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Comparison of Various Types of Hydrogen Bonds Involving Aromatic Amino Acids

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Abstract: Ab initio calculations are used to compare the abilities of the aromatic groups of the Phe, Tyr, Trp, and His amino acids (modeled respectively by benzene, phenol, indole, and imidazole) to form H-bonds of three different types. Strongest of all are the conventional H-bonds (e.g., OH··O and OH··N). His forms the strongest such H-bond, followed by Tyr, and then by Trp. Whereas OH··φ bonds formed by the approach of a proton donor to the π electron cloud above the aromatic system are somewhat weaker, they nonetheless represent an important class of stabilizing interactions. The strengths of H-bonds in this category follow the trend Trp > His > Tyr ∼ Phe. CH··O interactions are weaker still, and only those involving His and Trp are strong enough to make significant contributions to protein structure. A protonated residue such as HisH$^+$ makes for a very powerful proton donor, such that even its CH··O H-bonds are stronger than the conventional H-bonds formed by neutral groups.

Introduction

The hydrogen bond is one of the bedrocks upon which the structure of proteins is constructed. The participation of the peptide group in such bonds is a well-recognized factor in α-helices and β-sheets as well as a multitude of other structural components of proteins. There are a number of amino acid residues that can form H-bonds via their side chains in addition to their peptide group. Perhaps most notable of this category are side chains that contain a hydroxyl (Ser and Thr) or amide (Asn and Gln) group or charged residues such as Lys, Arg, Asp, and Glu. Also known to participate in H-bonds are some of the aromatic amino acids, such as His, Tyr, and Trp. Most attention has been focused upon the ability of these residues to form conventional H-bonds of the OH··O or NH··O type. This focus is understandable as these traditional H-bonds can be expected to represent the strongest sort of interaction, one that proteins will strive to take advantage of as they adopt their optimal structure.

On the other hand, the many factors that contribute to the final structure of a protein often mitigate against particular H-bonds adopting their preferred geometry. It is for this reason, for example, that the lengths of H-bonds within proteins cover a wide spectrum, some much longer than is optimal for the H-bond; it is also why many H-bonds are considerably bent from their preferred linear arrangement. Indeed, factors of a similar nature can conspire to keep some potentially H-bonding residues from forming a H-bond of the traditional type at all. However, this failure does not preclude such a residue from participating in a stabilizing interaction. One type of interaction that has gained increasing scrutiny involves the approach of a standard proton donor toward the π electron density that lies above and below the aromatic groups of Phe, Tyr, Trp, and His residues. Indeed, the potential importance of this phenomenon to protein structure has been underscored by recent analyses of gas-phase clusters,[1,2] wherein the preferred conformations of Trp analogues are altered by the presence of a H-bond of this type.

However, surveys of crystal structures of proteins remain inconclusive concerning the presence of such H-bonds. While some studies[3−5] suggest that proton-donating amino groups tend to make contact with the π electrons of the aromatic Phe, Tyr, and Trp side chains, these observations are contradicted by other work that noted that water molecules and hydroxyl and amine groups prefer the plane of the ring of the same residues with only relatively rare contacts with the ring faces.[6−8] This latter idea was reinforced by studies that suggested that interactions with the π clouds are less likely than those involving the CH groups of the phenyl ring[9,10] confirming earlier such indications.[11,12] Even in cases where the proton donor lies directly above the phenyl ring, its orientation seems in many cases to favor a stacked orientation rather than a geometry conducive

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to formation of a H-bond.[13,14] However, this preference may not be indicative of the possibility of H-bond formation with the π system, as it was attributed to the ability of the donor group to form a H-bond with another species rather than with the ring.[13] Indeed, the entire question is complicated in the sense that the trends seen in proteins may reflect a stronger preference for traditional H-bonding groups (e.g., the OH of tyrosine vs the phenyl ring).[8]

Other sorts of interactions are possible as well. There are, for example, some indications that water might act as a proton acceptor to CH groups of nonpolar aromatic rings,[9] just as the imidazole of His can form a H-bond via a CH group.[15−17] In fact, the latter notion brings up the possibility of yet another class of interaction in which an aromatic residue might involve itself. In addition to traditional OH••O H-bonds and those in which a proton donor approaches the aromatic ring from above in a OH••π configuration, there is the potential of CH groups to act as proton donors in H-bonds.[18] Although many of the observations of such interactions have involved very acidic CH groups, as in alkynes or substituted alkanes,[19−23] a number of observations of aromatic CH donors have surfaced as well.[24−29]

The current status of the analysis of protein structures thus raises the possibility of various sorts of interactions in which aromatic residues might participate (e.g., OH••O, OH••π, and CH••O) but leaves largely unanswered a number of important questions. Are all three of these interactions attractive, or do they appear in proteins merely as a result of steric constraints? Which sorts of interactions are preferred, and by how much from an energetic standpoint? How do the various aromatic residues compare with respect to their ability to form each of these types of potentially stabilizing interactions? What sorts of structural and spectroscopic markers are associated with each of these interactions that might be used to detect their presence?

Whereas crystal structures are highly informative regarding the geometries of various groups, they are largely silent on the question of the attractive or repulsive nature of each interaction and the magnitude of any stabilizing force. Quantum chemical calculations, on the other hand, are particularly useful in terms of computing energetics and so are well-equipped to provide answers to the questions above. There have been a number of quantum chemical studies that considered the π H-bonding capabilities of aromatic groups such as benzene,[30−32] phenol,[33] and indole.[34] The possibility of aromatic CH••O interactions has also been investigated to some extent.[35−40] However, there has been little in the way of a comprehensive comparison of all three sorts of interactions on an equal footing (i.e., at a similar level of theory) so that fair comparisons can be made. Nor has there been much effort to compare the different aromatic residues with one another.

