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Proton Transfer of Formamide + nH$_2$O (n = 0−3): Protective and Assistant Effect of the Water Molecule

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The interconversion process from formamide to its enol form formamidic acid (FM → FA) can be regarded as a model for tautomerization of larger nucleic acid bases which may be responsible for the spontaneous point mutation in DNA. The present paper describes a study of structural tautomer interconversion and the relative stabilizing influences of water for formamide−$(H_2O)_n$ and the enol form formamidic acid−$(H_2O)_n$ (n = 0−3), by means of B3LYP exchange and correlation functions. In the vicinity of formamide (FM) and formamidic acid (FA), three different regions are considered. Water in two of them can protect formamide from tautomerizing, while in the third one works oppositely. The protective and assistant effects of water molecules in the same and different regions have been discussed in detail with the number of water molecules increasing. The calculated results offer us a new insight into the structural tautomer interconversion of FM.

1. Introduction

Proton transfer (PT) is a common phenomenon in the chemical and biological sciences[1−7] and it can be viewed as the simplest model of a tautomerization reaction. Formamide contains both carbonyl and amino groups, and despite its simplicity, it contains the essential features of the peptide linkage and often is used as a model,[8−11] especially in theoretical studies, for example, high-level quantum calculations. Moreover, the interconversion process from formamide to its enol form formamidic acid (FM → FA) has been extensively studied previously[12∼18] because it can be regarded as a model for tautomerization of larger nucleic acid bases, in particular connecting the guanine and uracil system.[19∼20] The tautomerization process of the nucleic acids may be responsible for the spontaneous point mutation in DNA.[21]

Early theoretical studies of the tautomerization of FM were focused on the geometric change, relative stability of tautomers, and the energetic stabilization due to the hydrogen bonds in the gas phase or nonaqueous solution.[22] In fact, many structural features that are necessary for the biological functions of biomolecules depend on the interactions with the surrounding water. In the tautomerization process, besides serving as solvent, the water molecule also acts as a "hydrogen bridge", that is, it gives or accepts protons to promote the long-range PT. Simons and co-workers found that the tautomerism of isolated FM → FA has a classical barrier of 52 kcal/mol in the gas phase, while a single molecule lowers the barrier to 26 kcal/mol.[12] Their additional work performed the ab initio dynamics calculations based on a canonical variational transition-state theory and the rate constants of the reaction were given.[13] Kim et al. studied the solvent effect on the PES of the prototropic tautomerization of FM using the SCRF model, and water-assisted and dimer-assisted transitions were compared.[17] Fu et al. studied the superior catalytic effect of $(H_2O)_2$.[18] The works above enhance our perspective on the role of the water molecule in the PT process of FM. However, it is worth noticing that only one site S2 (Figure 1) was studied previously and the extension of several water molecules' effects were not systematically studied. Many of the theoretical investigations on the solvation of formamide pointed out that there were several possible structures for the formamide−water complex, and the water molecule can be placed in S1, S2, and S3[23−27] (Figure 1), respectively. How does H_2O in other sites affect the relative stability of FM and FA? What role do these water molecules play in the tautomerism process? The present work aims at answering these two question and (i) gives precise results of the geometries and energetics of 20 complexes of FM−$(H_2O)_n$ and FA−$(H_2O)_n$ (n = 0−3), (ii) investigates the PT processes from FM−$(H_2O)_n$ to the FA−$(H_2O)_n$ (n = 0−3) and determines some of the transition states in these courses, and (iii) summarize the differences when water molecules are located in different regions in the vicinity of FM and FA.

Figure 1. Preferential regions S1, S2, and S3 for water molecules in the vicinity of FM and FA.

2. Computational Methods

Kim et al. have shown that for FM and FA, DFT, MP2, and HF levels of theory gave similar results as far as the geometrical features were concerned.[17] Therefore, we optimize the structures of FM−$(H_2O)_n$ and FA−$(H_2O)_n$ (n = 0−3) at the cost-effective B3LYP/6-311++G** level of theory. Energy and frequency calculations, as well as zero-point energy (ZPE) correction, have been performed with the same theory. For FM/FA−H_2O, the most reliable QCISD method was used. Energies obtained at the equilibrium geometry of the complex for each subsystem are lower than those calculated at the same geometry with the basis functions of the respective subsystem alone. This so-called basis set superposition error (BSSE) may be important and can

