Formamide Tautomerization: Catalytic Role of Formic Acid

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Formic acid catalyzed tautomeric conversion of formamide to formamidic acid has been investigated by use of ab initio and density functional theoretical calculations. In a 1:1 dimeric complex between formamide and formic acid, the tautomeric conversion occurs via double-hydrogen transfer within an eight-member hydrogen-bonded cyclic network. The results predict that the energy barrier of the catalytic process is reduced by more than a factor of 4 compared to that in the isolated formamide molecule in the gas phase, and the tautomerization in the 1:1 complex is several kcal/mol less endothermic than that of the isolated molecule. The potential energy surface corresponding to this double hydrogen transfer process indicates that a concerted transfer of both the hydrogen atoms along the hydrogen bond directions is energetically favorable, and no minimum for an ionic intermediate, which may arise for stepwise transfer, was predicted. The unique configuration of the transition state has been identified by starting the reaction from both the tautomeric forms, and the transition state was subjected to IRC calculation.

1. Introduction

The formamide (FM)−formamidic acid (FMA) tautomeric pair has drawn much attention as a convenient molecular prototype for detailed mechanistic investigation of the prototropic isomerization processes.[1−18] Thermodynamically, the conversion of FM to FMA is endothermic, and the activation energy barrier in the gas phase is nearly 50 kcal/mol.[1,2,4,13] However, many recent investigations have predicted that the barrier is significantly reduced when the process is assisted by a water molecule[1,2−4,13] or by a second formamide molecule (self-assisted process).[2,3] Investigations of such catalytic influences by a wide range of proton donor−acceptor species would be valuable to understand the mechanisms of such processes in different physical conditions. Such information is important because many basic biochemical processes in living systems are related to tautomeric transformations analogous to that in formamide−formamidic acid system.[3−6,11,13,17−26]

In this paper, we discuss the catalytic role of formic acid on FM↔FMA tautomerization in the gas phase. The 1:1 complexes of both the tautomeric forms generate doubly hydrogen-bonded cyclic structures, and in the tautomerization reaction the formic acid molecule acts as H-donor as well as H-acceptor. In contrast to the self-assisted reaction, where the second formamide molecule is also tautomerized, the formic acid in the present case is regenerated at the end of the reaction. The process has been investigated by use of quantum chemistry theoretical methods.

2. Methods

The geometries of FM, FMA, their 1:1 complexes with formic acid (FM···FA and FMA···FA), and the transition states (TS) connecting the tautomers are calculated by MP2 as well as by DFT/B3LYP methods using two different basis sets (6-31G** and 6-311++G**) as implemented in the Gaussian-03 suite of programs.[27] The transition states have been located by the use of synchronous transit-guided quasi-Newton (STQN) method.[28] Normal-mode analysis has been performed to verify that the optimized geometries of FM···FA and FMA···FA have all positive frequencies, and transition-state species (TS) have only one imaginary frequency. The normal-mode frequencies of the reactant, product, and TS were used to estimate the effect of zero-point energy correction on barrier height of the tautomerization process and relative energies of various species. Basis set superposition errors in calculated binding energies (E_{HB}) in the two complexes are corrected by the counterpoise (CP) method of Boys and Bernardi.[29] Intrinsic reaction coordinate (IRC) calculations were performed at both the MP2 and B3LYP levels using the 6-31G (d, p) basis set to verify the transition states. The SCF convergence criterion *Tight* was used throughout, except in IRC and relaxed potential energy surface (PES) calculations.

3. Result and Discussion

3A. Energetic and Geometric Parameters. The optimized structures of the two doubly hydrogen-bonded complexes (FM··· FA and FMA···FA), along with the transition-state species (TS), are shown in Figure 1. It has been verified that the same transition state on the reaction path is achieved irrespective of the starting tautomeric form. Selected geometrical parameters of all the molecular species involved in the study are presented in Table 1. Results for two different calculations (MP2/6-311++G** and DFT/BLYP/6-311++G**) are given here. The energetic parameters of the three species predicted at the MP2/6-311++G** level of calculation are shown schematically in Figure 2. Here, the total energy of the isolated FM and FA molecules at infinite separation is taken as the reference of energy scale. The relative energies of all the species predicted at other levels of calculations are shown in Tables 2 and 3. Our results for the isolated FM and FMA agree with those reported by previous workers.[2,13]

