J. Phys. Chem. A **2002,** *106,* 12103−12109 **12103**

Double-Proton Transfer in the Formamidine−Formamide Dimer. Post-Hartree−Fock Gas-Phase and Aqueous Solution Study

Yevgeniy Podolyan, Leonid Gorb, and Jerzy Leszczynski*

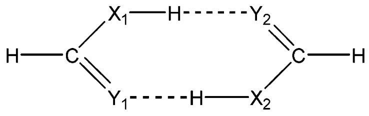
The Computational Center for Molecular Structure and Interactions, Department of Chemistry,
Jackson State University, 1400 J. R. Lynch Street, Jackson, Mississippi 39217-0510

Received: July 19, 2002; In Final Form: September 30, 2002

The mechanism of the double-proton transfer in the formamide−formamidine dimer, which is the simplest model resembling the hydrogen bonding pattern in the adenine−thymine base pair, has been studied by means of ab initio post-Hartree−Fock calculations. The optimizations of all local minima and transition states were performed for both the gas phase and water solution using density functional theory (B3LYP), second-order Møller−Plesset theory, and the quadratic configuration interaction method using various basis sets. Additional optimizations of the structures with explicitly included water molecules were performed at the B3LYP level of theory. The two-dimensional adiabatic surfaces have been calculated for the process of double-proton transfer in both the gas phase and a polar surrounding. The results of the calculations indicate that the gas-phase double-proton transfer possesses a concerted and asynchronous mechanism. However, due to the stabilization of the zwitterionic structure by a polar medium, the latter becomes a local minimum in the water solution where the reaction proceeds through a stepwise mechanism.

Introduction

Chemical reactions that involve multiple-proton transfers are among the most vital processes for biological and chemical systems.[1,2] However, they have not been studied as extensively as the reactions of a single-proton transfer. Multiple-proton-transfer reactions include proton relay systems in enzymes, proton transfers in hydrogen-bonded water complexes, and proton transfers in prototropic tautomerism.[1−5] One of the simplest examples of multiproton transfer is double-proton transfer. This phenomenon has been studied both experimentally and theoretically in the dimers of carboxylic acids,[6−15] in DNA base pairs and their models,[16−18] during water-assisted photo-tropic tautomerism in DNA bases,[19−21] etc. Even though many theoretical studies have been recently performed in this area,[22−30] the detailed mechanism of these processes still remains unclear even for such relatively simple systems as the hydrogen-bonded cyclic complexes having the following general structure:



where X and Y are oxygen or nitrogen atoms or NH groups. To clarify this point, the results of recent theoretical studies for such dimers are described briefly.

Formic Acid Dimer (X = Y = O). This complex is one of the most extensively studied systems both theoretically and experimentally because this is one of the simplest examples of the species where multiple-proton transfer occurs. All high level ab initio calculations that have been performed for the gas phase suggest that the protons in formic acid are transferred concertedly and synchronously via the transition state possessing D_{2h} symmetry.[22,23] The value of the calculated barrier, however, greatly depends on the level of calculation, size of the basis set, and the inclusion of correlation energy. Thus, the calculated values of the barrier height range from as high as 18.4 kcal mol^{-1} at the HF/6-311+G(d,p) level of theory to as low as 5.2 kcal mol^{-1} at the B3LYP/cc-pVDZ level of theory.[22,23] A surprising and completely unexpected result has been obtained from an ab initio molecular dynamics study[29] using the Hartree−Fock approximation and the 6-31G basis set. This simulation suggests the concerted asynchronous (successive) mechanism of the double-proton transfer.

The influence of the polar surrounding on the mechanism of this process has also been investigated using the self-consistent Onsager reaction field model.[23] The study has shown the dependence of the mechanism on the level of calculations and the value of the dielectric constant used. At the HF level it was concluded, for example, that the transition state possesses C_{2v} symmetry (successive mechanism) in the dielectric medium mimicking water. However, the mechanism remains the same as in the gas phase (at all values of the dielectric constant) when predicted at the B3LYP level.

Formic Acid−Formamidine Dimer ($X_1 = Y_1 = O$; $X_2 = Y_2 = NH$). Unlike the formic acid dimer, the gas-phase double-proton transfer in this dimer occurs asynchronously through an intermediate.[27] The relative energy of the intermediate varies from 1.3 kcal mol^{-1} at the B3LYP/6-31+G(d,p) level to 7.4 kcal mol^{-1} at the HF/6-31G(d,p) level with the values of the MP2 and CCSD(T) energies being in the middle. Similarly, the value of the calculated barrier height (note that there are two transition states, but because of the C_{2v} symmetry of the molecule, they are equivalent) varies from 1.6 kcal mol^{-1} at the B3LYP/6-31+G(d,p) to 8.3 kcal mol^{-1} at the HF/6-31G(d,p) level of theory.[27] The shape of the potential surface greatly depends on the value of the dielectric constant. The barrier height is reduced with an increase in the dielectric constant. It practically vanishes in the medium characterized by a dielectric constant from 2 to 5, meaning that the strongly H-bonded protons in the dimer move freely between the N and O atoms at room temperature in solution. In the solvent characterized

10.1021/jp021666d CCC: $22.00

by the values of a dielectric constant higher than 10, the only stable structure is the zwitterionic form in which the proton of the formic acid is transferred completely to the formamidine molecule. Even though this observation may seem to be unexpected, it is justified because the polar surrounding stabilizes ionic compounds more than neutral ones.

