

Quantum Mechanical Studies for Structures and Energetic of Double Proton Transfer in Biologically Important Hydrogen-bonded Complexes

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We have performed quantum mechanical calculations to study the geometries and binding energies of biologically important, cyclic hydrogen-bonded complexes, such as formic acid + H₂O, formamidine + H₂O, formamide + H₂O, formic acid dimer, formamidine dimer, formamide dimer, formic acid + formamide, formic acid + formamidine, formamide + formamidine, and barrier heights for the double proton transfer in these complexes. Various *ab initio*, density functional theory, multilevel methods have been used. Geometries and energies depend very much on the level of theory. In particular, the transition state symmetry of the proton transfer in formamidine dimer varies greatly depending on the level of theory, so very high level of theory must be used to get any reasonable results.

Key Words : Double proton transfer, Tautomerization, Hydrogen-bonded complex, Asynchronous mechanism, Multilevel

Introduction

Proton transfer is one of the simplest and the most fundamental reaction in chemistry and biology. Proton transfer involving many protons is also an important phenomenon. Most multiproton transfers occur, either concertedly or stepwise, through a hydrogen-bonded chain. A proton relay is thought to account for the high mobility of the proton in water. There are many examples of multiproton transfer such as proton relay systems in enzymes, certain proton transfers in hydrogen-bonded water complexes, and proton transfers in prototropic tautomerisms. H-bonding complexes of formic acid (FA), formamide (FM), and formamidine (FN), such as FA-water, FM-water, and FN-water, can serve as model systems for protein-water and protein-solvent interactions. Due to the simplicity of this model, the characterization of the hydrogen-bonding interactions between water and FA, FM, and FN, and prototropic tautomerization in these complexes have been of considerable interest to experimentalists and theoreticians.

FA dimer is one of the most extensively studied systems both experimentally and theoretically, since it is one of the simplest examples of a multiproton transfer system in which the constituents are held together by two hydrogen bonds. Therefore, it can be used as a model of many chemically and biologically important multiproton transfers. 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.¹ 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. The dynamics of double proton transfer (DPT) in FA dimer¹ has been studied.

DPT occurs in DNA base pair such as the adenine-thy-

mine base pair. In the hydrogen-bonding sites of thymine, uracil, cytosine, and guanine, and the amide and amidine hydrogen bonds are involved in the structure and function of DNA and RNA. Since such biological molecules are too large to be treated by highly accurate *ab initio* methods, FM-FM and FN-FN dimers can be used as the smallest model system to understand the local characteristics of H-bonding interactions and tautomerization. Limbach *et al.*² have studied the DPT in prototropic tautomerisms for many amidine systems and porphyrins using the dynamic NMR technique. They reported rates and the kinetic isotope effects for both concerted and stepwise DPT. Proton transfers in FN dimer can also be considered a prototype of multiproton transfer to provide information about hydrogen bonding, as well as the proton relay mechanism in enzymes. The prototropic tautomerization of FN has also been studied by several workers since it is important in proteins and can be used as a model for tautomerization in nucleic acid bases.^{3,4} In addition to serving as a model for hydrogen transfer reactions in bases of nucleic acids, FN has been extensively studied theoretically since it also forms homodimers and hydrogen bonds with water. The mechanism of DPT in this dimer greatly depends on the method and the presence of a polar surrounding. At the HF level, the protons are transferred concertedly through a transition state possessing *C*_{2v} symmetry in the gas phase,⁵ however at the B3LYP level, the protons are transferred concertedly with the *D*_{2h} symmetry of the transition state. The dynamics of DPT in monohydrated formamidine has been studied,⁶ which showed that the barrier height depends greatly on the computational level and the size of the basis set.

The interaction of amidines with carboxylic acids is of significant biological importance as a consequence of the presence of the amidine (more specifically, guanidine) moiety in arginine, which may serve as binding sites for carboxylic

acids in enzyme. The DPT in FA-FN complex occurs asynchronously through an intermediate.⁷ 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) depends very much on the computational level. The DPT in FM dimer occurs concertedly. However, 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.⁴ 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. The DPT in the FI-FA complex is probably the least studied. Podolyan *et al.*⁸ suggested that the DPT occurs concertedly and asynchronously.