It is the objective of the present paper to carry out just this sort of systematic comparison of the various interactions in which an aromatic residue might conceivably participate. All four sorts of aromatic residues (Phe, His, Tyr, and Trp) are considered separately and compared to one another. In each case, different possible conventional (e.g., OH••O or NH••O) H-bonds are considered and compared with an assortment of OH••π or CH••O bonds that might occur. Along with the energetic aspects of the interactions, structural and spectroscopic markers are computed.

Methods

Ab initio calculations were carried out using the Gaussian 98 set of codes[41] and the 6-31+G** basis set. Electron correlation was included via the second-order Møller−Plessset (MP2) treatment with frozen core.[42] (Only very small changes were introduced into the results by the latter approximation, relative to full MP2.) Interaction energies were corrected for basis set superposition error via the standard counterpoise method.[43] NMR chemical shifts were computed using the gauge-including atomic orbital (GIAO) approach[44] at the MP2 level, which has been shown to produce rather accurate data for hydrogen bonds.[45] Total interaction energies were decomposed via the Kitaura−Morokuma scheme[46] as implemented in the GAMESS program.[47]

The aromatic portion of the Phe amino acid was modeled here by benzene (Bz). Similarly, the active portions of Tyr, Trp, and His were modeled by phenol (Ph), indole (In), and imidazole (Im), respectively. The molecule chosen to interact with these species is water, in part

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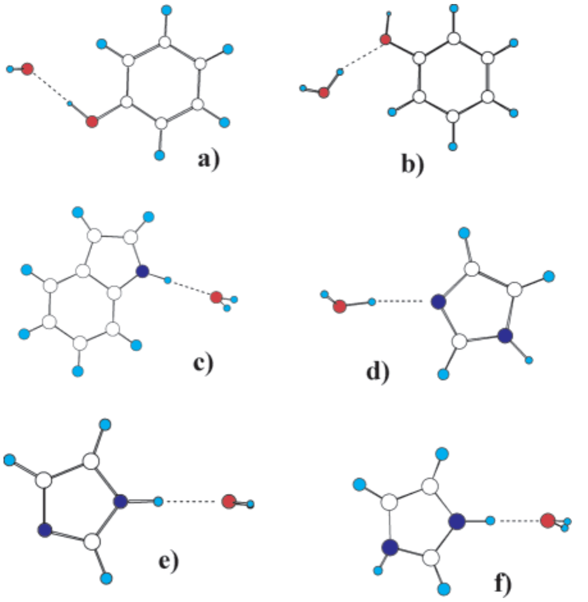

Figure 1. Conventional XH··Y H-bonds formed by HOH with aromatic molecules (a and b) phenol, (c) indole, (d and e) imidazole, and (f) protonated imidazole. C is indicated by open circles, H by light blue, O by red, and N by dark blue.

because of its ability to act as both proton donor and proton acceptor and also because of its widespread occurrence in biological systems.

As mentioned above, there are a variety of ways in which a molecule of water can interact with the aromatic species under consideration. One sort of interaction consists of a conventional H-bond in which a proton-donating OH or NH group approaches the lone pair of an O or N atom. These interactions are referred to herein as XH··Y and are shown in Figure 1. With no heteroatoms, benzene cannot form a classic H-bond and so is not included in this category. With its OH group, phenol can act as either proton donor or proton acceptor in a OH··O bond with water, illustrated in Figure 1, panels a and b, respectively. The NH group of indole can donate a proton to water, as indicated in Figure 1c. Neutral imidazole contains both an unprotonated N atom and a NH group, so it can accordingly act as acceptor or donor via these groups, represented in Figure 1, panels d and e, respectively. Protonated imidazole (ImH$^+$), on the other hand, can form only a NH··O bond (the two NH groups are equivalent), as illustrated in Figure 1f.

The second sort of interaction involves the approach of the OH group of the water molecule toward the aromatic (φ) ring from above, forming an interaction with the π cloud designated OH··φ. The optimized minimum for HOH··benzene, illustrated in Figure 2a, has a not quite linear arrangement between the approaching OH bond and the center of the benzene ring (indicated by the black dot). A similar configuration is observed in the OH··φ configuration of the phenol molecule, exhibited in Figure 2b. There are two rings in the indole system, and the water molecule was allowed to approach both the five-membered pyrrole (Figure 2c) and the six-membered phenyl ring (Figure 2d). The approach of water toward the unprotonated imidazole is illustrated in Figure 2e. When imidazole is protonated, it attracts not the H atom of water but rather the partially negatively charged O atom. Hence, the geometry exhibited for ImH$^+$ + HOH in Figure 2f is not classified as a H-bond. (The configurations illustrated in Figure 2 were optimized under the sole restriction that the water O atom lies directly above the aromatic's center to circumvent the tendency for displacement of the water toward the heteroatoms with which it can form a more stable conventional XH··Y H-bond.)

