Oxygen and Nitrogen in Competitive Situations: Which Is The Hydrogen-Bond Acceptor?

Abstract: In the design of novel protein ligands one of the major challenges is the replacement of functional groups to modify and improve the binding characteristics. Often nitrogen- and oxygen-containing groups are exchanged, or both atoms occur in a competitive situation. We have investigated the hydrogen-bonding abilities of oxygen atoms covalently bound to two non-hydrogen atoms of which at least one is formally assigned to an sp^2-type hybridization. In particular, examples in which such oxygen atoms compete with nitrogen atoms in the same molecular segment have been studied. Based on interaction energies obtained from ab initio calculations for complexes of these molecules with water, the oxygen atoms can be classified as rather weak hydrogen-bond acceptors; nitrogen atoms present in the same fragment exhibit much stronger interaction energies. The ab initio results are confirmed by the relative frequencies with which oxygen and nitrogen atoms are found to be involved in hydrogen bonding in the crystal structures of organic molecules containing the fragments of interest.

Keywords
ab initio calculations · binding studies · crystal packing · drug design · hydrogen bonds

The hydrogen bond is of fundamental importance for interactions in biological systems, especially those formed between O–H···O/N and N–H···O/N. In the present contribution we consider hydrogen-bonding properties related to protein–ligand interactions. Oxygen and nitrogen both frequently act as hydrogen-bond acceptors. The design of novel protein ligands often involves functional-group replacements. These bioisosteric replacements are performed to alter a molecular framework while retaining its hydrogen bonding, or to enhance hydrogen bonding in a well-planned and tailored fashion. In this context the question arises, which is the better hydrogen-bond acceptor? Can it be answered?

The knowledge of pK_a values of the compounds under consideration might help; however, these values are often not available. Since no straightforward method exists to reliably compute pK_a, calculated partial charges are often used to assess hydrogen-bonding capabilities of functional groups. Using ab initio calculations, Kollman established a correlation of the strength of noncovalent interactions with the magnitude of the electrostatic potential or its gradient in the lone-pair region.[1] In general, owing to its higher electronegativity, oxygen is expected to be a better hydrogen-bonding partner than nitrogen. In a hydrogen bond A–H···B, the proton donor ability and accordingly its strength increases with the electronegativity of A.[2] However, for the H-bond acceptor ability the situation is more complicated. Apparently, here the availability of the lone pair for donation is the determining factor.[2] This availability is dependent on the local electron delocalization, such as in a conjugated π system. Etter tried to rank the relative proton-accepting abilities of various functional groups by analyzing molecular packing in crystalline systems.[3, 4] These studies show that hydrogen bond accepting properties of functional groups clearly depend on the local intramolecular environment. Simple correlations with electronegativity or partial charges are not sufficient to explain the observed trends.

Accordingly, the question of relative hydrogen-bonding ability of acceptors cannot be answered in a straightforward manner. Nevertheless, the question arises whether we can collect evidence to provide some guidelines on the likelihood of oxygen and nitrogen, or functional groups containing the two atoms in a geometrically equivalent environment, being involved in hydrogen bonding, for example, as acceptors. We will use two different approaches to investigate the hydrogen-bonding properties of such systems: ab initio calculations on various functional groups complexed with water and statistical analyses of the packing in crystal structures containing the fragments of interest. As a starting point we have selected examples, such as, oxazoles, isoxazoles, methoxypyridines, and oxime ethers (Fig. 1), in which oxygen and nitrogen are at various degrees of proximity in the same molecular fragment. In principle, both polar atoms should be able to compete as acceptors in forming hydrogen bonds.