The energy diagram shows that the binding energy of the FMA···FA complex ($E_{HB} = 17.35$ kcal/mol) is about 2.88 kcal/mol larger than that of FM···FA (BSSE uncorrected). The zero-

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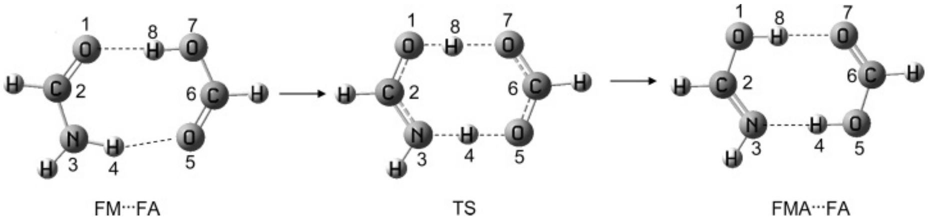

Figure 1. Optimized structures of the tautomers FM···FA and FMA···FA and the transition state (TS) between the two tautomers.

TABLE 1: Selected Bond Lengths (Å) and Bond Angles (Degree) of All the Molecular Species Optimized at Two Different Levels of Theoretical Calculations

geometrical parameters	MP2/6-311++G**							B3LYP/6-311++G**						
	FM	TS	FMA	FM--FA	TS	FMA--FA	FA	FM	TS	FMA	FM--FA	TS	FMA--FA	FA
O_1-O_7				2.682	2.467	2.705					2.672	2.505	2.687	
N_3-O_5				2.924	2.482	2.686					2.908	2.494	2.665	
C_2-C_6				3.953	3.637	3.863					3.938	3.662	3.842	
O_1-H_8			0.968	1.689	1.065	0.989				0.970	1.669	1.056	0.998	
O_1-C_2	1.216	1.283	1.346	1.232	1.286	1.319		1.211	1.282	1.346	1.229	1.288	1.315	
C_2-N_3	1.369	1.308	1.274	1.345	1.301	1.286		1.360	1.301	1.263	1.339	1.294	1.280	
N_3-H_4	1.009	1.321		1.019	1.219	1.674		1.009	1.342		1.023	1.258	1.637	
H_4-O_5				1.938	1.263	1.013					1.917	1.236	1.028	
O_5-C_6				1.219	1.272	1.313	1.205				1.216	1.273	1.306	1.199
C_6-O_7				1.321	1.255	1.224	1.348				1.316	1.247	1.222	1.346
O_7-H_8				0.995	1.402	1.715	0.969				1.003	1.449	1.689	0.971
$O_1-H_8-O_7$				175.5	177.7	178.4					177.5	179.9	178.4	
$N_3-H_4-O_5$				161.9	178.7	178.9					162.3	178.2	178.1	
$O_1-C_2-N_3$	124.7	108.5	121.8	125.0	124.6	123.9		124.9	108.5	122.1	125.0	124.7	124.3	
$C_2-N_3-H_4$	117.5	73.2		119.2	122.5	126.3		119.4	73.6		119.3	122.5	125.5	
$O_5-C_6-O_7$				126.6	126.9	126.4	125.2				126.5	126.6	126.3	125.1
$N_3-O_5-C_6\text{-}O_7$				0.0	0.0	0.7					0.0	0.0	0.0	
$N_3-C_2-O_1\text{–}O_7$				0.0	0.0	−2.2					0.0	0.0	0.0	

point energy-corrected barrier for tautomerization in the forward reaction is reduced by a factor of 4.5 in the H-bonded complex compared to that of the isolated molecule. The values of these reaction parameters can be compared with the results of other studies, where the roles of a water molecule and a second formamide molecule (self-catalysis) on the tautomeric conversion process have been discussed. For example, a very recent calculation of Liang et al.[1] (B3LYP/6-311++G**) predicts that the barrier in a doubly hydrogen-bonded 1:1 water complex can be reduced by a factor of 2. Likewise, in case of self-assisted tautomerization, Kim et al.[3] reported that according to MP2/6-31G** level of calculation, a doubly hydrogen-bonded second formamide molecule can lower the barrier by a factor of 2.5. Clearly, the comparisons of these results with the predictions of the present study indicate the efficient catalytic role of formic acid on this tautometic conversion process.

