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Short, Strong Hydrogen Bonds in the Gas Phase and in Solution: Theoretical Exploration of pK_a Matching and Environmental Effects on the Strengths of Hydrogen Bonds and Their Potential Roles in Enzymatic Catalysis

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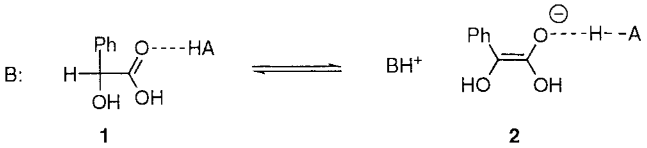
Short, strong hydrogen bonds are common in charged systems in the gas phase, but the importance of such bonding in enzymatic catalysis has been the subject of considerable controversy. Confusion has arisen about the relationship among bond strength, the "low-barrier" or "no-barrier" nature of the hydrogen bonding, the role of pK_a matching, the covalent or electrostatic nature of the bonding, and the role of solvation on the strengths of these types of hydrogen bonds. We have attempted to strip away the "Alice in Wonderland" quality of the definitions in this field by defining, through high-level calculations, when short-strong hydrogen bonds do and do not occur. The strengths and geometries of several types of hydrogen bonds involving anions have been investigated by ab initio quantum mechanical calculations. For a series of enols hydrogen-bonded to enolates, the strengths of the short, strong gas-phase hydrogen bonds are linearly related to the differences between the proton affinities (PA) of the two anions which share the proton. The bond strength is also related to the O···O distance between them. There is no discontinuity at $\Delta PA = 0$, and hydrogen-bonding becomes even stronger in a computational experiment when the PA of the H-bond acceptor exceeds that of the donor. "Low-barrier" hydrogen bonds with single-well minima after inclusion of zero-point energies occur when ΔPA is near 0, but no special stability accrues when the double-well minimum becomes single-well. The maleic/fumaric and mesaconic/citraconic systems studied by Drueckhammer have been investigated computationally. The influence of solvation on hydrogen-bond strength was studied using solvent cavity models. Small increases in dielectric constant from the gas-phase value ($\epsilon = 1$) rapidly reduce the strengths of charged hydrogen bonds. Short, strong hydrogen bonds occur only with charged systems, and only then in nonpolar ($\epsilon < 10$) environments. Alternative mechanisms are often available to account for enzymatic catalysis; the example of orotidine monophosphate decarboxylase is discussed.

Introduction

Hydrogen bonds are frequently separated into two categories:[1] weak or normal hydrogen bonds and strong or very strong hydrogen bonds. The normal hydrogen bonds are regarded as those with strengths of about 3−5 kcal/mol and of generally less than 12 kcal/mol. In such hydrogen bonds, the proton is significantly more strongly bound to one heavy atom than the other participant in the bond. Proton-transfer involves two minima separated by a significant barrier. Most neutral hydrogen bonds fall into this category. Strong hydrogen bonds may have energies in excess of 12 kcal/mol. Such strong hydrogen bonding always involves features such as a short bond distance and single minimum potential or double minimum with a very low barrier. Such bonds have significant covalent character. Strong hydrogen bonds are always found to be ionic hydrogen bonds.[2] The bifluoride FHF^- in the gas phase, with a "hydrogen bond" of 46 kcal/mol, is the prime example of such a bond.[3]

To explain some apparent anomalies in enzyme catalysis, Gerlt and Gassman[4] proposed that hydrogen bonds with strengths of 10−20 kcal/mol could be important stabilizing factors in enzymes. A typical example is illustrated in Scheme 1.

Scheme 1



Deprotonation of the α-proton of carboxylic acids is a key step in many enzyme-catalyzed processes, including carbon−carbon bond formation and racemization.[5] However, the formation of an enolate intermediate with a carboxylate base is highly endothermic.[6] According to Gerlt and Gassman, a general acid catalyst can stabilize the unstable intermediate by the formation of a short, strong hydrogen bond between the conjugate base of the general acid catalyst and the developing enolate when

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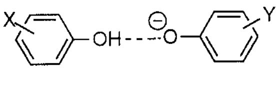
the pK_as are matched. A large stabilization energy is available when the hydrogen bond changes from a weak bond in the enzyme−substrate complex **1** to a strong one in the enzyme−intermediate or transition state complex **2**. Subsequently, Cleland and Kreevoy discussed the special stabilization arising from hydrogen-bonding between proton donors and acceptors of matched pK_a.[7] Frey applied this idea to serine proteases.[8]

The claims that short, strong hydrogen bonds are important in catalysis have been widely criticized, particularly the proposal that special stabilization occurs upon pK_a matching.[9] The very existence of short, strong hydrogen bonds in the condensed phase has been questioned.[10] A discussion of low-barrier hydrogen bonds (LBHB) and the catalytic advantage of covalent character in LBHB was also argued by Warshel.[11] The proponents of short, strong hydrogen bonds have responded strongly in favor of the importance of these in catalysis.[12]

Recently, Herschlag et al.[13] investigated hydrogen-bond energies as a function of ΔpK_a for homologous series of phenol−phenolate complexes, **3**, in solution. Linear relationships between hydrogen bond strength and ΔpK_a were observed in DMSO and THF solvent. Experimental studies and calculations in the literature[14−19] have also established that when pK_as are matched between donor and acceptor, maximum hydrogen bonding is achieved; however, the relationship at that point between hydrogen bond strength and ΔpK_a is still linear, and no special stabilization is observed due to the "pK_a match".



