The Role of a Short and Strong Hydrogen Bond on the Double Proton Transfer in the Formamidine−Formic Acid Complex: Theoretical Studies in the Gas Phase and in Solution

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Multiproton transfer in which more than one proton is transferred, either synchronously or asynchronously, is an important phenomenon in chemistry and biology. The hydrogen bonds with a very low barrier, leading to proton delocalization in the H-bond, are called "short strong" or "low-barrier" hydrogen bonds (SSHB or LBHB). It has recently been proposed that they may provide an unusually large amount of stabilization to high-energy enzyme-bound intermediates and/or transition states. In order to study the role of such hydrogen bonds in the multiproton transfer, we have performed high-level ab initio quantum mechanical calculations for the potential energy surface of the formamidine−formic acid complex. The double-proton transfer occurs asynchronously with a strongly hydrogen bonded intermediate, and the barrier height is 3.95 kcal mol^{-1}, which is about 5−12 kcal mol^{-1} lower than those of the concerted reactions in formamidine dimer and in formic acid dimer. The SSHB changes not only the barrier height but also the mechanism of the double-proton transfer. The strength of SSHB depends on environments. We have calculated the solvent effect at the HF and the B3LYP levels using the self-consistent isodensity polarized continuum model (SCIPCM). The strength of SSHB is reduced rapidly with increasing dielectric constants. It is about 29 kcal mol^{-1} at $\epsilon = 10$. The barrier height is also reduced with increasing dielectric constants, which indicates that the proton transfer becomes faster in a polar medium. These results suggest that the SSHB contribute to the proton transfer greatly, and the energetics is changed very much with environment.

Introduction

Proton transfer has been studied extensively for a long time, since it is one of the simplest and the most fundamental reactions in chemistry and is important in oxidation−reduction reactions in many chemical and biological reactions.[1,2] Multiproton transfer in which more than one proton is transferred, either synchronously or asynchronously, is also an important phenomenon in chemistry and biology. Examples of multiproton transfer are proton relay systems in enzymes, proton transfers in DNA base pairs and in prototropic tautomerisms.[3] Although many theoretical and experimental studies have recently been performed, there are few studies about detailed dynamics features of multiproton transfer. In terms of its mechanism, it is an important question whether multiproton transfer is just a repetition of single-proton transfer or not. Double-proton transfer in hydrogen-bonded systems has recently been studied since it is important in prototropic tautomerism in solution and in DNA base pair and can be used as a simple model of multiproton transfer. Proton transfer, in general, has a high energy barrier, but for a number of hydrogen-bonded systems it has only a very low barrier, leading to a proton delocalization in the hydrogen bond that strongly depends on the environments. Such hydrogen bonds are called "short strong" or "low-barrier" hydrogen bonds (SSHB or LBHBs), and it has recently been proposed that they may provide an unusually large amount of stabilization to high-energy enzyme-bound intermediates and/or transition states.[4,5] As a reaction proceeds from the ground state to the transition state, the increase in H-bond strength would be greater in a low-dielectric enzymatic active site than in aqueous solution. The different degree of strengthening of the hydrogen bond therefore allows greater transition state stabilization for the enzymatic reaction. There has been considerable debate recently about the existence, the strength, and the role of LBHBs in enzyme.[6−15] Herschlag and co-workers have reported that enzymes may use multiple interactions of moderate strength for transition state stabilization, rather than relying on a single, very strong interaction such as an LBHB.[14,15] They suggested that the high catalytic activity of enzymes can be explained by factors other than LBHBs, including cooperativity of hydrogen bonds, the presence and orientation of water molecules, electrostatic stabilization of ionic charges, and the preorganization of the enzyme for the substrate. On the other hand, the hydrogen bond between the Asp and His residues in the catalytic triad of serine protease would be an example of the potential contribution of LBHB in enzyme catalysis.[16−20] It is also a good example of SSHB in the process of multiproton transfers. Since SSHB has been known to reduce the energy barrier of proton transfer by stabilizing intermediates and/or the transition state, it will be necessary to understand its contribution to the potential energy surface of the reaction. However, most studies of SSHB are about the structure, strength, and the spectroscopic properties. There has been no study about the role of SSHB to the potential energy surface of multiproton transfer in the gas phase and in solution. In order to account for the role of the SSHB, we have performed high-level ab initio quantum mechanical calculation for the potential energy surface of the formamidine−formic acid complex (FFA). Since proton transfers occur mostly in solution, and the enzyme active site is not like a gas phase, it is important to consider environmental effects, so solvent effect was also calculated using the dielectric continuum model.