TABLE 2: Energy Barriers (kcal/mol) for Tautomeric Conversion of Formamide in Bare Molecule and in 1:1 Complex with Formic Acid

	FM → FMA		FM···FA → FMA···FA	
level of calculations	without ZPE correction[a]	ZPE corrected	without ZPE correction	ZPE corrected
MP2/6-31G**	46.78	43.95	12.88	9.63
MP2/6-311++G**	47.42	43.74	12.58	9.60
B3LYP/6-31G**	46.21	43.28	10.57	7.42
B3LYP/6-311++G**	48.52	45.41	12.02	8.98

[a] ZPE = Zero-point energy.

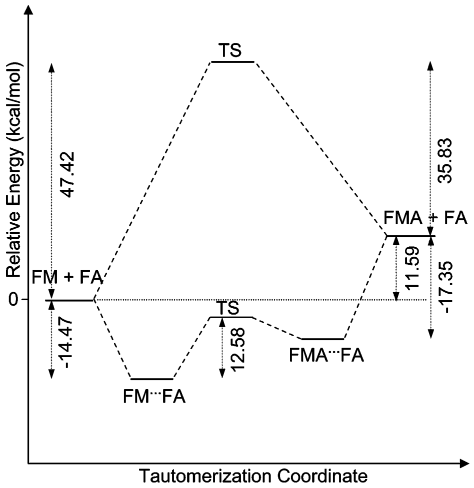

Figure 2. An energy level diagram showing the calculated (MP2/6-311++G**) relative energies of different molecular species and the transition states. The combined energy of the isolated formamide (FM) and formic acid (FA) molecules at infinite separation has been taken as zero (0) of the energy scale. Only the BSSE uncorrected energetic parameters of the hydrogen-bonded complexes (Tables 2 and 3) are shown in the figure.

The geometrical parameters of the molecular species (Table 1) indicate that the hydrogen bonding with formic acid induces notable geometry changes of the two tautomers, and it has been pointed out below that such changes favor formation of the TS. The C=O, N−H, and C−N bond lengths of FM are changed, respectively, from 1.216, 1.009, and 1.369 Å in an isolated molecule to 1.232, 1.019, and 1.345 Å in the FM···FA complex. The hydrogen bond induced changes of the first two parameters are quite obvious. Interestingly, C−N bond length is decreased on complex formation by 0.024 Å, that is, develops partial double bond character. Such changes are also noticed in the formic acid (FA) moiety; the C−O and C=O bond lengths are changed from 1.348 and 1.205 Å in the isolated molecule to 1.321 and 1.219 Å in the FM···FA complex. Thus, the C−O single bond length of FA is decreased by 0.027 Å from isolated molecule to FM···FA complex. These changes indicate that H-bonding promotes charge delocalization over the whole cyclic interface. The changes in geometrical parameters of the tautomer FMA on binding with formic acid are presented in Table 1.

TABLE 3: BSSE Corrected Binding Energies (kcal/mol) of the Doubly Hydrogen-Bonded FM···FA and FMA···FA Complexes

	FM···FA			FMA···FA		
level of calculation	without BSSE corrections[a]	BSSE corrected	BSSE and ZPE corrected	without BSSE corrections	BSSE corrected	BSSE and ZPE corrected
MP2/6-31G**	18.22	13.58	11.06	20.72	16.00	14.14
MP2/6-311++G**	14.47	12.38	11.20	17.35	14.80	13.25
B3LYP/6-31G**	19.11	15.12	12.96	22.49	18.72	17.36
B3LYP/6-311++G**	14.82	14.29	12.31	17.87	17.12	15.59

[a] ZPE = Zero-point energy.

TABLE 4: Differences in Geometrical Parameters (Δ*R*) between the TS and Reactants and the Corresponding Energy Changes (Δ*E* kcal/mol) Calculated at the MP2/6311++G Level Induced by Varying the Configurations of Isolated FM and the FM Moiety in FM···FA**

	FM		FM in FM···FA	
geometrical parameters	Δ*R*	Δ*E*	Δ*R*	Δ*E*
O_1-C_2 (Å)	0.067	3.52	0.054	3.29
C_2-N_3 (Å)	−0.061	1.79	−0.044	1.93
N_3-H_4 (Å)	0.312	29.65	0.200	16.00
$-O_1-C_2-N_3$ (degree)	−16.2	12.68	−0.4	−0.02
$-C_2-N_3-H_4$ (degree)	−44.3	46.52	3.3	0.13

The distortions of the five important geometrical parameters for formation of TS from the reactants FM and FM···FA and the corresponding energy change calculated by variation of the configurations at the MP2/6-311++G** level are presented in Table 4. The data indicate that the most significant factors responsible for a smaller energy barrier in case of FA-assisted tautomerization are the much smaller distortions of the $-O_1-C_2-N_3$ and $-C_2-N_3-H_4$ bond angles and the smaller changes of the N_3-H_4 bond length.

