardly accept any hydrogen bonds? Is it because of competition with the ester carbonyl O^1 oxygen, or is the ester O^2 a far worse acceptor than an ordinary ether oxygen? And, are the hydrogen bond properties of the carbonyl oxygen atoms in ester groups essentially the same as in ketones, despite the electrostatic and short range inductive effects of the bonded ester oxygen? Finally, is there an energetic preference for a linear O—H ⋯ O hydrogen bond angle, or is a slightly bent angle more favorable? These questions are answered by the following calculations of the energies of model systems containing these hydrogen bonds.

INTERMOLECULAR ENERGY STUDIES USING DISTRIBUTED MULTIPOLES-BASED MODEL POTENTIAL

Minimizations of the *exp*-6 + *DMA* intermolecular interaction energies between methanol and propanone, methoxymethane, or (*Z*, *E*)-methylacetate, respectively, led to a number of favorable dimer orientations. The most favorable minima all had (conventional) hydrogen bonds, and are shown in Figures 6−9 and described in Table I.
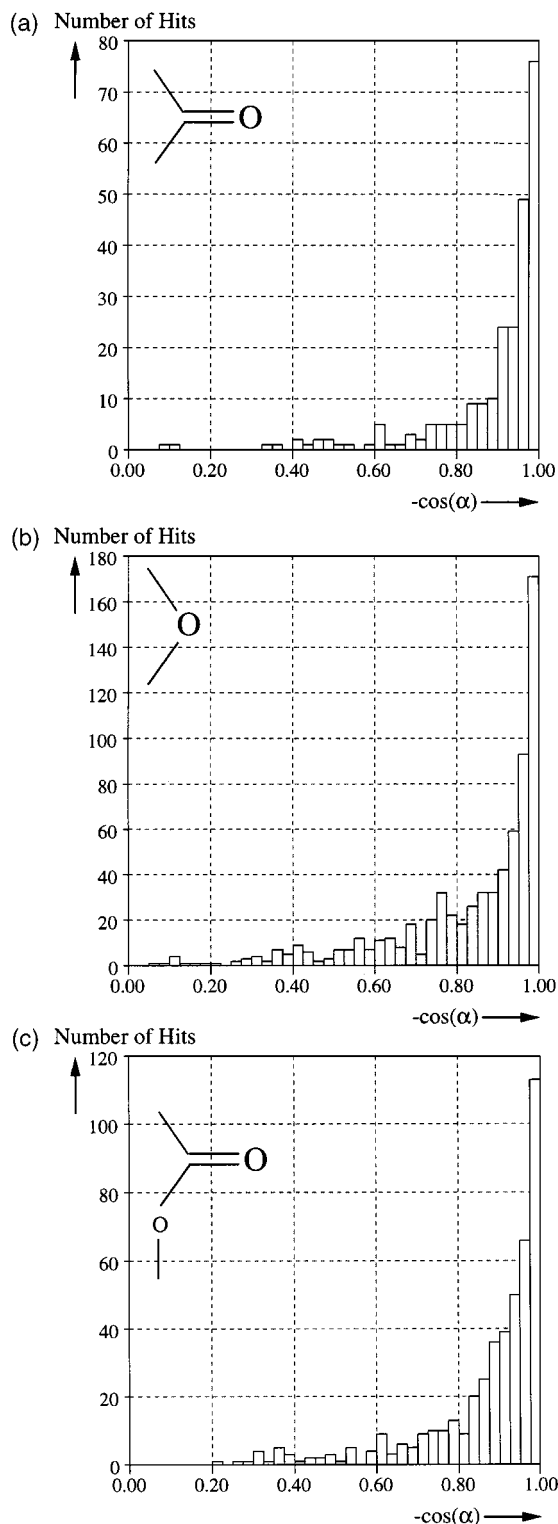
FIGURE 4. Statistically corrected distribution of hydrogen bond angles O—H ⋯ O, as found in the crystal structures in the CSD, for the following systems: (a) alkanol ⋯ ketone; (b) alkanol ⋯ ether, and (c) alkanol ⋯ (Z / E)-ester carbonyl.
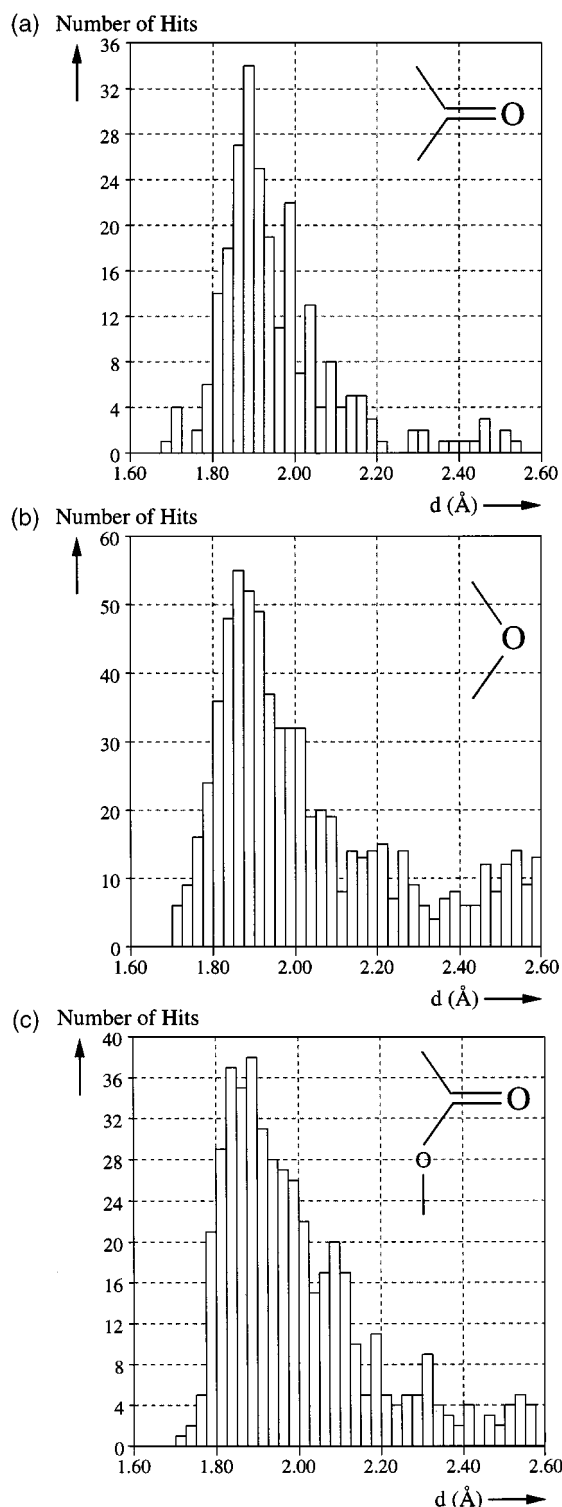
FIGURE 5. Distribution of hydrogen bond lengths H ⋯ O as found in the crystal structures in the CSD, for the following systems: (a) alkanol ⋯ ketone; (b) alkanol ⋯ ether, and (c) alkanol ⋯ (Z / E)-ester carbonyl.
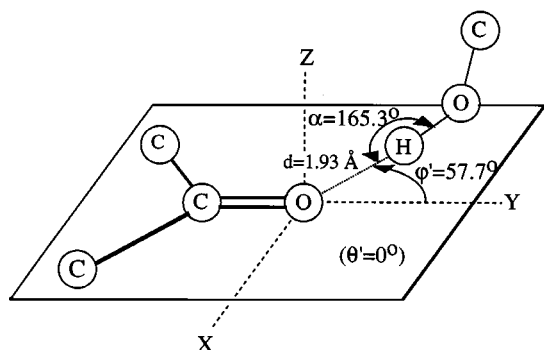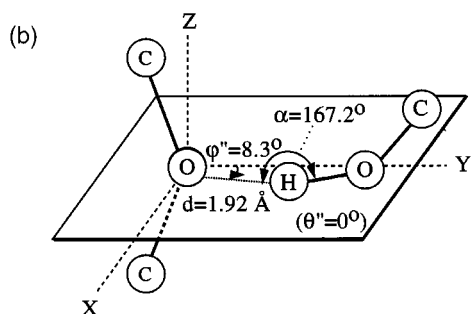
FIGURE 6. Geometry of the ORIENT minimum energy situation for the methanol ··· propanone hydrogen bonded system. In this minimum, the ORIENT interaction energy is −22.1 kJ / mol and the IMPT total intermolecular energy is −24.7 kJ / mol.