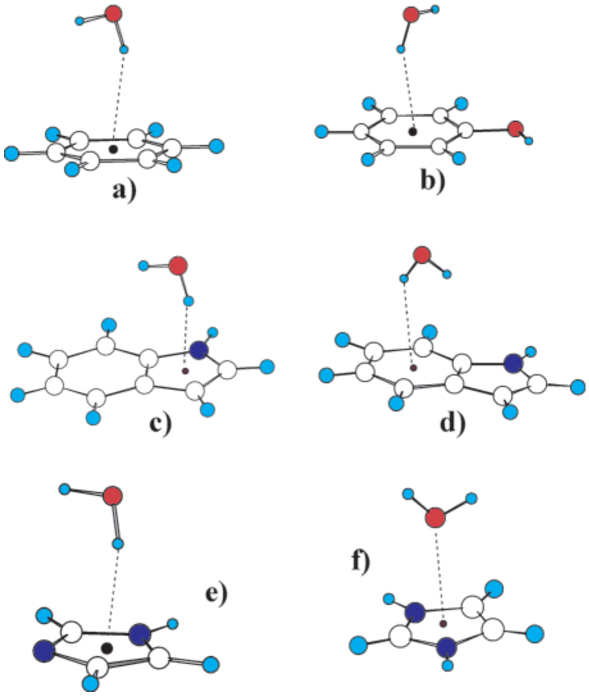

Figure 2. Optimized geometries of OH··φ complexes. Small black dot represents center of indicated ring.

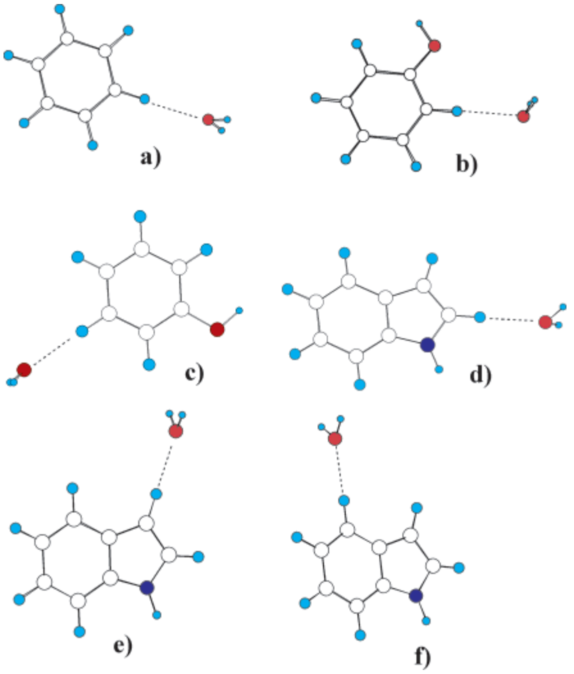

Figure 3. Optimized geometries containing CH··O interactions of (a) benzene, (b and c) phenol, and (d−f) indole.

The possibility of a CH group acting as proton donor is investigated in a number of different CH··O arrangements, shown in Figures 3 and 4. Only one such configuration is possible for benzene (Figure 3a), where all six H atoms are equivalent. Figure 3b illustrates the interaction of water with the CH group ortho to the OH of phenol; the meta CH group was considered in Figure 3c. There are quite a number of nonequivalent CH groups in indole. Those considered explicitly here included the two CH groups on the pyrrole ring, both adjacent to NH (Figure 3d) and one removed (Figure 3e), and one of the CH groups on the phenyl ring (Figure 3f). The CH group that lies between the two N atoms of imidazole was considered, as in Figure 4a, as was one of the other two CH groups (Figure 4b). The same two CH groups were taken as potential proton donors in the case of protonated imidazole (Figure 4, panels c and d). As in the OH··φ cases, in the absence of restrictions many of the CH··O configurations in Figures 3

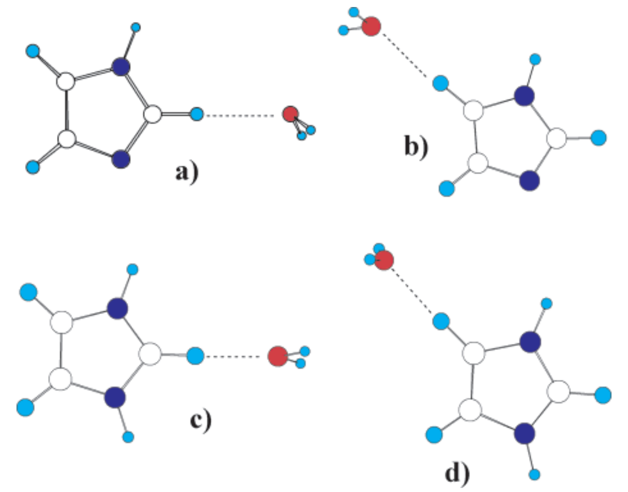

Figure 4. Optimized geometries containing CH··O interactions of (a and b) imidazole and (c and d) protonated imidazole.

and 4 decay to energetically preferred XH··Y structures; hence, linearity was imposed on the CH··O arrangements.

Results

Energetics. The uppermost section of Table 1 lists the calculated interaction energies for each of these sorts of interactions for the various aromatic systems. The classical XH··Y sorts of H-bonds are reported on the left side of the table. The OH group of phenol is an active H-bonder, forming an interaction with water of 6.2 or 4.0 kcal/mol, depending on whether phenol is the proton donor or acceptor, respectively. The NH··O H-bond formed by indole amounts to some 5.5 kcal/mol, slightly weaker than the preceding OH··O phenol case. The NH group of imidazole can donate a proton to water, or the unprotonated N atom can accept a proton from water. The OH··N bond of the latter configuration is somewhat stronger than the NH··O bond of the former and is in fact the strongest of the H-bonds formed by the neutral aromatic molecules. The greater strength of the NH··O bond in imidazole, as compared to indole, may be due to the presence of two electron-withdrawing N atoms in the former case. Of course, after the imidazole has been protonated, its only option is to form a H-bond of the NH··O variety. Because of the charged nature of the proton donor, the resulting ion−neutral interaction is particularly strong, 15.9 kcal/mol.