Formamidine Dimer (X = Y = NH). A description of the mechanism of double-proton transfer in this dimer greatly depends on the method and the presence of a polar surrounding. Thus, at the HF level, the protons are transferred concertedly through a transition state possessing C_{2v} symmetry in the gas phase and via a stepwise mechanism with an intermediate in the solution.[23] The results of the study at the B3LYP level suggest that the protons are transferred concertedly both in the gas phase and in the solution. However, the symmetry of the transition state is D_{2h} and C_{2v} in the gas phase and solution, respectively.[23] The height of the barrier also depends on the method and basis set used. Thus, the barrier height ranges from 9.0 to 25.4 kcal mol^{-1} for the gas-phase transfer. In the solution the value of the barrier height varies from 10.9 to 11.7 kcal mol^{-1} at the B3LYP level and from 19.7 to 23.8 kcal mol^{-1} at HF level depending on the value of the dielectric constant.

Formamide Dimer (X = NH; Y = O). The double-proton transfer occurs concertedly both in the gas phase and in solution. The structure of the transition state has C_s symmetry at the HF level and has C_{2h} symmetry at the B3LYP and MP2 levels of theory.[26] Thus, an HF study suggests asynchronous transfer of the protons and the B3LYP and MP2 levels suggest synchronous transfer of the protons. The barrier height depends greatly on the level of theory and is very sensitive to the size of the basis set. It varies from 18.8 kcal mol^{-1} (15.3 with zero-point energy) at the B3LYP/6-31G(d,p) level to 32.7 (28.5) kcal mol^{-1} at the HF/6-311G(d,p) level of theory. The reported barrier heights in the solvent are 32.4−33.4 kcal mol^{-1} at the HF level and 19.6−21.0 kcal mol^{-1} at the B3LYP level depending on the value of the dielectric constant.[26]

Formamidine−Formamide Dimer ($X_1 = X_2 = Y_1 =$ NH, $Y_2 =$ O). This system is probably the least studied. The geometry of this complex has been predicted at the HF/6-31G(d),[31] B3LYP/6-31G(d,p), and MP2/6-31G(d,p) levels of the theory.[16] The interaction energy has also been calculated.[32] However, only local minima have been located. The zwitterionic structure where the proton is completely transferred from formamide to formamidine was optimized at the HF level. However, because vibrational frequencies were not calculated for the studied system, it is unclear whether the zwitterionic structure is a local minimum or a transition state.

An analysis of the presented data suggests that a description of the mechanism of double-proton transfer in quite similar systems could be different and depends on the chemical structure, reaction conditions (vacuum or polar solvent), and sometimes even on the level of ab initio calculations. One may assume that the current state of knowledge is definitely far from a good understanding of the mechanism of this vital reaction. Therefore, new investigations, analysis, and conclusions are needed and this paper presents the results of reliable ab initio study of the proton-transfer mechanism in the formamidine−formamide (FIFA) dimer. There are two reasons to choose this system. First of all, until the structure of the transition state(s) is/are located at a reliable level of ab initio theory, the mechanism of proton transfer in this system should be considered unknown. And, second, this dimer closely mimics the hydrogen-bonding pattern in the adenine−thymine DNA base pair. Thus, the data obtained for this relatively small complex could also suggest the possible mechanism of proton exchange in the AT pair.

In the present study we have performed an extensive investigation of the mechanism of the double-proton transfer using high-level ab initio methods. We have carried out a search of all local minima and transition state structures for this process in the gas phase and in a water solution. The latter was implemented through the use of the PCM solvation model and the explicit inclusion of a selected number of water molecules. The data on the mechanism of the proton transfer of selectively hydrated prototypic DNA species are of importance due to a recent observation of selective hydration of the bases in a DNA strand.[33,34]

Computational Methods

The ab initio LCAO-MO method was used for the study of the FIFA dimer. The calculations were carried out using the Gaussian98[35] program package. All of the geometries of local minima and transition state structures were optimized without symmetry restrictions (C_1 symmetry was assumed) by the gradient procedure at the HF/6-31+G(d,p) and B3LYP/6-31+G(d,p) levels of theory. Additional optimizations were performed for gas-phase structures at the B3LYP/aug-cc-pVTZ, MP2/6-31+G(d,p), MP2/aug-cc-pVDZ, and QCISD/6-31+G(d,p) (with single-point energy calculations at CCSD(T)/aug-cc-pVDZ)) levels of theory. The characteristics of local minima and transition states were verified by establishing that the matrixes of the energy second derivatives (Hessians) at the corresponding level of theory (except QCISD where these calculations have not been performed due to a very high cost) have zero and one negative eigenvalues, respectively. The values of Gibbs free energy of formation have been calculated by the standard formula $\Delta G = \Delta H - T\Delta S$ at room temperature (298.15 K). The ΔS values have been calculated at the same levels of theory as the optimizations. To estimate the ΔH value, the thermal correction to enthalpy (H_T) calculated at the same level has been added to the calculated energy. (The values of entropy and thermal correction to enthalpy were not scaled due to the unavailability of the frequency scaling factor for the used basis sets; however, on the basis of the values for similar basis sets,[36] one can conclude that the correction would be negligible for the studied systems.)

The dimerization enthalpy of the monomers ($\Delta H_{\rm dim}$) has been obtained as a sum of the calculated energy of interaction ($E_{\rm int}$) corrected for the basis set superposition error,[37] deformation energy ($E_{\rm def}$), and thermal correction to enthalpy (H_T): $\Delta H_{\rm dim} = E_{\rm int} + E_{\rm def} + H_T$. The Gibbs free energy of dimerization was calculated by the subtraction of the $T\Delta S$ term from the dimerization enthalpy $\Delta H_{\rm dim}$.