METHANOL ··· PROPANONE

In the case of the methanol ··· propanone system, only one hydrogen bonded minimum orientation was obtained (see Fig. 6), having an *exp*-6 + *DMA* interaction energy of −22.1 kJ/mol. This hydrogen bond has the characteristics of the most frequently observed geometry in the CSD. The
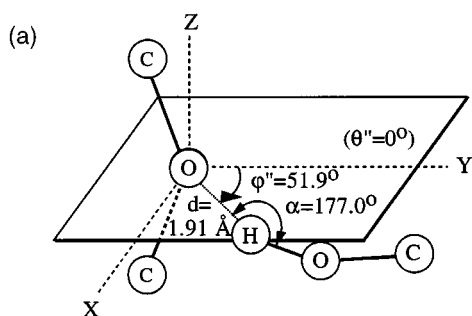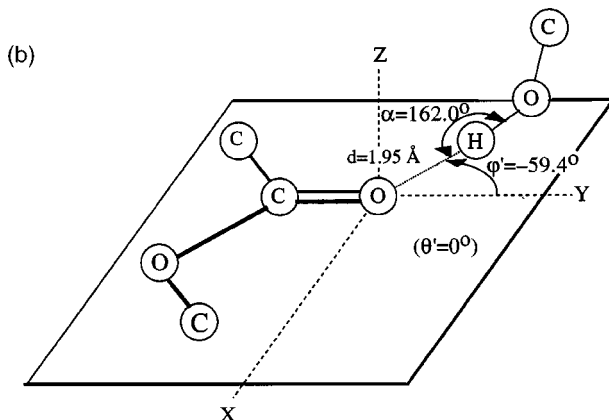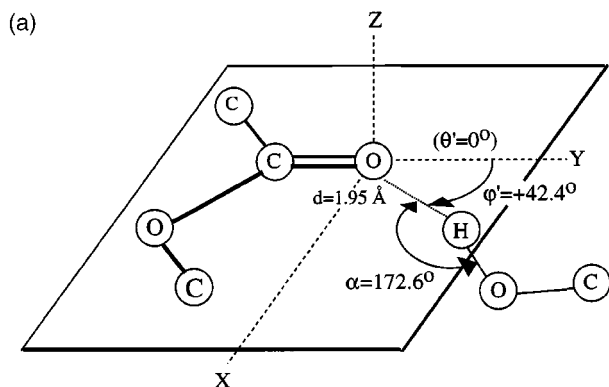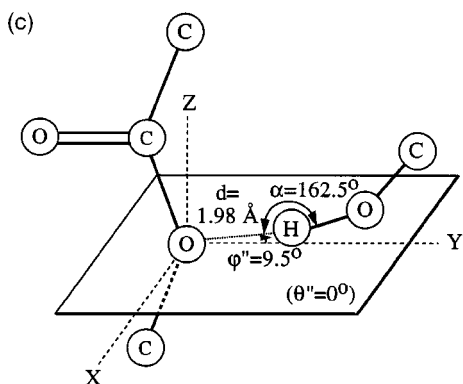

FIGURE 7. Geometries of the ORIENT minimum energy situations for the methanol ··· methoxymethane hydrogen bonded systems. In these minima, the ORIENT interaction energy and the IMPT total intermolecular energy are: (a) −21.9 and −20.7 kJ / mol; and (b) −21.7 and −21.9 kJ / mol.

FIGURE 8. Geometries of the ORIENT minimum energy situations for the methanol ··· (*Z*)-methylacetate hydrogen bonded systems. In these minima, the ORIENT interaction energy and the IMPT total intermolecular energy are: (a) −23.8 and −25.9 kJ / mol; (b) −22.9 and −24.6 kJ / mol; and (c) −17.6 and −14.5 kJ / mol.