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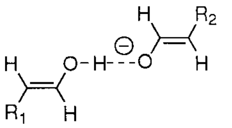

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Cleland and Kreevoy[7] suggested that "the requirements for forming low barrier hydrogen bonds appear to be the absence of a hydrogen bonding solvent such as water, and similar pK_a values of the two heteroatoms involved in the bond. The strongest bonds form when the two heteroatoms are the same (oxygen or nitrogen)..." As pointed out by Guthrie, this may be the requirement for a short hydrogen bond, but it does not indicate how strong the hydrogen bond will be.[10] In the gas phase, the existence of strong hydrogen bonds has been well-established. However, no strong hydrogen bonds >10 kcal/mol have been observed in solution.[10] For example, the strongest solution phase hydrogen bond ($\Delta G = -7.5$ kcal/mol) was measured in acetonitrile,[20] which has a dielectric constant of 36.

Drueckhammer et al.[21] studied the relative strengths of neutral and anionic hydrogen bonds in solution using the equilibrium between citraconic (**5a**) and mesaconic acid (**5b**) or between the corresponding anions (**5c** and **5d**).

5a **5b**

5c **5d**

The cis−trans equilibria were used to estimate the relative strengths of the intramolecular hydrogen bonds formed by the *cis*-diacid (**5a**−**5b**) and monoanion (**5c**, **5d**). The charged hydrogen bond in monanion **5c** was 4.4 kcal/mol stronger than the neutral hydrogen bond in diacid **5a** in DMSO solvent. It was also suggested that the difference might be enhanced in a lower polarity medium. Hydrogen-bond energies involving charged species generally decrease as the environment changes from the gas phase to nonpolar solvents and then to the water solvent. "Is it possible that some hydrogen bonds in the solution or active sites of enzymes have energies in the range of 10−20 kcal/mol?"[10] That is to say, do enzymes have dielectric environments that are low enough to allow short, strong hydrogen bonds? It is therefore of considerable interest to probe short, strong hydrogen bonds in low dielectric media.

Theoretical methods can describe a wider variety of properties than are available experimentally and allow a more detailed analysis of each result for the purpose of gaining insight and understanding and making predictions. In this paper, we report calculations on model systems which establish the strength of hydrogen bonds as a function of charge type, pK_a, and environment, and we establish guidelines for the strength of hydrogen bonds to be expected under given conditions.

We have carried out computational investigations on the complexes **4** formed by enols and enolates with different substituents. These are simpler model systems for the phenols, **3**, studied in solution by Herschlag.[13]

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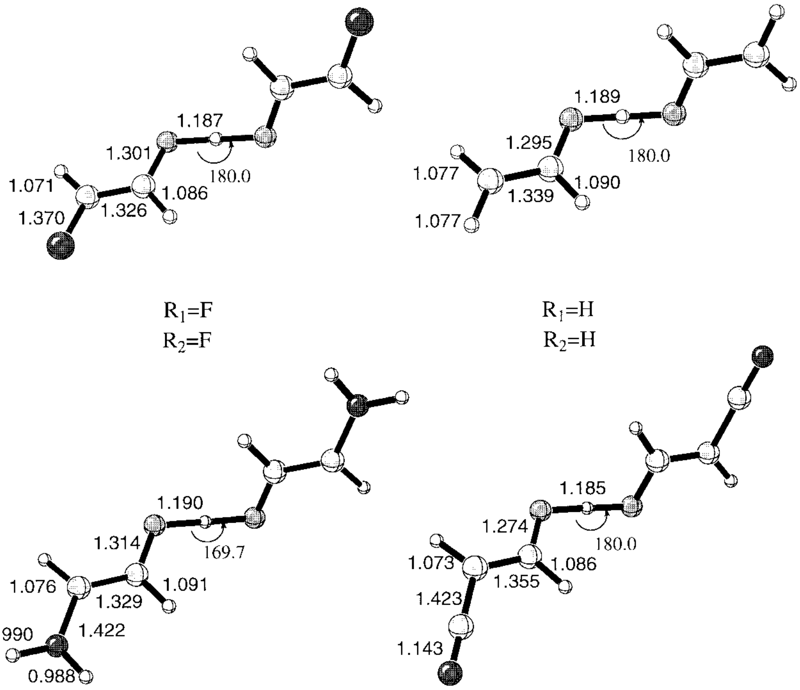

R_1=F
R_2=F

R_1=H
R_2=H

R_1=NH_2
R_2=NH_2

R_1=CN
R_2=CN

Figure 1. Calculated transition states for proton transfer in the degenerate cases. Distances in Ångstroms and angles in degrees.

Such complexes are closely related to enzymatic catalysis and also involve a homologous series.

We also investigated the compounds **5a**−**d**, studied experimentally by Drueckhammer. These molecules allow us to calculate the changing strengths of anionic hydrogen bonds in the gas phase and in polar media and to compare the calculations with experimental data in solution. The SCRF and SCIPCM methods were used to approximate environment effects. The effect of a hydrogen-bonding solvent was studied by incorporating an explicit water molecule hydrogen bonded to a carboxylate group. Finally, the implication of short, strong hydrogen bonds for enzymatic catalysis is briefly discussed on the basis of our theoretical results.