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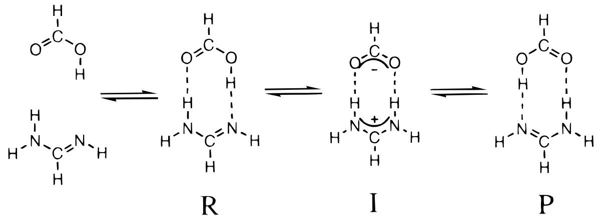


Figure 1. Schematic reaction diagram for double-proton procedures in FFA.

Computational Methods

All electric structure calculation were done using the Gaussian 94 quantum mechanical program.[21] Geometries, energies, and frequencies at the stationary points were calculated at the Hartree−Fock (HF) and the second-order Møller−Plesset (MP2) levels of theory using the 6-31G(d,p) and 6-31+G(d,p) basis sets. Density functional theory calculations were also performed with the B3LYP functional using the same basis sets. The solvent effect was calculated by using the SCRF method such as the SCIPCM[22] implemented in Gaussian 94. The isodensity value of 0.0004 was used for all calculations. The energies for FFA, the transition state, and the intermediate were calculated by the coupled cluster method including singles, doubles, and triples terms (CCSD(T)) using the geometries optimized at the MP2 level in the gas phase. The covalent bond orders were calculated using the atoms in molecules (AIM) methodology,[23] as implemented by Ciolowski and co-workers[24,25] in the Gaussian 94 program.

The formation energies for the H-bonded complexes, E_{HB}, were calculated from the difference in energies between the complex and two different monomers. The basis set superposition error (BSSE) may be important in the calculation of the formation energies.[26] The BSSE was corrected by the Boys and Bernardi counterpoise correction scheme,[27]

$$\mathrm{BSSE} = [E_m(M_1) - E_d(M_1')] + [E_m(M_2) - E_d(M_2')] + E_{reorg} \quad (1)$$

$$E_{reorg} = [E_m(M_1') - E_m(M_1)] + [E_m(M_2') - E_m(M_2)] \quad (2)$$

where $E_m(M)$ and $E_d(M')$ are the energies of the monomer in its own basis set and in the basis set of the H-bonded complex, respectively, and M and M′ denote the optimized geometry of the monomer and the geometry of the monomer in the optimized H-bonded complex, respectively. The reorganization energy (E_{reorg}), i.e., the energy associated with the transition from the optimized geometry of monomer to the geometry the monomer has in the H-bonded complex, should be also included in the correction of the BSSE. The corrected formation energy is determined as follows:

$$\begin{aligned} E_{HB}(\mathrm{corr}) &= E(D) - [E_m(M_1) + E_m(M_2)] + \mathrm{BSSE} \\ &= E(D) - [E_d(M_1') + E_d(M_2')] + E_{reorg} \quad (3) \end{aligned}$$

where $E(D)$ is the energy of the H-bonded complex.

Results

There is a high-energy intermediate along the reaction coordinate for the prototropic tautomerization of FFA, so two protons are transferred asynchronously via a stepwise mechanism, as shown in Figure 1. The geometries for FFA, the intermediate (I), and the transition state (TS) were calculated at various levels of theory. The geometric parameters for R, I, and TS, calculated at the HF, B3LYP, and MP2 levels using the 6-31+G(d,p) basis set are shown in Figure 2. The H-bond lengths of NH---O in R are 2.069, 1.888, and 1.936 Å at the HF, B3LYP, and MP2 levels, respectively. The B3LYP level predicts smaller H-bond lengths. The OH---N distances of 1.636 Å at the MP2 levels is a little bit short, but that of 1.810 Å at the HF level agrees very well with experiments.[28] The H-bond length in I is 1.518 Å, which is very short and comparable to those of SSHBs reported in the literature.[4,6,9,29] The geometric parameters for TS are also shown in Figure 2.

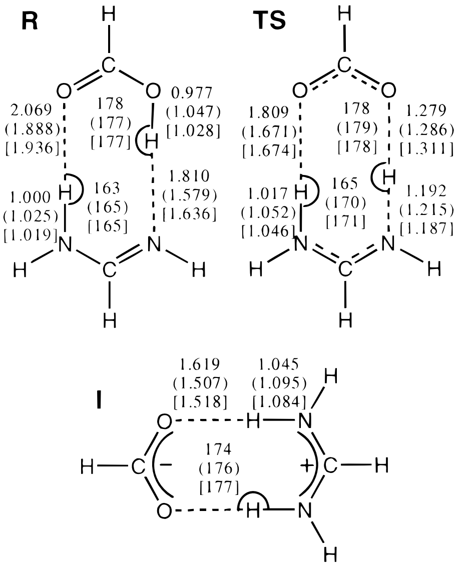


Figure 2. Geometric parameters for R, TS, and I optimized at the HF, B3LYP, and MP2 levels using the 6-31+G(d,p) basis set. Numbers in parentheses are for B3LYP and brackets for MP2 levels. Lengths in Å and angles in degree.