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TABLE 1: Geometrical Parameters of Isolated FM, Fts, and FA

	FM				Fts		FA		
	this work[a]	this work[b]	CCSD(T)/PVTZ[c]	exptl[d]	this work[a]	this work[b]	this work[a]	this work[b]	MP2/6-31G** [d]
bond									
N1−C2	1.361	1.363	1.356	1.352	1.302	1.306	1.263	1.273	1.274
C2=O3	1.212	1.224	1.211	1.219	1.282	1.293	1.347	1.354	1.350
C2−H4	1.103	1.100	1.097	1.002	1.089	1.085	1.091	1.087	1.088
N1−H5	1.010	1.007	1.003	1.002	1.342	1.325			
N1−H6	1.007	1.004	1.000	1.098	1.013	1.010	1.017	1.016	1.016
O3−H5					1.332	1.328	0.970	0.970	0.971[e]
angle									
N1C2O3	121.9	124.5	125.0	124.7	108.6	107.8	122.1	121.8	121.6
C2N1H5	119.5	119.4	112.2	118.5	73.6	73.6			
C2N1H6	121.4	121.3	119.3	120	125.8	125.8	111.6	110.4	110.0
N1C2H4	112.4	112.9	112.2	112.7	128.6	129.0	127.6	127.6	128.1
C2O3H5					74.5	73.9	107.2	106.8	105.4[e]

[a] At the RB3LYP/6-311++G** level. [b] At the QCISD/6-31++G** level. [c] Reference 34. [d] Reference 12. [e] Reference 22.

TABLE 2: Free Energy Changes (kJ/mol) and Activation Energy (kJ/mol) of FM−$(H_2O)_n$ Tautomerism[a]

	ΔG	$\Delta(\Delta G)$[b]	$\Delta G^{\neq}$
FM → FA	51.50[c] 57.28	0	200.53[c] 191.01
FM−W1 → FA−W1	57.80,[c] 61.50 (61.64)	−6.30,[c] 4.22 (4.36)	200.92,[c] 188.67
FM−W2 → FA−W2	47.93,[c] 51.18 (52.60)	−3.57,[c] −6.10 (−4.68)	104.81,[c] 87.10
FM−W3 → FA−W3	62.97,[c] 63.20 (63.31)	11.47[c,] 5.92 (6.03)	210.56,[c] 194.77
FM−2W1 → FA−2W1	66.98 (66.94)	9.70 (9.66)	190.52
FM−2W2 → FA−2W2	48.92 (50.27)	−8.36 (−7.01)	76.41
FM−W1−W2 → FA−W1−W2	56.12 (57.44)	−1.16 (0.16)	88.54
FM−W1−W3 → FA−W1−W3	73.64 (73.61)	16.36 (16.33)	197.07
FM−W2−W3 → FA−W2−W3	56.38 (56.96)	−0.90 (−0.32)	89.84
FM−W1−W2−W3 → FA−W1−W2−W3	61.37 (61.26)	4.09 (3.98)	91.64

[a] Values listed are calculated at the B3LYP/6-311++G** level, including ZPE correction; values in parentheses indicate the free energy changes with BSSE correction, including the E_{FR} terms proposed by Xantheas.[31−35] [b] $\Delta(\Delta G) = \Delta G_{(FM-nW1-mW2\rightarrow FA-nW1-mW2)} - \Delta G_{(FM\rightarrow FA)}$ $(0 \leq n + m \leq 3)$. [c] Values are obtained at the QCISD/6-31++G** level.

TABLE 3: Binding Energies (kJ/mol) of FM/FA to Water Molecules[a]

	ΔE_{BE}^{MW}		ΔE_{BE}^{MW}
FM−W1	−22.40 (−21.10) −22.9[b]	FA−W1	−9.89 (−8.44)
FM−W2	−31.51 (−29.38) −30.9[b]	FA−W2	−39.73 (−36.17)
FM−W3	−17.26 (−14.57) −19.3[b]	FA−W3	−9.46 (−6.66)
FM−2W1	−37.62 (−31.92)	FA−2W1	−23.53 (−17.87)
FM−2W2	−56.62 (−49.11)	FA−2W2	−66.66 (−57.80)
FM−W1−W2	−50.74 (−46.75)	FA−W1−W2	−51.94 (−46.63)
FM−W1−W3	−40.35 (−36.16)	FA−W1−W3	−20.71 (−16.54)
FM−W2−W3	−48.95 (−44.03)	FA−W2−W3	−49.96 (−44.46)
FM−W1−W2−W3	−70.78 (−63.87)	FA−W1−W2−W3	−63.51 (−56.71)