Methods

All the ab initio calculations were performed using GAUSSIAN 94.[22] Geometries were optimized with the standard basis set 6-31G(d) or 6-31+G(d) at the Hartree−Fock level. Frequency calculations were carried out to confirm the nature of transition states and to obtain the zero point vibrational energies. Solvent effects were modeled by the Onsager reaction field method[23] or the SCIPCM method.[24−26] The effect of hydrogen-bonding solvent was studied by adding one water molecule hydrogen bonded to the solute.

Table 1. Optimized Structural Parameters and Energies of Enol−Enolate Complexes[a]

R_1(enol)	R_2(enolate)	E_{HB} (kcal/mol)	R(O⋯O) (Å)	O⋯H⋯O (deg)
NH_2	NH_2	25.4	2.57	169.7
NH_2	H	23.2	2.61	168.6
NH_2	F	22.5	2.62	168.4
NH_2	CN	16.7	2.71	166.5
H	NH_2	31.6	2.52	171.0
H	H	28.9	2.56	169.4
H	F	28.1	2.57	169.2
H	CN	21.3	2.67	166.3
F	NH_2	34.6	2.48	172.4
F	H	31.6	2.53	170.4
F	F	30.8	2.54	169.9
CN	CN	32.2	2.55	167.9

[a] Obtained at HF/6-31G* level. Energies are evaluated with ZPVE correction.

Results and Discussion

1. Short, Strong Hydrogen Bonds as a Function of Bond Length and ΔPA. Single or Double Minima? Optimized geometries and energies have been obtained at the HF/6-31G* level for complexes **4**, where R_1, R_2 = NH_2, H, F, CN. The hydrogen-bonding energies and several geometrical parameters for 12 complexes which are formed by different combinations of monomers are given in Table 1. As seen in Table 1, all these hydrogen bonds involving ions in the gas phase are strong, with bond energies varying from 16.7 kcal/mol (R_1 = NH_2, R_2 = CN) to 32.2 kcal/mol (R_1 = CN, R_2 = CN). There is also a very significant change in the distance between the heavy atoms involved in hydrogen bonding, from 2.44 to 2.71 Å. However, the bond angles are very similar: all are within 3.5° of 170°.

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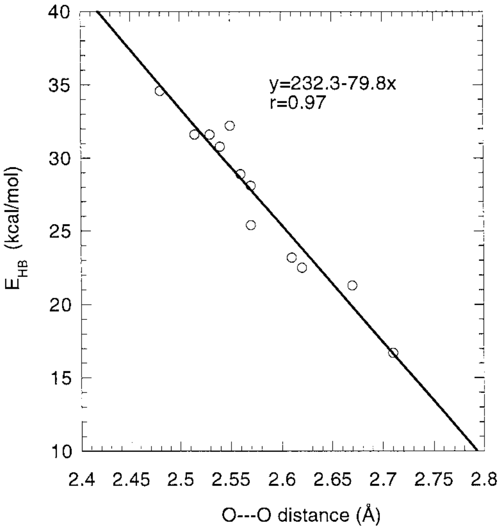

Figure 2. Hydrogen bond strength versus O···O distance.

Table 2. Calculated Barriers of Proton Transfer in PK_a-Matched Hydrogen-Bonded Species

R_1(enol)	R_2(enolate)	E_A (kcal/mol)	E_A (+ZPVE) (kcal/mol)
NH_2	NH_2	2.6	−0.1
H	H	2.4	−0.3
F	F	2.1	−0.6
CN	CN	2.5	−0.3

The transition states for the proton transfers in the degenerate cases are shown in Figure 1. All the geometries indicate a centrosymmetric proton with a linear O···H···O arrangement, except the complex of R_1, R_2 = NH_2 where the bond angle OHO is 170°. Energetic results listed in Table 2 reveal modest classical barriers for proton transfer. After zero point energy correction, the barriers become negative. That means the vibrational ground state of the proton lies above the activation barrier of proton transfer. Therefore, the proton is allowed to freely move in a single well effective potential, which leads to the so-called "low-barrier hydrogen bond." That is, there is a single-well potential after inclusion of zero point energy.

The relationship of the hydrogen bond length, R(O···O), and the hydrogen bond strength, E_{HB}, is presented in Figure 2. A linear correlation is found for 12 stable complexes. The correlation is $E_{HB} = 232.33 - 79.78R$(O···O). It is clear that when a hydrogen bond becomes shorter, it becomes stronger, with the shortest bonds being the strongest. Hibbert and Emsley have compared the experimental energies of OHO hydrogen bonds with the O···O distances found in crystal structures for a series of compounds.[27] It was shown that the energy of the OHO hydrogen bond changes dramatically around R(O···O) = 2.45 Å. It was further suggested that 2.45 Å was the threshold value for very strong hydrogen bonds. However, our calculations indicate that there is no dramatic change when R(O···O) is shortened from 2.8 to 2.4 Å. E_{HB} displays a smooth inverse relationship with R(O···O). Allen et al. also described the correlations among the geometries and energies of the cationic strong H-bond complexes.[19] A linear relationship was observed for R(A···H)/R(A···B) and dissociation energy, E_D, where R(A···H) is designated as the distance between the donor atom and the bridging proton and R(A···B) is designated as the distance between donor and acceptor atoms. The linear correlation of E_{HB} with bond length is a reflection of the similar electronic structures of this series of complexes.