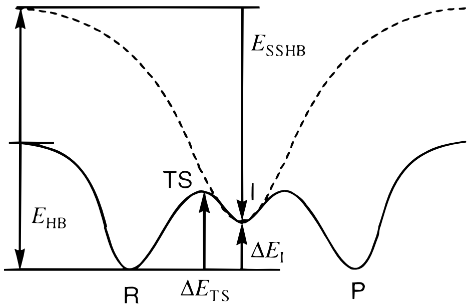


Figure 3. Schematic energy diagram for the double-proton transfer in FFA.

TABLE 1: Formation Energies of the FFA Complex from Formamidine and Formic Acid and of the Intermediate from Formamidinium Cation and Formate Anion Calculated at Various Levels of Theory[a]

	E_{HB}	E_{reorg}	BSSE	E_{HB}(corr)	E_{SSHB}
HF/6-31G(d,p)	−16.6	1.81	2.01	−14.6	
HF/6-31G+(d,p)	−14.9	1.51	0.88	−14.0	−122
B3LYP/6-31G(d,p)	−22.3	5.21	3.81	−18.5	
B3LYP/6-31G+(d,p)	−18.7	4.76	0.84	−17.9	−129[b]
MP2/6-31G(d,p)	−20.4	4.04	4.89	−15.5	
MP2/6-31G+(d,p)	−18.2	3.34	2.89	−15.3	−126[b]

[a] Energies in kcal mol^{-1}. [b] BSSEs were corrected.

Figure 3 shows the schematic potential energy curve for the double-proton transfer and energetic parameters in the gas phase. The calculated formation energies of FFA from formamidine and formic acid, E_{HB}, are listed in Table 1. The BSSEs were corrected. In general, adding diffuse functions to the basis set

TABLE 2: Calculated Barrier Heights and the Relative Energy of the Intermediate in Terms of Two Monomers at Various Levels of Theory[a]

	ΔE_{TS}	ΔE_1
HF/6-31 G(d,p)	8.27 (5.72)	7.40
HF/6-31 +G(d,p)	7.80 (5.14)	6.39
B3LYP/6-31 G(d,p)	2.16 (0.14)	2.11
B3LYP/6-31+G(d,p)	1.64 (−0.52)	1.34
MP2/6-31G(d,p)	3.69 (1.86)	3.67
MP2/6-31+G(d,p)	2.86 (0.31)	2.61
CCSD(T)//MP2/6-3lG(d,p)	4.74 (2.91)	4.69
CCSD(T)//MP2/6-31+G(d,p)	3.95 (1.40)	3.65

[a] Energies in kcal mol^{-1}. Numbers in parentheses are with zero-point energies.

of heavy atoms reduces the H-bond strengths and the BSSEs. The values for E_{HB}(corr) at HF, B3LYP, and MP2 levels using the 6-31+G(d,p) basis set are −14.0, −17.9, and −15.3 kcal mol^{-1}, respectively. These results indicate that the H-bond strength depends on electron correlation and levels of calculation.[30] The density functional theory slightly overestimates the strength of hydrogen bonds. The formation energies of intermediate from formamidinium cation and formate anion (structure I), which represents the strengths of SSHBs, E_{SSHB}, were also calculated and listed in Table 1. The BSSE-corrected value of E_{SSHB} at the MP2/6-31G+(d,p) level is −126 kcal mol^{-1}. Glusker and co-workers[28] have also calculated structures and energies for FFA in the gas phase at the MP2/6-311++G(2d,p)//MP2/6-31+G(d,p) level and obtained −132 kcal mol^{-1} for the E_{SSHB} value. This value agrees very well with ours listed in Table 1, although it is a little bit smaller since they did not correct the BSSE. They have also reported the values of $\Delta H°$ and $\Delta G°$ of formation at 298 K, which are −131 and −120 kcal mol^{-1}, respectively. The values of $\Delta H°$ and E_{SSHB} are approximately the same. The structure of I is analogous to the ion pair of carboxylic acid and a base. We have calculated covalent bond orders for I using the atoms in molecules (AIM) methodology[23] at the MP2/6-31+G(d,p) level and found that the covalent bond order for the SSHB between O and H is 0.18, which is very small.

