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Water-Assisted Proton Transfer of Cyanuric Acid

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Abstract

On the basis of the reliable B3LYP/6-311++G** approach, the water-assisted proton transfer of cyanuric acid were explored. Results reveal that water molecules hold an assisting effect on proton transfer. In the tautomeric process of the hydrated cyanuric acid, the protons transfer step by step and the activation energies decrease gradually. Compared with the subsequent water molecules attached to cyanuric acid, the first water molecule donates the strongest assisting effect. The assisting effect is not always increasing with the number of water molecule. Two water molecules in the hydrated systems are proved to be the optimal number in assisting the proton transfer. Analysis reveals that the side water is in favor of the proton transfer. The formation of the water cluster with two water molecules in the side chain is most favorable for proton transfer.

1 Introduction

In 2008, contaminated infant milk that contains melamine caused thousands of infants' kidney damaged, making people afraid of melamine. In fact, the culprit is not melamine. However, when melamine enters into the organism, a kind of by-product, cyanuric acid, is produced. Melamine is of low toxicity and has been used illegally as a food additive because it boosts the apparent protein content based on certain testing methods. Cyanuric acid is used as a stabilizer in chlorine tablets for swimming pools. Experimental studies have shown that combination of melamine with cyanuric acid leads to crystal formation and exhibit higher toxicity than the individual compounds [1-3]. In 2007, pet food containing both melamine and cyanuric acid has caused kidney failure in cats

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and dogs in the USA. Large sheets (rosettes and one-dimensional tapes) of melamine cyanurate can be generated through hydrogen bonding, as causes the functional disability and the organism dying. The stability and solubility of melamine and cyanuric acid have significant effect on the product of solid urine stones. Therefore, the properties of cyanuric acid are explored here.

It is known that the hydrogen bond (H-bond) plays a key role in the structure and function of biological molecules. The arrangement of protons in the H-bond not only carries the fundamental biological information of the cell, but also determines the properties, shapes and functions of biomolecules. Cyanuric acid is a unique cyclic amide having three hydrogen bond donor and three acceptor sites, leading to a range of hydrogen bonding possibilities, not only with water molecules but also with other polar solvents. Two stable isomers of cyanuric acid have been determined in solution: enolic form (C_E) and keto form (C_K) (Figure 1). The tautomeric process of cyanuric acid is fulfilled with the proton transfer (PT), which is ubiquitous in chemistry and biology, often occurs in acid-base reactions, electrochemistry and biological processes [4-5]. Organism itself is a huge water environment. When cyanuric acid enters into the organism, it can form hydrogen bond inevitably. Therefore, it is required to take the effect of water molecules into account for the PT process of cyanuric acid. Water-assisted PT has been investigated extensively [6-14], while the water involved PT of cyanuric acid remains unknown. In addition, water molecules could affect the stability and solubility of cyanuric acid. It is believed that the research on the stability and solubility of cyanuric acid will be helpful to resolve the stone problem.

Due to the importance of hydration effect on the tautomeric process of $C_E \rightarrow C_K$, the investigation on water-assisted PT will shed light on the following questions. (1) How about the coupling mode of cyanuric acid and water molecules? (2)How does water molecule affect the stability and solubility of cyanuric acid? (3)How does water molecule influence the tautomeric process of cyanuric acid? (4) Which route is preferred in the tautomeric process? (5) What is the optimized condition for water-assisted PT?

2. Computational Methods:

The hybrid density functional theory (DFT) is proven to be an excellent compromise between computational cost and reasonable results. This method has been successfully used in determination of electronic structure and in description of large free radicals and intermolecular complexes [15-17], harmonic frequencies and binding energies [18-19]. It has been confirmed that B3LYP could give reliable results for the geometrical and vibrational features of melamine and cyanuric acid system [20-21], B3LYP and MP2 could give very similar results for this kind of PT system [22-23]. Compared with the experimental data, good agreement is established for the B3LYP and MP2 approaches in the present paper, all other calculations are performed using B3LYP method in conjunction with a 6-311++G** basis set and carried out with Gaussian 03 program [24]. At this level, the hydrated cyanuric acid complexes (C_E-mW and C_K-mW, "m" represents the number of water molecules) are also optimized for the investigation of the hydration effect on their relative stability and the intramolecular PT. Vibrational frequency analyses for all optimized configuration structures are performed at the same level to verify whether the optimized structures correspond to the genuine local minima in the global potential energy surface (PES) or not. The corrections of the basis set superposition error (BSSE) and the zero point vibrational energies (ZPE) are carried out for the related energy calculations. The natural bond orbital (NBO) analyses are performed to obtain the information about the OH bond order. Solvent effects are considered with the polarizable continuum model (PCM) at the same basis set level.

3. Results and discussion

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On the basis of the reliable B3LYP/6-311 ++G** method, different coupling modes of hydrated cyanuric acid were determined through geometry optimization. The primary parameters of C_E and C_K are collected in Table 1 and the optimized structures of C_E and C_K are represented in Figure 1. The calculated bond order of C_E-mWn ("n" represents different structures of hydrated cyanuric acid complexes) is represented in Table 2. The calculated binding energies of

Table1: Optimized Bond Distances (Å) and Bond Angles (deg) of the Two Stable Cyanuric Acid Isomers

	C_K			C_E	
	X-ray	B3LYP[a]	MP2[b]	B3LYP[a]	MP2[b]
C_1-O_8	1.215	1.206	1.217	1.332	1.327
C_3-O_7	1.210	1.206	1.217	1.332	1.327
C_1-N_4	1.345	1.391	1.382	1.333	1.327
C_3-N_4	1.355	1.391	1.382	1.330	1.334
C_3-N_6	1.365	1.391	1.382	1.333	1.333
N_5-C_1-N_4	116	113.2	114.1	126.6	126.2
C_2-N_5-C_1	125	126.8	125.9	113.4	113.8
N_6-C_2-N_5	114	113.2	114.1	126.6	126.2
C_3-N_6-C_2	125	126.8	125.9	113.4	113.8
O_9-C_2-N_6	122	123.4	123.0	116.1	115.3

[a] Calculated at the B3LYP/6-311++G** level. [b] Calculated at the MP2/6-311++G** level.