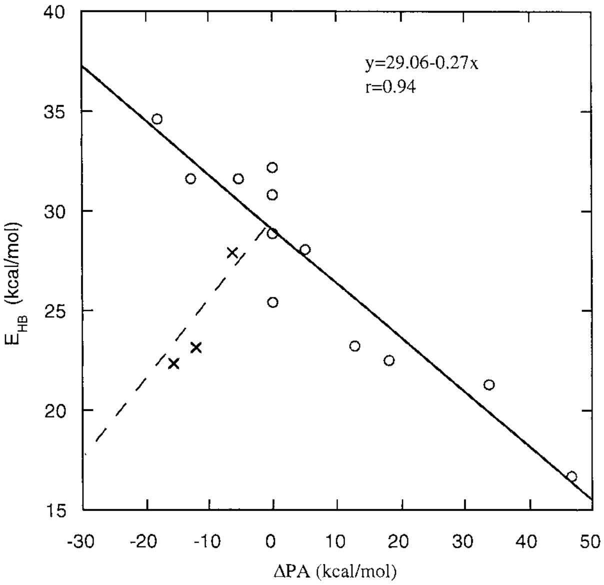

Figure 3. Hydrogen bond strength versus ΔPA.

Table 3. Calculated Total Electronic Energies (au) for the Enol and Enolate Monomers and Proton Affinities (kcal/mol) for the Enolate Monomers

	energy (hartree)	proton affinity (kcal/mol)
	Enolate	
NH_2	−207.278 271	−390
H	−152.283 928	−377
F	−251.133 710	−372
CN	−244.077 532	−344
	Enol	
NH_2	−207.900 025	
H	−152.885 389	
F	−251.726 847	
CN	244.625 153	

We then probed the strength of hydrogen bonds as a function of acidity of the two partners in the enol−enolate pairs. We have performed calculations of proton affinities for the enolate monomers as shown in Table 3. Geometries were optimized and energies were evaluated at the RHF/6-31G* level. Proton affinities are obtained by taking the difference of the enol and corresponding enolate energies. Figure 3 shows the E_{HB} vs ΔPA correlation for those complexes. As expected, the strength of the hydrogen bond increases with increasing acidity of donor and with increasing basicity of acceptor. A linear correlation ($E_{HB} = 29.76 - 0.32\Delta P$A) is found between the hydrogen-bond energy and the difference between the proton affinities (ΔPA) of the donor and acceptor. Clearly, there is no significant deviation in E_{HB} at ΔPA = 0, although we found a low-barrier hydrogen bond (a single-well potential) at ΔPA = 0. This is in contrast to the proposal that the hydrogen bond becomes *especially* strong when the pK_a of the donor and acceptor are equal.[7]

We continued the computational experiment beyond what is possible experimentally by calculating E_{HB} for

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Table 4. Calculated Atomic Charges (CHELPG) on Enol and Enolate Monomers

	enol				enolate			
	NH_2	H	F	CN	NH_2	H	F	CN
O	−0.77	−0.76	−0.76	−0.74	−0.93	−0.90	−0.91	−0.81
H	0.49	0.49	0.50	0.51				

values of $\Delta PA < 0$, where proton transfer is exothermic. We investigated those metastable complexes computationally by constraining the proton to be affixed to the more acidic enol and optimizing all other variables. It is very interesting to note that ΔE_{HB}s for $\Delta PA < 0$ are even larger than those of $\Delta PA = 0$, because the hydrogen bond involves a very strong donor and very strong acceptor. Experimentally, proton transfer is highly exothermic, and the unusually strong hydrogen bond cannot be formed. Thus, experimentally the dashed line in the Figure 3 should be observed. There is symmetric linear falloff in the hydrogen-bond strength on both sides of $\Delta PA = 0$. However, our purpose is to understand the relationship between hydrogen bond strength and ΔPA. A single line fits all the data including those of the constrained complexes with the OH bond maintained on the better H-bond partner. There is no discontinuity at the point of $\Delta PA = 0$, indicating that no fundamental change occurs in the nature of hydrogen bond when ΔPA passes from positive values to negative values through $\Delta PA = 0$.

Figure 3 is analogous to the solution-phase experimental results observed by Herschlag et al.[13] However, the complexes studied in our work encompass a much larger variation of electronic structure than those studied experimentally. As seen from Figure 3, ΔPA changes in a wide range from −50 to 50 kcal/mol. The maximum pK_a change in the experimental work is only 5 pK_a units, or about 7 kcal/mol. In addition, the bond strengths of the complexes in our system, in the range of 17−47 kcal/mol, are much larger than those studied experimentally, which are around 3−6 kcal/mol.

Herschlag et al.[13] suggested that a simple electrostatic model (eq 1),

$$E_{HB} = \frac{K}{\delta r} q_1 q_2 \tag{1}$$

where ϵ is the dielectric constant of the environment, r is the distance between donor and acceptor, and q_1 and q_2 are atomic charges on the donor and acceptor atoms,[28] could explain the observed energetics of H-bonds. However, our calculations indicate that simple electrostatics fail to reproduce the order of H-bond strength in this series of complexes. The CHELPG charges[29] on the enol and enolate monomers are given in the Table 4. For the enol with substituents R = NH_2, H, F, CN, the atomic charge on the enol oxygen is on the order of NH_2 > H, F > CN. According to the eq 1 above, the E_{HB}s of the complexes with R_2(enolate) = NH_2, R_1(enol) = NH_2, H, F, CN will decrease in the order of NH_2, H, F, CN. Indeed, the reverse order is obtained from the calculational results, which is consistent with the acidity order of enols: NH_2 < H < F < CN. It appears that a simple electrostatic model is not adequate to describe the short, strong hydrogen bond. Covalent factors must be included to account for the strengths of strong hydrogen bonds.[9,10]