Statistical analyses of intermolecular interactions in the crystal structures of organic molecules have been used to derive

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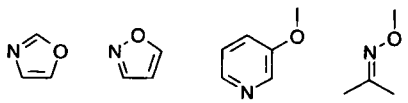

Fig. 1. Fragments used to examine the relative abilities of oxygen and nitrogen to act as hydrogen-bond acceptors.

information about favorable contact geometries of oxygen and nitrogen atoms.[5] In a comprehensive study, Murray-Rust and Glusker investigated ketones, ethers, esters, and epoxides.[6] In another detailed study we analyzed the geometry around functional groups present in amino acids.[7] The environment of oxygen atoms bound to two non-hydrogen atoms of which at least one is formally assigned an sp^2-type hydridization and involved in an unsaturated π system were not covered in both studies. Such oxygen atoms, referred to as $O_=$ in the following, are found in the examples shown in Figure 1 as well as in esters, anisoles, furans, and enol ethers. In this paper, we report on the relative strengths of $O-H\cdots O_=$ hydrogen bonds with respect to other hydrogen bonds, especially in competitive situations.

Methods

For the ab initio calculations, we used the program TURBOMOLE with a "split-valence" basis set [8] for the geometry optimization of all coordinates: C,N,O (7s,4p,1d)/[3,2,1], H (4s)/[2]. The geometry-optimized structures were subsequently used in a single-point calculation using a triple-zeta plus polarization (TZP) basis set to obtain interaction energies. The following TZP basis set was used (GTO primitive sets taken from Huzinagas tables [9]): C,N,O (9s,5p,1d)/[5,3,1], H (5s,1p)/[3,1]. The exponents of the polarization functions were chosen as 0.8 (d on C), 1.0 (d on N), 1.2 (d on O), and 0.8 (p on H). All calculations were performed at the SCF-MP2 level. To check the accuracy of the presently used calculation strategy, we also calculated the interaction energy and hydrogen-bond length of the water dimer. We obtain for $(H_2O)_2$: $R_{OO} = 2.931$ Å, $\Delta E = -23.7$ kJ mol^{-1} (-5.67 kcal mol^{-1}) using the above-mentioned basis sets. This is in good agreement with experimental values [10] and earlier ab initio calculations using larger basis sets [11].

Abstract in German: *Ein zentrales Problem beim Entwurf neuer Proteinliganden ist die Abwandlung von deren Molekülgerüsten durch den gezielten Austausch funktioneller Gruppen. Dadurch sollen die Bindungseigenschaften verändert und verbessert werden. Oft werden Stickstoff- gegen Sauerstoff-haltige Gruppen ausgetauscht, oder beide Atomarten kommen in konkurrierenden Umgebungen vor. Wir untersuchten die Fähigkeiten von Sauerstoffatomen, die über kovalente Bindungen an zwei Nichtwasserstoffatome gebunden sind, von denen zumindest eines formal in einer sp^2-Hybridisierung vorliegt, als Wasserstoffbrückenbindungspartner zu fungieren. Vor allem konkurrierende Situationen, in denen dieser Sauerstoffatomtyp gleichzeitig mit einem Stickstoffatom im selben Molekülbaustein auftritt, wurden untersucht. Anhand von ab-initio-Rechnungen bestimmte Wechselwirkungsenergien dieser Gruppen im Komplex mit Wasser klassifizieren die betrachteten Sauerstoffatomtypen als sehr schwache H-Brücken-Acceptoren. Die im gleichen Fragment auftretenden Stickstoffatome weisen deutlich höhere Wechselwirkungsenergien auf. Die Ergebnisse der ab-initio Rechnungen werden durch die unterschiedlichen Häufigkeiten bestätigt, mit denen Sauerstoff und Stickstoff in diesen Fragmenten in Kristallstrukturen organischer Moleküle an Wasserstoffbrückenbindungen beteiligt sind.*

Results

The results from the ab initio calculations on the complexes of oxazole, methoxypyridine, and oxime ethers with water are summarized in Figure 2. In all cases the $H-O-H\cdots O_=$ hydrogen bond is calculated to be substantially weaker than the $H-O-H\cdots N$ hydrogen bond. Energy differences of more than 10 kJ mol^{-1} are found for oxazole and methoxypyridine. For oxime ethers this difference is somewhat smaller. The calculations suggest that nitrogen is a much stronger hydrogen-bond acceptor than oxygen $O_=$ in the investigated molecules.