Many theoretical studies with *ab initio* quantum chemical methods at various levels have been carried out to predict the structures of the cyclic hydrogen-bonded complexes and the potential energy surface for the various double proton transfer processes. Hobza *et al.*⁹ have studied the potential energy surface (PES) for DPT in the adenine-thymine base pair using various computational methods. They have reported that the character of the PES, such as the barrier for the DPT, strongly depends on the theoretical level of calculation: the size of the basis set and the inclusion of correlation energy.

Most of the theoretical studies have focused on the geometric change, relative stability of tautomers, and the energetic stabilization due to the hydrogen bonds, and barrier height of the tautomerization in the gas phase. They play a key role in determining the structure and function of biomolecules, such as proteins and nucleic acids. Therefore it is necessary to determine the geometries and energetic of hydrogen-bonded systems accurately in order to quantify their impact on biological systems. Density functional theory (DFT) has been successfully applied to the reliable predictions of the geometries and stabilization energies of some hydrogen-bonded complexes. MP2 theory can account for the full range of intermolecular interactions: electrostatic, induction and dispersion effects. However, recent studies suggested that a very large basis set is required to study interactions of hydrogen-bonded complexes with MP2 level.¹⁰ Such large basis sets, however, are practically impossible to use for biological molecules. In the present study, a systematic study of hydrogen-bond interactions at selected quantum mechanical (QM) levels of theory is performed including DFT, MP2, and recently developed multilevel methods. Comparison is made with available experimental data and previously reported high level QM calculations.

Computational Methods

All electronic structure calculations were done using the Gaussian 03 quantum mechanical packages.¹¹ Geometries for FA-H₂O, FM-H₂O, FN-H₂O, FA-FA, FM-FM, FN-FN, FA-FM, FA-FN, FM-FN, and transition state (TS) for the DPT were optimized. Computational methods include MP2,

CCSD, B3LYP, BH&HLYP, MPW1K, M06-2X, BMC-CCSD, MC-QCISD,¹² MC3BB, MC3MPW,¹³ MCCM-UT-CCSD, and MCCM-UT-MP4SDQ.¹⁴ The basis sets used in this study include 6-31G(d,p), 6-311G(d,p), 6-31+G(d,p), 6-311+G(d,p), cc-pVTZ, aug-cc-pVDZ, aug-cc-pVTZ, and G3Large. All of the multicoefficient correlated quantum mechanical methods have been described elsewhere in detail.^{12,14} The multilevel structure, energy, and Hessian are calculated by using the Multilevel 4.0 program.¹⁵ The BMC-CCSD calculation is performed using the Mlgauss 2.0 program.¹⁶

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

$$BSSE = 2[E_m(M) - E_d(M')] + E_{reorg} \quad (1)$$

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

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 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 which 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:

$$\begin{aligned} E_d(\text{corr}) &= E(D) - 2E_m(M) + BSSE \\ &= E(D) - 2E_d(M') + E_{reorg} \end{aligned} \quad (3)$$

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

Results and Discussion

Optimized structures of FA-H₂O, FM-H₂O, FN-H₂O, FA-FA, FM-FM, FN-FN, FA-FM, FA-FN, and FM-FN were depicted in Figures 1-3, and the formation energies of cyclic H-bonded complexes were listed in Table 1. The H-bond distances depend on the level of theory and the size of the basis sets. It is clear that the linear H-bonds are shorter than the bent ones. The H-bonds made of acidic O-H in FA were quite short, which means that these H-bonds are quite strong. The H-bonds OH...N in the FA-FN complex is the shortest, and therefore the strongest.