[a] Calculated at the B3LYP/6-311++G** level. [b] Taken from ref 27, calculated at the HF/6-311++G** level with BSSE corrections.

be checked by the Boys and Bernardi's counterpoise procedure (CP),[28−30] taking into account the fragment relaxation energy (E_{FR}) as well.[31−35]

The binding energy of FM/FA to water molecules has been determined by eq 2.1, where subscripts W and bW denote free H_2O and the best cluster containing nH_2O, respectively. A negative value of ΔE_e^{MW} indicates that the molecules interact favorably with the corresponding most stable $(H_2O)_n$ cluster.[36]

$$\Delta E_{BE}^{MW} = E_{M-n(W)} - E_M - \sum E_{n(bW)} \tag{2.1}$$

The natural bond orbital (NBO) analysis was used for a better understanding of the nature of corresponding intermolecular interactions.[21,37] The NBO second-order perturbation stabilization energies $\Delta E_{ij}^{(2)}$ are calculated by eq 2.2. $\hat{F}$ is the Fock operator, and ϵ_i and ϵ_j correspond to the energy eigenvalues of the donor molecular orbital Φ_i and the acceptor molecular orbital Φ_j.[37] In Table 4 we list the significant donor−acceptor NBO intreractions of most complexes we studied.

$$\Delta E_{ij}^{(2)} = 2\frac{|\langle\Phi_i|\hat{F}|\Phi_j\rangle|^2}{\epsilon_i - \epsilon_j} \tag{2.2}$$

All calculations have been performed with the Gaussian 98 program.[38]

3. Results and Discussions

3.1. The Tautomerization Process from Isolate FM to Its Tautomer FA. The optimized geometrical parameters of FM, FA, and the transition state Fts are listed in Table 1. Our results for FM agree well not only with Fogarasi's high-level electron correlation calculations,[39] but also with those obtained by experiments.[12] The optimized geometrical parameters of FA show good agreement with MP2/6-31G** calculations.[12,22] The relative free energy change of the transition from keto form to enol form FM → FA is listed in Table 2. The result shows clearly that the keto form is more stable than the enol form, which had also been pointed out by King using an IR study in the vapor phase in argon matrix.[40]

The transition state Fts (Figure 6) possesses an imaginary frequency 1953i cm^{-1} assigned to a single-proton transfer. The greatest changes of geometrical parameters in the tautomerism process are those relating to N1−C2−O3. The C2−O3 bond lengths of FM, Fts, and FA are 1.224, 1.293 and 1.354 Å, respectively. It is worth noticing that, to reach Fts, ∠N1C2O3 becomes flexural from 124.5 → 107.8 → 121.8. Such great

TABLE 4: Some Significant Donor−Acceptor Natural Bond Orbital Interaction of Fm, FA, and Water Molecules and Their Second-Order Pertubation Stabilization Energy $\Delta E^{(2)}$ [a]