The barrier height, ΔE_{TS}, and the energy of I relative to R, ΔE_I, were calculated at various levels, and the results are listed in Table 2. The ΔE_{TS} values including zero-point energies are also listed. All values from the HF levels are about 4 or 5 kcal mol^{-1} larger than the corresponding CCSD(T) values obtained from the single-point energy calculations using the MP2-optimized geometries. Adding diffuse function to the basis sets reduces the ΔE_{TS} and ΔE_I values at all levels of calculation. The ΔE_{TS} and ΔE_I values at the CCSD(T) level are slightly larger than the corresponding values at the MP2 and the B3LYP levels, and they are 3.95 and 3.65 kcal mol^{-1}, respectively. Since electron correlation is very important to the energetics of double-proton transfer, density functional theory has usually reproduced experimental and high-level theoretical results better than the HF theory.[31,32] The ΔE_{TS} and ΔE_I values at the B3LYP/6-31+G(d,p) level are both 2.3 kcal mol^{-1} smaller than the corresponding CCSD(T) values, but those from the HF/6-31+G(d,p) method are 3.85 and 2.74 kcal mol^{-1} larger, respectively. The results from the B3LYP method are slightly closer to those from CCSD(T) than are those from HF, but the differences are comparable. The barrier heights including zero-point energies, which is called the adiabatic energy barrier, are also listed in Table 2. The adiabatic barrier at the CCSD(T)//MP2/6-31+G(d,p) level is 1.40 kcal mol^{-1}, which is about 2.5 kcal mol^{-1} smaller than the ΔE_{TS} value without zero-point energies. The well depth in which the intermediate is located was estimated from the energy differences between I and TS. It is about 0.3 kcal mol^{-1}, which is smaller than the thermal energy at 300 K, which is about 0.6 kcal mol^{-1}. Therefore the intermediate cannot exist alone at room temperature, and two moving protons are delocalized between their positions in structures of I and TS. These results imply that entire structures between I and TS can behave as an activated complex and that the two protons are transferred asynchronously, but pseudoconcertedly.

Since proton transfer occurs mostly in solution or in an enzyme active site, it is important to consider environmental effects. SSHB or LBHB form a charged species in which the charge may be delocalized over several atoms, thus some component of the interaction will be electrostatic, and therefore the strength of the interaction will depend on the local effective dielectric constant. We have calculated the solvent effect at the HF and B3LYP levels with the 6-31+G(d,p) basis set using the SCIPCM.[22] The calculated H-bond lengths of R and I as a function of the dielectric constant are listed in Tables 3 and 4. When the dielectric constant is increased, the O−H bond distance r_1 in R is increased but the H−N distance r_2 is decreased. The proton is gradually shifted toward the H-bond center and the distance between two heavy atoms, $r_1 + r_2$, is decreased. The H-bond distance r_1 in I is increased but the N−H bond distance r_2 decreased with increasing dielectric constant. The distance between two heavy atoms $r_1 + r_2$ in I is increased with increasing dielectric constant. These results suggest that the partial negative and positive charges in I are localized at formate and formamidinium moieties, respectively, and they are further apart from each other, so the strength of SSHB becomes weaker in a polar environment. The value of r_1 in I is about 1.7−1.8 Å at the dielectric constant of 10, which agrees well with experimental observation from crystallographic studies.[28] This distance is not changed much in a medium of larger dielectric constant. A correlation between H-bond distance r_1 and r_2 has been obtained from the concept of bond order−bond length by several researchers.[33−36] This correlation can be described by

$$(r_1 + r_2) = 2r_{02} + (r_1 - r_2) + 2b \ln[1 + \exp\{(r_{01} - r_{02} - r_1 + r_2)/b\}] \quad (4)$$

where r_{01} and r_{02} represent the distances of free H-bond donors O−H and H−N$^+$, respectively. The parameter b is given by