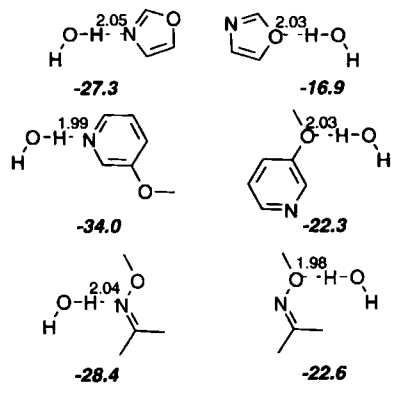

Fig. 2. Calculated hydrogen-bond lengths $R(H\cdots O/N)$ [Å] and interaction energies (in italics) [kJ mol^{-1}] from ab initio calculations on complexes of bifunctional molecules with a water molecule.

In order to obtain further evidence for the diverging acceptor strengths of oxygen and nitrogen in the present examples, we carried out statistical analyses of hydrogen-bond geometries in crystalline oxazoles, isoxazoles, methoxypyridines, and oxime ethers. Data were retrieved from the Cambridge Crystallographic Database (CSD).[12] The analyses were performed as described in detail elsewhere.[7] The results are summarized in Table 1.

To our surprise, in all the competitive examples we found no or very few hydrogen bonds formed to oxygen in an X(sp^2)-O-C

Table 1. Results from a search in the Cambridge Structural Database (CSD) for hydrogen bonds with oxazoles, isoxazoles, methoxypyridines, oxime ethers, furans, enol ethers, and sterically unhindered esters and ethers.

Fragment [a]	Total no. of fragments [b]	Fragments with H-bond to N [c]	Fragments with with H-bond to $O_=$
oxazole [d]	32(36)	15(17)	1(1)
isooxazole [d]	66(75)	22(25)	-
o-methoxypyridine [d]	13(21)	1(4)	-
m-methoxypyridine [d]	7(12)	4(7)	-
p-methoxypyridine [d]	21(28)	3(3)	-
oxime ether	64(136)	4(4)	-
furan	382(499)	n.p. [e]	4(4) [f]
enol ether	106(279)	n.p. [e]	-
ester [g]	146(177)	51(56) [h]	2(2) [f]
ether [g]	487(653)	n.p.	35(44) [i]

[a] Version 5.09 of the Cambridge File used; only data with $R(F) \leq 0.10$ considered. [b] Number of CSD Refcodes; in parenthesis, number of fragments found in these Refcodes. [c] Entries with N/O$\cdots$H*O,N* distances of 2.0–3.2 Å, N/O$\cdots$*H*O,N distances of 1.4–2.2 Å, and O/N$\cdots$H–O,N angles of 135–180° were considered as hydrogen bonds. [d] Fragments with direct metal coordination were excluded. [e] Not present. [f] Search ranges extended to N/O$\cdots$H*O,N* of 2.0–3.4 Å and N/O$\cdots$*H*O,N of 1.4–2.5 Å. [g] Only fragments with CH_2 groups adjacent to the functional group considered. [h] For oxygen in the ester carbonyl. [i] Oxygen atom embedded in an environment of two sp^3 carbons.

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environment. Virtually all hydrogen bonds were formed with the nitrogen atom. In a first approximation we assumed that in these examples both atoms are capable of hydrogen bonding and that steric factors do not prevent H-bond formation. In addition, we looked at the total number of structures containing these functional groups in the database. Since the chemical composition of the individual molecules was not analyzed in detail, it could well be that for some of the retrieved examples the formation of a hydrogen bond is simply not possible for geometric (e.g., absence of donor functional groups) or stochiometric reasons (e.g., imbalance in the number of donor and acceptor groups). Furthermore, crucial in such comparisons is the definiton of relevant limits for classifying an intermolecular contact as a hydrogen bond (see Table 1). Recently, the distance criteria in hydrogen-bond formation was discussed in detail by Jeffrey and Saenger.[13] Nevertheless, as a rough estimate for oxazoles, isoxazoles, and methoxypyridines, we can say that the nitrogen atoms are involved in a hydrogen bond in 23–47% of the cases (Table 1). Oxime ethers form hydrogen bonds much less frequently. This contrasts with the computational results that give similar interaction energies for oxime ethers and oxazoles.