hydroxyl group hydrogen is situated in the plane of the lone pairs of the acceptor oxygen ($\theta' = 0°$), and points roughly in the direction of one of the lone pairs ($\varphi' = 57.7°$). The bond angle O—H ··· O is slightly off-linear ($\alpha = 165.3°$), in which the hydroxyl oxygen has a position nearer to the proximal propanone methyl group than it would have
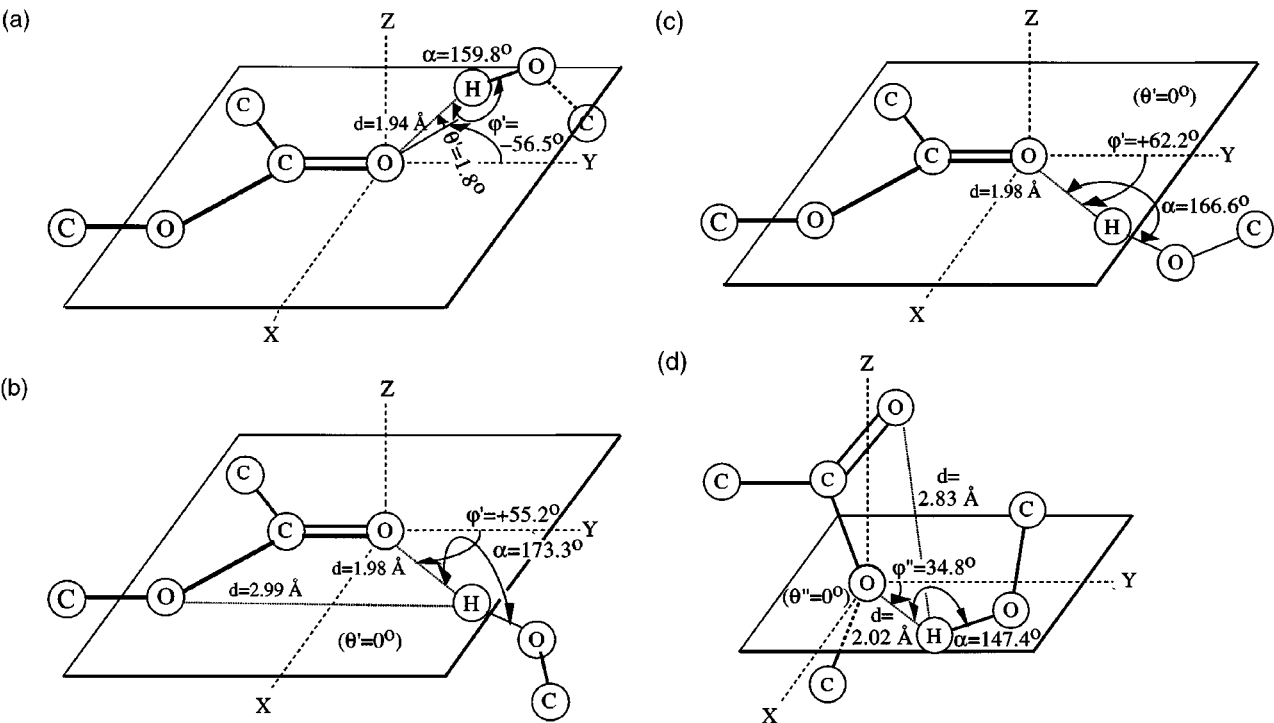
FIGURE 9. Geometries of the ORIENT minimum energy situations for the methanol $\cdots$ (*E*)-methylacetate hydrogen bonded systems. In these minima, the ORIENT interaction energy and the IMPT total intermolecular energy are: (a) -24.2 and -27.2 kJ/mol; (b) -22.8 and -24.1 kJ/mol; (c) -22.2 and -23.7 kJ/mol; (d) -21.5 and -20.4 kJ/mol.

had in a linear position on the extension of the $O \cdots H$ hydrogen bond axis.

No hydrogen bonds were present in the two other minor minima, which have the methanol molecule in a position above the plane of the pro-panone molecule, one minimum where the C—O bond is roughly on top of, and the other antiparallel with respect to the C=O bond. Their interaction energy of about -12.0 kJ/mol is only half the energy of the hydrogen bonded orientation.

TABLE I.

Geometries and Total Interaction Energies for Hydrogen-Bonded *exp*-6 $\pm$ *DMA* Minimum Energy Orientations.[a]

Dimer	Figure	$\theta°$	$\varphi°$	$\alpha°$	d (Å)	*exp-6* + *DMA* (kJ/mol)	IMPT (kJ/mol)
MeOH $\cdots$ propanone	6	0.0	57.7	165.3	1.93	-22.1	-24.7
MeOH $\cdots$ methoxymethane	7a	0.0	51.9	177.0	1.91	-21.9	-20.7
	7b	0.0	8.3	167.2	1.92	-21.7	-21.9
MeOH $\cdots$ (*Z*)-methylacetate	8a	0.0	+42.4	172.6	1.95	-23.8	-25.9
	8b	0.0	-59.4	162.0	1.95	-22.9	-24.6
	8c	0.0	9.5	162.5	1.98	-17.6	-14.5
MeOH $\cdots$ (*E*)-methylacetate	9a	1.8	-56.5	159.8	1.94	-24.2	-27.2
	9b	0.0	+55.2	173.3	1.98	-22.8	-24.1
	9c	0.0	+62.2	166.6	1.98	-22.2	-23.7
	9d	0.0	34.8	147.4	2.02	-21.5	-20.4

[a]Corresponding schematic drawings are referred to. The *exp*-6 + *DMA* energies consist of the multipolar electrostatic and empirical repulsion–dispersion interaction energies, whereas for the IMPT method the total intermolecular energy ($E_{er} + E_{es} + E_{ct} + E_{pol} + E_{disp}$) has been given.

METHANOL ⋯ METHOXYMETHANE

Two major hydrogen bonded minima are found for the methanol ⋯ methoxymethane dimer (see Fig. 7a, b). These minima have very similar interaction energies of −21.9 and −21.7 kJ/mol. The first is a typical hydrogen bond geometry with the hydroxyl group in the plane of the lone pairs, pointing almost in the direction of the lone pair ($\varphi'' = 51.9°$), with a nearly linear hydrogen bond angle ($\alpha = 177.0°$). The other minimum is also in the plane of the lone pairs, but the hydrogen position is between both lone pairs ($\varphi'' = 8.3°$), and again the hydrogen bond angle is off-linear ($\alpha = 167.2°$). This latter orientation is more typical for the experimental data observed in the CSD: hydrogen bonding in between the lone pairs with a slightly off-linear bond angle.

Besides these two hydrogen bonded dimers, three other minor minimum energy orientations were found. One has the methanol above the C—O—C plane; one at the "back" of the two methyl groups; and, in the least favorable one, near one of the methyl groups (interaction energies: −6.8, −5.2, and −4.7 kJ/mol, respectively).