The influence of the polar solvent was included using the polarizable continuum model.[38−40] All structures were optimized at the B3LYP/6-31+G(d,p) level of theory in the framework of PCM. The complexes of the dimers with water molecules were optimized in the gas phase using the same procedure as described above for isolated dimers at the B3LYP/6-31+G(d,p) level of theory. The water molecules were initially located in positions of the strongest interaction with the dimers' polar groups without breaking the hydrogen bonds between formamidine and formamide.

Results and Discussion

Gas-Phase Proton Transfer. The topology of a two-dimensional adiabatic potential energy surface for the double-proton transfer in the formamidine−formamide complex cal-

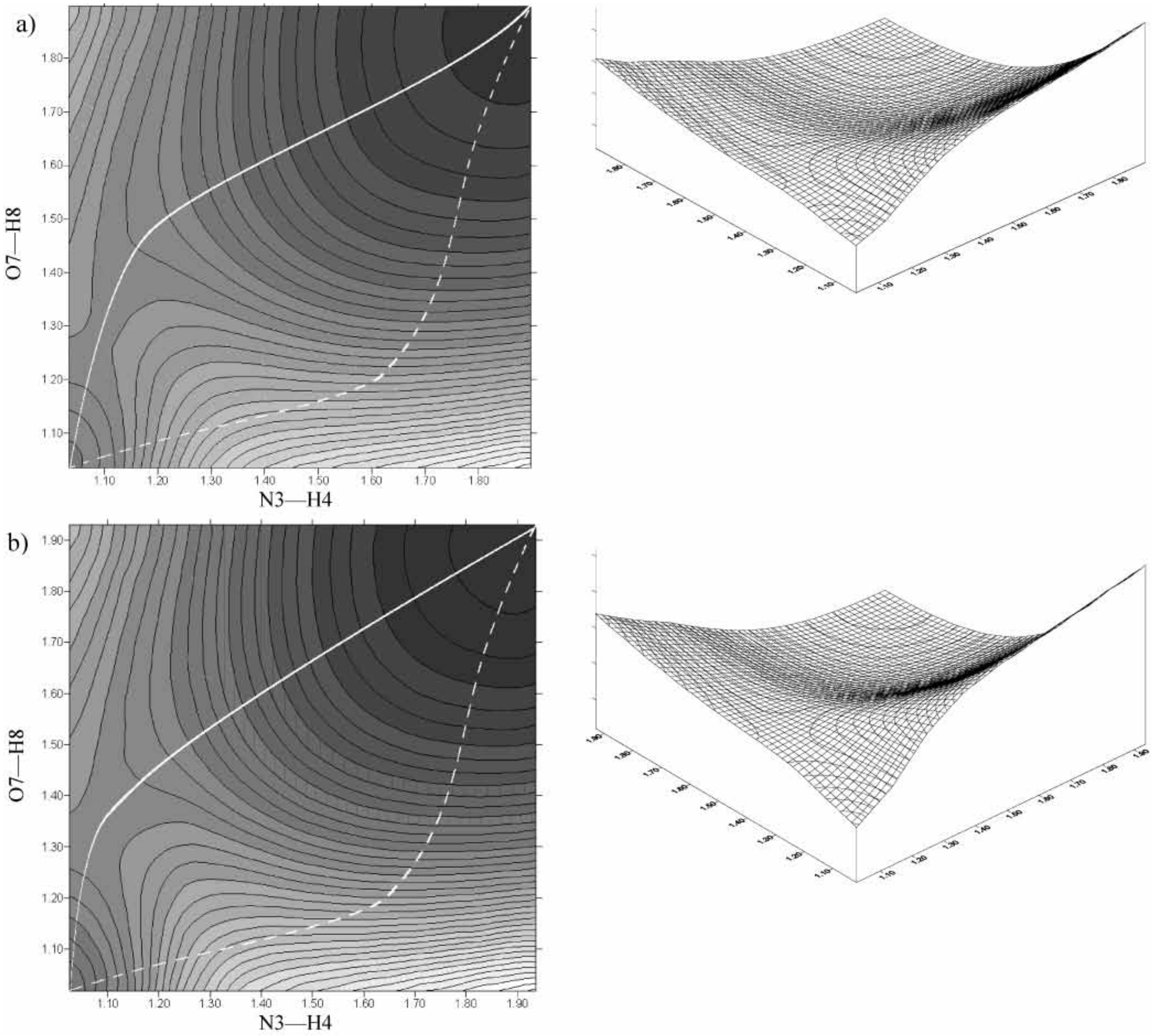


Figure 1. Two-dimensional adiabatic potential energy surfaces for gas-phase double-proton transfer in the FIFA dimer calculated at the (a) B3LYP/6-31+G(d,p) and (b) MP2/6-31+G(d,p) level. The solid line shows the actual pathway; the dashed line shows alterative path which is not realized.

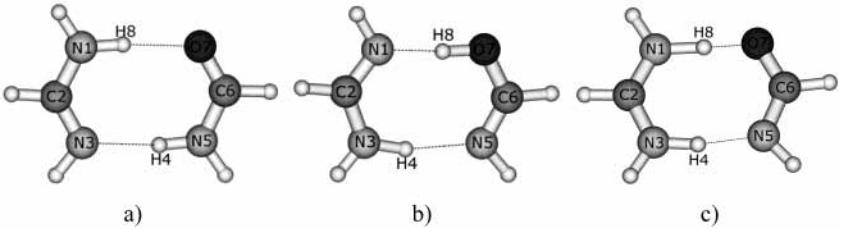


Figure 2. Structure of (a) the hydrogen bonded FIFA, (b) the DPT complex and (c) the transition state species.

culated at the B3LYP/6-31+G(d,p) and MP2/6-31+G(d,p) levels of theory are shown in Figure 1. The surfaces have been constructed on the basis of two optimized geometries—the FIFA dimer and its double-proton transfer (DPT) complex—by varying the O−H and N−H distances. One may see that there are just three critical points on the surface. Two correspond to the aforementioned hydrogen bonded FIFA and the DPT complexes. The third critical point characterizes the transition state (TS) for the proton transfer. The structures of all three species are shown in Figure 2. Selected geometrical parameters of those structures optimized at different levels of ab initio approximation are collected in Tables 1−3. The following results have been obtained for all considered methods and basis sets.