In order to further validate our observation that $O_{=}$ is a very weak H-bond acceptor we retrieved structures with the functional groups shown in Figure 3 (Table 1). Since ethers and

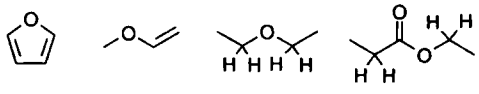

Fig. 3. Additional fragments used to show that $O_{=}$ is a very weak hydrogen-bond acceptor.

esters are rather abundant in the database we limited our search to sterically unhindered examples with CH_2 groups adjacent to the functional group. Furans and enol ethers only contain oxygen atoms in the type of environment under investigation (i.e., $O_{=}$). In these structures, they turn out to be rare hydrogen-bond acceptors, especially if one compares the number of hydrogen-bonded examples with the total occurrence of the fragment in the database.[14] For esters, we also have competition between two different types of oxygen atoms, one of which is in the $O_{=}$ environment. In agreement with the previous observations in N/O examples, the $O_{=}$ oxygen is very rarely involved in a hydrogen bond. As expected, the carbonyl oxygen is a frequent acceptor in such interactions. For comparison, we also considered aliphatic ethers. The statistics in Table 1 indicate that aliphatic ether oxygens have a tendency to act as acceptors in the formation of hydrogen bonds.

To further understand these observations, we performed ab initio calculations on the systems shown in Figure 3 (Fig. 4).

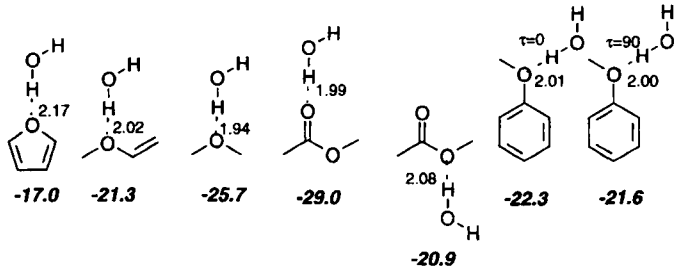

Fig. 4. Calculated hydrogen-bond lengths $R(H\cdots O)$ [Å] and interaction energies (in italics) [kJ mol^{-1}] from ab initio calculations on complexes of mono- and bifunctional molecules with a water molecule. For anisole the values for the planar ($\tau = 0°$) and perpendicular arrangement ($\tau = 90°$) are given.

They confirm the experimental evidence. The interaction energy of complexes of furan, enol ether, and methyl acetate (H-bond to the ester oxygen) with water is calculated to be between -17 and -21 kJ mol^{-1}. The interaction of a water molecule with the carbonyl oxygen of methyl acetate is stabilized by more than 8 kJ mol^{-1} with respect to that with the $O_{=}$-type oxygen. The interaction to ethers displays an intermediate value approaching that of the water dimer.

We analyzed the directionality of the hydrogen bond for the different functional groups observed in the CSD in terms of polar coordinates, as described previously.[7] The results are summarized in Figure 5. For oxazoles and isoxazoles, corresponding hydrogen-bond donors are observed in a narrow section around the lone-pair direction at nitrogen. This hydrogen-bonding geometry is very similar to that found with pyridine and imidazole. Angular deviations in the plane of the heterocycle are more pronounced toward the side where the oxygen is found, especially in isoxazoles. Distortions perpendicular to the ring plane amount to about 40° in either direction. Esters display properties very similar to those of peptide groups.[7] Donor groups are found on a spherical cap about the carbonyl oxygen. More pronounced steric repulsion appears to be present toward the ester oxygen, since less examples are found with the donor group lying on this side of the functional group. Ethers show much stronger deviations perpendicular to a plane through the probe fragment (about 65°) than in the plane of the $-CH_2-O-CH_2-$ moiety (30°).