METHANOL ⋯ (Z)-METHYLACETATE

The methanol ⋯ (Z)-methylacetate system results in three major minima, all hydrogen bonded. Two involve the carbonyl oxygen O^1, one near each of its lone pairs, and one the ester oxygen O^2 (see Fig. 8a−c). The most favorable formation of a hydrogen bond is found at the cis side of the carbonyl group (Fig. 8a: −23.8 kJ/mol). In this minimum the complete methanol molecule is in the plane of the (Z)-ester, with the hydroxyl group pointing slightly off the lone pair direction of O^1 ($\varphi' = +42.4°$). This is mainly due to repulsion of the methanol hydroxyl group with the C^3-methyl group of the ester (O[methanol] ⋯ $C^3 = 3.28$ Å). Despite this repulsion, the O—H ⋯ O bond angle is slightly bent toward the C^3 methyl group ($\alpha = 172.6°$), which is also found for the methanol ⋯ propanone system. The in-the-plane position of the methyl group of the methanol molecule is probably an effect of electrostatic repulsion between this methyl group and the C^3-methyl group of the ester.

The hydrogen bond at the trans position of the carbonyl axis is very similar in orientation and interaction energy to the propanone case (Fig. 8b, cf. Fig. 6). It is remarkable that the presence of the ester oxygen O^2 does not seem to affect this hydrogen bond. The energy of −22.9 kJ/mol is just 1 kJ/mol less favorable than at the cis side of the ester carbonyl axis. For the acceptor ester "ether-like" oxygen, O^2, only one hydrogen bonded minimum orientation is obtained (see Fig. 8c), which is similar to the second minimum found for the methoxymethane acceptor, but having a lower energy (−17.6 kJ/mol, in contrast to ether: −21.7 kJ/mol). The methanol molecule is in the plane of and approximately in between the lone pairs of O^2 and the bond angle is off-linear ($\alpha = 162.5°$). However, whereas the carbonyl oxygen of the (Z)-methylacetate molecule forms hydrogen bonds with similar energy as in the case of propanone, the hydrogen bond to O^2 has a loss of more than 4 kJ/mol in comparison with methoxymethane. It will be shown later, analyzing the IMPT calculations, that the decrease of this interaction energy is due mainly to a decrease in electrostatic attraction. Starting the *exp*-6 + *DMA* minimization in the orientation where the methanol hydroxyl group points to the O^2 lone pair of (Z)-methylacetate, found as the major minimum in the case of methoxymethane oxygen, also results in a final orientation of the hydroxyl group between the acceptor lone pairs (cf. Fig. 8c). The "disappearance" of that minimum in the lone pair direction is likely to be caused by dipolar repulsion with the carbonyl group of the ester, as will be explained later.

Besides these three minimum energy conformations seven other non−hydrogen bonded minima were also found for the methanol ⋯ (Z)-methylacetate system, all having interaction energies less than or equal to −10.0 kJ/mol.

METHANOL ⋯ (E)-METHYLACETATE

The methanol ⋯ (E)-methylacetate system results in four significant minima (Figs. 9a−d). It was expected, following the result of its (Z)-conformer, that the stronger hydrogen bond would also be formed at the cis side of the carbonyl of (E)-methylacetate. However, hydrogen bonding at the trans side turns out to form the lowest minimum energy orientation (−24.2 kJ/mol), again in a position similar to the methanol ⋯ propanone or methanol ⋯ (Z)-methylacetate dimers (Fig. 9a), but having a larger interaction energy. The second lowest energy minimum is found at the cis side, almost in a mirrored position to the plane that mirrors the carbonyl lone pairs (Fig. 9b), but about 1.4 kJ/mol less favorable than at the transposition (−22.8 kJ/mol). The third minimum (Fig. 9c) has a

geometry at the same side of the ester carbonyl with the methanol methyl group in a different position, which is similar to that of the global minimum as found for the (Z)-conformer (Fig. 8a). The whole methanol molecule is in plane with the ester, having a slightly bent hydrogen bond angle. The largest difference with the (Z)-ester, not unexpectedly, is that the φ' angle is now proximate to the lone pair direction ($\varphi' = +62.2°$), and not hindered by the C^3 methyl group, as was the case in the (Z)-conformer. Surprisingly, this unhindered (E)-complex is less favorable than the sterically distorted corresponding minimum with the (Z)-conformer by 1.6 kJ/mol. This is probably due to the lack of an extra, attractive interaction of the methanol molecule with the C^3 methyl group, as the hydrogen bonds to the ketone and ester group are slightly bent toward the adjacent methyl groups. Thus, for the (Z)-ester an extra hydroxyl$\cdots$O methyl interaction improves the total interaction, as opposed to intrinsic atomic properties of the hydrogen bond being responsible for this effect.

The fourth minimum orientation features the only hydrogen bond to the (E)-ester oxygen, O^2. This hydrogen bond, having $\varphi'' = 34.8°$, is quite near the O^2 lone pair direction ($\varphi'' = 55°$), but with the methanol methyl group out of the O^2 lone pair plane, pointing to the carbonyl side of the ester (Fig. 9d). The energy of this dimer (-21.5 kJ/mol) is 4 kJ/mol more attractive than the hydrogen bonded minimum to O^2 in the (Z)-conformer (Fig. 8a). This can be explained by the energetic difference in the orientation of the O—H vector with respect to the O=C vector of the ester carbonyl group in the (Z)- and (E)-esters (Fig. 10). The opposite directions of the O—H and O=C dipole moments in the (Z)-ester will reduce the total interaction energy for hydrogen bonding to O^2. This also explains the stronger hydrogen bonds to the ether in comparison to O^2 of the (Z)-ester, as the ether lacks such a "repulsive" carbonyl group. Thus, it can be concluded that the ester O^2 oxygen is not intrinsically a worse hydrogen bond acceptor than the sp^3 oxygen of, for instance, an ether molecule, but that the whole (molecular) environment should be considered for the resulting total interaction energy.