	donor	acceptor	$\Delta E^{(2)}$ (kJ/mol)
FM−W1	LP(1)O3	BD*(1)O(W1)−H(W1)	6.69
	LP(2)O3	BD*(1)O(W1)−H(W1)	30.93
FA−W1	LP(1)O3	BD*(1)O(W1)−H(W1)	9.53
FM−W2	LP(1)O3	BD*(1)O(W2)−H(W2)	7.23
	LP(2)O3	BD*(1)O(W2)−H(W2)	29.68
	LP(2)O(W2)	BD*(1)N1−H5	19.27
FA−W2	LP(1)N1	BD*(1)O(W2)−H(W2)	44.27
	LP(2)O(W2)	BD*(1)O3−H5	63.37
FM−W3	LP(2)O(W3)	BD*(1)N1−H6	28.01
FA−W3	LP(2)O(W3)	BD*(1)N1−H6	18.18
FM−W1−W3	LP(1)O3	BD*(1)O(W1)−H(W1)	9.11
	LP (2)O3	BD*(1)O(W1)−H(W1)	35.53
	LP(2)O(W3)	BD*(1)N1−H6	32.35
FA−W1−W3	LP(1)O3	BD*(1)O(W1)−H(W1)	16.51
	LP(2)O(W3)	BD*(1)N1−H6	19.86
FM−W1−W2	LP(1)O3	BD*(1)O(W1)−H(W1)	7.40
	LP(2)O3	BD*(1)O(W1)−H(W1)	28.59
	LP(1)O3	BD*(1)O(W2)−H(W2)	7.36
	LP(2)O3	BD*(1)O(W2)−H(W2)	22.95
	LP(2)O(W2)	BD*(1)N1−H5	22.07
FA−W1−W2	LP(1)O3	BD*(1)O(W1)−H(W1)	13.79
	LP(1)N1	BD*(1)O(W2)−H(W2)	43.01
	LP(2)O(W2)	BD*(1)O3−H5	72.06
	BD(1)O(W2)−H(W2)	BD*(1)O3−H 5	4.35
FM−W2−W3	LP(1)O3	BD*(1)O(W2)−H(W2)	8.65
	LP(2)O3	BD*(1)O(W2)−H(W2)	36.74
	LP(2)O(W2)	BD*(1)N1−H5	15.05
	LP(2)O(W3)	BD*(1)N1−H6	29.8
FA−W2−W3	LP(1)N1	BD*(1)O(W2)−H(W2)	57.48
	LP(2)O(W2)	BD*(1)O3−H5	55.89
	LP(2)O(W3)	BD*(1)N1−H6	18.06
FM−W1−W2−W3	LP(1)O3	BD*(1)O(W1)−H(W1)	10.45
	LP(2)O3	BD*(1)O(W1)−H(W1)	31.39
	LP(1)O3	BD*(1)O(W2)−H(W2)	9.28
	LP(2)O3	BD*(1)O(W2)−H(W2)	27.84
	LP(2)O(W2)	BD*(1)N1−H5	17.64
	LP(2)O(W3)	BD*(1)N1−H6	32.06
FA−W1−W2−W3	LP(1)O3	BD*(1)O(W1)−H(W1)	19.65
	LP(1)N1	BD*(1)O(W2)−H(W2)	52.38
	LP(2)O(W2)	BD*(1)O3−H5	68.59
	LP(2)O(W3)	BD*(1)N1−H6	18.56
	BD(1)O(W2)−H(W2)	BD*(1)O3−H5	4.35

[a] NBO analyses were at the B3LYP/6-311++G** level. BD denotes the occupied bond orbital, and BD* denotes the formally empty antibonding orbital. LP denotes the occupied lone pair. The interaction type between LP−BD* belongs to n−σ*, and that between BD−BD* belongs to σ−σ*.

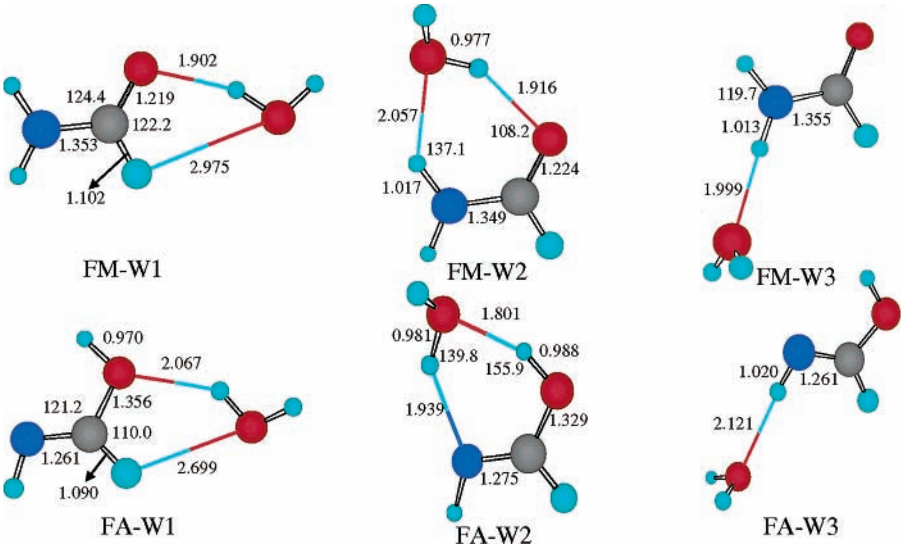

Figure 2. Optimized structures of monohydrated formamide and formamidic acid with water in regions S1, S2, and S3. The number values refer to bond lengths (in Å) and bond angles (in deg).

geometric variations make the proton transfer difficult,[18] which has been proved by the high barrier of 200.53 kJ/mol at the QCISD/6-31++G** level.