Discussion

In the present study we have used a combination of quantum-mechanical ab initio calculations and statistical analyses of the crystal packing of small organic molecules to compare the properties of different hydrogen bonds. According to our ab initio results, oxygen atoms bound to two non-hydrogen atoms of which at least one can be formally assigned to an sp^2-type hybridization are very weak acceptors in a hydrogen bond. This is consistent with the very low frequency of crystalline systems in which these groups are involved in hydrogen bonding.

The results presently available from different sources indicate similar trends. It appears to be self-evident that, if a hydrogen bond between a particular functional group and a water molecule is computed to be weak, a statistical evaluation of crystal structures will show low "involvement frequencies" or reduced "probabilities for H-bond interactions" for this group. With more negative interaction energies, these frequencies also increase. However, it should be noted that the computed energies correspond to complexes of the isolated test molecule with a water molecule, whereas the probabilities from crystal packing relate to the properties of the test fragment embedded in larger molecular entities interacting with various hydrogen-bond donors in crystalline environments. In each crystal structure, the molecules pack in such a way that the entire structure corresponds to a minimum of free enthalpy (neglecting kinetically metastable states). Therefore, the computed interaction energies of the isolated complexes cannot be used to estimate the strength of hydrogen-bonding in these crystals. Nevertheless, with some caution, the observed trends lead us to conclude that $O_{=}$ atoms only act as weak hydrogen-bond acceptors.

In biological systems, protein–ligand interactions compete with interactions with water molecules. Several contributions need to be considered: interactions of the functional groups in the protein binding site and of the ligand with water in the solvated state. Upon binding, water molecules, previously en-