$$b = [(r_1 + r_2)_{min} - (r_{01} + r_{02})]/(2 \ln 2) \quad (5)$$

where $(r_1 + r_2)_{min}$ represents a minimum distance. The heavy atom distances $r_1 + r_2$ were plotted with respect to the proton-transfer coordinate $r_1 - r_2$ in Figure 4 using the values of r_1 and r_2 in Tables 3 and 4. The solid line was fitted to eq 4. Limbach and co-workers[37] have previously studied the influence of dielectric field on H-bond distances in various H-bonded complexes and ion pairs and found that there is a good correlation between $r_1 + r_2$ and $r_1 - r_2$. The plot in Figure 4 agrees very well with Limbach and co-workers' results. The distances $r_1 + r_2$ in I are increased when the dielectric constant is increased, which is consistent with those of ion pairs.[37] The $(r_1 + r_2)_{min}$ value was estimated from the solid line in Figure 4, which is 2.396 Å. It was suggested that the $(r_1 + r_2)_{min}$ value refers to the most compressed geometry where the proton transfer is characterized by a single well potential; it could correspond to a stationary point with an imaginary frequency, i.e., to a transition state of proton transfer.[37] However, the

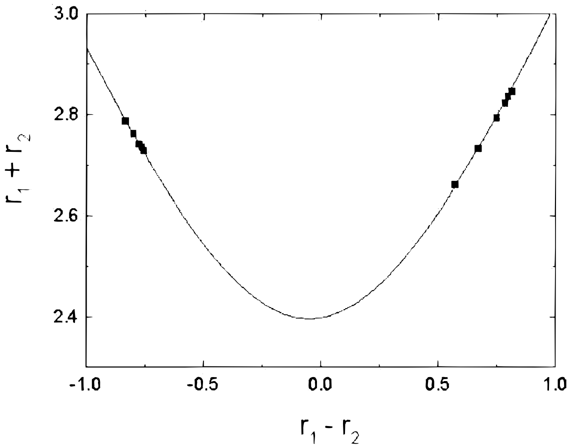
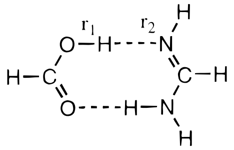


Figure 4. Correlation between the H-bond heavy atom distance $r_1 + r_2$ and the proton transfer coordinate $r_1 - r_2$. The HF values of r_1 and r_2 in Tables 3 and 4 were used. The solid line was fitted to eq 4. The r_{01} and r_{02} values were 0.950 and 0.999 Å, respectively, and the $(r_1 + r_2)_{\min}$ value was 2.396 Å.

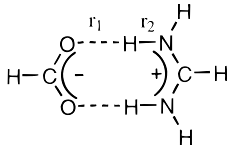
TABLE 3: Calculated H-Bond Lengths in the FFA Complex in Terms of the Dielectric Constant at the HF and B3LYP Level with the 6-31+G(d,p) Basis Sets Using the SCIPCM[a]



	HF/6-31+G(d,p)		B3LYP/6-31+G(d,p)	
ϵ^b	r_1	r_2	r_1	r_2
gas	0.977	1.810	1.047	1.579
2	0.981	1.781	1.065	1.529
5	0.984	1.758	1.119	1.414
10	0.985	1.750	*c*	*c*
20	0.985	1.750	*c*	*c*
78.4	0.987	1.742	*c*	*c*

[a] Lengths in Å. [b] Dielectric constant. [c] The R structures do not exist at this level of theory.

TABLE 4: Calculated H-Bond Lengths of the Intermediate in Terms of the Dielectric Constant at the HF and B3LYP Levels with the 6-31+G(d,p) Basis Sets Using the SCIPCM[a]



	HF/6-31+G(d,p)		B3LYP/6-31+G(d,p)	
ϵ^b	r_1	r_2	r_1	r_2
gas	1.618	1.045	1.507	1.095
2	1.702	1.031	1.578	1.074
5	1.772	1.022	1.642	1.060
10	1.804	1.019	1.668	1.056
20	1.817	1.018	1.683	1.054
78.4	1.830	1.016	1.695	1.051

[a] Lengths in Å. [b] Dielectric constant.

geometry at a single well is not necessarily correlated with the geometry of a transition state since it is at the top of the potential surface. Although there is no direct relation between these two, the $r_1 + r_2$ values at the transition state in the gas phase is 2.471 Å, which is slightly larger than the $(r_1 + r_2)_{\min}$ value, but the difference is very small.

TABLE 5: Energetics for Double-Proton Transfer in the Dielectric Medium at the HF/6-31+G(d,p) Level with the SCIPCM[a]

ϵ^b	E_{HB}	ΔE_{TS}	ΔE_{I}	$\Delta E_{\mathrm{I-2M}}{}^c$	E_{SSHB}
gas	−14.9	7.80	6.39	−8.49	−122.4
2.0	−12.4	5.55	1.76	−10.4	−66.1
5.0	−10.2	*d*	−2.32	−12.5	−33.2
10.0	−9.44	*d*	−4.04	−13.5	−22.5
78.4	−8.39	*d*	−5.71	−14.1	−13.3

[a] Energies in kcal mol^{-1}. [b] Dielectric constant. [c] Relative energies of I in terms of formic acid and formamidine. [d] The TS structures do not exist.