IMPT ANALYSIS

The *exp*-6 + *DMA* model potential calculations give a good estimate of dominant electrostatic con-
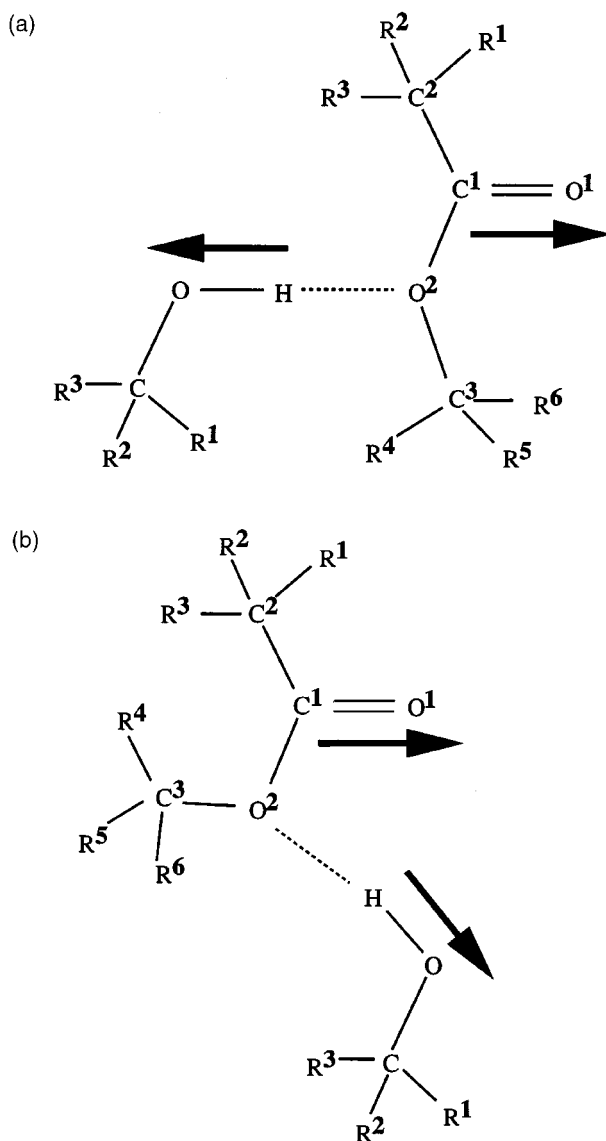
FIGURE 10. Orientation of the methanol hydroxyl group with respect to the carbonyl group for hydrogen bonds to O^2 of: (a) (Z)-esters; and (b) (E)-esters. Arrows indicate the direction of the hydroxyl and carbonyl dipole moments, which are repulsive in (a).

tributions, but rely on semiempirical potentials for other contributions. At hydrogen bond distances, intermolecular polarization and charge transfer energies, as well as electrostatic penetration effects, are important. Furthermore, the repulsion energy can be anisotropic, thus contributing to the directional preference.[15, 37] These effects are not accounted for in the *exp*-6 + *DMA*, and therefore IMPT calculations were carried out at the minima.
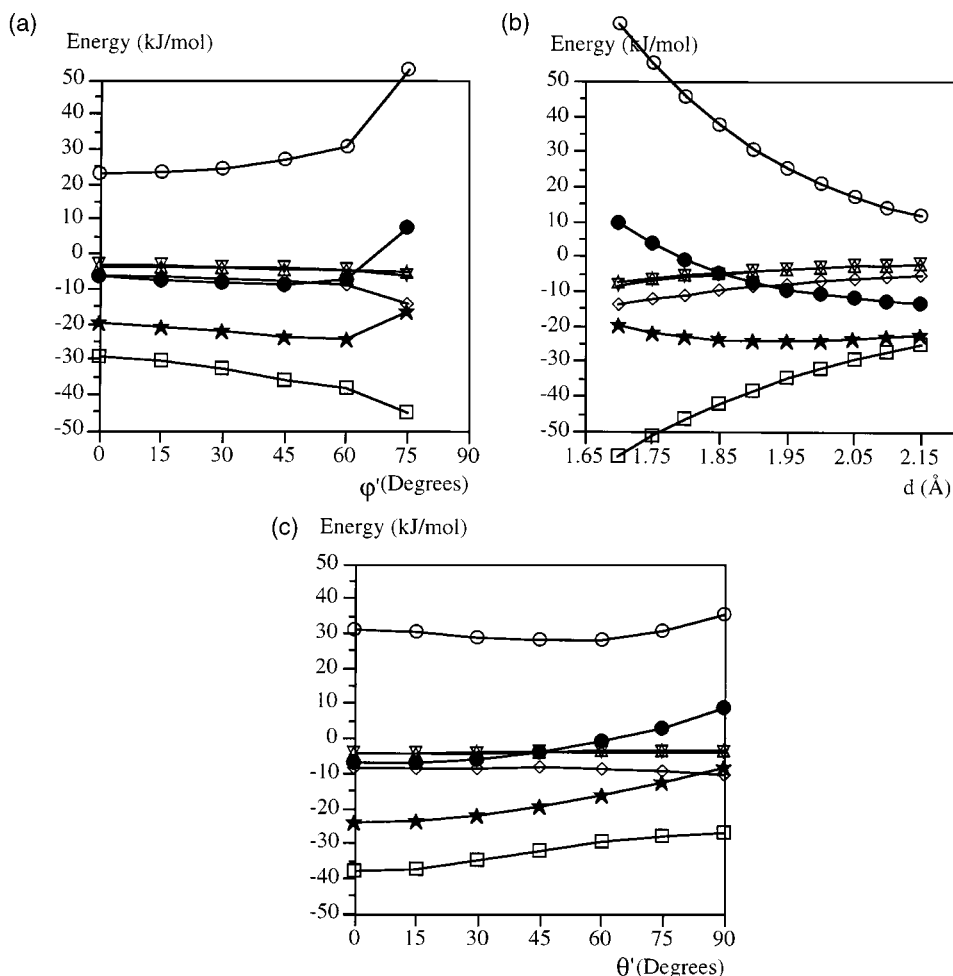
FIGURE 11. Contributions of the intermolecular energy terms in the hydrogen bonded model system methanol $\cdots$ propanone as calculated by applying the IMPT method using 6-31G* basis sets. $\bigcirc$: Exchange repulsion (E_{er}); $\square$ electrostatic interaction (E_{es}); $\triangle$: charge transfer (E_{ct}); $\triangledown$: polarization (E_{pol}); $\diamondsuit$: dispersion (E_{disp}); $*$: total energy $(E_{er} + E_{es} + E_{ct} + E_{pol} + E_{disp})$; $\bullet$: total first order energy $(E_{er} + E_{es})$. (a) Dependence of the φ' angle in the plane of the lone pairs $(\theta' = 0°)$ at a fixed hydrogen bond length of 1.9 Å with a linear hydrogen bond angle $(\alpha = 180°)$. Considering the electrostatic term only, it is -11.0 kJ / mol more attractive than that calculated using the *exp-6 + DMA* model potential in the minimum at $\varphi' = 60°$, which is attributable to the electrostatic penetration energy $(E_{pen\text{-}es}, 29\%$ of the total electrostatic energy). (b) Hydrogen bond length dependence in the "ideal" lone pair direction (at $\varphi' = 60°$ and $\theta' = 0°$) with a linear hydrogen bond angle $(\alpha = 180°)$. (c) Dependence of the out-of-the-lone-pair-plane θ' angle with $\varphi' = 60°$ at a fixed hydrogen bond length of 1.9 Å with a linear hydrogen bond angle $(\alpha = 180°)$.