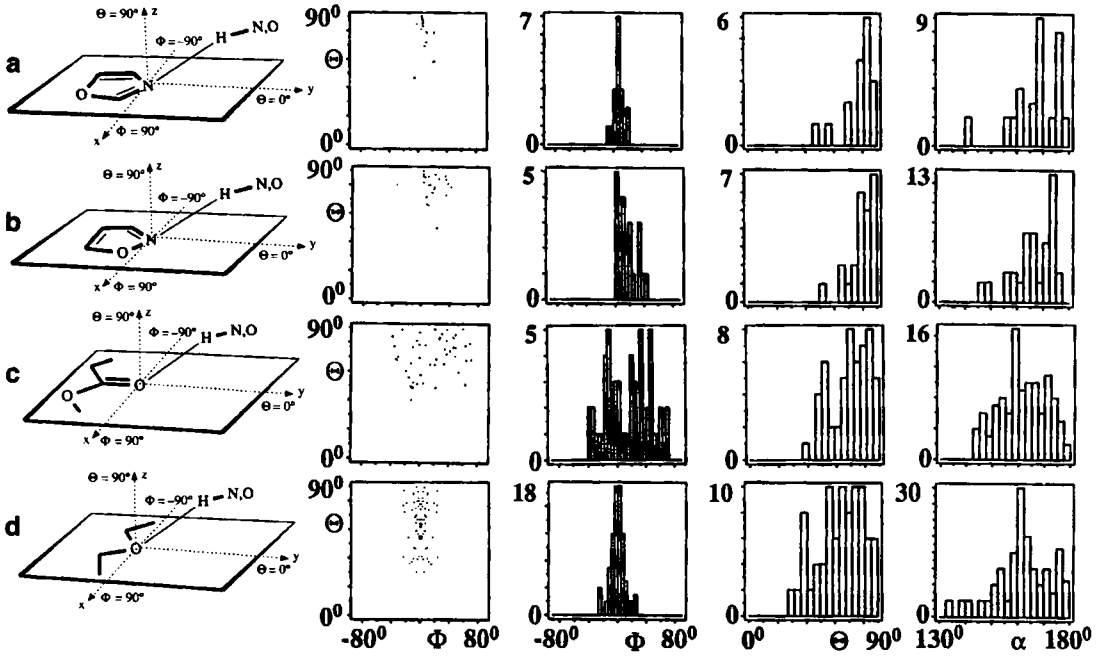

Fig. 5. Scatter and histograms of the spatial distribution of donor sites about different acceptor functional groups: nitrogen in oxazoles (a) and isoxazoles (b), and oxygen in ester carbonyl groups (c) and ethers (d). The definition of spherical polar coordinates with respect to the probe fragment is indicated. Column 1, Φ/θ scattergram; column 2, histogram of Φ; column 3, histogram of θ; column 4, histogram of H-bonding angle α (A···H–D). In the examples considered the mean acceptor-to-donor distances A···D and hydrogen-bond angles A···H–D are: oxazoles 2.88(11) Å, 167(9)°, isoxazoles 2.87(10) Å, 167(8)°, esters 2.89(10) Å, 162(10)°; ethers 2.83(11) Å, 162(9)°.

gaged in interactions with the protein and the ligand are liberated and can then interact with each other. Clearly, all these processes involve enthalpy and entropy changes.[15] Nevertheless, in terms of the enthalpy balance, weak hydrogen bonds to $O_=$ have to compete with stronger $H-O-H\cdots OH_2$ interactions. This significant enthalpy difference indicates that $H-O-H\cdots O_=$ interactions are only of minor importance under physiological conditions. It must be considered that a newly formed protein–ligand hydrogen bond only contributes in terms of enthalpy to the binding affinity if it is stronger than the competing water interaction. If a ligand has several ways of satisfying a donor functional group at a protein binding site, it appears rather unlikely that oxygen atoms $O_=$ adjacent to sp^2 centers control molecular recognition and the binding properties. This will especially be the case if "better" acceptors are present.

Perhaps it is more appropriate to describe oxygen atoms of this type as nonpolar. Such a description is also suggested by the comparison of experimentally determined free energies of solvation ΔG_{solv} in water.[16] For ethylbenzene, ΔG_{solv} is $-3.33\ kJ\,mol^{-1}$. The corresponding value for methoxybenzene is $-4.34\ kJ\,mol^{-1}$. Thus, the replacement of $-CH_2-$ by -O- reduces ΔG_{solv} by only $1\ kJ\,mol^{-1}$. Similarly, the differences in ΔG_{solv} between the methyl or ethyl ester of acetic acid (CH_3COOCH_3, $CH_3COOCH_2CH_3$) and the corresponding ketones 2-butanone and 2-pentanone ($CH_3COCH_2CH_3$, $CH_3COCH_2CH_2CH_3$) are very small (less than $2\ kJ\,mol^{-1}$).[16]

The results obtained from the present investigation have several implications. In drug design, one is often attempting functional group replacements to improve the binding affinity, to avoid specific metabolic pathways, or to allow better synthetic accessibility. Several of these bioisosteric replacements involve oxygen atoms bound to sp^2-type carbon atoms. For example, it is known that a phenyl group can be replaced by a furan moiety without loss of biological activity.[17] In the complex of dihydrofolate reductase with trimethoprim, a lipophilic binding site is occupied by the 3,4,5-trimethoxyphenyl substituent.[18] None of the ether oxygens forms a hydrogen bond with the protein. Nevertheless, the ligand binds with high affinity. Further examples are known in which a tight-binding ligand buries an $O_=$-type oxygen atom in the protein binding site without forming a hydrogen bond.[19] The current results provide an explanation for why high-affinity ligands are still found.

The present conclusions are also of relevance for the development of pharmacophore hypotheses that are frequently used to explain the binding of ligands to receptors of unknown 3D structure. For example, Schulman et al. proposed a pharmacophore model for muscarinic agonists.[20] For acetylcholine and closely related analogues, they assume that the ester oxygen is involved in an essential hydrogen bond with the receptor. In view of the present results, this model appears rather unlikely.