Recently, BMC-CCSD, MC3BB, and MC3MPW method gives the best performance to predict structures and energetic for chemical reaction of small molecular system,¹⁷ therefore, the formation energies at the BMC-CCSD level were used as a benchmark in this study. All MP2 levels overestimated the formation energies of all cyclic complexes. The M06-2X values agreed very well with the BMC-

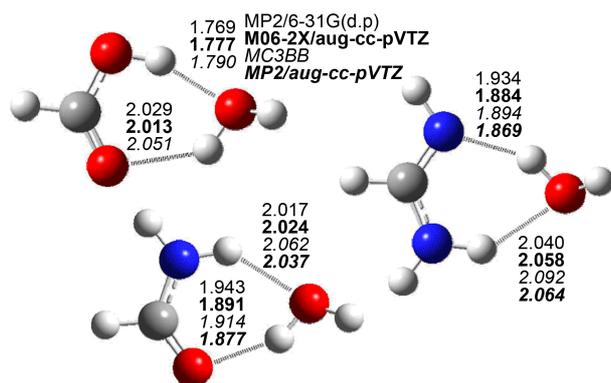


Figure 1. Optimized cyclic hydrogen-bonded structures for FA-H₂O, FN-H₂O, and FM-H₂O. The MP2/aug-cc-pVTZ results were from ref. 25.

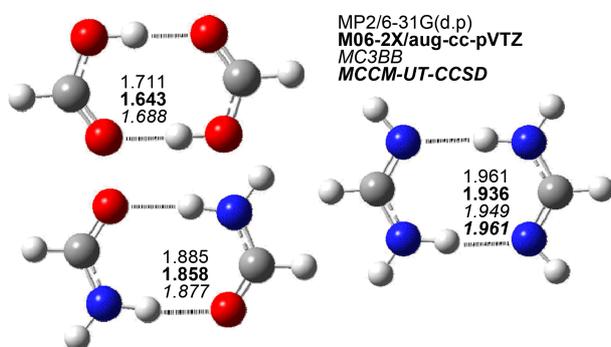


Figure 2. Optimized cyclic hydrogen-bonded structures for FA-FA, FN-FN, and FM-FM.

CCSD within 1 kcal/mol except two values for the FN-FN complex. The MCCM-UT-CCSD method was used very successfully to reproduce structures and H-bond energies of water dimer and HF dimer,¹⁸ which agreed quite well with the BMC-CCSD. The complex formation energies of mono-

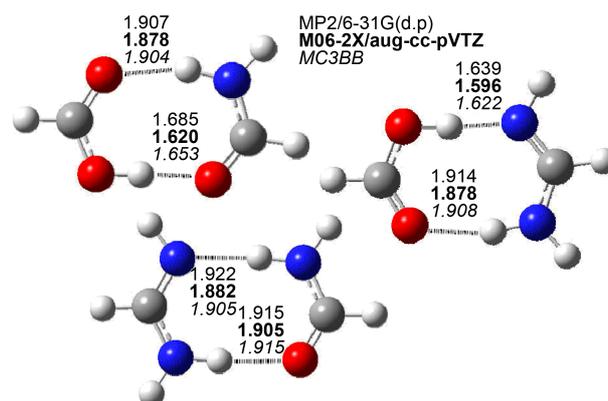


Figure 3. Optimized cyclic hydrogen-bonded structures for FA-FM, FA-FN, and FN-FM.

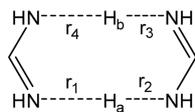
hydrate are in the range of -10.4 and -11.5 kcal/mol, whereas those of homo-dimer and hetero-dimer are in the range of -15.2 and -18.8 kcal/mol. The strongest complex formation energy is for the FA-FN dimer due to the strong H-bonds between acid and base. The FA and FM dimers were used as a reference in the database of H-bonded complexes, so the structures and complex formation energies have been studied extensively.¹⁹⁻²⁴ The best estimate of the formation energy was at the CCSD(T) level with complete basis set (CBS) limit, which are -18.61 and -15.96 kcal/mol for FA-FA and FM-FM complexes, respectively. However, deformation energies of monomer were not included in these calculations, which act as a repulsive interaction to give smaller (less negative value) formation energies.