1. The local minima are represented by hydrogen bonded complexes characterized by interatomic and intermolecular distances that are typical for hydrogen bonded systems. One may see that the intermolecular distances in the DPT complex are shorter than in the FIFA, which means that the corresponding hydrogen bonds are significantly stronger in the DPT complex than in the FIFA. As expected, these intermolecular distances are the most sensitive to the method of calculation. The greatest difference between predicted distances is approximately 0.1 Å

TABLE 1: Selected Geometrical Parameters of the Optimized FIFA Dimer

	B3LYP/6-31+G(d,p)	MP2/6-31+G(d,p)	QCISD/6-31+G(d,p)	B3LYP/aug-cc-pVTZ	MP2/aug-cc-pVDZ
N1−O7	2.92	2.95	2.98	2.91	2.89
N3−N5	2.93	2.96	3.00	2.94	2.91
N1−H8	1.03	1.02	1.02	1.02	1.03
N1−C2	1.35	1.36	1.35	1.34	1.36
C2−N3	1.29	1.30	1.29	1.28	1.30
N3−H4	1.90	1.94	1.98	1.91	1.88
N5−H4	1.04	1.03	1.02	1.03	1.04
N5−C6	1.34	1.35	1.35	1.34	1.35
C6−O7	1.23	1.24	1.24	1.23	1.24
O7−H8	1.90	1.93	1.96	1.89	1.86
N1−H8−O7	174.7	175.0	174.9	174.8	176.4
N3−H4−N5	172.8	173.1	172.5	172.6	173.3

TABLE 2: Selected Geometrical Parameters of the Optimized DPT Form of the FIFA Dimer

	B3LYP/6-31+G(d,p)	MP2/6-31+G(d,p)	QCISD/6-31+G(d,p)	B3LYP/aug-cc-pVTZ	MP2/aug-cc-pVDZ
N1−O7	2.65	2.69	2.75	2.68	2.68
N3−N5	2.93	2.97	3.03	2.94	2.92
N1−H8	1.62	1.67	1.75	1.65	1.66
N1−C2	1.30	1.30	1.29	1.29	1.30
C2−N3	1.35	1.35	1.35	1.34	1.35
N3−H4	1.04	1.03	1.02	1.03	1.03
N5−H4	1.91	1.97	2.02	1.93	1.90
N5−C6	1.27	1.29	1.28	1.28	1.30
C6−O7	1.32	1.32	1.33	1.31	1.33
O7−H8	1.03	1.02	1.00	1.02	1.02
N1−H8−O7	175.6	174.8	174.5	175.4	174.0
N3−H4−N5	166.6	166.8	165.8	166.6	167.0

TABLE 3: Selected Geometrical Parameters of the Optimized Transition State of the FIFA Dimer

	B3LYP/6-31+G(d,p)	MP2/6-31+G(d,p)	QCISD/6-31+G(d,p)	B3LYP/aug-cc-pVTZ	MP2/aug-cc-pVDZ
N1−O7	2.51	2.52	2.52	2.51	2.51
N3−N5	2.71	2.69	2.73	2.72	2.70
N1−H8	1.19	1.15	1.13	1.18	1.17
N1−C2	1.31	1.31	1.31	1.30	1.32
C2−N3	1.32	1.32	1.32	1.32	1.33
N3−H4	1.09	1.08	1.07	1.08	1.09
N5−H4	1.63	1.62	1.67	1.66	1.62
N5−C6	1.31	1.32	1.31	1.30	1.32
C6−O7	1.29	1.29	1.29	1.28	1.29
O7−H8	1.32	1.37	1.39	1.33	1.34
N1−H8−O7	178.7	178.3	178.5	178.5	177.4
N3−H4−N5	169.7	170.4	169.7	169.5	170.4

between the longest (QCISD/6-31+G(d,p)) and the shortest (MP2/aug-cc-pVDZ) values. So, to attain convergence of the geometrical parameters, higher levels of theory and extended basis sets are required.

2. Much more attention should be paid to the analysis of the geometry of TS. All considered methods predict a structure that corresponds to a practically complete transfer of the H4 proton to the formamidine molecule. Indeed, the values of interatomic distances for chemical bonds N3−H4 are predicted to be at almost equilibrium N−H value at all considered levels of theory, and the interatomic distance N1−H8 is just slightly elongated compared to the equilibrium distance in FIFA.

The majority of the structures of the gas-phase transition states that have been discussed in the Introduction correspond to a concerted mechanism; i.e., the protons are transferred in one step and mostly synchronously. A one-step mechanism is also suggested for the double-proton transfer in the FIFA dimer at all considered levels of theory. However, in contrast to a synchronous transfer, it should be considered as asynchronous, or successive. In other words our data suggest that there should be some time lag between the movement of the H4 proton, which is moving first, and the H8 proton, which is moving after the H4 proton has virtually reached the N4−H4 equilibrium interatomic distance. Thus, the structure of the gas-phase proton-transfer transition state is zwitterionic. It possesses the protonated formamidine and deprotonated formamide units as counterparts.