Table 1. Features of H-Bonds Contained within Optimized Complexes Pairing Water with Benzene (Bz), Phenol (Ph), Indole (In), Imidazole (Im), and Protonated Imidazole (ImH^+)

	XH··Y	OH··φ	CH··O
		$-\Delta E$,[a] kcal/mol	
Bz		2.1	1.1
Ph	6.2,[b] 4.0[c]	2.3	1.3,[d] 1.2[e]
In	5.5[f]	3.5,[g] 3.2[h]	2.1,[i] 1.1,[j] 0.9[h]
Im	6.7,[k] 6.0[f]	3.1	2.4,[l] 2.3
ImH^+	15.9	8.1[m]	11.3,[l] 9.5
		R,[n] Å	
Bz		3.370	3.412
Ph	2.858,[b] 2.918[c]	3.347	3.410,[d] 3.408[e]
In	2.966[f]	3.212,[g] 3.299[h]	3.349,[i] 3.392,[j] 3.426[h]
Im	2.917,[k] 2.955[f]	3.225	3.339,[l] 3.336
ImH^+	2.752	2.898[m]	3.053,[l] 3.105
		Δr,[o] mÅ	
Bz		+2.8	−0.8
Ph	+11.1,[b] +6.0[c]	+0.7	−0.1,[d] −0.8[e]
In	+6.1[f]	+4.8,[g] +3.8[h]	+0.4,[i] +0.3,[j] −0.9[h]
Im	+13.4,[k] +6.7[f]	+3.5	+0.6,[l] +1.0
ImH^+	+22.0		+7.8[l], +5.7
		$\Delta\nu$,[p] cm^{-1}	
Bz		−27	+33
Ph	−147,[b] −71/−39[c]	−23/−30	+21,[d] +26[e]
In	−102[f]	−48/−52,[g] −32/−47[h]	0,[i] +3,[j] +17[h]
Im	−216/−55,[k] −113[f]	−34/−41	−2,[l] −5
ImH^+	−414	−	−118,[l] −78
		$\Delta\sigma(H)_{iso}$,[q] ppm	
Bz		+2.3	−1.3
Ph	−1.0,[b] −2.9[c]	+2.1	−1.4,[d] −1.3[e]
In	−2.9[f]	+1.8,[g] +2.4[h]	−1.6,[i] −1.5,[j] −1.3[h]
Im	−4.9,[k] −2.7[f]	+1.6	−1.5,[l] −1.5
ImH^+	−4.9		−2.7,[l] −2.5

[a] Corrected for basis set superposition error by counterpoise method. [b] Ph is proton donor, see Figure 1a. [c] Ph is acceptor, see Figure 1b. [d] CH ortho to OH group, see Figure 3b. [e] CH meta to OH group, see Figure 3c. [f] NH··O. [g] Five-membered ring. [h] Six-membered ring. [i] Five-membered ring ortho to N (Figure 3d). [j] Five-membered ring meta to N (Figure 3e). [k] OH··N. [l] CH between two N atoms. [m] Direct O··φ connection with no bridging H. [n] Distance between non-hydrogen atoms, or in case of OH··φ between O and center of ring. [o] Change in AH (A = O, N, C) bond length of proton donor molecule. [p] Shift in stretching frequency of AH bond; s/as frequencies of water when water is proton donor. [q] Change in isotropic chemical shift of bridging hydrogen caused by complexation.

Turning next to the less traditional H-bonds, we consider the approach of one of the water protons toward the delocalized π cloud of the aromatic system (designated here as φ, i.e., from above the ring). The properties calculated for these optimized complexes are indicated by the next column of Table 1, from which it may be seen that the binding energy of water to benzene is some 2.1 kcal/mol. The addition of a hydroxy group to form phenol enhances the binding energy by a small amount, up to 2.3 kcal/mol. Larger increments arise when the aromatic system is enlarged to an indole system or when two N atoms are added to the ring as in imidazole. In either case, the interaction energy surpasses 3 kcal/mol. Indole forms the strongest of the OH··φ bonds, particularly if the pyrrole ring is involved. When the imidazole is protonated, it becomes a far less inviting target to the proton of water; in fact, the preferred arrangement turns the water so that it approaches the aromatic ring oxygen-first, forming a sort of O··φ interaction. As in the XH··Y case of traditional H-bonds, the ion−dipole nature of this interaction makes it much stronger than the neutral−neutral situations, resulting in an interaction energy here of 8.1 kcal/mol.

The weakest of the H-bond types considered here involves the approach of the O atom of water toward one of the CH groups of the aromatic molecule. The CH group of benzene is rather weakly acidic, so the interaction amounts to only 1.1 kcal/mol. Addition of the hydroxy group in phenol strengthens the CH··O interaction somewhat, by 0.2 kcal/mol if the CH is adjacent to the hydroxy and by 0.1 kcal/mol if once removed. There are a variety of CH groups on the indole moiety. The one that binds a water most strongly is located on the five-membered ring, adjacent to the N atom. This interaction energy is evaluated at 2.1 kcal/mol. This quantity drops by 1.0 kcal/mol if one moves away to the next CH group, one removed from the N. The CH group on the six-membered phenyl ring binds slightly more loosely than this, comparable to the binding strength of benzene itself. The presence of two N atoms in imidazole makes for a more acidic CH between them. This CH group binds to water with a strength of 2.4 kcal/mol. The other two CH groups are only marginally weaker, at 2.3 kcal/mol. Of the neutral aromatic CH donors then, it is imidazole that binds most tightly to water with an interaction energy comparable to that of the $C^{\alpha}H$ of amino acids[48] and perhaps half that of the water dimer.