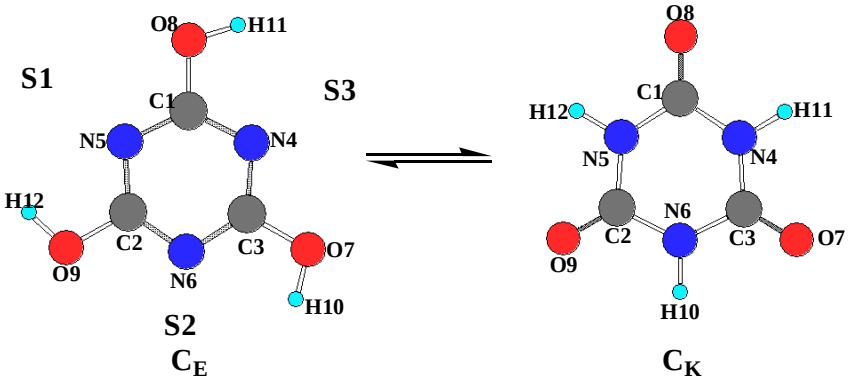

Figure 1 Two Isomers (C_E and C_K) of Cyanuric Acid

Table 2 The Calculated Bond Order of C_E-mWn (m= 0-3, n=1-3)

Bond	C_E	C_E-1W	C_E-2W_1	C_E-2W_2	C_E-3W_1	C_E-3W_2	C_E-3W_3
O_9-H_{12}	0.742	0.654	0.621	0.653	0.621	0.652	0.620
O_8-H_{11}	0.742	0.740	0.738	0.652	0.649	0.652	0.737
O_7-H_{10}	0.742	0.741	0.741	0.740	0.740	0.652	0.741
O_{13}-H_{14}	---	0.722	0.685	0.719	0.684	0.718	0.670
O_{16}-H_{17}	---	---	0.702	0.720	0.701	0.718	0.687
O_{19}-H_{20}	---	---	---	---	0.719	0.719	0.704

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cyanuric acid molecule and water molecules are listed in Table 3. The relative free energies (ΔG) of C-mWn are listed in Table 4. The calculated activation energies for the direct PT reaction of cyanuric acid with different methods in gas phase are represented in Table 5. Table 6 lists the calculated activation energies for the direct PT reaction of cyanuric acid in gas phase and in solution. The steady states, the transition states, and the corresponding isomerization processes are reflected in Figures 2-6. The activation energy changes of the different structures of TS11-6Wn and TS21-6Wn are reflected in Figure 7. The harmonic vibrational IR spectra of the enolic isomers are exhibited in Figure 8.

Table 3 The Calculated Binding Energy (E_{bind} in kcal/mol) of Cyanuric Acid Molecule and Water Molecules with the BSSE and ZPE Corrections

	C_E	C_K		C_E	C_K
1W	-7.9	-6.3	$6W_1$	-41.6	-34.8
$2W_1$	-13.2	-11.6	$6W_2$	-25.1	-22.5
$2W_2$	-16.0	-12.6	$6W_3$	-25.9	-20.3
$3W_1$	-21.5	-17.8	$6W_4$	-18.1	-14.7
$3W_2$	-24.4	-19.1	$6W_5$	-10.7	-9.2
$3W_3$	-12.0	-11.3	$6W_6$	---	-15.7
$3W_4$	---	-7.8	$6W_7$	---	-20.7

Table 4 Relative Free Energies (ΔG in kcal/mol) of C-mWn

	0	1W	$2W_1$	2W2	$3W_1$	$3W_2$	$3W_3$	$3W_4$
C_E	0.0	0.0	-0.3	0.0	-1.6	-1.5	0.0	---
C_K	-30.1	-28.7	-28.8	-26.9	-28.5	-26.6	-29.6	-25.5

	$6W_1$	$6W_2$	$6W_3$	$6W_4$	$6W_5$	$6W_6$	$6W_7$
C_E	-6.0	-1.8	-1.4	-1.2	0.0	---	---
C_K	-29.6	-29.9	-27.5	-27.9	-28.3	-22.4	-26.2

Table 5 Calculated Activation Energies for the Direct Proton Transfer Reaction of Cyanuric Acid at Different Methods in Gas Phase (Kcal/mol)

	C_E	TS21	Int1	TS22	Int2	TS23	C_K
MP2/6-311++G**	0.0	35.8	-0.1	31.2	-11.3	18.4	-28.0
B3LYP/6-311++G**	0.0	34.8	-1.7	30.3	-12.8	17.4	-29.5

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Table 6 Calculated Activation Energies for the Direct Proton Transfer Reaction of Cyanuric Acid in Gas Phase and in Water Solvent (kcal/mol)

	C_E	TS21	Int1	TS22	Int2	TS23	C_K
gas phrase	0.0	34.8	-1.7	30.3	-12.8	17.4	-29.5
Water solvent	0.0	35.4	-2.2	27.5	-19.4	14.0	-28.6

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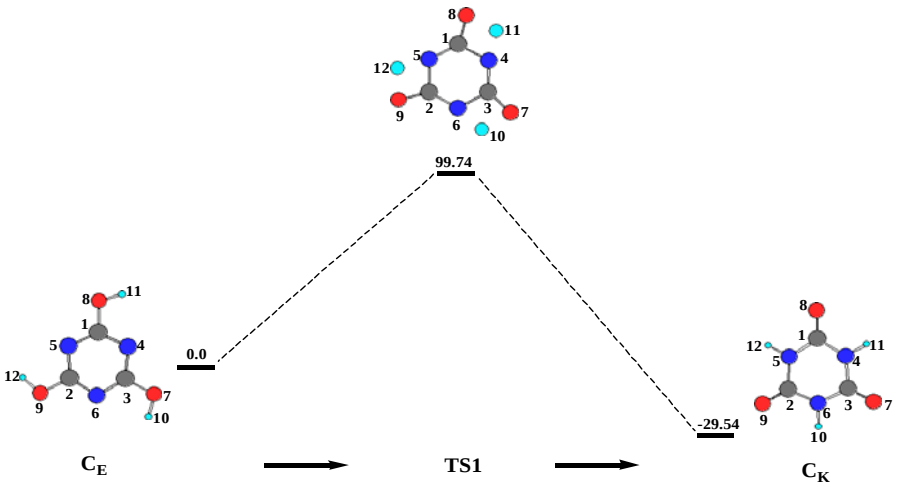

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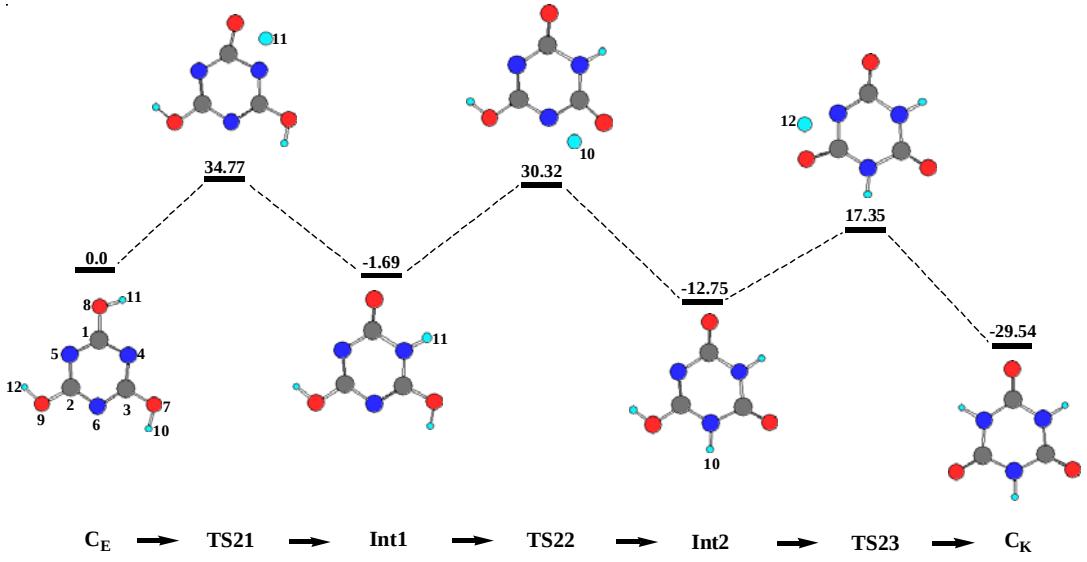