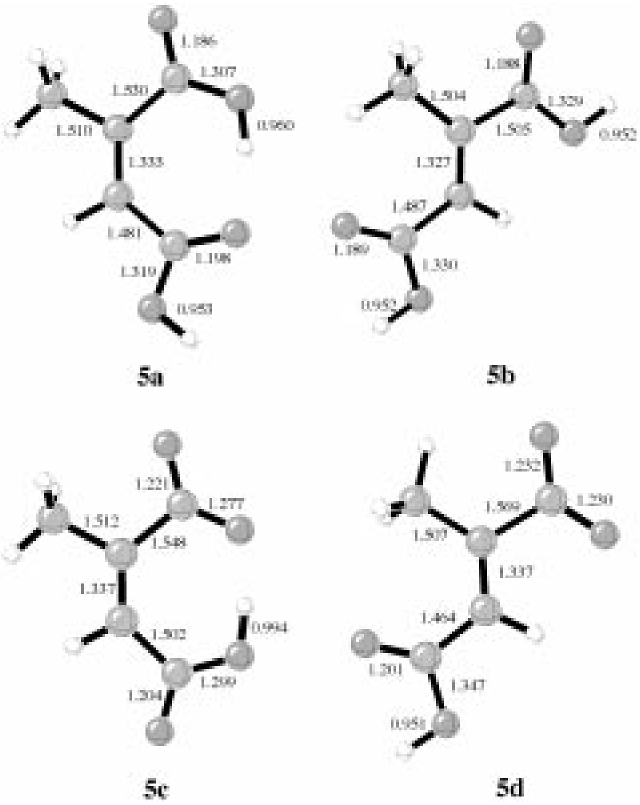

Figure 4. 6-31G*-optimized geometries of trans and cis conformations of diacids **5a** and **5b**, and 6-31+G*-optimized geometries of trans and cis conformations of monoanions **5c** and **5d**. Bond lengths are given in Ångstroms.

2. Environmental Effects on the Relative Strengths of Normal and Short, Strong Hydrogen Bonds. In this section, we explore the influence of solvation on hydrogen-bond strength. We began with the calculations of **5a**−**d** in the gas phase. Compounds **5a** and **5b** were calculated at the RHF/6-31G* level. For a proper description of anions, it is often necessary to supplement the basis set with a set of diffuse s- and p-functions.[30] We have, therefore, performed RHF/6-31+G* calculations on anions **5c** and **5d**. Substrates **5a**−**d** were fully optimized and are shown in Figure 4. All structures are planar with C_s symmetry. The geometrical parameters for intramolecular hydrogen bonds are shown in Figure 4. The energy difference between the cis and trans compounds was used to estimate the relative strength of the intramolecular hydrogen bonds formed by the *cis*-diacid or monoanion. It was found that the intramolecular anionic hydrogen bond in **5c**, defined by the energy difference between **5c** and **5d**, is 11.2 kcal/mol. By contrast, the trans form of the diacid (**5b**) is more stable than the cis (**5a**), due to steric repulsions and the *s*-trans nature of one acid required to achieve hydrogen-bonding. The energy difference between the

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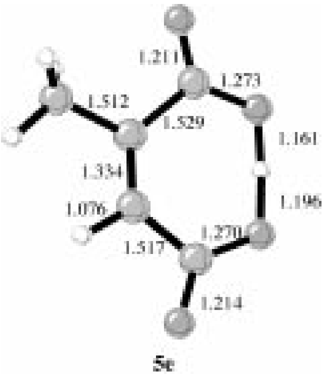

Figure 5. Transition structure for hydrogen transfer of **5c**.

two hydrogen bonds gives a useful measure of the added strength of the anionic hydrogen bond. The negatively charged hydrogen bond is estimated to be 15.8 kcal/mol stronger than that of neutral hydrogen bond in the gas phase. Recently Garcia-Viloca and co-workers calculated the same system at the RHF/6-31+G(d,p) level.[31] They reported a $\Delta\Delta G$ of 15.2 kcal/mol, which compares favorably with our result.

The transition structure **5e** for proton transfer in the mesaconic system, **5c**, was also located and is shown in Figure 5. The energy difference between transition state **5e** and the global minimum, **5c**, is found to be 3.0 kcal/mol, and it decreases to a negligible 0.002 kcal/mol after zero point energy corrections. This indicates that the bridging proton in the cis monoanion **5c** is located in a broad flat minimum between the two oxygen atoms; it is an authentic low-barrier hydrogen bond.

We then computed the effect of a dielectric medium on the proton-transfer barrier. To model the effect of the medium, we have employed the SCRF method, based on Onsager reaction field theory. In this model, the solvent is represented by a continuum dielectric, characterized by a dielectric constant, ϵ. The solute is assumed to be embedded in a spherical cavity with radius a_0.[32] The Born correction is added to the calculated solvation energy of charged species using eq 2,[33]

$$\Delta G_{\mathrm{Born}} = -166\left(1 - \frac{1}{\delta}\right)\left(\frac{q^2}{\alpha}\right) \text{ kcal/mol} \qquad (2)$$

where ϵ is the solvent dielectric constant, q is the solute charge, and α is the Onsager radius. To parallel the experimental conditions, we conducted the calculations on **5a**−**d** with $\epsilon = 4.81$ (chloroform) and $\epsilon = 45.0$ (DMSO). The introduction of a dielectric medium seems to have little effect on the calculated barriers. The calculated barrier in a nonpolar medium ($\epsilon = 4.81$) is 3.0 kcal/mol. With a continuum dielectric constant of $\epsilon = 45.0$, the barrier is still 3.0 kcal/mol. After zero point energy corrections, we obtain very low barriers for proton transfer in the two solvents. The calculational result is consistent with the experimentally observed extremely deshielded NMR signal in chloroform and DMSO which is used as a indicator of a low-barrier hydrogen bond. Regardless of solvent, a single minimum potential energy well is predicted.