The total intermolecular energies as calculated by the *exp-6 + DMA* model potential and the IMPT method in the *exp-6 + DMA* minima are given in Table I. The qualitative trends in the IMPT total interaction energies between the various hydrogen bonded systems are very similar to that of the *exp-6 + DMA* potential. The largest energetic differences are found in the case of hydrogen bonding to the carbonyl groups of the propanone and the (Z, E)-esters, where the IMPT method gives in a slightly larger attractive energy.

To explore the surface around the acceptor oxygen atom in greater detail by the IMPT method, several "idealized" orientations of methanol to the acceptor molecule were constructed. Only the hydrogen bond directionality toward the acceptor oxygen lone pairs $(\varphi'$ and θ' or φ'' and $\theta'')$, the intermolecular O $\cdots$ H distance (d), and O—H $\cdots$ O bond angle (α) were varied within the different systems (see Fig. 2). Considering the database analysis, an initial O $\cdots$ H distance of 1.90 Å was taken (Figs. 5a–c).

METHANOL · · · PROPANONE

For the methanol · · · propanone system, the φ' angular dependency is shown in Figure 11a with the complete methanol molecule in the plane of the lone pairs ($\theta' = 0°$) and a linear hydrogen bond angle ($\alpha = 180°$). The first order energy terms clearly dominate the orientational dependency of the total interaction energy. The electrostatic energy (E_{es}) and the second order term energies (E_{ct}, E_{pol}, and E_{disp}) all get more attractive from the position between both lone pairs ($\varphi' = 0°$) toward the lone pair direction of the acceptor oxygen ($\varphi' = 60°$) and further. The exchange repulsion energy term (E_{er}) gets slightly more repulsive toward the lone pair position. But, because of the approach to the propanone methyl group, E_{er} increases exponentially at $\varphi' > 60°$ and, as a result, an optimum total energy is obtained around the lone pair direction ($E_{tot} = -24.0$ kJ/mol).

The distance dependency in this orientation was checked by increasing and decreasing the O · · · H distance in steps of 0.05 Å (see Fig. 11b). The optimum distance turns out to be in between 1.90 and 1.95 Å, which is in excellent agreement with the bulk of data found in the CSD (Fig. 5a). It is interesting to observe that the first order energy terms of the IMPT, $E_{er} + E_{es}$, would result in an optimum distance of more than 2.15 Å. The attractive second order terms, E_{pol}, E_{ct}, and E_{disp}, play a major role in determining the hydrogen bond distances. The optimum distance may be somewhat shorter because E_{disp} is underestimated.[37] The out-of-plane position of the complete methanol molecule with respect to the carbonyl group lone pair ($\theta' > 0°$) shows a quick decrease of the electrostatic energy (Fig. 11c). As the exchange–repulsion energy hardly changes, the total energy also quickly becomes less favorable.

So far only linear hydrogen bond angles O—H · · · O have been considered. Although the hydrogen bond angle in the CSD was found to be most abundant at 165°, this can be explained on grounds of geometrical factors (see Figs. 4a–c). Nevertheless, the energetic effect of nonlinear hydrogen bonds was investigated using a O—H · · · O angle of 165° at a fixed H · · · O distance (1.90 Å) and keeping H in the lone pair direction ($\varphi' = 60°$). Seven distinct orientations with the O—H group in or out of the plane of the propanone molecule and the methanol methyl group in or out of this plane were considered. A slightly more attractive interaction was obtained where the complete methanol molecule is in the plane of the propanone molecule, with the hydroxyl group slightly bent toward the nearby propanone methyl group (similar to the *exp*-6 + *DMA* minimum energy orientation, cf. Fig. 6). Although in this position the exchange–repulsion energy obviously increases, due to the shorter distance between the hydroxyl oxygen and the methyl group ($\Delta E_{er} = +2.4$ kJ/mol), the electrostatic energy term gets more attractive and almost compensates for this increased repulsion ($\Delta E_{es} = -2.2$ kJ/mol). In addition, the second order energy terms all get slightly more attractive as well, leading to an overall energy gain of 1.1 kJ/mol in comparison with the linear hydrogen bond. This supports the *exp*-6 + *DMA* results which show that the slightly off-linear hydrogen bonds can be slightly energetically favorable as a result of the molecular environment, leading to an extra intermolecular attraction.

METHANOL · · · METHOXYMETHANE

Similar IMPT calculations were carried out for the methanol · · · methoxymethane system. The φ'' angular dependency for the in-the-lone-pair-plane position of the complete methanol molecule is shown in Figure 12. A very slight increase of E_{es} attraction can be observed going from a position between the ether oxygen lone pairs toward one of the one pairs ($\varphi'' = 55°$). The exchange–repulsion energy term increases slightly more rapidly. In combination with E_{pol}, E_{ct}, and E_{disp}, the total energy shows a flat optimum around $\varphi'' = 15°$ ($E_{tot} = -21.9$ kJ/mol), but in fact all φ'' angles up to the lone pair direction are favorable orientations. Comparison of the nearly equal energies of both *exp*-6 + *DMA* minima with those obtained from the IMPT calculations in the same orientations (Table I) also shows that the IMPT calculations only slightly favor the position of the hydroxyl group in between the assumed lone pair positions. This agrees with the CSD observations. The main cause for a more favorable position between the lone pairs is not an increased electrostatic interaction, but rather a decreased exchange–repulsion (Fig. 12). This anisotropy of the exchange–repulsion was also found for the ketone oxygen acceptor, but it was overcompensated by a stronger electrostatic attraction in the lone pair direction.