3.2. The Tautomerism Process of Formamide−(H$_2$O)$_n$ to Formamidic Acid−(H$_2$O)$_n$ (n = 1−3).

In the vicinity of FM/FA, S1, S2, and S3 (Figure 1) are all favorable regions for water

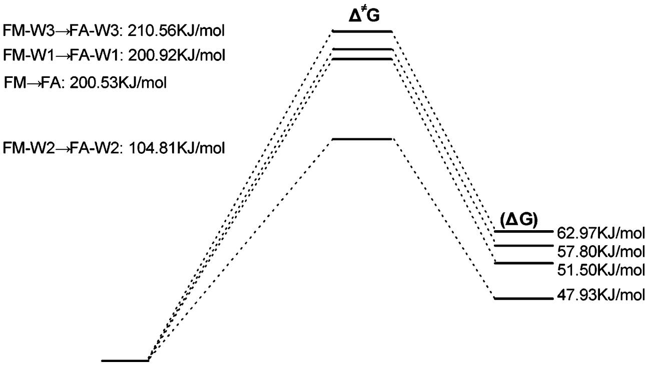

Figure 3. Relative potential energy profiles based on calculations at the QCISD/6-31++G** level of theory including zero-point corrections.

molecules, which can be demonstrated by the negative values of the binding energy presented in Table 3. We consider water as an H-bond acceptor and donor via the interactions occurring through its oxygen or hydrogen atoms, respectively, because the relevant structure is energetically favored over the alternative double donor or double acceptor hydrogen bonding.[41,42]

In the following part, we adopted energy change to investigate the role of water in the tautomerism process. The energetic perspective has been successfully used to study spontaneous DNA mutation induced by proton transfer.[21,43~44] Values obtained in the present BSSE corrections are in almost the same order as those without BSSE emendation (Table 2). We will focus on the results with BSSE corrections.

3.2.1. The Tautomerism of Monohydrate-FM. In this part, a single water molecule has been placed in S1, S2, and S3, respectively. The corresponding configurations were optimized (Figure 2). The free energy changes and activation energies are listed in Table 2. The relative order of activation energy obtained from DFT and QCISD methods is different. It is considered that DFT calculations may underestimate the potential energy barrier,[17] and the QCISD results are more reliable.

When a single water molecule W1 is located in S1, it can protect the FM from tautomerizing to FA. As shown in Figure 2, W1 acts as an H-bond donor as well as a weak H-bond acceptor,[27] which can also be concluded by our NBO analyses. Comparing with isolated FM and FA, C2−O3 bonds in both FM−W1 and FA−W1 are lengthened; however, C2−H4 is not obviously changed because the interaction between H4 and W1 is a bit weak. Comparing with FM → FA, the free energy change becomes 4.36 kJ/mol larger, and the activation energy is also higher (Table 2). This indicates that the transition process is more difficult than the isolated FM both thermodynamically and dynamically. We can go deeper into this question by NBO analysis, which has been demonstrated as a powerful tool for examining hydrogen bonding. The comparison of $\Delta E_{ij}^{(2)}$ of FM−W1 and FA−W1 shows that the hydrogen bonds between FM and W1 are stronger, which makes the FM−W1 complex more stable, so that the transition process is difficult.

On the other hand, the water molecule in S2 provides facile interconversion routes between tautomers and assists in the tautomerization process. Comparing with isolated FM → FA, it is a double-proton transfer. W2 lowers ΔG by 4.68 kJ/mol, and the activation energy falls drastically to 104.81 kJ/mol. NBO results show that the electronic structure changed a lot during the tautomerization reaction, which has also been pointed out by Wang et al.[12] However, the comparison of $\Delta E_{ij}^{(2)}$ between FM−W2 and FA−W2 shows that FA becomes more stable by W2's hydrogen bonding. Hence, FA−W2 is more structurally favored and the transition occurs more easily.