Not surprisingly, the cationic protonated imidazole is a potent proton donor. As mentioned above, the $NH\cdots OH_2$ interaction energy amounts to 15.9 kcal/mol. The corresponding $CH\cdots OH_2$ binding energy is also quite large, stronger than most neutral H-bonds, even those involving only electronegative atoms such as O and N. The interaction energy is computed to be 11.3 kcal/mol for the CH that lies between the two N atoms and 9.5 kcal/mol for the others.

Geometries and Spectroscopic Features. In reference to equilibrium H-bond lengths, the optimized distances are reported as R in the second section of Table 1. The various O··O and O··N distances for the conventional H-bonds are the shortest of those considered, all less than 3 Å. Shortest of all at 2.75 Å is the NH··O distance in the cationic system containing protonated imidazole. The values of R tabulated for the OH··φ systems refer to the distance between the water O atom and the center of the indicated aromatic ring. These distances are generally between 3.2 and 3.4 Å for the neutral systems and are roughly correlated with the strengths of the H-bonds. That is, the shortest distances correspond to the most negative values of ΔE. The weaker nature of the CH··O interaction leads to the longer R(C··O) distances in Table 1, in the 3.3−3.4 Å range. The exceptions include the protonated imidazole, where the strong binding leads to H-bond lengths in the neighborhood of 3.1 Å.

One of the more interesting manifestations of a H-bond is its effect upon the X−H covalent bond of the proton donor molecule. Whereas the vast majority of such bonds are elongated by the formation of the H-bond and undergo a red shift in its stretching frequency, recent experimental measurements and calculations have revealed a small subset of interactions, wherein the opposite effect of a bond contraction and blue shift occur.[18,23,49−51] The Δr data for the conventional XH··Y H-bonds in Table 1 are all positive, indicating the stretches characteristic of such bonds. The $\Delta \nu$ shifts below them are all negative; this red shift is typically associated with bond stretches. One might also note a correlation between the two quantities in that the larger bond stretches are associated with a greater red shift in the frequency.

In the case of the OH··φ interactions, it is the water molecule that is the donor, so it is one of the water OH bonds that is undergoing a stretch in the H-bonding interactions. These stretches are considerably smaller than those in the traditional XH··Y H-bonds, where the acceptor is a lone pair of an electronegative atom rather than the π cloud of the aromatic system. These smaller stretches, along with the accompanying smaller red shifts of the frequency, are consistent with the weaker nature of these OH··φ interactions.

The results for the CH··O interactions are interesting first in the sense that the changes in the CH bond lengths are rather small, generally less than 1 mÅ. More intriguing perhaps is the observation that the CH bond contracts in some of the systems and elongates in others. The contractions occur in the more weakly bound systems, involving benzene and phenol, and elongations are associated with unprotonated and protonated imidazole. Indole is intermediate in that the changes are small and can occur in either direction. There is a general correlation that the weaker CH··O interactions tend to contract the CH bond, while it is elongated in the stronger cases. The next section of data in Table 1 indicates that CH contractions are associated with blue shifts and stretches with red shifts.

The bottom section of Table 1 reports the calculated changes in the isotropic chemical shift of the bridging hydrogen, caused by complexation. The typical result of H-bond formation is the drop in this quantity by several ppm, exemplified by the XH··Y data in Table 1. Earlier calculations[52] had suggested that similar changes, albeit generally to a lesser degree, occur in CH··O H-bonds, a result that is confirmed in the pertinent section of Table 1, where the changes are typically between 1 and 2 ppm. The exception is the stronger set of CH··O H-bonds involving protonated imidazole, where the downfield shifts of the bridging hydrogen approach 3 ppm.

Most interesting perhaps are the results for the OH··φ interactions, wherein the bridging H of the water molecule approaches the aromatic ring from above. The proton's chemical shift moves upfield, rather than down, as it approaches the π electrons. It is further intriguing that the magnitude of this shift bears no obvious correlation with either the strength of the interaction (ΔE) or the optimized distance of approach (R). Indeed, the largest shift (of +2.3 ppm) is associated with the weakest interaction, between water and benzene.

Energy Decomposition. A breakdown of the full molecular interaction energy into a number of components can offer insight into the fundamental nature of the interaction. One popular means of such decomposition is via an approach attributed to Kitaura and Morokuma[46] in which the electrostatic energy (ES) represents the classical Coulombic force between the charge distributions of the two partner molecules. The exchange energy (EX) corresponds to the steric repulsion between the electron clouds of the two molecules. The remaining components arise when the two molecules are permitted to perturb the electron clouds of one another. The polarization (POL) and charge transfer (CT) contributions represent the energetic consequences of electronic redistributions that occur within the confines of a single molecule and those that cross from one molecule to the other, respectively. Finally, the correlation component to the interaction energy (CORR) contains dispersion as its major contributor as well as additional factors.