To test for the possibility of a synchronous concerted proton-transfer mechanism in the considered system, we have investigated the nature of the structure where the H4 and H8 protons were placed in the middle between the N1−O7 and N3−N5 atoms, respectively. The interatomic distances N3−N5 and N1−O7 have been chosen as an average between the ones calculated for these distances in the FIFA and DPT forms. The calculated structure has two imaginary frequencies at both the MP2/6-31+G(d,p) and B3LYP/6-31+G(d,p) levels. The search for the transition state structure was always a failure when using this structure as a starting point. Thus, the structure that formally describes the transition state for synchronous concerted proton transfer actually cannot be considered as the species that characterizes the true transition state.

Because the topology of such a reaction has not been investigated precisely even at the Hartree−Fock level[31] (i.e., the zwitterionic structure was not attributed to either a local minimum or transition state), we have performed geometry optimization and vibrational frequencies calculations using the

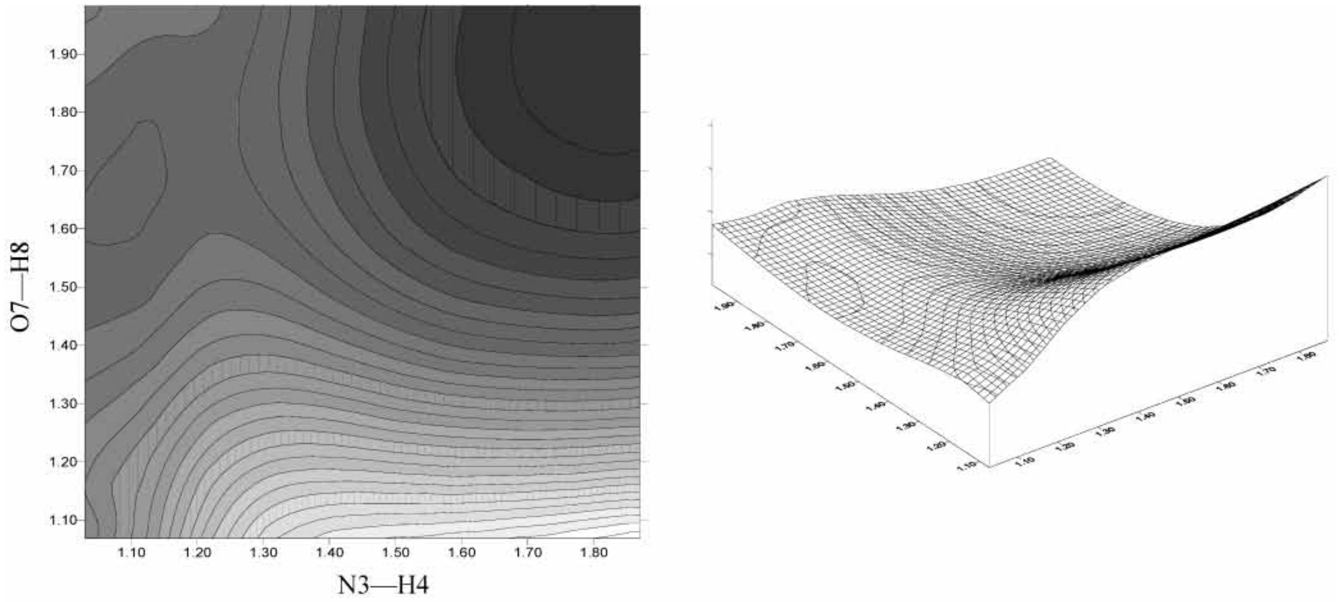


Figure 3. Two-dimensional adiabatic potential energy surface for proton transfer in the FIFA dimer in water (calculated at the B3LYP/6-31+G-(d,p) level using the PCM solvation model).

TABLE 4: Calculated Gibbs Free Energies for the Double-Proton Transfer (ΔG°_{298}), Potential Energy ($\Delta E^{\ddagger}$) and Gibbs Free Energy ($\Delta G^{\ddagger}_{298}$) Barrier Heights in the Forward Direction, Dimerization Enthalpies ($\Delta H^{\circ}_{298\text{dim}}$) and Gibbs Free Energies of Dimerization ($\Delta G^{\circ}_{298\text{dim}}$) at Room Temperature (kcal mol^{-1})

method	ΔG^{0}_{298}	$\Delta E^{\ddagger}$	$\Delta G^{\ddagger}_{298}$	$\Delta H^{\circ}_{298\text{dim}}$	$\Delta G^{\circ}_{298\text{dim}}$
B3LYP/6-31+G(d,p)	9.6	12.0	10.3	−11.7	−1.3
MP2/6-31+G(d,p)	9.9	14.0	11.8	−10.3	0.0
CCSD(T)/aug-cc-pVDZ// QCISD/6-31+G(d,p)	8.3	13.0	10.9	−11.2	−0.9
B3LYP/aug-cc-pVTZ	9.6	12.5	10.8	−14.2	−3.6
MP2/aug-cc-pVDZ	9.0	12.3	10.8	−11.6	−1.2

6-31+G(d,p) basis set. In contrast to electron-correlated methods, the results of the HF study suggest that the zwitterionic species, which has a structure closely resembling that of the TS in Figure 2c (with the exception of the N1−H8 bond being shorter), is actually a local minimum.

Theoretically, there could be two pathways for asynchronous concerted double-proton transfer through two different transition states. The transition state corresponding to the first pathway (solid line in Figure 1) with both protons transferred to formamidine is described above. The second pathway (dash line in Figure 1) could be formally initiated by the movement of the H4 proton ahead of H8. However, as one can see from the potential energy surfaces in Figure 1, this pathway is not realized. The reason may lie in the fact that the proton affinity of the formamidine monomer is 29.8 kcal mol^{-1} higher than that of formamide (calculated at CCSD(T)/aug-cc-pVDZ// QCISD/6-31+G(d,p) level).