At this point it is interesting to compare our results with data from the literature. A number of studies have investigated hydrogen bonding between water and methoxymethane.[39–41] Results of

Energy (kJ/mol)
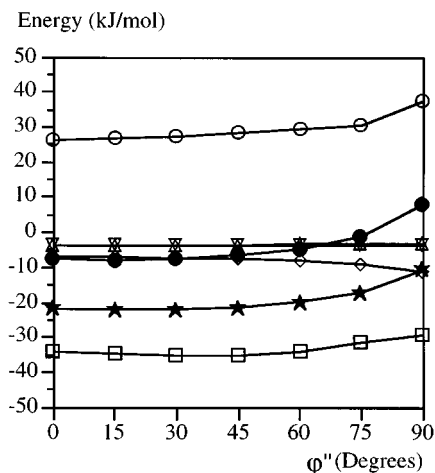
FIGURE 12. Contributions of the intermolecular energy terms in the hydrogen bonded model system methanol $\cdots$ methoxymethane as calculated by applying the IMPT method using the 6-31G* basis sets. Shown is the dependence of the φ' angle in the plane of the lone pairs ($\theta' = 0°$) at a fixed hydrogen bond length of 1.9 Å with a linear hydrogen bond angle ($\alpha = 180°$). The same symbols as in Figure 11 are used.

these studies show that the optimum hydrogen bond orientation of water is in the ether oxygen lone pair direction, rather than between the lone pairs.[39,40] We repeated our methodology for the water $\cdots$ methoxymethane system and found only one major minimum using the *exp*-6 + *DMA* model potential, in which the hydroxyl is pointing into the ether oxygen lone pair. IMPT calculations on this system, focusing on the φ'' angle dependence, also resulted in a shifted minimum orientation to $\varphi'' = 30°$ (data not shown) in comparison with the methanol $\cdots$ methoxymethane system ($\varphi'' = 15°$). These observations demonstrate that water as a hydrogen bond donors differs significantly from alkanol hydroxyl groups. The matter of methyl substitution in donors or acceptors has already been addressed previously.[39,41] However, the energy well for hydrogen bonds in the lone pair plane of the ether oxygen is very shallow in both cases, so the different directional preferences in this plane are very weak. Varying the other geometrical parameters of the methanol $\cdots$ ether hydrogen bond gives similar results to those of the methanol $\cdots$ propanone case (not shown). The O $\cdots$ H distance at $\varphi'' = 0°$ gives an optimum around 1.90 Å. An out-of-the-lone-pair-plane position of the whole methanol molecule ($\theta'' > 0°$, $\varphi'' = 0°$) is not favorable, mainly because of the rapid increase of steric hindrance of the

methoxymethane methyl group. Changing the hydrogen bond angle, α, to 165° at fixed $\varphi'' = 0°$ in various directions gives, at best, the same energy ($E_{tot} = -21.6$ kJ/mol) in an orientation very similar to that given in Figure 7b. Here, the increase in exchange repulsion energy ($\Delta E_{er} = +0.9$ kJ/mol) is not compensated by a stronger electrostatic ($\Delta E_{es} = -0.1$ kJ/mol), but the second order energy terms again contribute [$\Delta(E_{pol} + E_{ct} + E_{disp}) = -0.8$ kJ/mol].

METHANOL $\cdots$ (*Z*)-METHYLACETATE

In case of the methanol $\cdots$ (*Z*)-methylacetate dimer, both carbonyl oxygen lone pairs were investigated for their ability to accept the methanol hydrogen bond donor. As found by the *exp*-6 + *DMA* potential energy model, the trans side of the C=O axis has very similar characteristics to those of the propanone carbonyl group. A minimum energy orientation ($E_{tot} = -23.9$ kJ/mol) is found for the in-the-plane position of the whole methanol molecule ($\theta = 0°$) in the lone pair direction ($\varphi' = -60°$) having a nonlinear hydrogen bond angle ($\alpha = 165°$).

The cis side shows a slightly different picture (Fig. 13). The total and the electrostatic interaction at all φ' ($\varphi' \geq +0°$) angles is more attractive in comparison with the trans side ($\varphi' \leq -0°$). This preference for hydrogen bonding at the cis side does not exist in case of (*E*)-methylacetate, as found by DMA as well as IMPT results (discussed later), where the trans side forms the strongest hydrogen bonds. This suggests that it is not the O^2 ester oxygen alone that improves the hydrogen bond strength at the cis side, but rather that the CH_3 group contributes to a stronger interaction. Again, this points to a significant influence of the molecular environment on the total interaction.

Except for this cis/trans difference, the features for the hydrogen bond at the cis side of the (*Z*)-ester are similar to those of the propanone $\cdots$ methanol system. The φ' angle finds its optimum for an in-the-plane position of the whole methanol molecule already around +45°, due to the strong increase in exchange–repulsion energy with the C^3H_3 group for larger φ'. The position in the ester plane of the hydroxyl group as well as of the whole methanol molecule is clearly favored over an out-of-plane position. Setting the hydrogen bond angle to 165°, at fixed O $\cdots$ H distance with $\varphi' = 45°$, the best position is again found for the hydroxyl oxygen bending toward the nearby ester C^3H_3 group.

Energy (kJ/mol)
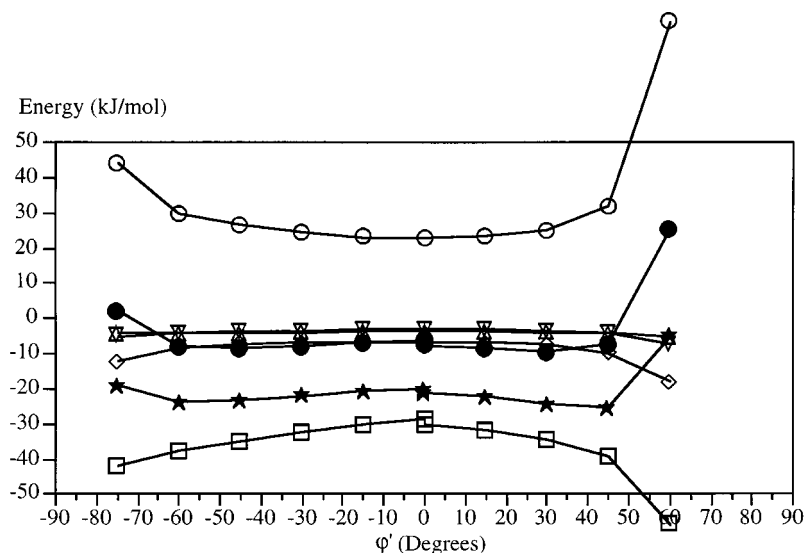
FIGURE 13. Contributions of the intermolecular energy terms in the hydrogen bonded model system methanol $\cdots$ (Z)-methylacetate as calculated by applying the IMPT method using the 6-31G* basis set. Shown is the dependence of the φ' angle in the plane of the lone pair ($\theta' = 0°$) at the "cis" and "trans" sides of the carbonyl group ($\varphi' > 0°$ and $\varphi' < 0°$, respectively), having a fixed hydrogen bond length of 1.9 Å and a linear hydrogen bond angle ($\alpha = 180°$). The same symbols as in Figure 11 are used. Note that the discontinuity at $\varphi' = 0°$ is due to the 180° flip of the methanol $\cdots$ methyl group around the O—H axis.