The data in Table 1 also show that the geometric parameters of the TS are quite closer to those of the product FMA···FA. For example, the bond length between the O_1 and H_8 atoms at the TS (1.065 Å) is quite closer to that in the product (0.989 Å) than to that in the reactant (1.689 Å). Similar behavior is also noticed for the bond length between O_5 and H_4 atoms; the values of this parameter in the TS, FMA···FA, and FM···FA are 1.263, 1.013, and 1.938 Å, respectively. The hydrogen bond involving N_3, H_4, and O_5 atoms is not linear in the reactant; the $-N_3-H_4-O_5$ bond angle is 162°. However, the three atoms are nearly collinear ($-N_3-H_4-O_5 \sim 179°$) at the TS and product. Such linearity in hydrogen bond geometry also possibly contributes to larger binding energy in the product (FMA···

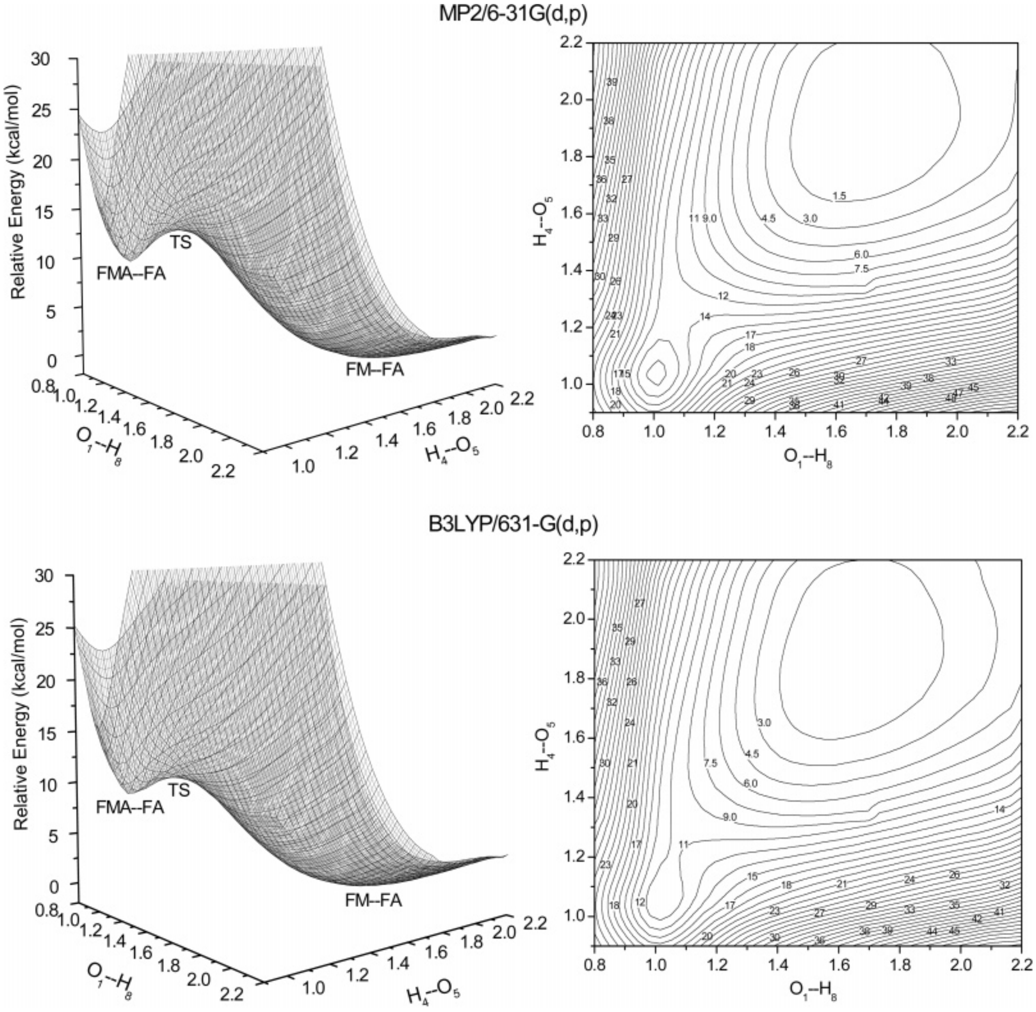

Figure 3. The potential energy surface and the corresponding contour plot as a function of $O_1\cdots H_8$ and $O_5\cdots H_4$ bond lengths. Predictions for both the MP2 and B3LYP calculations are shown.

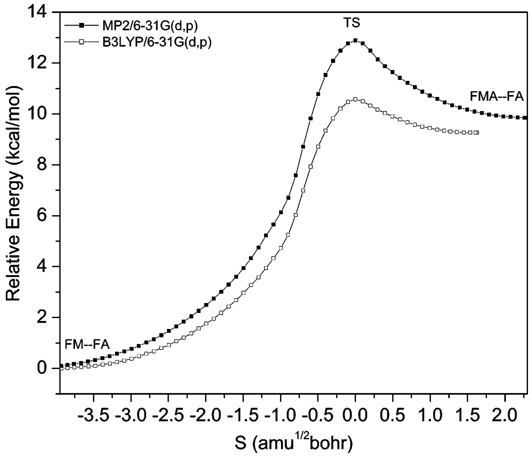

Figure 4. The energy profile of the tautomeric conversion as a function of intrinsic reaction coordinate (S).

FA) than in the reactant (FM···FA). These similarities in geometrical parameters of the TS with the product are reflected also in energetic parameters. In the 1:1 complex, the energy difference between the TS and product is much smaller than that between the TS and reactant (Figure 2).

It has been pointed out before that the predicted barrier for the water-assisted tautomerization is more than a factor of 2 larger than the present case. The reason for such differences can be understood on examining how a few key geometrical parameters in the two systems are affected on transition from the reactant to the respective TS configuration. For example, in the present system, the bond angle $-O_1-C_2-N_3$ (Table 1) has almost the same value in FM···FA, TS, and FMA···FA. In contrast, Table 1 in ref 1 shows that this bond parameter changes from 125° in the reactant complex to 108° in the TS, and in the product it is ∼122°.