Figure 2 Proton Transfer Processes between Isomers C_E and C_K

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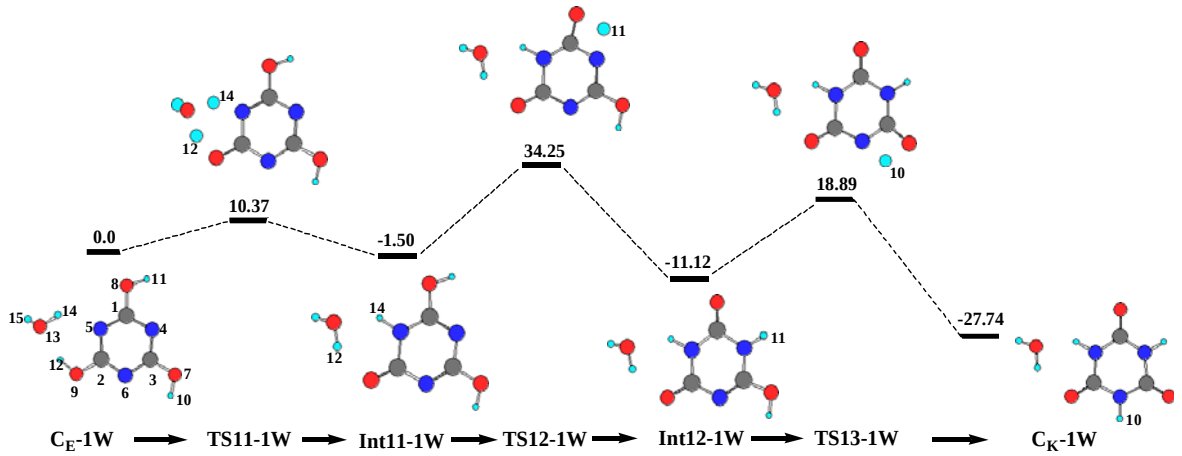

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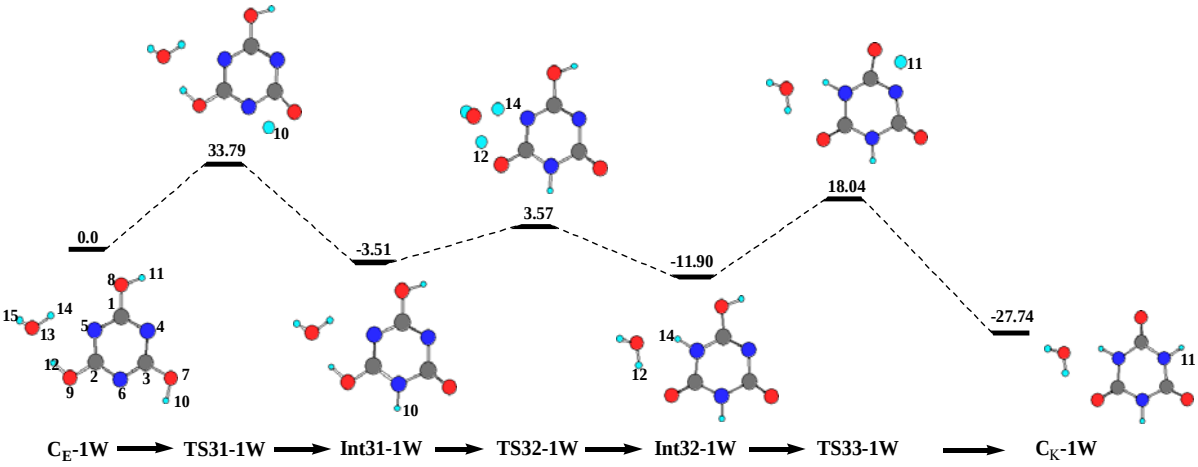

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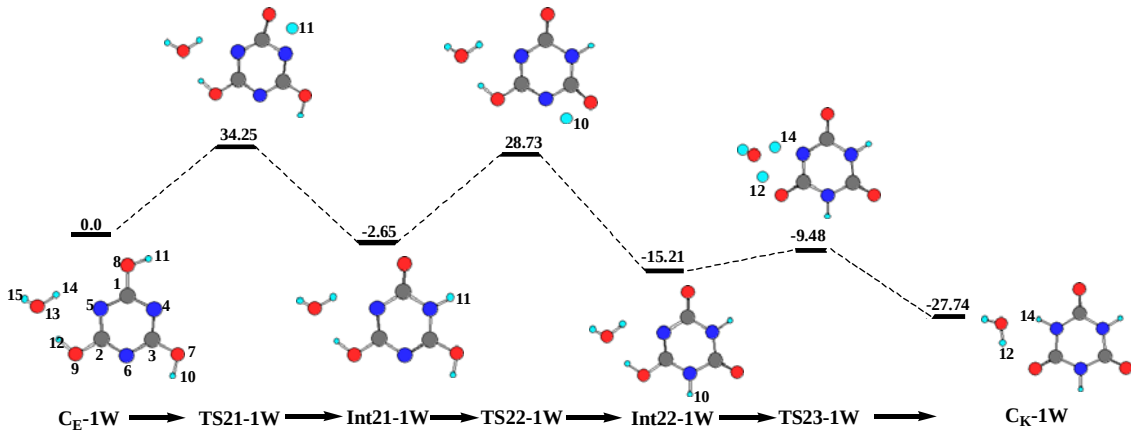

Figure 3 Proton Transfer Processes between C_E-1W and C_K-1W

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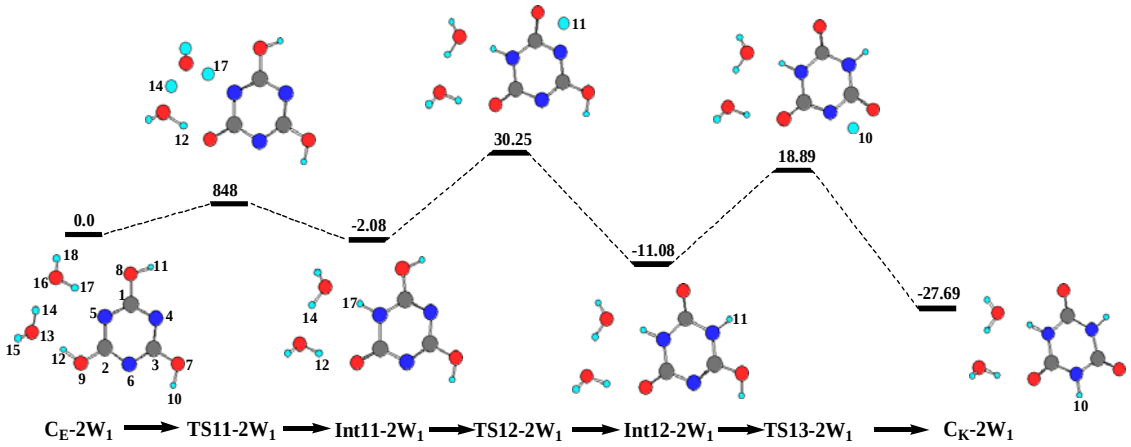
2W1:



2W2:

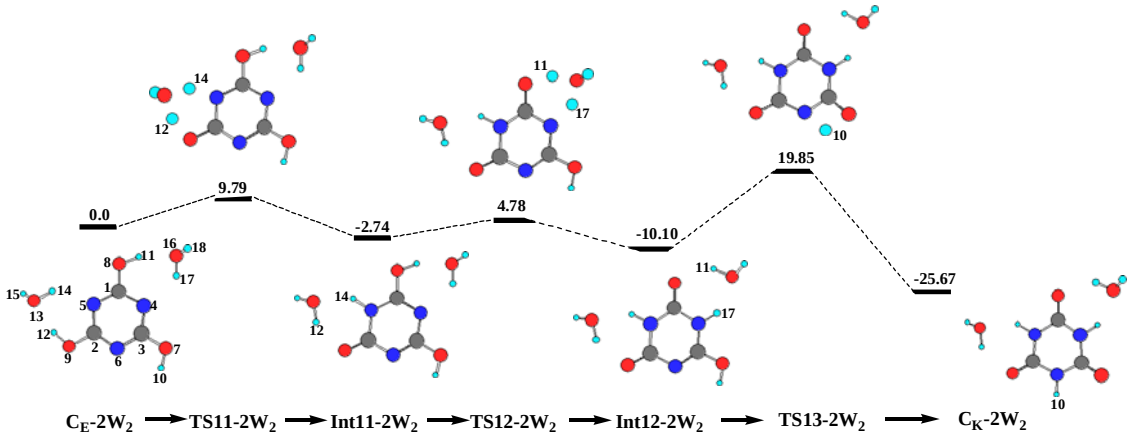


Figure 4 Proton Transfer Processes between C_E-2W and C_K-2W

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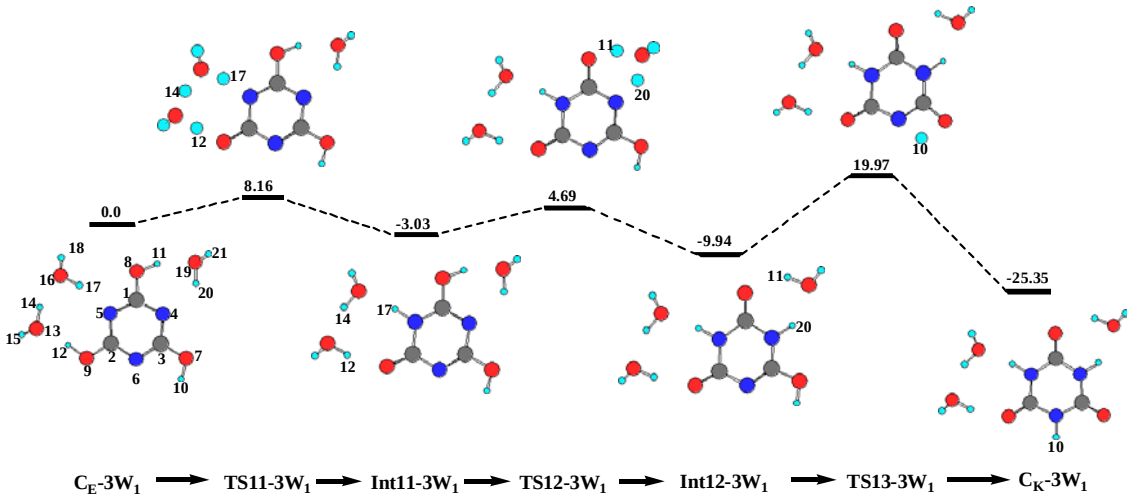
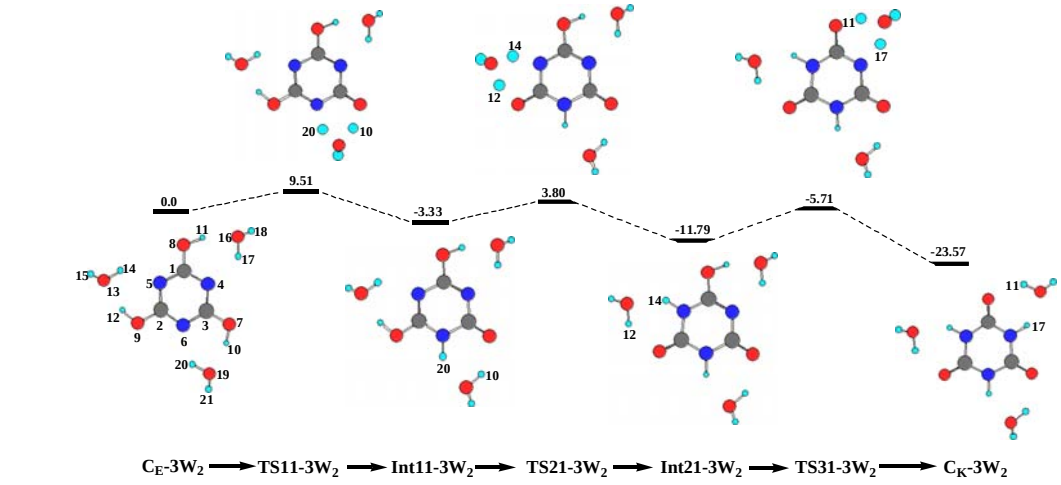
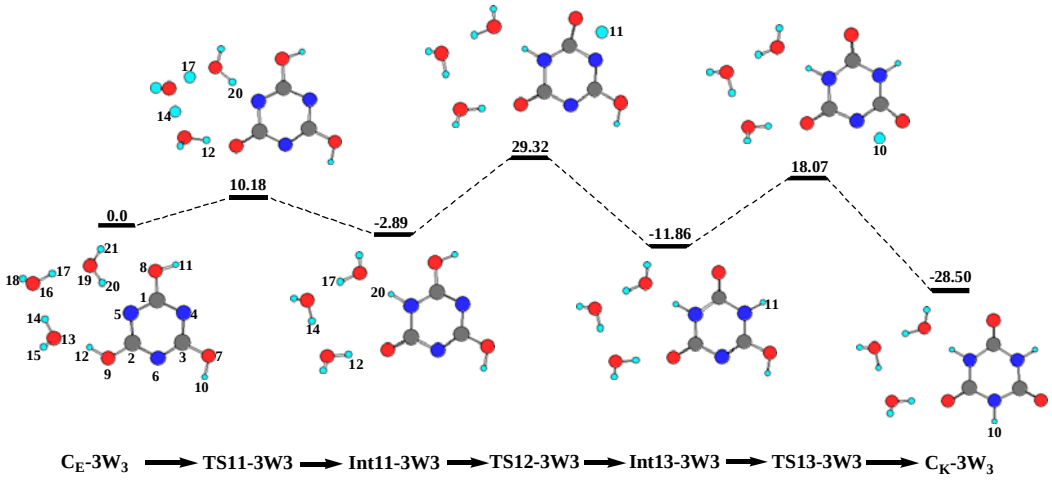
3W1:



3W2:



3W3-Path1:



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3W3-Path2:

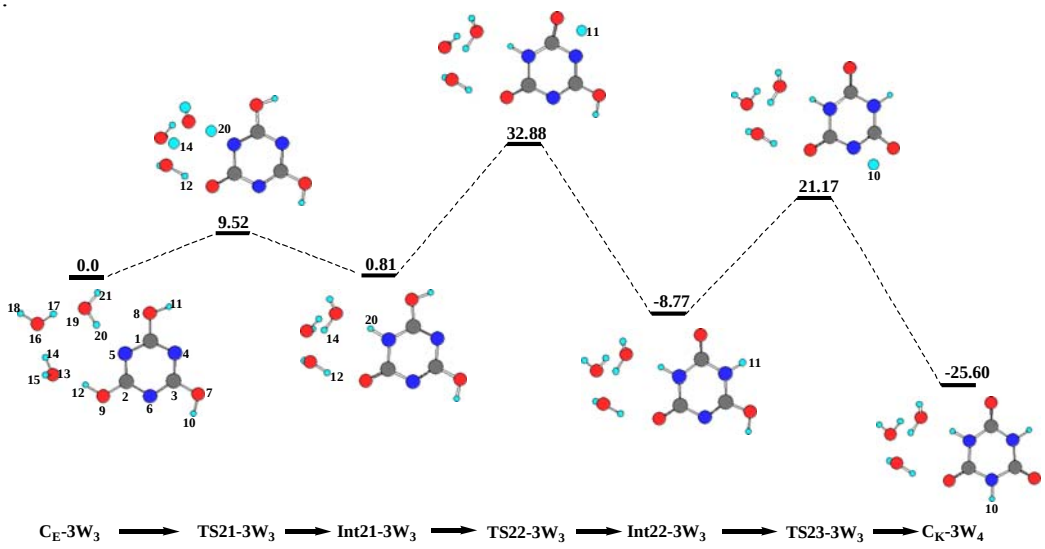

Figure 5. Proton Transfer Processes between C_E-3W and C_K-3W

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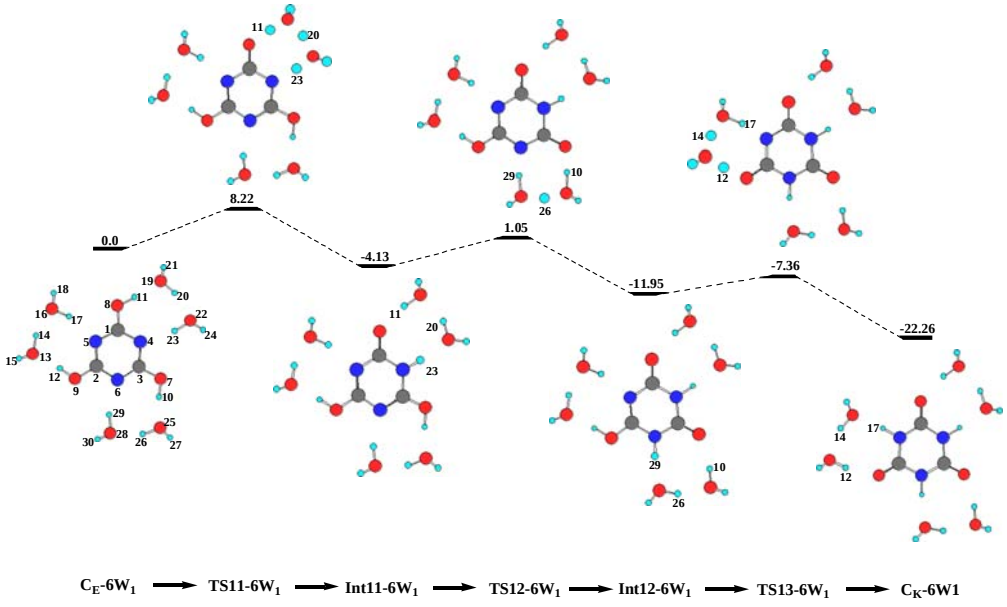

6W2:

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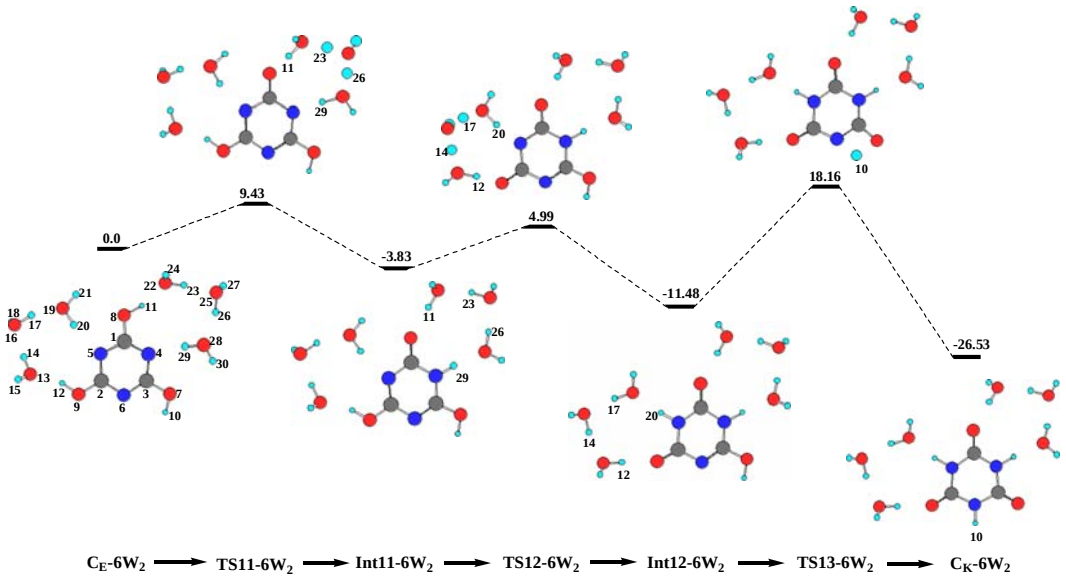
Path1:



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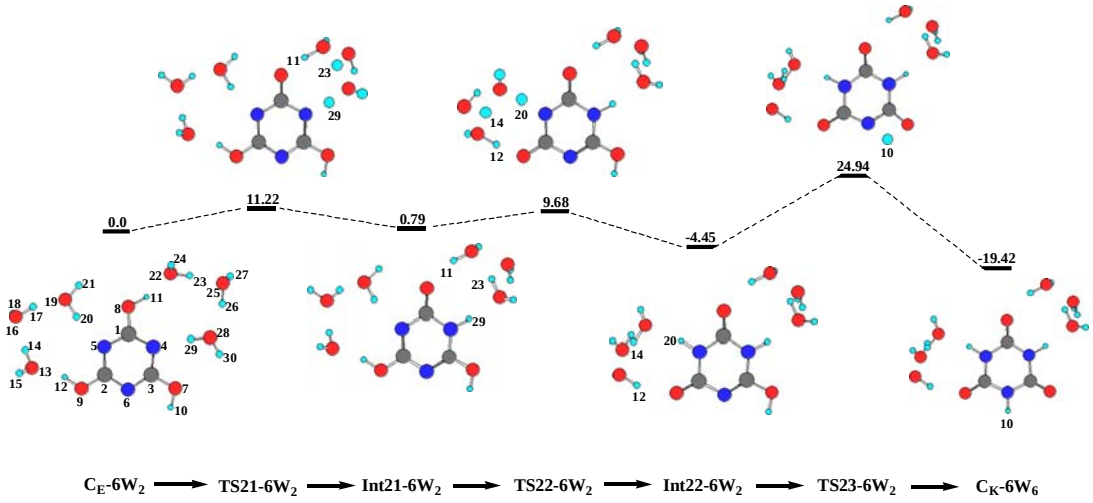