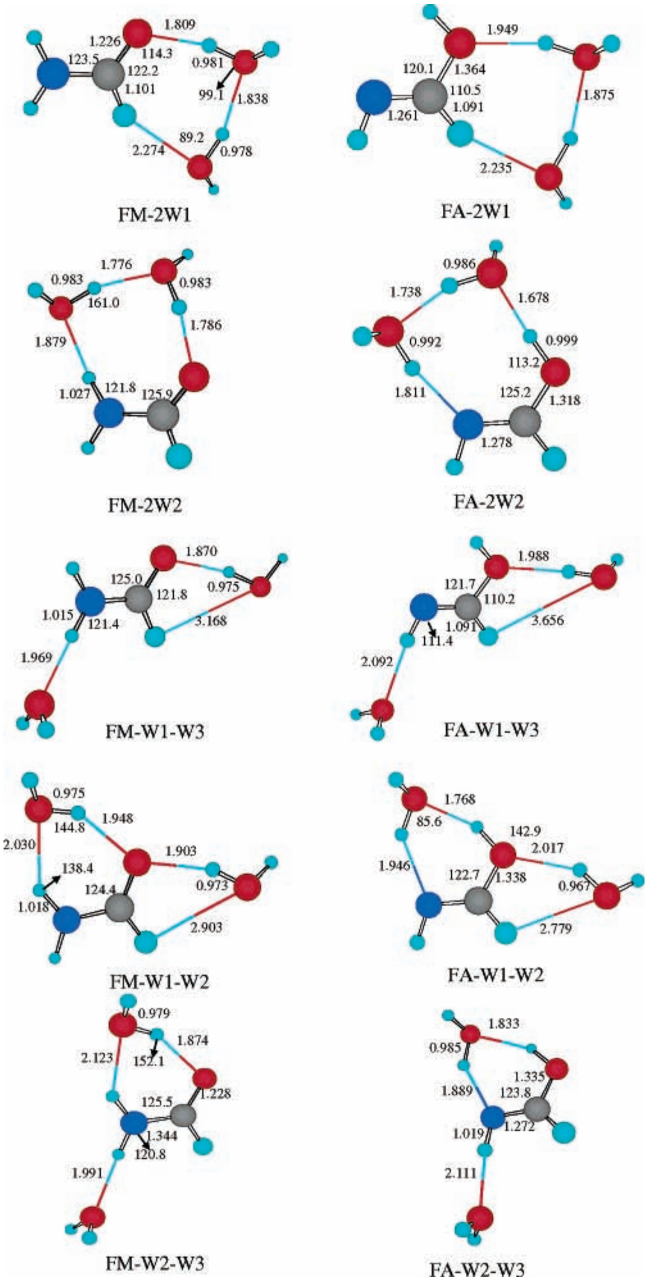

Figure 4. Optimized structures of dihydrated formamide and formamidic acid with water molecules. The number values refer to bond lengths (in Å) and bond angles (in deg).

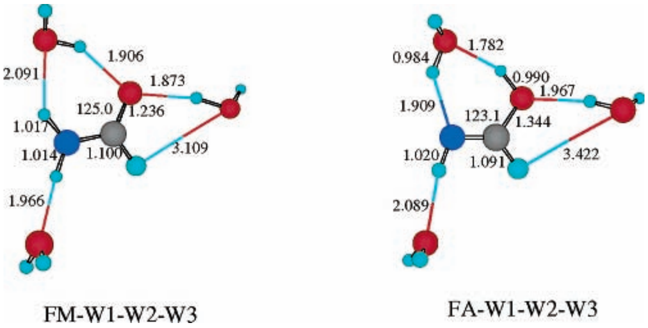

Figure 5. Optimized structures of trihydrated formamide and formamidic acid with water molecules. The number values refer to bond lengths (in Å) and bond angles (in deg).