TABLE 6: Energetics for Double-Proton Transfer in the Dielectric Medium at the B3LYP/6-31+G(d,p) Level with the SCIPCM[a]

ϵ^b	E_{HB}	ΔE_{TS}	ΔE_{I}	$\Delta E_{\mathrm{I-2M}}{}^c$	E_{SSHB}
gas	−18.7	1.64	1.34	−17.4	−129.4
2.0	−16.9	0.39	−1.20	−18.1	−73.0
5.0	−15.5	*e*	−3.45	−19.0	−39.6
10.0	*d*	*e*	−5.49^f	−19.4	−28.7
78.4	*d*	*e*	−7.52^f	−19.7	−19.2

[a] Energies in kcal mol^{-1}. [b] Dielectric constant. [c] Relative energies of I in terms of formic acid and formamidine. [d] R was unable to locate. [e] The TS structures do not exist. [f] Energies are in terms of R at $\epsilon = 5$.

The energetics for double proton transfer in a dielectric medium at the HF and B3LYP levels are listed in Tables 5 and 6, respectively. At both HF and B3LYP levels, the H-bond strength, E_{HB}, becomes weaker, and the ΔE_{TS} and ΔE_{I} values become smaller with increasing dielectric constant. The HF level calculation also predicts larger barrier heights for the proton transfer in solution than the B3LYP level, as it does in the gas phase. The ΔE_{TS} and ΔE_{I} values at the B3LYP level in the gas phase are both about 2.3 kcal mol^{-1} smaller than those at the CCSD(T) level. If we assume that these errors are approximately the same in a dielectric medium, we can adjust the ΔE_{TS} and ΔE_{I} values in Table 5 by adding 2.3 kcal mol^{-1}. The estimated ΔE_{TS} and ΔE_{I} values at $\epsilon = 2$ are about 2.7 and 1.1 kcal mol^{-1}, respectively. The adiabatic barrier height at the CCSD(T) level is about 2.5 kcal mol^{-1} lower than the potential energy barrier in the gas phase. If we assume that frequencies in the gas phase and in a medium at $\epsilon = 2$ are approximately the same, the estimated adiabatic barrier height at $\epsilon = 2$ will be about 0.2 kcal mol^{-1}. The TS structure does not exist at $\epsilon = 5$. The thermal energy at room temperature is about 0.6 kcal mol^{-1}, which is larger than the adiabatic energy barrier. These results suggest that strongly H-bonded protons in FFA can move freely between N and O atoms at room temperature in solution. In other words, the proton transfer becomes extremely fast in a medium at $\epsilon = 2-5$. The characteristics of potential energy surface in terms of dielectric constants are shown in Figure 5. At $\epsilon \geq 10$, the structure of R is not stable (not a stationary point) any longer; thus the only existing structure is I. In this case two protons are captured at the I structure, and thus proton transfer stops at this point.

The formation energies of I from separate neutral monomers $\Delta E_{\mathrm{I-2M}}$ are also listed in Tables 5 and 6. In the gas phase, the E_{HB}(corr) value at the MP2/6-31+G(d,p) level is −15.3 kcal mol^{-1}, and the ΔE_{I} value at the CCSD(T) level is 3.65 kcal mol^{-1}; therefore, the best estimated value for $\Delta E_{\mathrm{I-2M}}$ in this study will be −11.7 kcal mol^{-1}. The $\Delta E_{\mathrm{I-2M}}$ value at the B3LYP level in the gas phase is −17.4 kcal mol^{-1}, overestimating the CCSD(T) binding energy by 5.7 kcal mol^{-1}; this value is reduced with increasing dielectric constant. The estimated $\Delta E_{\mathrm{I-2M}}$ values in solution can be obtained by adding 5.7 kcal