6W3 (C_E-6W$_3$):

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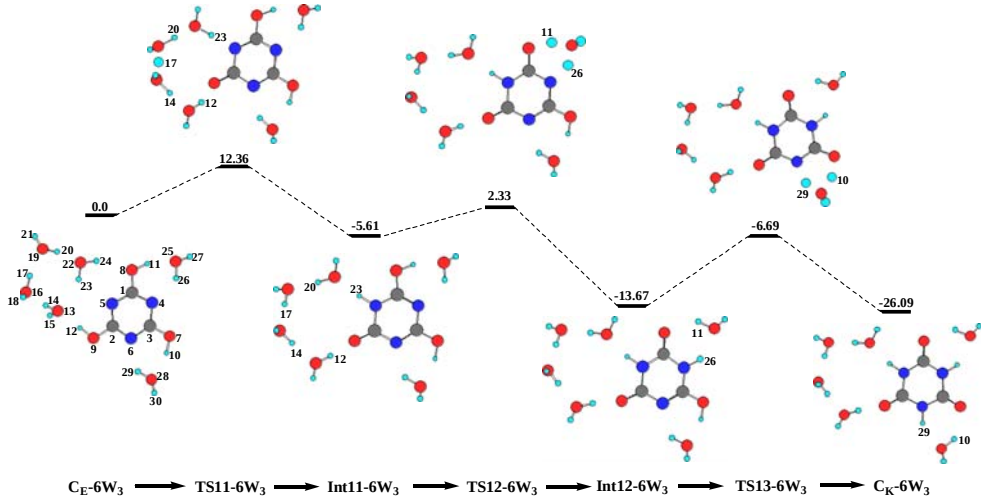

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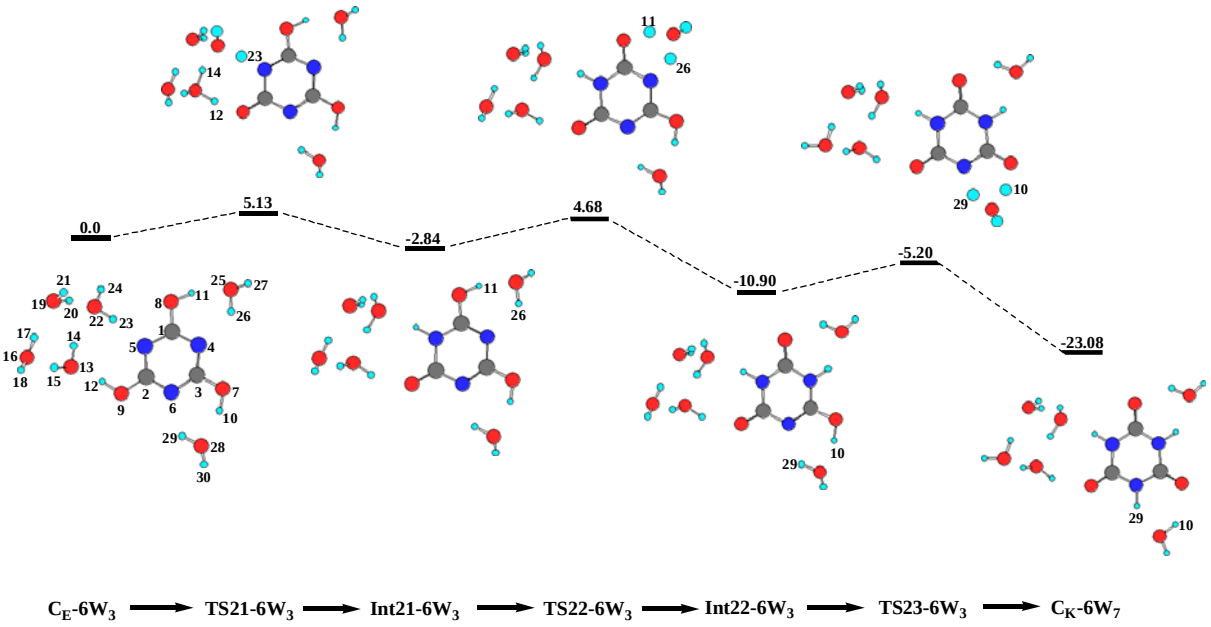

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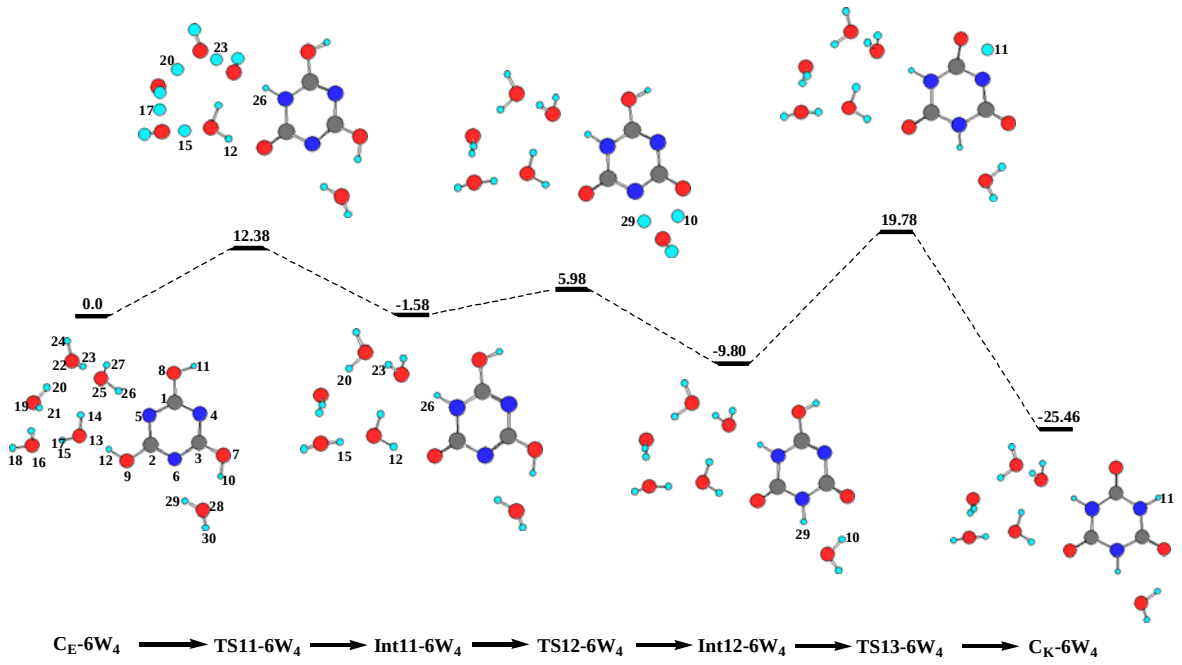