Table 5. Calculated Dielectric Dependence of the H−Bond Energy Difference (Energies in kcal/mol)

dielectric constant	anionic H-bond in monoanion (**3c** and **3d**)	neutral H-bond in diacids (**3a** and **3b**)	relative strength $\delta\delta E$
		Gas Phase	
	11.18	−4.59	15.77
		Onsager Reaction Field[a]	
2.00	8.72	−3.75	12.47
4.81	6.52	−3.01	9.53
10.00	5.42	−2.67	8.09
20.00	4.84	−2.49	7.33
30.00	4.64	−2.43	7.07
40.00	4.38	−2.40	6.78
45.00	4.35	−2.39	6.74
50.00	4.32	−2.38	6.70
60.00	4.31	−2.37	6.68
70.00	4.30	−2.36	6.66
78.30	4.30	−2.35	6.65
		SCIPCM	
4.81	6.96	−4.15	11.11
45.00	5.39	−4.02	9.41

[a] Corrected by Born correction for charged species.

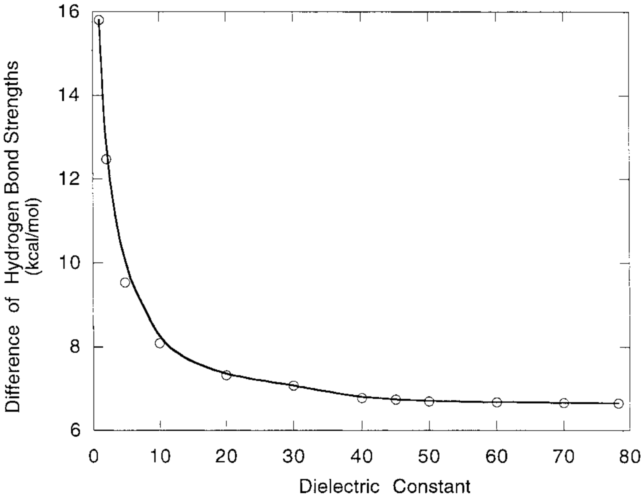

Figure 6. The dielectric dependence of the relative strengths of normal hydrogen bond in **5a** and short, strong hydrogen bond in **5c**.

Next, we consider the *cis*/*trans*-diacid and monoanion energy difference in solvents of different polarity. The results are summarized in Table 5. Figure 6 presents the dependence of the difference between the anion and neutral cis/trans energies (ΔE_{HB}) on the solvent polarity given by the ab initio SCRF calculations. The hydrogen bond energy difference (ΔE_{HB}) decreases with increasing solvent polarity, which is primarily due to the greater solvation energy of the anion.

The Hartree−Fock calculations give energy differences somewhat larger than the experimental values. However, SCRF calculations at the Hartree−Fock level reproduce the solvent effect trend. Our theoretical estimation of anionic hydrogen bond strength for **5c** with $\epsilon = 45$ is 4.2 kcal/mol, which is similar to the experimental estimates of 3.0 kcal/mol. The calculated energy difference between **5a** and **5b** with $\epsilon = 45$ is −2.4 kcal/mol, which is also in good agreement with the experimental value of −1.4 kcal/mol. The predicted ΔE_{HB} is

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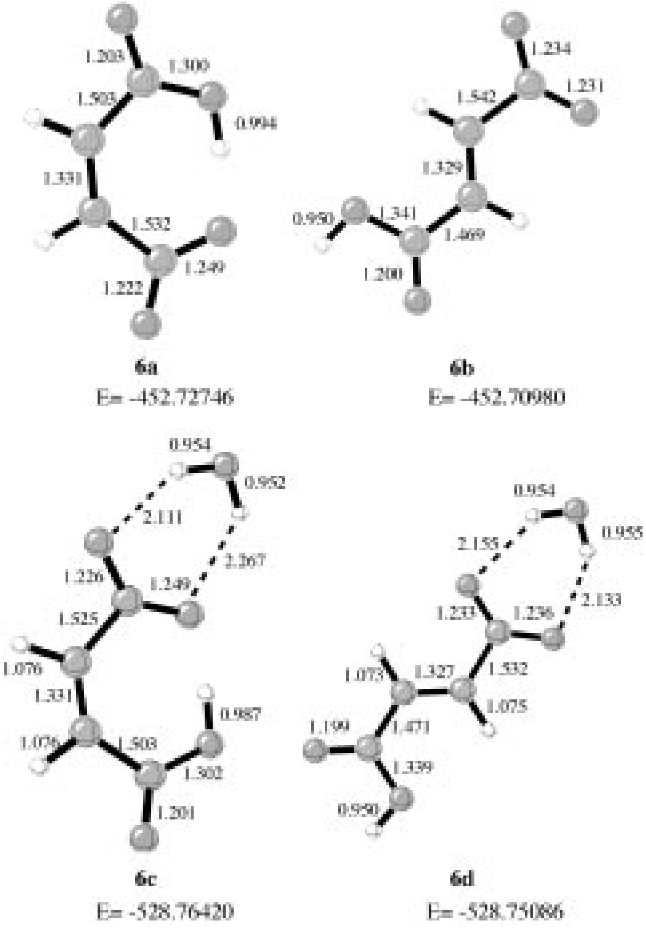
6.6 kcal/mol. It is 9.2 kcal/mol lower than the gas-phase value of 15.8 kcal/mol and is higher than the experimental value of 4.4 kcal/mol. The very low barrier calculated for the intramolecular hydrogen transfer in DMSO indicates that a low barrier or single minimum does not require a strong bond strength in solution.