Incorporation of zero-point vibrational energies has a large effect on the energetic parameters of the reaction. The predicted changes are summarized in Tables 2 and 3. It shows that the effect is sensitively dependent on the level of calculation. At the MP2/6-311++G** level, the zero-point energy-corrected barrier for the forward reaction is 9.6 kcal/mol. However, for the reverse reaction the barrier is predicted to be only 0.5 kcal/mol.

3B. Potential Energy Surface. The potential energy surface for conversion of FM···FA to FMA···FA has been constructed on the basis of optimized geometries of the above two complexes where we allow the two H-atoms (H_8 and H_4) of the FMA···FA complex in the hydrogen-bonded ($H_8\cdots O_7$ and $H_4\cdots N_3$) interface to move independently starting from a separation of 0.8 Å and scanned up to 2.2 Å with the step size of 0.1 Å in each case. Both MP2 and B3LYP methods have been used with 6-31G** basis set. Except the proton positions, the geometries were fully optimized with respect to all other parameters. The surface thus generated and the corresponding contour plots are presented in Figure 3. The two minima corresponding to the reactants and products and the saddle point corresponding to the TS are clearly shown. The identification of the TS configuration is subjected to IRC calculation and the energy profile as a function of the reaction coordinate is shown in Figure 4. The normal vibrational frequencies corresponding to the three points on the surface have been calculated at the MP2 and DFT levels using 6-31G** basis set. The mode of the TS species having negative frequency has been identified as the reaction coordinate.