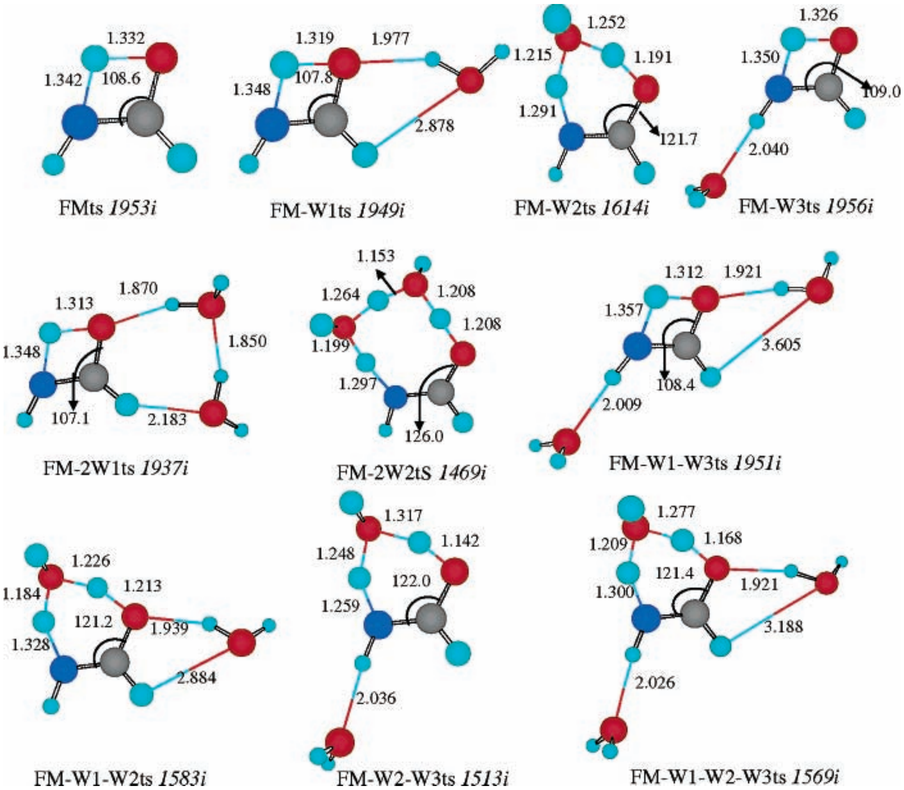

Figure 6. The optimized structures of the transition states of the transition process at the B3LYP/6-311++G** level. The number values refer to bond distances (in Å) and intramolecular angles (in deg). Italic numbers are the corresponding imaginary frequencies of the transition states.

The water molecule in S3 also can play a protective role as W1, and its protective effect is even higher. There is only one hydrogen bond N1−H6···O(W3) in the FM/FA−W3 complexes. The ΔG of FM−W3 → FA−W3 is 6.03 kJ/mol higher than that of FM → FA, even 1.67 kJ/mol higher than that of FM−W1. The active energy of FM−W3 → FA−W3 is 10.03 kJ/mol higher than that of FM−W1 → FA−W1 (Table 2). It reveals that water in S3 possesses a greater protective ability.

To sum up, the relative order of the equilibrium constant for the transition is FM−W2 → FA−W2 > FM → FA > FM−W1 → FA−W1 > FM−W3 → FA−W3, and the corresponding reaction speed is exactly in the same order. We presented a profile of potential energy changes induced by the water molecule in different regions in Figure 3. We can tell from the figure that compared with the transition process of isolated FM, W1 and W3 can protect FM from transition to FA both on thermodynamics and dynamics, whereas W2 works contrarily.

3.2.2. The Tautomerism of Dihydrate-FM. In this part we introduce another water molecule to study the transition from FM−(H$_2$O)$_2$ to FA−(H$_2$O)$_2$. Totally 10 different configurations were optimized (Figure 4). The relative free energy change and activation energy are also listed in Table 2.

When a water monomer is replaced by a water dimer in S1, considerable shortening of C2═O3····H(W1,upper) and C2−H4···O(W1,lower) hydrogen bonds and reasonable lengthening of the C2−O3 bond are observed. The water dimer located in S1 reinforces the protection effect of the tautomerism from FM to FA, which can be proven by the increment of the free energy change by 9.66 kJ/mol. $\Delta(\Delta G)$ induced by the water dimer is larger than the double $\Delta(\Delta G)$ induced by the water monomer in S1. This suggests that there is a cooperative protection effect between the two water molecules.

Similarly, when a water dimer is put in S2, hydrogen bonds between water molecules and FM/FA become shorter, whereas the C2−O3 bonds are not changed much. The water dimer also involves the transition process: it is a triproton transfer via a transition state FM−2W2ts, which possesses an imaginary frequency of 1469i cm^{-1} (Figure 6). The $\Delta(\Delta G)$ is −7.01 kJ/mol, whcih is much less than the double $\Delta(\Delta G)$ value induced by the water monomer in the same region. Therefore, we may conclude that the two waters in S2 assist in the tautomerization process anti-cooperatively. The variation of ∠N1C2O3 is very small, 125.9° → 126.0° → 125.2°. Accordingly, the activation energy is very low.