The energy components to the interaction energy of phenol and imidazole with water are reported in Table 2 for each of the three main types of H-bonds. These two aromatics were chosen for examination so as to encompass both the rather weak OH··φ and the CH··O bonds formed by phenol (similar to benzene) as well as the stronger such bonds formed by imidazole and indole. The classical OH··O H-bonds are reported on the left of the table for both cases in which phenol or imidazole acts as proton donor or acceptor. The CH··O interaction, displayed on the right, is that in which the water accepts a proton from the CH adjacent to the OH group of phenol, the strongest

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Table 2. Decomposition Elements[a] (kcal/mol) of Interaction Energies of Complexes Involving Phenol and Imidazole with Water, Calculated with 6-31+G** Basis Set

	XH··Y		OH··φ	CH··O
	Phenol−Water Complex			
ES	−12.7[b]	−8.4[c]	−3.4	−1.9
(MP)[d]	(−5.2)	(−1.0)	(−7.9)	(−1.1)
EX	9.5	7.1	3.2	1.1
CT	−2.3	−1.7	−0.9	−0.4
POL	−1.8	−1.5	−0.7	−0.2
CORR[e]	−2.2	−2.1	−2.4	−1.4
	Imidazole−Water Complex			
ES	−10.3[f]	−8.7[g]	−3.1	−4.0
(MP)[d]	(−5.6)	(−4.1)	(−3.8)	(−2.5)
EX	6.5	4.5	1.3	2.2
CT	−1.7	−1.0	−0.6	−0.6
POL	−2.1	−1.0	−0.5	−0.4
CORR[e]	−2.1	−2.0	−2.4	−1.1

[a] Uncorrected for BSSE. [b] φOH is proton donor. [c] φOH is acceptor. [d] Multipole expansion of electrostatic energy through R^{-5} term. O atom was taken as center for expansion around water molecule and the centers of the aromatic rings of phenol and imidazole for the other. [e] CORR = ΔE(MP2) − ΔE(HF). [f] OH··N. [g] NH··O.

such interaction, or the CH of imidazole that lies between the two N atoms.

Inspection of Table 2 suggests that all three sorts of H-bonds behave in much the same way. In all cases, the largest attractive component is electrostatic. (This quantity is very poorly reproduced by consideration of the interaction between the molecular dipoles, which yields values far smaller than ES. A more complete molecule-centered multipole expansion, carried through the fifth power of the distance separating the two molecules,[53] provides an undependable approximation, as is clear from comparison of the MP row of Table 2 with ES.) CT and POL make smaller but not insignificant contributions as well; the CT component tends to be slightly larger in magnitude than POL in most cases. The only repulsive component is the exchange term, which is consistently smaller than ES in magnitude. Correlation is attractive in all cases. With certain notable exceptions, the magnitudes of the various terms follow the same pattern as do the total interaction energies: XH··Y > OH··φ > CH··O.

It is only upon closer examination of the magnitudes of the various terms that one is able to discern any differences between the three sorts of H-bonding. In the case of the OH··φ bond involving phenol, the EX energy is nearly equal in magnitude to ES, while it is considerably smaller than ES in the other modes of bonding. The OH··φ bond also has proportionately greater contributions from the CT and POL energies that amount to 26 and 21% of the ES term, respectively, higher percentages than in the two other sorts of H-bonds. It is correlation, however, that shows the most marked difference. Whereas correlation is equal to more than 70% of the ES term for the OH··φ and CH··O bonds, it represents only 25% or less in the OH··O situations.

Turning next to the imidazole−water complexes, the various terms for the conventional XH··Y H-bonds are comparable to the corresponding values for phenol with some minor exceptions. The EX repulsions in the two bonds involving imidazole are somewhat smaller than in the phenol cases. Similarly, the CT and POL terms are smaller for the NH··O bond of imidazole, and the POL energy in the OH··N bond is proportionately somewhat higher than for the phenol case. These minor differences can be attributed in part to the participation of a N atom in the two imidazole H-bonds and probably do not denote any fundamental differences.

With regard to the OH··φ interactions, the various components are smaller for the imidazole−water complex than for the phenol−water complex. But this smaller magnitude is particularly striking in the case of the EX repulsion, 2 kcal/mol smaller for Im as compared to Ph. Since the attractive components are reduced in magnitude in Im, it is this more severely lowered repulsion that is responsible for the greater strength of the OH··φ interaction of Im as compared to Ph. Just as in the Ph case, correlation accounts for a large fraction of the OH··φ binding energy in Im··water, nearly as much as electrostatics.

As noted above, the CH··O interaction is also stronger for Im than for Ph. Inspection of the last column of Table 2 suggests that this difference cannot be attributed to any single component, as most terms are considerably larger in magnitude for Im than for Ph. The exception is the CORR energy, which is slightly smaller in the former. The stronger CH··O binding in Im as compared to Ph is thus attributed to magnification of all factors with the exception of dispersion. The proportional contributions of the various terms to the CH··O interaction in Im··water are in fact quite similar to their contributions to the conventional XH··Y bonds, reaffirming prior conclusions that the two sorts of bonds are quite similar in fundamental nature.[49,54−58]

Of course, there is more than one way to skin a cat or to decompose the total interaction energy. An alternate scheme, based upon symmetry-adapted perturbation theory (SAPT), was applied to an OH··φ complex pairing HOH with benzene,[59] comparable to our phenol··water complex, and revealed much the same trends as exhibited in the appropriate column of Table 2. Like the Morokuma decomposition, the SAPT analysis indicated the important role played by dispersion energy, as contained in the correlation component, also highlighting the importance of the induction terms (CT and POL).