The dependence of $\Delta E_{\rm HB}$ on a wide range of dielectric media has been estimated using ab initio SCRF methods. As seen from Figure 6, $\Delta E_{\rm HB}$ is very sensitive to dielectric constant. The difference between the two types of hydrogen bonds is largest, 16 kcal/mol, in the gas phase. It drops to 10 kcal/mol when ϵ reaches 4, and to half of the gas-phase value when ϵ reaches 10. The rapid decrease of $\Delta E_{\rm HB}$ indicates that the substantial stabilization effect of the charged hydrogen bond can be achieved only in a narrow range of low-polarity media.

We also examined the SCIPCM model recently implemented in Gaussian94. SCIPCM involves a PCM calculation in a cavity determined self-consistently from an isodensity surface. We carried out SCIPCM calculations in chloroform and DMSO using the same model system. The results at HF/6-31+G* are also listed in Table 5. The hydrogen-bond energies calculated by SCIPCM are larger than those calculated by the Onsager model and are in worse agreement with the experimental estimations of cis/trans energy differences. Similarly, Truong et al.[34] have recently shown that SCIPCM gives an overestimate of the solvation energy in the study of hydration effects on the profiles of an S_N2 reaction. It also has been suggested by Friesner and co-workers[35] that the use of simple, automated models for cavity size derived from first principles, such as a solute charge distribution isosurface, are unlikely to give greater accuracy, although this approach is appealing on the grounds of simplicity.

These calculations give a qualitative picture of the change in $\Delta E_{\rm HB}$ in a wide range of dielectric media that is in good agreement with available experimental results. The calculations reproduce the experimentally observed dramatic differences between energies of strong anionic hydrogen bonds and weak neutral hydrogen bonds in aprotic solvents and show that although LBHB in the geometric sense of the word can exist in a variety of dielectrics, short, *strong* hydrogen bonds can only exist in low dielectric media.

3. Specific Solvation Models. The solvation model in the previous section does not consider specific interactions between the solute and solvent. While it works well for aprotic solvents such as DMSO, it will not be accurate for solvents which can form hydrogen bonds with the anion. For example, for methanol ($\epsilon = 35$), SCRF calculations give $\Delta E_{\rm HB} = 6.7$ kcal/mol, while the experimental observation is 1.0 kcal/mol. To investigate the effect of hydrogen-bonding solvents on short, strong hydrogen-bond strengths, we performed ab initio calculations with partially solvated model compounds. The cis and trans monoanions, **6a** and **6b**, and their monohydrated species, **6c** and **6d**, were studied. Calculations were carried out at the HF/6-31+G* level in the gas phase. Optimized structures and energies of the monoanions with and without water are displayed in Figure 7. The energy difference between **6a** and **6b** is 15.7 kcal/mol, while the energy difference between **6c** and **6d** is 13.0 kcal/mol.



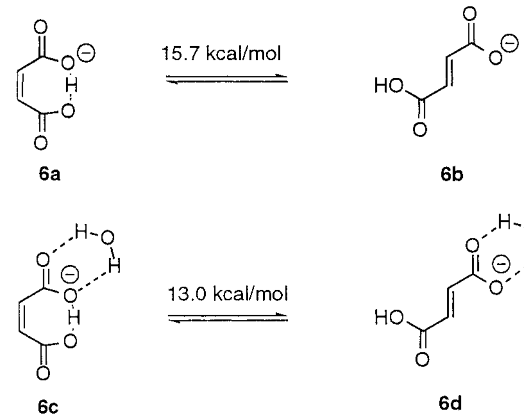
6a E= -452.72746

6b E= -452.70980

6c E= -528.76420

6d E= -528.75086

Figure 7. Geometries and related energies of **6a-d** at the RHF/6-31+G* level. Bond lengths are given in angstroms. Energies are given in hartrees.



Adding a hydrogen-bonding water molecule results in a 2.7 kcal/mol reduction in the hydrogen-bond strength of the cis monoanion. This is in a good agreement with the experimental result of 2.3 kcal/mol, which is derived from electrospray mass spectrometry measurement.[36] Our one water complex models very crudely the asymmetric solvation which occurs in the disordered bulk

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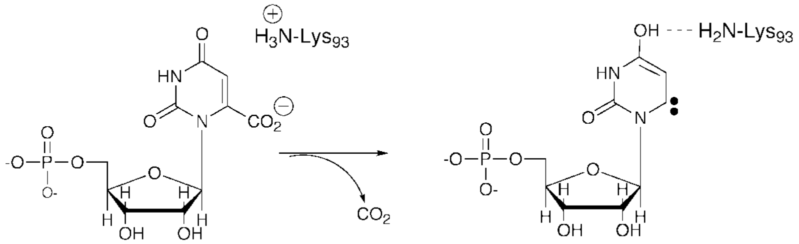
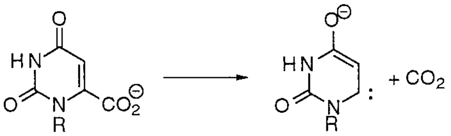


Figure 8. The catalyzed orotidine monophosphate decarboxylation in ODCase.