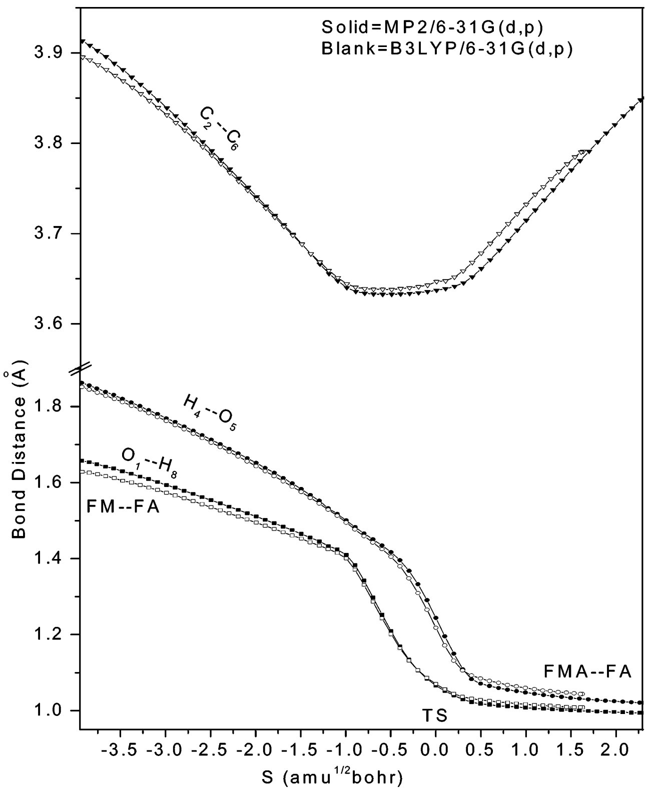

Figure 5. Evolution of the three key geometrical parameters of the 1:1 complex as a function of the intrinsic reaction coordinate (S).

In Figure 5, we have presented how three key internal coordinates evolve as a function of the intrinsic reaction coordinate. The configuration of the TS has been corresponded to the origin of the coordinate system. It shows that the two hydrogen bond distances sharply increase within one unit of the reaction coordinate in the direction of the reactant (FM···FA) side, but in the product (FMA···FA) direction for the same change of the reaction coordinate the O−H distance remains practically unaltered. This happens because of more similarities of the TS with the product. On the other hand, the distance between C_2 and C_6 atoms remains practically the same within one unit of reaction coordinate in the reactant side.

The absence of any other minimum on the potential energy surface indicates that the most favorable mechanism of tautomerization in the ground electronic state is via a concerted hopping of two protons. Sequential proton transfer would generate ionic intermediate. There has been a lot of discussion in recent years concerning sequential versus concerted mechanism for occurrence of double proton transfer in similar systems, for example, 7-azaindole dimer.[30,31] The potential energy surface indicates that ionic configuration does not correspond to any distinct minimum. We have also searched for this possibility (i.e., ionic intermediate) by partially optimizing such configurations using higher basis sets, but frequency calculations never support them to be local minima. A detailed knowledge of the mechanism of such processes in diverse systems is important to understand the tautomerizations in DNA bases, which are thought to be important in point mutations.[32−36]

4. Summary and Conclusion

We have performed an extensive, high-level quantum chemistry theoretical study for the formic acid catalyzd tautomeric conversion of formamide to formamidic acid in a 1:1 molecular complex. Thermodynamically, the process is endothermic, and the predicted energy difference between the two tautomeric forms in the isolated molecule and in the hydrogen-bonded complex with formic acid is 11.6 and 8.7 kcal/mol at the MP2/6-311++G** level of theory. The formic acid catalyzed energy barrier for the conversion of formamide to formamidic acid is predicted to be ~12.5 kcal/mol at the same level of theory, and it is about 4 times smaller compared to the barrier calculated for tautomerization in the isolated molecule. Zero-point energy correction further lowers the barrier to ~9.5 kcal/mol. These energetic and kinetic parameters are quite sensitive to the level of theoretical calculations. However, both the MP2 and the DFT/B3LYP calculations predict almost similar results when a large basis set (6-311++G**) is used. The mechanistic aspects of the process have been investigated by computing the intrinsic reaction coordinate (IRC) for unambiguous location of the TS and a two-dimensional potential energy surface to look for additional local minima with respect to hydrogen transfer coordinates. The results show that in the cyclic hydrogen-bonded network, the tautomeric conversion occurs through a concerted hopping of the two hydrogen atoms.

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References and Notes

(1) Liang, W.; Li, H.; Hu, X.; Han, S. *J. Phys. Chem. A* **2004**, *108*, 10219.