The IMPT calculations on hydrogen bonds to the O^2 oxygen of the (Z)-methylacetate molecule confirms the *exp*-6 + *DMA* results. Varying the φ'' angle of the most favorable in-the-plane position of the whole methanol molecule leads to an optimum to around $\varphi'' = 15°$ ($E_{tot} = -14.2$ kJ/mol, in an orientation like that in Fig. 8c). This interaction is almost 8 kJ/mol less favorable than in a comparable hydrogen bond to an ether oxygen, with most of the difference being in the electrostatic energy ($\Delta E_{es} = -6.5$ kJ/mol, $\Delta E_{DMA} = -6.0$ kJ/mol). This confirms the *exp*-6 + *DMA* results which indicate that the ester oxygen is a much poorer hydrogen bond acceptor than the ether oxygen, mainly because of long range electrostatic terms.

METHANOL $\cdots$ (*E*)-METHYLACETATE

The IMPT calculations for methanol $\cdots$ (*E*)-methylacetate were limited to the ORIENT minima only. The total energies are given in Table I, which shows that the IMPT results also point to a most favorable orientation in which methanol forms a hydrogen bond at the trans side of the carbonyl group (-27.2 kJ/mol). The lower number of hydrogen bonds at the trans side, as found in the CSD (43% of the total number hydrogen bonds involving the carbonyl group), is likely due to

steric hindrance of bulky groups attached to C^2, whereas such hindrance is not possible at the cis side.

Both minima at the cis side result in a slightly decreased strength of the hydrogen bond in comparison with the (Z)-ester. This supports the conclusion made that the methyl group in the (Z)-conformer helps to improve total interaction energy, despite the fact that it sterically hinders an optimum hydrogen bond geometry at around $\varphi' = +60°$.

The O^2 ester oxygen atom still acts as a reasonably strong hydrogen bond acceptor ($E_{tot} = -20.4$ kJ/mol), having a strength comparable to hydrogen bonding with ether oxygens (-21.9 kJ/mol). Again, this points to the fact that the O^2 atom is not intrinsically a worse hydrogen bond acceptor, but rather that the overall interaction of a hydrogen bonded orientation is dependent on the complete molecular environment involved. Despite this reasonably strong interaction, only a few hydrogen bonds involving O^2 have been found in the CSD. This has to be explained in terms of competition with the carbonyl hydrogen bond acceptor next to O^2. The energy barrier for hydrogen bonding between both acceptor oxygen atoms will not be very high, favoring the stronger interaction with the carbonyl oxygen.

Conclusions

We have raised several specific questions regarding hydrogen bonds to ketone, ether, and ester functional groups, which are potentially very important for understanding biochemical processes.

It has been shown that a lone pair preference exists for carbonyl (sp^2) but not for ether (sp^3) oxygen atoms. Nevertheless, for both types of oxygen all positions of the hydroxyl groups in or between their lone pairs result in strong total interaction, which is mainly driven by a strong electrostatic preference for a position in the plane of the lone pairs. In the case of the ether oxygens the lone pair directionality vanishes as a consequence of only a very weak electrostatic preference in the lone pair direction, which makes the balance between the exchange–repulsion and the attractive energy terms favor a position between the lone pairs.

The strength of hydrogen bonds to ether and ketone groups in their optimum geometries turns out to be similar, but hydrogen bonds to the ketone carbonyl oxygens are marginally stronger. From CSD searches it is clear that ester oxygens (O^2) hardly accept hydrogen bonds. In the case of (Z)-esters, this is due to the strongly reduced interaction energy of hydrogen bonds for O^2 in comparison with ether oxygens or with the (E)-ester O^2. The reduced interaction energy arises from the intramolecular environment around the (Z)-ester O^2: specifically, the (Z)-ester carbonyl group causes a repulsive dipolar interaction with any hydroxyl group hydrogen bonded to O^2. In the case of (E)-esters, the hydrogen bond strength to O^2 is comparable with that to an ether oxygen. However, owing to direct competition with the adjacent carbonyl group and a low intermediate energy barrier, the hydrogen bond is usually formed to the carbonyl oxygen.

No large differences in strength or geometry between carbonyl groups of ketones and of esters to accept hydrogen bonds have been found. CSD data have pointed to a similar behavior with a geometrical preference in the acceptor oxygen lone pair direction, and this has been confirmed by the energy calculations. A slightly more favorable interaction energy only was calculated for hydrogen bonds to the carbonyl groups of the esters. The hydrogen bond at the cis side in (Z)-esters appeared to be slightly stronger than at the trans side. However, in the CSD more hydrogen bonds were found at the trans side, which must obviously be explained in terms of a better steric accessibility at that side of the ester carbonyl group.

Finally, the question of linearity of hydrogen bonds was addressed. It has been found that a slightly bent hydrogen bond angle is often slightly more favorable as a result of an improved total interaction between the donor molecule and the acceptor molecule, rather than the consequence of an intrinsic property of the hydrogen bond. This, combined with the geometrical factor, explains the relative abundance of slightly nonlinear hydrogen bonds in the CSD.

Generally, the calculated energy data and optimum geometries obtained from exp-6 + DMA and IMPT calculations, using simple model systems which represent hydrogen bonding of alkanol donors to ketone, ether, and ester acceptor oxygen acceptors, are in excellent agreement with the experimental statistical data found with the CSD. Thus, the classical Coulombic interaction energy dominates the orientation dependence of these hydrogen bonds, as previously concluded for this and other types of hydrogen bonds.[19–21, 25, 31] The difference between the long range electrostatic energy calculated from exp-6 + DMA and the electrostatic term of the IMPT demonstrates that the electrostatic energy gain due to penetration is considerable. The charge transfer term is relatively small, so these hydrogen bonds have hardly any intermolecular (covalent) bond character, and the hydrogen bond strength results from a strong intermolecular electrostatic attraction. Nevertheless, the charge transfer term together with the other second order energy terms, the polarization or induction and dispersion terms, are essential to describe adequately the characteristic hydrogen bond lengths.

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