Summary and Discussion

The calculated results confirm the expectation that conventional H-bonds of the XH··Y type are the strongest and will usually be preferred. In cases where such bonds cannot be attained by these amino acid residues for structural or other reasons, nontraditional types of H-bonds can afford a certain degree of stability. OH··φ interactions offer a reasonable alternative, providing roughly half of the energetic stabilization of the conventional H-bonds, generally between 2 and 4 kcal/mol. CH··O bonds are somewhat weaker still, with interaction energies in the neighborhood of 1−2.5 kcal/mol. Moreover, one should not consider these alternative types of H-bonds as necessarily forming to the exclusion of traditional bonds but can occur as supplementary interactions, offering additional stabilization and perhaps further refinement to the protein structure.

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The computed data provide comparisons of the relative strengths of H-bonds within a given class. For example, the hydroxyl of phenol represents the most potent proton donor in the XH••Y category. The NH of imidazole is a better donor than the same group of indole, probably because of the presence of a second electronegative N atom on the former. With regard to accepting a proton, the N atom of imidazole is superior to the O of phenol. Indeed, the OH••N bond involving imidazole is the strongest of all H-bonds involving neutral aromatic groups. These strengths of the various H-bonds incorporating aromatic groups are comparable to, and sometimes stronger than, the more prevalent H-bonds in proteins (e.g., the interpeptide NH••O interactions comprising α-helices or β-sheets).

The presence of two electronegative N atoms on imidazole makes this species the most active CH donor. Indole is only slightly weaker, provided the CH group lies adjacent to the nitrogen of the pyrrole ring. The other CH groups of indole, as well as those in phenol and benzene, are considerably weaker. The calculated CH••O binding energies of the aromatic groups are comparable to those involving the peptide $C^{\alpha}H$ of the protein backbone.[48] With regard to OH••φ bonds, indole is the strongest acceptor of the aromatic residues, particularly its smaller five-membered ring. Imidazole is somewhat weaker, followed by phenol and then by benzene.

As noted above, the OH••φ and CH••O binding energies of phenol and benzene to water are rather small, the latter just barely above 1 kcal/mol. One might naturally wonder whether these weak interactions constitute a real H-bond or indeed a substantive attraction over and above the London/dispersive forces that would be experienced by a pair of nonpolar species. To address this question, the water molecule was replaced by CH_4, which clearly cannot form a H-bond. This methane molecule may be thought of as a model of the nonpolar hydrocarbon groups within proteins but of the same approximate size as a water molecule so as to offer parallel dispersion forces. When this methane molecule was placed directly above the benzene ring in a configuration similar to that in Figure 2a, the interaction energy was computed to be 0.5 kcal/mol. If we consider this quantity to be a sort of baseline (the attraction experienced by a nonpolar species above the benzene ring), then the 2.1 kcal/mol computed for the interaction energy of benzene with water represents an additional attractive force, attributable to the H-bond, of 1.6 kcal/mol. In the same vein, the interaction energy of methane with benzene in a CH••C geometry, parallel to Figure 3a, was computed to be 0.2 kcal/mol. The difference between this quantity and the CH••O binding energy of water is 0.9 kcal/mol, which represents perhaps a truer measure of the CH••O H-bond strength than does the binding energy (1.1 kcal/mol) itself.

The OH••φ interactions considered above position the approaching O atom directly above the center of the pertinent aromatic ring. An alternate potential target for the OH might be the pair of electrons in the nitrogen p orbital of the NH of Im and In. However, placement of the HOH directly above the NH of indole weakens the interaction by nearly 1 kcal/mol as compared to its preferred location over the center of the five-membered ring. In the case of Im too, the NH lone pair is a less attractive target for the approaching OH than is the center of the Im ring, with a similarly reduced interaction energy. The poor proton-accepting ability of this N is also reflected by the fact that the water turns its OH away from the N and toward the center of the ring even when the O atom is positioned directly above the N. This observation is not surprising in that the two N electrons are an integral ingredient of the aromatic system of the Im and In. (The other N atom of Im, the unprotonated nitrogen, is a better π proton acceptor, binding to an overhead water by an amount comparable to the situation where the water lies over the center of the ring.)

The structural aspects of these H-bonds conform to the notion that stronger interactions typically lead to a shorter equilibrium separation and hence follow the pattern that XH••Y bonds are the shortest and CH••O the longest, with an OH••φ intermediate between the two. Like the standard XH••Y H-bonds, OH••φ bonds too exhibit a red shift of the proton donor's OH stretching vibration along with a small lengthening of the OH bond. CH••O bonds, on the other hand, are not consistent in this regard. Whereas the stronger bonds of this subset (i.e., with interaction energies greater than 1 kcal/mol) undergo a similar red shift, the weaker CH••O bonds are contracted and shifted to the blue. NMR chemical shifts of the bridging proton of the CH••O H-bonds behave much as do traditional XH••Y, albeit to a lesser degree, whereas the bridging hydrogens in the OH••φ bonds are shifted in the opposite direction by between 1.6 and 2.4 ppm.

After it is protonated, the imidazole ring behaves quite differently in some ways. Its overall positive charge prevents the formation of an OH••φ bond with its π electron cloud. On the other hand, ImH^+ is a very potent proton donor, forming a NH••O H-bond of more than twice the strength of its neutral analogue. Its CH••O H-bonds are very strong as well, in the neighborhood of 10 kcal/mol, and exhibit all the features of a strong XH••Y bond, including red-shifted ν(CH) and downfield chemical shifts.