The TS structures of DPT for the water-assisted and dimer assisted tautomerization were depicted in Figures 4-6, and the barrier heights were listed in Table 2 except for the FN-FN complexes. The TS structures of monohydrated complexes (Fig. 4), FA-H₂O and FN-H₂O, have C_s symmetry. In the FA-H₂O complex, the H-bond with water oxygen is

Table 1. Formation energies (in kcal/mol) of cyclic hydrogen-bonded complexes

	FA-H ₂ O	FM-H ₂ O	FN-H ₂ O	FA-FA	FM-FM	FA-FM	FA-FN	FM-FN
MP2/6-31G(d,p)	-13.90	-12.83	-13.47	-18.13	-17.17	-18.23	-20.35	-16.69
G3*(without ZPE)	-10.27	-9.59	-10.44	-16.27	-14.87	-16.15	-18.28	-14.74
MCCM-UT-CCSD//MP2/6-31G(d,p)	-10.03	-10.48	-10.48	-15.71	-14.53	-15.76	-17.55	-14.18
MC3BB	-9.92	-10.08	-10.08	-15.00	-13.05	-14.64	-17.24	-13.12
MC3MPW	-10.61	-10.89	-10.89	-16.33	-14.17	-15.88	-18.86	-14.38
M06-2X/6-31+G(d,p)	-11.62	-10.97	-12.02	-16.29	-14.49	-16.18	-19.48	-14.73
M06-2X/cc-pVTZ	-11.08	-10.15	-10.90	-16.59	-14.21	-16.11	-18.41	-14.05
M06-2X/aug-cc-pVTZ	-11.09	-10.36	-11.19	-16.78	-14.48	-16.32	-18.83	-14.31
BMCCSD//M06-2X/aug-cc-pVTZ	-10.85	-10.36	-11.50	-16.83	-15.22	-16.57	-18.88	-15.44
B97d/TZV(2df,2pd) ¹⁹				-18.89	-15.86			
CCSD(T)/CBS ^{22,a}				-18.61	-15.96			
W1 ²⁴				-16.15	-14.94			
CCSD(T)/aug-cc-pVDZ//RI-MP2/TZVPP ²¹				-16.41	-14.13			-14.23
CCSD(T)/cc-pVTZ//RI-MP2/TZVPP ²¹				-17.28	-14.45			-14.77
MP2/cc-pV5Z//MP2/DZ(d,p) ²³					-15.77			
MP2/cc-pVQZ ²⁰					-16.26			

^aDeformation energy is not included

Table 3. Formation energies, potential energy barriers (in kcal/mol), and some geometrical parameters (in Å) for the TS of formamidine dimer at various levels of theory

	E_d	V^\ddagger	TS				TS Symm
			r_1	r_2	r_3	r_4	
MP2/6-31G(d,p)	-15.68	14.98	1.280	1.280	1.280	1.280	D_{2h}
MP2/6-311G(d,p)	-15.05	15.29	1.281	1.281	1.281	1.281	D_{2h}
MP2/6-31+G(d,p)	-14.09	15.28	1.394	1.188	1.188	1.394	C_{2v}
MP2/6-311+G(d,p)	-13.61	14.64	1.355	1.218	1.217	1.355	C_{2v}
MP2/aug-cc-pVDZ	-15.44	13.21	1.374	1.210	1.210	1.355	C_{2v}
MP2/cc-pVTZ	-15.29	13.65	1.293	1.268	1.268	1.293	C_{2v}
MP2/TZ2P	-14.22	14.96	1.434	1.165	1.165	1.434	C_{2v}
B3LYP/6-31G(d,p)	-16.64	11.69	1.288	1.288	1.288	1.288	D_{2h}
B3LYP/6-31+G(d,p)	-13.55	12.41	1.355	1.231	1.231	1.355	C_{2v}
B3LYP/aug-cc-pVTZ	-12.71	13.68	1.422	1.184	1.184	1.422	C_{2v}
B3LYP/G3Large	-12.77	13.52	1.410	1.190	1.190	1.410	C_{2v}
BH&HLYP/6-31G(d,p)	-16.16	15.53	1.277	1.277	1.277	1.277	D_{2h}
BH&HLYP/6-31+G(d,p)	-13.79	15.85	1.279	1.279	1.279	1.279	D_{2h}
MPW1K/6-31G(d,p)	-17.01	11.97	1.275	1.275	1.275	1.275	D_{2h}
MPW1K/6-31+G(d,p)	-14.92	12.57	1.276	1.276	1.276	1.276	D_{2h}
M06-2X/6-31+G(d,p)	-14.20	10.93	1.285	1.285	1.285	1.285	D_{2h}
M06-2X/cc-pVTZ	-13.36	12.42	1.286	1.286	1.286	1.286	D_{2h}
M06-2X/aug-cc-pVTZ	-13.66	12.53	1.286	1.286	1.286	1.286	D_{2h}
MC-QCISD	-13.35	15.99	1.478	1.140	1.140	1.476	C_{2v}
MCCM-UT-MP4SDQ	-13.26	16.27	1.448	1.147	1.147	1.448	C_{2v}
MCCM-UT-CCSD	-12.20	15.16	1.447	1.149	1.149	1.447	C_{2v}
MC3BB	-12.63	14.37	1.400	1.182	1.182	1.400	C_{2v}
MC3MPW	-14.02	12.59	1.318	1.242	1.242	1.318	C_{2v}
BMCCSD//M06-2X/aug-cc-pVTZ	-15.18	15.69					
MP2/cc-pV5Z//MP2/DZ(d,p) ²³	-16.32						
CCSD(T)/aug-cc-pVDZ//RI-MP2/TZVPP ²¹	-13.70						
CCSD(T)/cc-pVTZ//RI-MP2/TZVPP ²¹	-14.37						