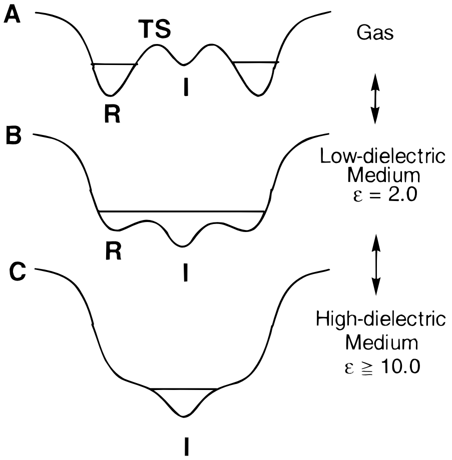


Figure 5. Schematic diagram of the potential energy curve for double-proton transfer in FFA depending on the polarity of the environments. Horizontal lines represent the thermal energy at room temperature. R: Formamidine formic acid complex (FFA). I: Intermediate with SSHBs.

mol^{-1} to the values in Table 6. The estimated $\Delta E_{\mathrm{I-2M}}$ value at $\epsilon = 10$ is -13.7 kcal mol^{-1}. This would be the well depth of the potential curve shown in Figure 5c. Protons are transferred very fast at $\epsilon = 2$, but they are captured in a single potential well at $\epsilon = 10$. This potential well becomes even deeper when the dielectric constant is increased further.

The strength of SSHB is reduced (the E_{SSHB} value is increased) rapidly with increasing dielectric constants. The E_{SSHB} value is changed from -28.7 to -39.6 kcal mol^{-1} by reducing the dielectric constant from 10 to 5 in Table 6. A relatively small variation of dielectric constant results in about 11 kcal mol^{-1} of change in the strength of SSHB. If we assume that the effective dielectric constant of an enzyme is 10,[38,39] the E_{SSHB} value will be about -29 kcal mol^{-1}. This is a little bit larger than typical standard formation energies of SSHB in the range of -10 to -15 kcal mol^{-1}.[6] Although the E_{SSHB} value depends very much on the polarity of the medium, the change in the $\Delta E_{\mathrm{I-2M}}$ value is not large. The $\Delta E_{\mathrm{I-2M}}$ value at the B3LYP level is reduced only 2.3 kcal mol^{-1} going from gas to $\epsilon = 78.4$. The E_{SSHB} value is determined from the energy difference between I and two charged species, formate and formamidinium cation. The charged species are stabilized more than the neutral in a polar medium, so the E_{SSHB} value is increased (the H-bond strength weakened) with increasing dielectric constant. However, the $\Delta E_{\mathrm{I-2M}}$ value is determined from the energy difference between I and two monomers, formic acid and formamidine. This value depends mostly on the size of dipole moments of I and two monomers in a polar medium. Since the dipole moment of I is larger than those of two monomers, the $\Delta E_{\mathrm{I-2M}}$ value is reduced with increasing dielectric constant. These results suggest that the reaction coordinate of proton transfer is different from that of formation of the SSHB. However, these two coordinates are strongly coupled with each other near the structure of I, as shown in Figure 3, so it is not possible to change one coordinate without changing the other.

Discussion

The mechanism and barrier height of the double-proton transfer in FFA are quite different from those in the homodimers, formic acid dimer and formamidine dimer. The double-proton transfer in formic acid dimer has been studied extensively both experimentally and theoretically.[32,40] The barrier height depends very much on the theoretical levels of calculation: the size of basis set and inclusion of correlation energy. Two protons in formic acid dimer are transferred synchronously, and the barrier at the G2* level is 8.94 kcal mol^{-1}.[32] The double-proton transfer in formamidine dimer has recently been studied theoretically, and not only the barrier height but also the mechanism depend on the levels of theory.[41,42] However, all higher level calculations including electron correlation predict that the double-proton transfer occurs synchronously. Truhlar and co-workers[41] has reported that the barrier height is 11.0 kcal mol^{-1} at the SAC2//HF/6-31G(d,p) level. Limbach and co-workers[43,44] have recently studied the double-proton transfer in substituted formamidine dimers using dynamic NMR techniques and showed that the two protons are transferred synchronously.

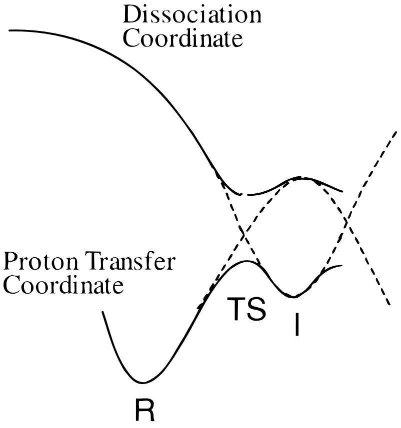


Figure 6. Schematic diagram for the strong coupling between the proton transfer and the dissocation of SSHB. Only half of the entire reaction (from R to I) is shown.