(2) Fu, A. P.; Li, H.; Du, D.; Zhou, Z. *Chem. Phys. Lett.* **2003**, *382*, 332.

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

(4) Bell, R. L.; Taveras, D. L.; Truong, T. N.; Simons, J. *Int. J. Quantum Chem.* **1997**, *63*, 861.

(5) Adalsteinsson, H.; Maulitz, A. H.; Bruice, T. C. *J. Am. Chem. Soc.* **1996**, *118*, 7689.

(6) Pranata, J.; Davis, G. D. *J. Phys. Chem.* **1995**, *99*, 14340.

(7) Puhovski, Y. P.; Rode, B. M. *J. Phys. Chem.* **1995**, *99*, 1566.

(8) Ventura, O. N.; Rama, J. B.; Turi, L.; Dannenberg, J. J. *J. Phys. Chem.* **1995**, *99*, 131.

(9) Engdahl, A.; Nealnder, B.; Åstrand, P. O. *J. Chem. Phys.* **1993**, *99*, 4894.

(10) Wang, X. C.; Facelli, J. C.; Simons, *Int. J. Quantum Chem.* **1993**, *45*, 123.

(11) Wong, M. W.; Wiberg, K. B.; Frisch, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1645.

(12) Kwiatkowski, J. S.; Leszczynski, J. *J. Mol. Struct.* (*THEOCHEM*) **1992**, *270*, 67.

(13) Wang, X. C.; Nichols, J.; Feyereisen, M.; Gutowski, M.; Boatz, J.; Haymet, A. D. J.; Simons, J. *J. Phys. Chem.* **1991**, *95*, 10419.

(14) Lovas, F. J.; Suenram, R. P.; Fraser, G. T.; Gillies, C. W.; Zozom, J. *J. Chem. Phys.* **1988**, *88*, 722.

(15) Kwiatkowski, J. S.; Bartlett, R. J.; Person. W. B. *J. Am. Chem. Soc.* **1988**, *110*, 2353.

(16) Jasien, P. G.; Stevens, W. J. *J. Chem. Phys.* **1986**, *84*, 3271.

(17) Zielinski, T. J.; Poirier, R. A. *J. Comput. Chem.* **1984**, *5*, 466.

(18) Schlegel, H. B.; Gund, P.; Fluder, E. M. *J. Am. Chem. Soc.* **1982**, *104*, 5347.

(19) Li, P.; Bu, Y. *J. Phys. Chem. A* **2004**, *108*, 10288.

(20) Podolyan, Y.; Gorb, L.; Leszczynski, J. *J. Phys. Chem. A* **2002**, *106*, 12103.

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

(22) Hrouda, V.; Florián, J.; Polá×f0ek, M.; Hobza, P. *J. Phys. Chem.* **1994**, *98*, 4742.

(23) Oie, T.; Loew, G. H.; Burt, K. S.; MacElroy, R. D. *J. Am. Chem. Soc.* **1983**, *105*, 2221.

(24) Pullman, A.; Berthod, H.; Giessner-Prettre, C.; Hinton, J. F.; Harpool, D. *J. Am. Chem. Soc.* **1978**, *100*, 3991.

(25) Ottersen, T. *J. Mol. Struct.* **1975**, *26*, 365.

(26) Ottersen, T.; Jensen, H. *J. Mol. Struct.* **1975**, *26*, 375.

(27) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B. et al. *GAUSSIAN 03*, Revision B.05; Gaussian Inc.: Pittsburgh, PA, 2003.

(28) Peng, C.; Ayala, P. Y.; Schlegel, H. B.; Frisch, M. J. *J. Comput. Chem.* **1996**, *17*, 49.

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

(30) 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.

(31) Sakota, K.; Sekiya, H. *J. Phys. Chem. A* **2005**, *109*, 2722.

(32) Löwdin, P. O. *Rev. Mod. Phys.* **1963**, *35*, 724.

(33) Pullman, B.; Pullman, A. *Quantum Biochemistry*; Wiley-Interscience: New York, 1963.

(34) Topal, M. D.; Fresco, J. R. *Nature* **1976**, *263*, 285.

(35) Shi, K.; Wahl, M.; Sundaralingam, M. *Nucleic Acids Res.* **1999**, *27*, 2196.

(36) Hu, X.; Li, H.; Ding, J.; Han, S. *Biochemistry* **2004**, *43*, 6361.