Path2:

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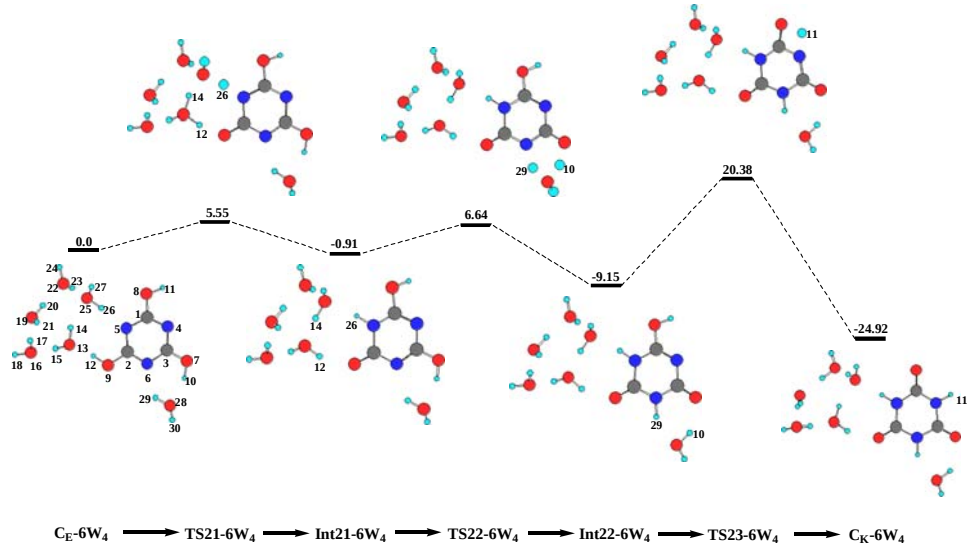

6W5 (C_E-6W$_5$)

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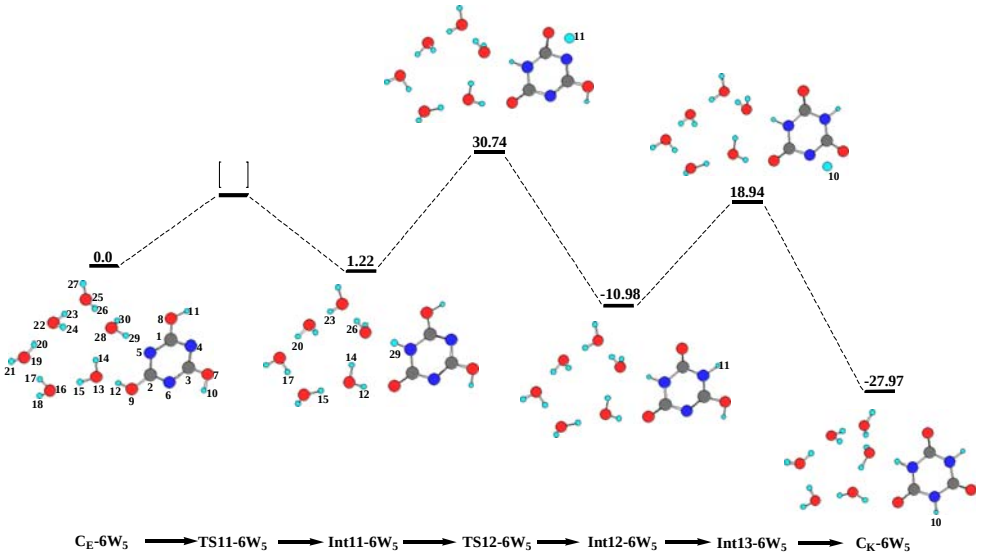

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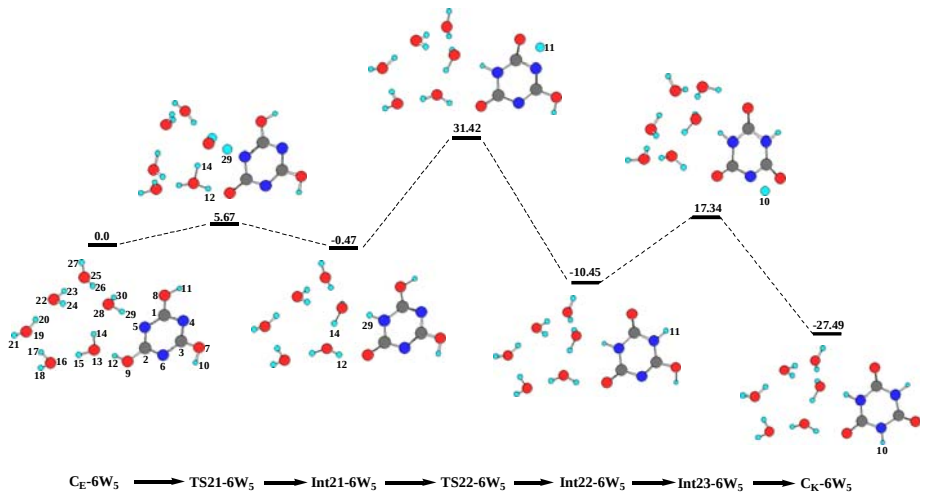

Figure 6 Proton Transfer Processes between C_E-6W and C_K-6W

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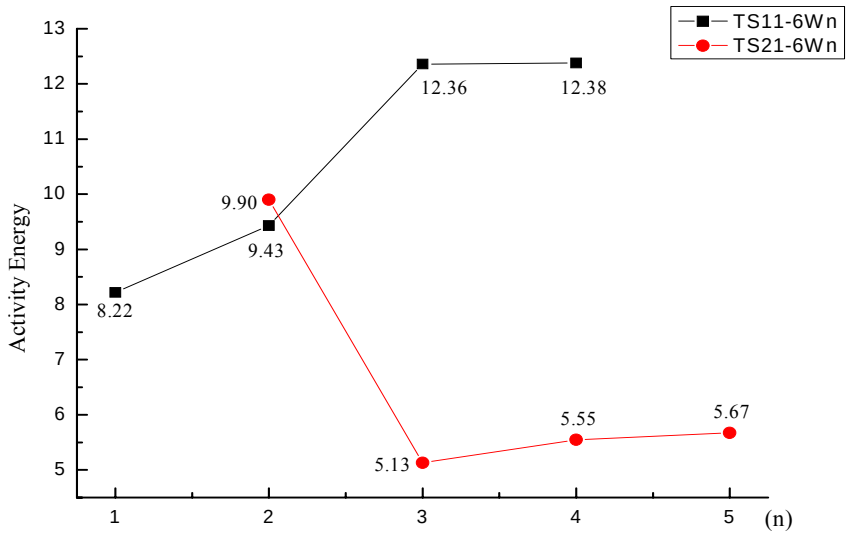

Figure 7 Activation Energy Changes of the Different Structures of TS11-6Wn and TS21-6Wn