The proton transfer in FFA does not occur synchronously, since there is a stable intermediate with a SSHB. The reaction coordinate of formation for the SSHB is different from the proton transfer coordinate. However, these two coordinates are strongly coupled around the structure of I, as shown in Figure 6, which reduces the potential energy barrier and makes the reaction stepwise. If these two coordinates are not strongly coupled, the double-proton transfer in FFA would occur synchronously without forming SSHB, and the potential energy barrier would be higher. The barrier height for the hypothetical synchronous double-proton transfer in FFA will be a value between those for formic acid dimer and formamidine dimer. We have calculated the barrier heights for formic acid dimer and for formamidine dimer at the CCSD(T)//MP2/6-31G(d,p) level, which are 9.33 and 16.8 kcal mol^{-1}, respectively. Therefore, the barrier height for the hypothetical synchronous double-proton transfer in FFA will be a value between these two. These values are about 5−12 kcal mol^{-1} larger than the barrier of stepwise double-proton transfer in FFA at the same level in Table 2. These results suggest that the SSHB reduce the potential energy barrier by about 5−12 kcal mol^{-1} compared with that of the possible concerted reaction and make the reaction stepwise and faster. The SSHB changes not only the barrier height but also the mechanism of the double-proton transfer in FFA.

The calculated covalent bond order of SSHB in I is 0.15, which is very small. There is a correlation between $r_1 + r_2$ and $r_1 - r_2$ in this SSHB with respect to the polarity of medium, which is consistent with that of an ion pair.[37] These results suggest that this H-bond has more ion-pair character although it is short and strong, so the strength of this H-bond originates mostly from the electrostatic interaction between two ions, formamidinium cation and formate anion. This result suggests that the H-bond is not a “Speakman−Hadzi” type of SSHB.[45,46]

In a Speakman−Hadzi type compound, the proton is usually delocalized between H-bond donor and acceptor, so there would be more covalent character in the H-bond. The IR spectra of this compound contain a very broad and intense band between 2000 and 500 cm^{-1}, which is called Hadzi type II band.[45,47] The IR spectrum of formamidine acetate is available,[48] and there is no Hadzi-type II band in it. The H-bonds in the structure like I turn out to be much stronger than the Speakman−Hadzi type of SSHB. In order to differentiate this H-bond from the Speakman−Hadzi type, we may call it a “Coulomb-type SSHB”. This Coulomb-type SSHB may exist in and take an important role in many biological systems, such as H-bonded complexes between aspartate and guanine or guanidinium groups. Bachovchin and co-workers[13] have shown that the LBHB in the catalytic diad (Asp^{l02}−His^{57}) of serine protease is not a Speakman−Hadzi type but a Coulomb-type by using NMR techniques. The proton in the protonated diad is not delocalized between H-bond donor and acceptor, but it is essentially 85% localized on N$^{\delta 1}$ of the active site histidine.[13] They suggest that the N$^{\delta 1}$−H proton could be no more than 15% delocalized when His^{57} is protonated. These results are consistent with the characteristics of I that the proton is not delocalized between the H-bond donor and acceptor, but it is located on N, as shown in Figure 2, and the covalent bond order for the H-bond is 0.18, except that there are two H-bonds in I but only one in the protonated dyad. Since the SSHB in protonated dyad is not a Speakman−Hadzi type but a Coulomb type, its strength would be also very sensitive to the polarity of the medium.

Concluding Remarks

We have performed high-level ab initio quantum mechanical calculation for the potential energy surface of the formamidine−formic acid complex to study the role of SSHB in multiproton transfer. The double-proton transfer occurs asynchronously with a strongly hydrogen-bonded intermediate, and the barrier height is 3.95 kcal mol^{-1}, which is about 5−12 kcal mol^{-1} lower than those of the concerted reactions in formamidine dimer and in formic acid dimer. The SSHB reduces the potential energy barrier by about 5−12 kcal mol^{-1} compared with that of the possible concerted reactions and makes the reaction stepwise and faster. It changes not only the barrier height but also the mechanism of the double-proton transfer in FFA. We have calculated the solvent effect at the B3LYP level using the 6-31+G(d,p) basis set with the SCIPCM model. The strength of SSHB is reduced rapidly with increasing dielectric constants. The barrier height is also reduced with increasing dielectric constants, which indicates that the proton transfer becomes faster in a polar medium. These results suggest that strength of SSHB depends greatly on the local effective dielectric constant, and the energetics is changed very much with environment.

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