The calculated energy parameters, which characterize the process of double-proton transfer in the FIFA dimer, are collected in Table 4. The low values of the Gibbs free energy of dimerization are attributed to the large loss of entropy accompanying the dimerization, which originates from the transformation of translational and rotational degrees of freedom of the monomers into vibrational ones in the complexes. This is a general phenomenon for all associative reactions of type A + B → C.[41] The data in the table also suggest that in contrast to the results obtained for formic acid, formamide, and formamidine dimers, the calculated values of barrier height and energies of tautomerization are quite close at all levels of electron-correlated methods. The barrier heights correspond to the gas-phase equilibrium constants within the range 8.3×10^{-7} to 5.6×10^{-8}.[42]

Recently, we estimated the rate constants for similar intramolecular tautomeric transitions in isolated and water-mediated guanine molecules.[42] We have found that the value of the rate constant amounts to 8.6×10^{-6} s^{-1} for the 35.4 kcal/mol barrier, which characterizes intramolecular proton transfer in isolated guanine. However, the barrier of 15.3 kcal/mol, which is observed in the water-mediated proton transfer, increases the rate constant to 9.5×10^{4} s^{-1}. Using these values, we have found that the time to reach preequilibrium concentration of the rare form in the water-mediated tautomerization process is about 10^{-8} s. Let us now take into account that all predicted values for barrier heights in FIFA are smaller than the values considered in ref 42. Therefore, one may expect that the calculated rate constant for the proton transfer in the FIFA complex will be larger than for guanine and the time to reach preequilibrium concentration of the DPT form will be less than 10^{-8} s. Thus the obtained data suggest the following kinetic and thermodynamic behavior for the gas-phase FIFA complex. As soon as hydrogen bonds are formed, the equilibrium between the FIFA and DPT forms is reached virtually instantly. However, the equilibrium amount of the DPT form is extremely small and practically undetectable with modern equipment.

As was mentioned above, the FIFA complex could be considered the smallest prototypic system for modeling a double-proton transfer in the adenine−thymine base pair. Thus, we expect that tautomeric transformations in the AT base pair, even being reached instantly, are not significant for contributions to spontaneous point mutations because the predicted concentration of rare tautomeric form is expected to be too small. The comprehensive study of the proton transfer in AT and GC base pairs are in progress.[43]

Proton Transfer in Water. The influence of a water surrounding has been addressed in this study through the implicit addition of four water molecules, which connect to all polar groups of the dimer without breaking the hydrogen bonds, and also through the polarizable continuum model. The topology of a two-dimensional adiabatic proton-transfer surface in the

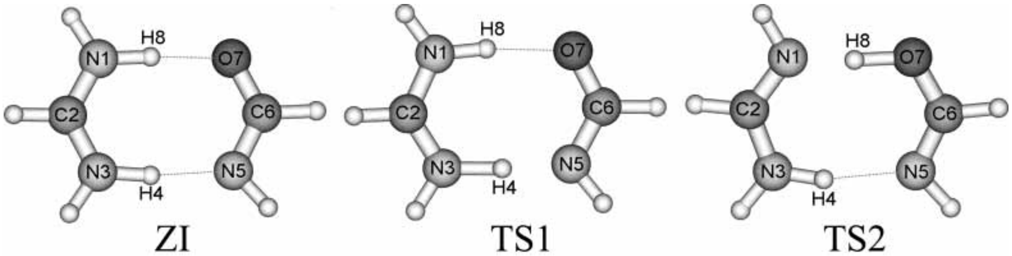


Figure 4. Structures of the optimized zwitterionic intermediate and two transition states for proton transfer in water.

TABLE 5: Selected Geometrical Parameters and Relative Total Energies and Gibbs Free Energies of Formation (kcal mol^{-1}) of the Optimized at the PCM B3LYP/6-31+G(d,p) Level Structures of FIFA Dimer

	FIFA	TS1	ZI	TS2	DPT
N1−O7	3.00	2.79	2.71	2.51	2.59
N3−N5	2.91	2.60	2.76	2.88	2.95
N1−H8	1.02	1.04	1.06	1.34	1.53
N1−C2	1.35	1.33	1.32	1.30	1.30
C2−N3	1.29	1.31	1.31	1.33	1.34
N3−H4	1.87	1.21	1.08	1.04	1.03
N5−H4	1.04	1.39	1.69	1.87	1.94
N5−C6	1.33	1.32	1.31	1.29	1.28
C6−O7	1.25	1.27	1.28	1.31	1.32
O7−H8	1.98	1.76	1.65	1.17	1.06
N1−H8−O7	171.7	172.6	176.9	174.9	174.4
N3−H4−N5	173.5	176.0	173.1	163.2	164.9
ΔG_f^{298}	0.0	4.9	4.9	6.7	6.3
ΔE^a	0.0	8.2	6.9	9.9	8.9

[a] Energies are not corrected for zero-point vibrational energy.