The transition structure of FN dimer depends very much on the computational level and the size of the basis set. The N-H bond distances and symmetry of the TS, formation energies, and the barrier heights were listed in Table 3. No intermediate was found at all level of theory, which means that the DPT occurs in a concerted mechanism. The complex formation energies also depend very much on the computational level. In general, the formation energy decreased (became less negative) with increasing the size of the basis set. It is very interesting that the TS symmetry depends very much on the computational level. The D_{2h} and C_{2v} symmetry of TS results from the synchronous and asynchronous mechanism of DPT, respectively, thus, the predicted DPT mechanism depend very much on the computational level. At the MP2 level using 6-31G(d,p) and 6-311G(d,p) basis sets, D_{2h} symmetry of TS was predicted, but C_{2v} symmetry was predicted by adding diffuse functions. Using aug-cc-pVDZ, cc-pVTZ, and TZ2P basis sets, D_{2h} symmetry was predicted again. DFT methods, namely, BH&HLYP, MPW1K, M06-2X, predicted D_{2h} symmetry of TS. Only B3LYP with

6-31+G(d,p), aug-cc-pVTZ, and G3Large basis sets predicted C_{2v} symmetry. It is very important to obtain correct TS structure for the reaction dynamics of tautomerization. Interestingly, all multilevel methods predicted C_{2v} symmetry, so it is more likely that the DPT occurs *via* an asynchronous mechanism.

The change in the TS structure can be understood clearly by monitoring the correlation between the hydrogen bond length and the proton transfer coordinate. The correlation plot between the hydrogen bond length and the proton transfer coordinate is shown in Figure 7. Limbach *et al.*⁴⁴⁻⁴⁶ defined the hydrogen bond coordinates $q_1 = (1/2)(r_{AH} - r_{BH})$ and $q_2 = r_{AH} + r_{BH}$ to represent the correlation between r_{AH} and r_{BH} in many hydrogen-bonded complexes (A-H...B). For a linear H-bond, q_1 represents the distance of H from the H-bond center and q_2 represents the distance between atoms A and B. A strong H-bond results in short r_{BH} and slightly elongated r_{AH} distances. Bond distance depends on bond energy and bond order. In the A-H...B complexes, the r_{AH} and r_{BH} distances depend on each other, leading to allowed