There are a number of prior studies that buttress the computational results presented here. The combination of phenol with molecules such as water has indicated the conventional OH••O H-bond, with phenol acting as donor, is most favorable.[33,60,61] (There were earlier indications that a π complex might also be present,[62] but this contention has been largely dispelled by later refinements.)[63] The computed binding energy of 6.2 kcal/mol for this phenol••water complex lies comfortably within the range of 5.6−7.3 kcal/mol emerging from a mixed experimental and theoretical study.[33]

A set of DFT calculations[34] confirmed experimental indications[64−66] that water prefers forming a NH••O H-bond with indole to its placement above the plane of the ring. Likewise, the H-bond energy of 5.5 kcal/mol computed here for indole plus water is in nice coincidence with an experimental estimate of the same quantity.[26,67]

Regarding OH••φ interactions, the benzene••water system has been the subject of a number of studies. In the gas phase,

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benzene clearly does form stabilizing contacts with water, as evidenced by the rotationally resolved spectra,[68−70] which suggest both hydrogens of the water molecule point toward the ring from above similar to the configuration pictured in Figure 2a. This result is consistent with data emerging earlier from inert gas matrixes.[71] Our calculated interaction energy of 2.1 kcal/mol fits well with experimental measurements of this quantity,[67] estimated to lie in the 1.4−2.8 kcal/mol range,[68,72,73] and with most other recent calculations.[73−76] In a related system, acetylene, comparable to water in its proton-donating ability, has been computed to bind to benzene's π face with an interaction energy of 2.2 kcal/mol at the MP2 level.[77] Our calculated OH••φ interaction energy for HOH + In (3.5 kcal/mol) is close to an experimental measurement of 4.1 kcal/mol for a N-methylated variant of In.[66]

The strength of the OH••φ interaction was found here to build in the order benzene < phenol < indole. This observation matches precisely with a survey of 593 proteins that indicated a much higher proportion of Trp residues participate in π H-bonds (18%) than do Tyr (8%) or Phe (6%).[5] Indeed, our calculations support the idea that the greater participation of Trp in OH••φ interactions is due primarily to the energetics and is not merely the product of its larger size. In greater detail, our calculations indicate that a proton donor prefers π association with the five-membered ring that contains the heteroatom (3.5 kcal/mol) than to the larger all-carbon ring (3.2 kcal/mol). This conclusion confirms an earlier DFT calculation that found an identical preference of 0.3 kcal/mol for the OH••φ associated with the smaller ring.[34]

With respect to CH••O interactions, the CH group of benzene is weakly acidic, so the interaction amounts to only 1.1 kcal/mol. This value is slightly higher than 0.9 kcal/mol in ethylene•••water,[39,78,79] another system in which the donor C atom is formally sp^2-hybridized but which lacks the aromaticity of benzene. A recent calculation found that NH_3 prefers donation of a proton to the π face of benzene to accepting a proton in a CH••N configuration[80] consistent with the same preference of HOH observed here. The greater proton-donating potential of the CH of imidazole that lies between the two N atoms is consistent with a survey of His residues in proteins, which found that it is usually this same CH that is involved in H-bonding configurations.[15] Prior calculations[37] confirm the relative strengths of the H-bonds involving Im computed here. Strongest of all was the conventional OH••N interaction followed by NH••O. Of the two CH••O bonds considered, the CH group that lies between the two N atoms was found to be the more potent donor. This work also supports our finding of a stretch of the CH bonds when involved in a CH••O interaction.

Vibrational aspects of the calculations are consistent with earlier work as well. For example, the 147 cm^{-1} red shift calculated for the OH stretch in the classical H-bond of phenol with water agrees nicely with an experimental assessment of this quantity of 133 cm^{-1}.[60] The red shift of 102 cm^{-1} calculated for the indole−water complex is in similarly good accord with an experimentally measured shift of 85−89 cm^{-1}.[34,65] In terms of nontraditional H-bonds, the red shift of 27 cm^{-1} calculated for the OH••φ interaction in the benzene−water system is consistent with earlier calculated and experimental assessments[59,75] in the 20−30 cm^{-1} range. When located above the indole system, the OH stretches of a water molecule are shifted to the red by 48−73 cm^{-1}[2], consistent with our calculated shifts in the range of 32−52 cm^{-1}, particularly as the experimentally observed system contains a second water molecule interacting with the first. And finally, very recent high-pressure measurements[81] verify our finding of a red shift of the Im CH stretching frequency when the imidazole is protonated.

In conclusion, aromatic group constituents of amino acids such as Tyr and Trp will prefer to form H-bonds of the conventional sort. The OH••N bond involving His is the strongest, followed by the OH••O bond where Tyr acts as donor and then by the NH••O bond of Trp. If such bonds are unattainable, or in the case of Phe that contains no heteroatoms, other stabilizing interactions are possible, albeit somewhat weaker. The π electron clouds above these aromatic groups may attract a proton donor to form a OH••φ H-bond. Trp forms the strongest bond in this category, followed by His, and then by Tyr and Phe. The CH groups of the aromatics offer an alternative proton donor site for CH••O interactions. Most notable in this class are His and Trp; Tyr and Phe offer only very marginal stabilization. A protonated residue such as HisH$^+$ is a far more potent proton donor, and even its CH••O H-bonds are stronger than the conventional OH••O interactions between neutrals.

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