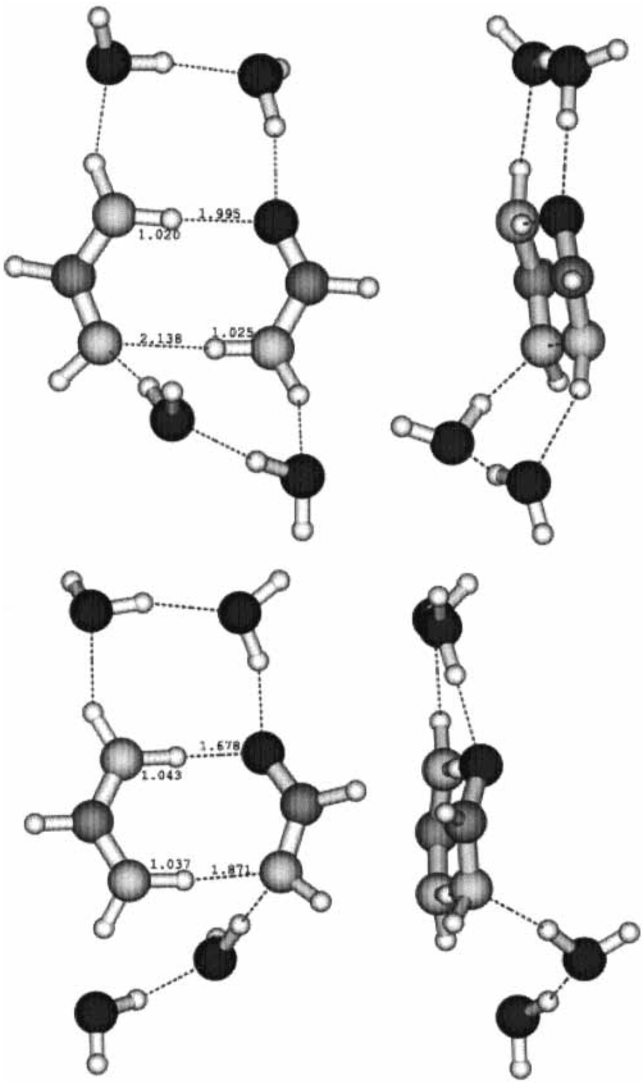


Figure 5. Structures of hydrated FIFA and ZI species.

FIFA dimer calculated at the PCM B3LYP/6-31+G(d,p) level is presented in Figure 3. The surface has been constructed in the same way as for the gas-phase proton transfer. One may see dramatic changes that take place when a FIFA complex is immersed in water. There are three local minima on this surface. In addition to local minima that characterize the FIFA and DPT complexes, the zwitterionic gas-phase structure of TS becomes a local minimum (ZI, see Figure 4) in solution. These results mean that the double-proton transfer in solution occurs via a stepwise mechanism that proceeds through two single-proton-transfer reactions.

Selected optimized geometrical parameters and relative Gibbs free energies of formation of considered forms are collected in Table 5. One can see that the changes in the geometry of the predicted structures gradually increase when going from the FIFA to the DPT and to ZI forms in comparison to the gas-phase structures. The most significant change in the geometry of the FIFA form is the increase in the distance between the N1 and O7 atoms and, therefore, the increase in the O7−H8 hydrogen bond. In contrast, the N1−O7 distance decreases and the N3−N5 distance increases in the DPT form when immersed in a polar solvent. The most considerable change occurs in the zwitterionic form of the dimer, in which both the N1−O7 and the N3−N5 distances between the monomers increase by 0.2 and 0.06 Å, respectively. Also, the N1−H8 covalent bond becomes shorter by 0.13 Å than in the gas-phase transition state structure calculated at the same B3LYP/6-31+G(d,p) level of theory.

The relative Gibbs free energy for the zwitterionic intermediate is 4.9 kcal mol^{-1} higher than that for the FIFA form. The Gibbs free energy of the DPT form of the dimer is 6.3 kcal mol^{-1} higher than that of the FIFA form, which makes it 1.4 kcal mol^{-1} less stable than the zwitterionic form. The reason for this phenomenon is probably the effect of strong stabilization of the zwitterionic form by a polar medium. We have also optimized the transition state structures for each proton transfer (Figure 4). Selected geometrical parameters of those structures are presented in Table 5. One may see that the depth of the zwitterionic local minimum on the potential energy surface is not big and that its value of Gibbs free energy equals that of the TS1. This result suggests that higher levels of theory and/or other solvation models should be applied to study the problem in depth.

The optimized geometries of the FIFA and ZI forms of the dimer with four water molecules are shown in Figure 5. The geometries of these forms are close to the ones obtained in the PCM model optimizations with the exception of hydrogen bonds, which are predicted to be longer with actual water molecules (see Figure 5). We were not able to optimize the structure of the DPT form of the dimer, which indicates that this minimum does not exist at the B3LYP/6-31+G(d,p) level or it is very shallow. However, this result supports the outcome of calculations performed using the PCM solvation model. The stabilizing influence of four water molecules is sufficient to decrease the Gibbs free energy of formation of the zwitterionic structure to 6.8 kcal/mol over the FIFA structure.

Summary

The results of the study on the double-proton transfer in the FIFA dimer suggest that different paths for this process should be observed in the gas phase and in a water solution. In the gas phase the reaction occurs concertedly and asynchronously. In the water solution, however, due to the stabilization of the zwitterionic structure by a polar medium, the latter becomes a local minimum. Thus, the reaction occurs through a stepwise mechanism with the zwitterionic intermediate. However, because the energy of the zwitterionic structure is 1.4 kcal/mol lower than that of the DPT form at the PCM B3LYP level of theory, the reaction of a single-proton transfer in solution becomes more likely than the double-proton transfer. The fact that we were not able to locate a minimum for the DPT form with four water molecules also supports this conclusion. However, an analysis of the energetics of all reactions suggests that the hydrogen-bonded FIFA form is significantly more stable than any other form in both the gas phase and a polar medium. Thus, it is unlikely that any minor tautomeric form of the formamidine−formamide dimer will be detected experimentally.

Acknowledgment. This work was facilitated by the ONR grant No. N00014-98-1-0592, NIH grant No. G1 2RR13459-21, and NSF grant No. 9805465. We also thank Prof. Andrzej Sokalski for a helpful discussion.