When two water molecules are put in two protection sites S1 and S3, respectively, the proton-transfer process is a single proton transfer, and the $\Delta(\Delta G)$ is 16.33 kJ/mol, whcih is 5.94 kJ/mol larger than the sum of that of FM−W1 → FA−W1 and FM−W3 → FA−W3. Moreover, it is interesting to find that the $\Delta E_{ij}^{(2)}$ of the primary interactions in FM−W1−W3 are all larger than the corresponding one in FM−W1 and FM−W3. This can explain why the protective effect is cooperatively reinforced to some extent. The activation energy of FM−W1−W3 → FA−W1−W3 is 6.06 kJ/mol larger than that of the FM → FA at the B3LYP/6-311++G** level, which means the tautomerization process becomes slow because of the influence of W1 and W3's.

For FM−W1−W2 and FM−W2−W3, the complexes contain both a protective and an assistant water molecule. Because of the participation of W2, proton-transfer processes of the two complexes are both double proton transfer. The NBO analyses indicate that the double proton transfer processes are complicated: some interactions we listed are attenuated and some are strengthened. Without BSSE correction, the $\Delta(\Delta G)$ of both FM−W1−W2 → FA−W1−W2 and FM−W2−W3 → FA−W2−W3 are negative; however, comparing with the double proton transfer FM−W2 → FA−W2, the negative extent is lessened nevertheless, specifically, ΔG of FM−W1−W2 → FA−W1−W2 is 4.84 kJ/mol more positive than that of FM−

W2 → FA−W2, and for FM−W2−W3 → FA−W2−W3, it is 4.36 kJ/mol larger than that of FM−W2 → FA−W2. When BSSE corrections are present, the $\Delta(\Delta G)$ of FM−W1−W2 → FA−W1−W2 even becomes positive. Simultaneously, the activation energies of these two clusters' transitions are all higher than that of the FM−W2. All the above suggest that for the double proton transfer process the protective effect induced by W1 and W3 can never be ignored.

3.2.3. The Tautomerism of Trihydrate-FM. The free energy change of FM−W1−W2−W3 → FA−W1−W2−W3 is 8.66 kJ/mol higher than that of FM−*W*2 → FA−W2, but 12.35 kJ/mol lower than that of FM−W1−W3 → FA−W1−W3 (Table 2). The active energy changes present the same variation trend. This comparison highlights the protective effect of W1 and W3 and the assistant effect of W2 for the complex's tautomerization process. It indicates that the transition process is a collaborative result for all the impacts induced by the water molecules in different sites. The positive $\Delta(\Delta G)$ suggests that FM in this molecular cluster prefers to stay in its keto form rather than isolated FM. It is reasonable because both W1 and W3 protect against this process, but only W2 assists in the tautomerization.

4. Conclusions

To investigate the structural tautomer interconversion of formamide induced by proton transfer, we have studied the interaction of FM/FA with (water)$_n$ ($n = 0-3$). Eighteen complexes of formamide tautomers with water molecules have been chosen for this purpose. On the basis of the results obtained from our calculations, the following can be stated: (1) There are three different sites in the vicinities of formamide for water molecules. In S1 and S3, water molecules can protect FM from tautomerizing to FA, whereas water molecules in S2 can assist in the tautomerism from FM to FA. These results are credible from both the thermodynamics and dynamics perspective. (2) As the number of water molecules located in S1 increases to 2, the protection ability that avoids tautomerization is reinforced. Simultaneously, the two water molecules in S1 or S3 show a cooperative effect to some extent. When a water dimer is located in S2, the assistive effect on the tautomerism is strengthened; however, the two water molecules may work anticooperatively. (3) For FM−W2−W3, the protective effect induced by W3 plays the subordinate role. However, FM−W1−W2−W3's tautomerizaiton becomes more difficult than isolated FM, FM−W1−W2, and FM−W2−W3, because W1 together with W3 get the upper hand rather than W2. The results obtained here allow us to have a new insight into the structural tautomer interconversion of formamide and may extend to nucleic acids induced by proton transfer. Such a phenomena for water molecules in different regions of formamide having stabilization or mutagenicity on formamide could provide an incentive for future development of research on the tautomerism of nucleic acid and related gene mutation.

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Supporting Information Available: The *Z*-matrix of calculated results. This material is available free of charge via the Internet at http://pubs.acs.org.

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