Another consequence of our results relates to the use of theoretical models to describe nonbonded interactions. Electrostatic interactions contribute significantly to nonbonded interactions. Frequently, these interactions are described by a point-charge model with the partial charges derived from bond polarities. Such a scheme will assign more negative charge to oxygen than to nitrogen, owing to the higher electronegativity of oxygen. Furthermore, most of the current molecular mechanics force fields use standard atomic radii for the calculation of the repulsive part of the nonbonded interaction. Usually, smaller van der Waals radii are used for oxygen atoms than for nitrogen atoms. Therefore, one can expect that most of the currently used standard force fields will predict $O_=\cdots H-O$ hydrogen bonds to be shorter and stronger than the $N\cdots H-O$ hydrogen bond. Indeed, we observed this artificial stabilization of the $O_=\cdots H-O$ hydrogen bond in the oxazole–water system using the force fields MaxiMin 5.2,[21] CVFF,[22] and CHARMM.[23] Accordingly, some care should be taken in interpreting results from such simple force-field calculations involving oxygens adjacent to unsaturated systems. More elaborate force-field models that use an explicit electrostatic potential fitting to derive appropriate partial charges[24–27] or that fit the charges to reproduce

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hydrogen-bonding energies from ab initio studies should perform better. Recently, it has been shown[28] that a 6-31 G* electrostatic potential based model accurately reproduces the relative hydrogen-bonding energies of water as proton donor to the nitrogen and oxygen of oxazole in the AMBER force field.[25–27]

The present results are also important in the development of more sophisticated models to handle solvation effects. Oxygen atoms bonded to two atoms of which at least one is sp^2-hybridized should be described by atomic solvation parameters that are distinct from those for oxygen atoms with two sp^3-type neighbors. For example, in their study, Scheraga et al.[29] used the same ΔG_h value for both oxygen atoms in esters. We suggest the use of a significantly smaller value for the $O_=$ oxygen.

The question remains as to the origin of the reduced hydrogen-bonding ability of $O_=$. Clearly, its local electronic environment will have a determining influence. In very simple models, the degree of electron delocalization in extended π systems is related to the planarity of the framework involved. In all the systems considered, $O_=$ and its nearest neighbors lie close to the plane of the adjacent unsaturated π system. Thus, delocalization and the corresponding reduction in electron density at the oxygen atom may lead to a reduction in the ability to act as a hydrogen-bond acceptor. In an earlier study we investigated the crystal packing around anisoles.[7] Hydrogen bonds to $O_=$-type oxygens are present in several of these structures. However, only about 3% of the total number of anisoles found in the Cambridge File are observed to be involved in H-bonding. These anisoles (86) were inspected more closely. They were separated into examples with the methoxy group coplanar (0–30°) or twisted (60–90°) with repect of the phenyl plane. In the latter cases, delocalization should be disrupted to some extent. For both groups, the mean hydrogen-bond lengths were determined. For planar examples (73), a mean of 2.99(12) Å is found;[30] for "perpendicular" ones (13) 2.94(15) Å. No clear dependence of the distance on the deviation from planarity is apparent. These findings are mirrored by our ab initio calculations (anisole complexed by water), which reveal nearly unchanged interaction energies and distances in the planar and perpendicular arrangement (Fig. 2). Accordingly, simple geometry versus delocalization arguments appear insufficient to explain the reduced hydrogen-bonding properties of $O_=$-type oxygens.

Summary

A combined approach based on quantum mechanical ab initio calculations and statistical analyses of nonbonded contacts in the crystal packing of organic molecules suggests that $O_= \cdots H-O/N$ hydrogen bonds formed with oxygen atoms bonded to two atoms of which one is sp^2-type hybridized ($O_=$) are rather weak. In competitive situations, such as that found in oxazoles, isoxazoles, methoxypyridines, or esters, the nitrogen—or, in esters, the carbonyl oxygen—nearly exclusively acts as the acceptor. Molecular fragments possessing only $O_=$ atoms as hydrogen-bond acceptor are less likely to be involved in hydrogen bonding. Similar trends are observed in the calculated changes in interaction energies for complexation between model fragments and water, on the one hand, and the "involvement frequencies" of these fragments as hydrogen-bond acceptors in organic crystal structures, on the other.

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