References and Notes

(1) *Proton Transfer in Hydrogen-bonded Systems*; Bountis, T., Ed.; Plenum: New York, 1992.

(2) Limbach, H. H.; Manz, J. *Ber. Bunsen-Ges. Phys. Chem.* **1998**, *102*, 289.

(3) Bell, R. P. *The Tunnel Effect in Chemistry*; Chapman and Hall: New York, 1980.

(4) Melander, L.; Saunders, W. H. J. *Reaction Rates of Isotopic Molecules*; John Wiley & Sons: New York, 1980; p152.

(5) Bender, M. L. *Mechanism of Homogeneous Catalysis from Protons to Proteins*; John Wiley & Sons: New York, 1971; Chapters 2, 4, and 5.

(6) Millikan, R. C.; Pitzer, K. S. *J. Am. Chem. Soc.* **1958**, *80*, 3515.

(7) Costain, C. C.; Srivastava, G. P. *J. Chem. Phys.* **1964**, *41*, 1620.

(8) Bertie, J. E.; Michaelian, K. H. *J. Chem. Phys.* **1982**, *76*, 886.

(9) Wilson, C. C.; Shankland, N.; Florence, A. J. *Chem. Phys. Lett.* **1996**, *253*, 103.

(10) Wilson, C. C.; Shankland, N.; Florence, A. J. *J. Chem. Soc., Faraday Trans.* **1996**, *92*, 5051.

(11) Neuheuser, T.; Hess, B. A.; Reutel, C.; Weber, E. *J. Phys. Chem.* **1994**, *98*, 6459.

(12) Qian, W.; Krimm, S. *J. Phys. Chem. A* **1997**, *101*, 5825.

(13) Liedl, K. R.; Sekusak, S.; Mayer, E. *J. Am. Chem. Soc.* **1997**, *119*, 3782.

(14) Qian, W.; Krimm, S. *J. Phys. Chem. A* **1998**, *102*, 659.

(15) Hage, W.; Liedl, K. R.; Hallbrucker, A.; Mayer, E. *Science* **1998**, *279*, 1332.

(16) Bertran, J.; Oliva, A.; Rodriguez-Santiago, L.; Sodupe, M. *J. Am. Chem. Soc.* **1998**, *120*, 8159.

(17) Fiebig, T.; Chachisvilis, M.; Manger, M.; Zewail, A. H.; Douhal, A.; Garcia-Ochoa, I.; de La Hoz Ayuso, A. *J. Phys. Chem. A* **1999**, *103*, 7419.

(18) Florian, J.; Leszczynski, J. *J. Am. Chem. Soc.* **1996**, *118*, *3010*.

(19) Tor, Y.; Dervan, P. B. *J. Am. Chem. Soc.* **1993**, *115*, 4461.

(20) Gorb, L.; Leszczynski, J. *Int. J. Quantum Chem.* **1997**, *65*, 759.

(21) Gorb, L.; Leszczynski, J. *Int. J. Quantum Chem.* **1998**, *70*, 855.

(22) Kim, Y. *J. Am. Chem. Soc.* **1996**, *118*, 1522.

(23) Lim, J.-H.; Lee, E. K.; Kim, Y. *J. Phys. Chem. A* **1997**, *101*, 2233.

(24) Loerting, T.; Liedl, K. R. *J. Am. Chem. Soc.* **1998**, *120*, 12595.

(25) Miura, S.; Tuckerman, M. E.; Klein, M. L. *J. Chem. Phys.* **1998**, *109*, 5290.

(26) Kim, Y.; Lim, S.; Kim, H.-J.; Kim, Y. *J. Phys. Chem. A* **1999**, *103*, 617.

(27) Kim, Y.; Lim, S.; Kim, Y. *J. Phys. Chem. A* **1999**, *103*, 6632.

(28) Kohanoff, J.; Koval, S.; Estrin, D. A.; Laria, D.; Abashkin, Y. *J. Chem. Phys.* **2000**, *112*, 9498.

(29) Ushiyama, H.; Takatsuka, K. *J. Chem. Phys.* **2001**, *115*, 5903.

(30) Wei, D.; Truchon, J.-F.; Sirois, S.; Salahub, D. *J. Chem. Phys.* **2002**, *116*, 6028.

(31) Zhanpeisov, N. U.; Leszczynski, J. *J. Phys. Chem. A* **1999**, *103*, 8317.

(32) Sponer, J.; Hobza, P. *Chem. Phys.* **1996**, *204*, 365.

(33) Poltev, V. I.; Tepluchin, A. V.; Malenkov, G. G. *Int. J. Quantum Chem.* **1992**, *42*, 1499.

(34) Schneider, B.; Berman, H. M. *Biophys. J.* **1995**, *69*, 2661.

(35) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.7; Gaussian: Pittsburgh, PA, 1998.

(36) Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502.

(37) Boys, S. F.; Bernardi, F. *Mol. Phys.* **1970**, *19*, 553.

(38) Miertus, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117.

(39) Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys. Lett.* **1996**, *255*, 327.

(40) Amovilli, C.; Barone, V.; Cammi, R.; Cances, E.; Cossi, M.; Mennucci, B.; Pomelli, C. S.; Tomasi, J. *Adv. Quantum Chem.* **1998**, *32*, 227.

(41) Searle, M. S.; Williams, D. H. *J. Am. Chem. Soc.* **1992**, *114*, 10690.

(42) Gorb, L.; Podolyan, Y.; Leszczynski, J.; Siebrand, W.; Fernandez-Ramos, A.; Smedarchina, Z. *Biopolymers* **2002**, *61*, 77.

(43) Gorb, L.; Podolyan, Y.; Leszczynski, J. To be submitted for publication.