Scheme 2



solution.[37] It is suggested that ordered water molecules need not disrupt short, strong hydrogen bonds.[10] Indeed, short hydrogen bonds have been observed in a hydrated crystalline environment.[38] It is possible that a preorganized enzyme active site could provide such a microenvironment that facilitates the formation of a symmetrically dihydrated hydrogen bond. The effect of symmetrical versus asymmetrical hydration on hydrogen-bond energetics needs further investigation. However, one will still expect that the H-bond strength will decrease upon the increasing polarity of the surrounding environment, no matter how it is solvated.

4. Alternatives to Short, Strong Hydrogen Bonds in Enzymatic Catalysis: The Role of Environment in Orotidine Monophosphate Decarboxylase. Gerlt and Gassman[4] and, later, Cleland and Kreevoy,[7] proposed that short, strong hydrogen bonds can provide a large acceleration of certain enzyme-catalyzed reactions. While low-barrier hydrogen bonds could be important in enzymatic catalysis involving active sites with effective dielectric constants less than $\epsilon = 10$ or so, other mechanisms can often be invoked to explain cases postulated to involve short, strong hydrogen bonds.[8,9]

One such case involves the remarkable enzyme orotidine monophosphate decarboxylase (ODCase). Cleland and Kreevoy suggested that the enormous acceleration of the decarboxylation of orotidylate (Scheme 2) provided by ODCase could be explained by the formation of a low-barrier hydrogen bond in the transition state.[7] However, we have found that an alternative mechanism involving proton transfer facilitated by a low dielectric environment can plausibly explain the catalysis. The novel mechanism of this reaction, as predicted by MP2 and DFT calculations, involves general acid catalysis concomitant with loss of CO_2 (Figure 8).[39] The reaction involves proton transfer from an ammonium cation to the orotate anion. The reaction is enormously exothermic in the gas phase, due to the elimination of charge upon proton transfer. The reaction involves development of a carbene stabilized by an enol.

The catalyzed decarboxylation of orotate would generate a carbene, stabilized by an adjacent enolate (see Scheme 2).[38]

In an aqueous environment, this intermediate could not be stabilized much by the ammonium, a weak acid in water. However, in a nonpolar environment, which is believed to be present in the active site of orotidine monophosphate decarboxylase, the proton transfer from lysine becomes exothermic, and the reaction is highly facilitated by proton transfer and hydrogen bonding of the enolate carbene. The influence of the dielectric constant is enormous, and the acceleration of this reaction by proton transfer ($k_{cat}/k_M/k_{uncat} = 10^{23}$ M^{-1}) can be attributed to the influence of dielectric constant on the exothermicity of proton transfer. In a nonpolar medium, exothermic proton transfer (general catalysis), rather than special hydrogen-bonding stability, can account for catalysis.

Therefore, it is not the special stabilization of a hydrogen bond developing in the transition state but the even larger stabilization which results from exothermic proton transfer in the transition state that produces catalysis. This example harkens back to Figure 3. When the pK_a of the hydrogen-bond donor matches or becomes smaller than that of the acceptor, a very large hydrogen-bond strength occurs; however, experimentally this energetic effect will be manifested in highly exothermic proton transfer, which provides just as much stabilization with no special hydrogen-bond strength.

Conclusions

A systematic series of ab initio quantum mechanics calculations was carried out in the gas phase on a series of enol−enolate complexes. The maleic/fumaric and mesaconic/citraconic systems studied by Drueckhammer have also been investigated computationally. The calculations lead to the following generalizations:

(1) Calculated hydrogen-bond energies, E_{HB}, correlate linearly with the differences in monomer proton affinity, ΔPA. There is no discontinuity at $\Delta PA = 0$, although low-barrier hydrogen bonds with a single energy minimum do occur at this point.

(2) E_{HB} displays a smooth inverse relationship to hydrogen-bond length, $R(O\cdots O)$. There is no special stabilization from pK_a matching, although it does give a maximum hydrogen bond strength.

(3) In aprotic solvents, the strength of short, strong hydrogen bonds involving ionic species is always stronger than that of the normal hydrogen bonds between neutral species. Catalysis involving hydrogen bonding can be substantial when a neutral hydrogen bond is converted to a charged hydrogen bond, as in Scheme 1, *if* the environment is appropriately nonpolar.

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(4) The energy difference between short, strong and normal hydrogen bonds is sensitive to the surrounding environment and falls off rapidly upon increasing polarity. An enzyme would need a very low dielectric environment in the enzyme active site in order for short, strong hydrogen bonds to provide substantial stabilization.[40] Of course, forming an ionic hydrogen bond in nonpolar media costs energy.[10] It has been proposed that enzymes could exploit the binding interaction to pay for the price of desolvating the hydrogen-bonded complexes and fixing them in the low dielectric environment.[40,42] Some of the cases previously discussed in the terms of low-barrier hydrogen bonds[4,7] may be explained by related thermodynamic factors caused by a relatively nonpolar enzyme environment. The mechanism proposed for orotidine monophosphate decarboxylase is a dramatic example of this type.[39] Alternative explanations have been offered for other enzymes.[41]

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