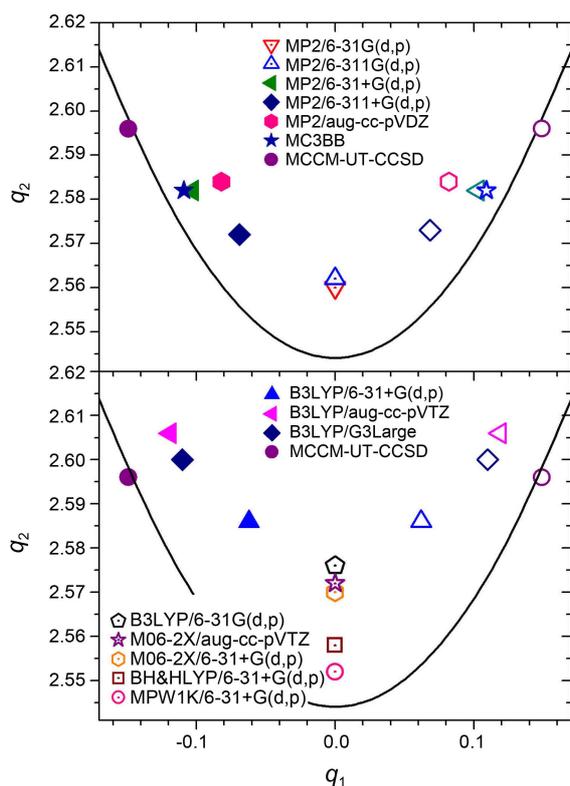


Figure 7. Correlation of the N-H bond distances $q_2 = r_1 + r_2$ with the proton transfer coordinate $q_1 = (1/2)(r_1 - r_2)$ at the TS of DPT for the FN-FN complex. Open and closed symbols are for H_a and H_b , respectively. Symbols with dot in the center are for the TS with D_{2h} symmetry, where the points of H_a and H_b are overlapped. The solid line designates the correlation that satisfies conservation of the bond order. Parameters for Pauling equations were from literature.⁴⁵ The region above the solid line is where the sum of bond order is smaller than unity. Top and bottom plot are for MP2 and DFT levels, respectively.

r_{AH} and r_{BH} values based on the following Pauling equations under the assumption that the sum of two bond orders is conserved, $n_{AH} + n_{BH} = 1$:

$$n_{AH} = \exp\{-(r_{AH} - r_{AH}^0)/b_{AH}\} \quad (4)$$

$$n_{BH} = \exp\{-(r_{BH} - r_{BH}^0)/b_{BH}\} \quad (5)$$

where r_{AH}^0 and r_{BH}^0 are the equilibrium lengths of the free AH and BH bonds, and b_{AH} and b_{BH} are the parameters describing the decrease of the AH and the HB unit bond valences with the corresponding distances. This type of correlation, i.e., the “bond energy bond order method”, has been used for many years to study hydrogen atom transfer. When H is transferred from A to B in the A-H...B complex, q_1 increases from negative to positive values and q_2 goes through a minimum, which is located at $q_1 = 0$. This correlation can be used to study the characteristics of transition state, such as earliness or lateness, bond order, and synchronicity. The q_1 value of TS is negative or positive when the TS is either early or late, respectively. In addition, the two q_1 values of two protons in TS of double proton transfer should be very similar and different in the synchronous and

asynchronous mechanism, respectively.

In Figure 7, all TS with D_{2h} symmetry have single points at $q_1 = 0$, since the correlation points of H_a and H_b overlap. Other TS with C_{2v} symmetry have two points for H_a and H_b with either positive or negative q_1 values with the same magnitude. Two close points of H_a and H_b indicate small asynchronicity of DPT, and the points remote from each other indicate large asynchronicity. All points except MCCM-UT-CCSD lie above the solid line, which means that the predicted bond orders are not conserved but decreased at the TS. Using the large basis sets increased the asynchronicity. The MCCM-UT-CCSD method, which gave consistently good results for both structures and energetic of most cyclic H-bonded complexes, predicted the largest asynchronicity of DPT. Since all multilevel methods predicted C_{2v} symmetry of TS consistently with large asynchronicity, one can conclude that the tautomerization in FN dimer occurs in the concerted but asynchronous mechanism.

Conclusions

We have performed high-level quantum mechanical calculations for structures and energetic of cyclic H-bonded complexes, which include three monohydrated complexes, FA-H₂O, FM-H₂O and FN-H₂O, and three homo-dimers, FA-FA, FM-FM, and FN-FN, an three hetero-dimers, FA-FM, FM-FN, and FM-FN. The structures and energetic of all cyclic H-bonded complexes depend very much on the level of theory and the size of the basis sets. In particular, the TS symmetry of FN dimer (and the mechanism of tautomerization as a result) depends very much on the computational level. Multilevel methods gave very good results in most cases comparing with the best estimates, which predicted C_{2v} symmetry of TS consistently with large asynchronicity, suggesting that the DPT of FN dimer occurs in a concerted but asynchronous mechanism.

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