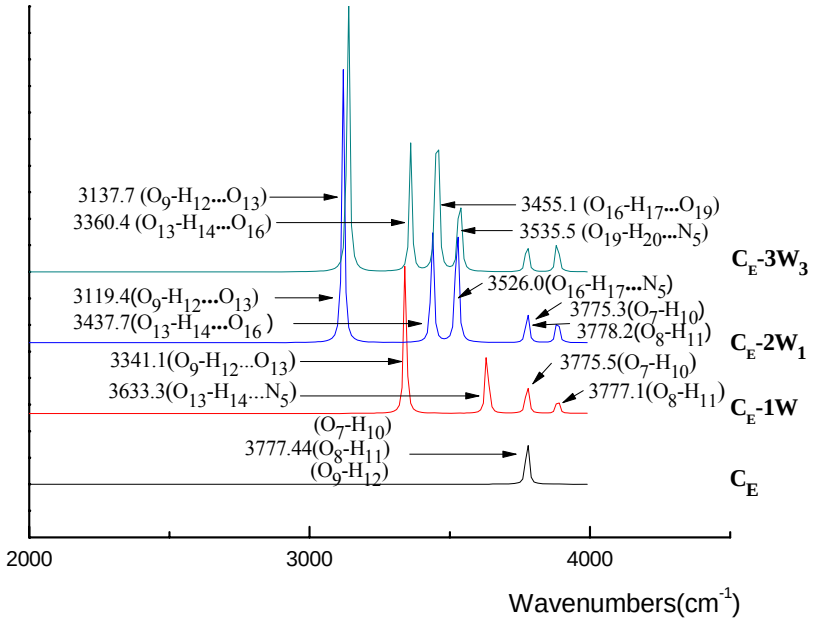

Figure 8 IR spectra of C_E-mWn (m=1,2,3 and n=1,3)

3.1 Geometry structures

3.1.1. Two Isomers of Cyanuric Acid (C_E and C_K).

The geometries of the two isomers of cyanuric acid (C_E and C_K) were fully optimized at the B3LYP/6-311++G** level (Figure 1). The optimized geometrical parameters of cyanuric acid isomers listed in Table 1 are in good agreement not only with the result obtained at the MP2/6-311++G** level but also with the experimental results obtained by X-ray [25]. The

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calculation results reveal that C_K (0.0) is more stable than C_E (29.5 kcal/mol), in good agreement with theoretical [15] and experimental [16-17] results.

3.1.2. The structures of C-1W

The structure feature that is necessary for the biological functions of cyanuric acid depend normally on their interactions with surrounding water. Thus, different coupling modes of hydrated cyanuric acid are investigated to illustrate the role of water in the PT process.

In the vicinity of C_E, three different regions (S1, S2, S3 in Figure1) are same for water molecules. Two stable structures are found for the monohydrated cyanuric acid, denoted with C_E-1W and C_K-1W. The corresponding atomic serial numbering is depicted in Figure 3. In C_E-1W, the bare N atom and OH group of cyanuric acid molecule interact with the O-H group of water through H-bond. The distance of O-H···O H-bond (2.73 Å) is shorter than that of O-H···N H-bond (3.02 Å). The structure of C_K-1W is a little different from that of C_E-1W. The bare O atom and NH group of cyanuric acid molecule interact with the O-H group of water through the N-H···O and O-H···O H-bonds. The distance of N-H···O and O-H···O H-bond is about 2.94 and 3.04 Å, respectively. In C_E-1W, the formation of O_9-H_{12}···O_{13} H-bond leads to the weakening of O_9-H_{12} interaction, which can be reflected from the changes of bond order of O_9-H_{12} according to the NBO analysis (0.742 in C_E and 0.654 in C_E-1W). The bond length of O_9-H_{12} is lengthened by 0.02 Å. As a result, transfer of H_{12} from O_9 is easier than the case without water. This indicates that the presence of water is in favor of PT.

3.1.3. The isomeric structures of C-2W

Four different isomers are optimized for dihydrated cyanuric acid, denoted as C_E-2W_1, C_E-2W_2, C_K-2W_1, and C_K-2W_2. From Figure 4 and Figure S2, it can be seen that the two water molecules are in the same side of cyanuric acid molecule in C_E-2W_1 and C_K-2W_1. But in C_E-2W_2 and C_K-2W_2, the two water molecules are in the different sides of cyanuric acid molecule. The O-H···N and O-H···O H-bonds are involved in C_E-2W_1 and C_E-2W_2. An eight-member ring is formed in C_E-2W_1. The water dimer fits quite nicely into the O_9-H_{12} and N_5 region. The distances of two O-H···O H-bonds of C_E-2W_1 (2.65Å and 2.72 Å) are shorter than the distance of O_9-H_{12}···O_{13} in C_E-1W (2.74Å). The length of O_{16}-H_{17}···N_5 H-bond in C_E-2W_1 (2.91 Å) is also shorter than that of O_{13}-H_{14}···N_5 H-bond in C_E-1W (3.02 Å). As the second water molecule is added to the system, the bond order of O_9-H_{12} is reduced to 0.621 and the bond length of O_9-H_{12} is further lengthened by 0.01 Å. That is to say, the interaction between O_9 and H_{12} is reduced. The geometric parameters of C_E-2W_2 are almost equal to those of C_E-1W. In C_E-2W_2, two water molecules interact with cyanuric acid molecule, stabilizing the cyanuric acid molecule.

3.1.4. The structures of C-3W

Seven isomers are determined for the trihydrated cyanuric acid, denoted with C_E-3$W_{1\text{-}3}$ and C_K-3$W_{1\text{-}4}$, respectively (Figure S3). According to the population of these water molecules, three different coupling mode complexes are determined. In C_E-3W_1 and C_K-3W_1, two water molecules populate on one side of cyanuric acid and the third locates on the other side. In C_E-3W_2 and C_K-3W_2, three water molecules locate separately in three areas. In C_E-3W_3, C_K-3W_3 and C_K-3W_4, three water molecules are on the same side of cyanuric acid molecule. In C_K-3W_4, the cyanuric acid molecule interacts directly only with two water molecules. These two water molecules and C_K are almost coplanar. The other water molecule interacts with the former two through intermolecular H-bonds, forming an eight-member ring and a six-member ring (side-water-chain structure). These two rings are almost perpendicular to each other. However, the corresponding enolic structure is not found.

3.1.5. The structures of C-6W

Twelve isomers are found for the hexahydrated

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cyanuric acid, denoted with C_E-$6W_{1-5}$ and C_K-$6W_{1-7}$ (Figure S4). It is found that when three or more water molecules lies on the same side of the cyanuric acid molecule, a side-water-chain structure is generated (like C_K-$3W_4$) to make themselves more stable, such as C_E-$6W_{3-5}$ and C_K-$6W_{4-7}$. In this kind of side-water-chain structure, cyanuric acid molecule interacts directly with only two water molecules and the rest of water molecules interact with these two through intramolecular H-bonds. In C_E-$6W_1$ and C_K-$6W_1$, six water molecules located separately on different sides of cyanuric acid molecules. In C_E-$6W_2$, C_K-$6W_2$, and C_K-$6W_6$, six water molecules distribute on two sides of cyanuric acid molecules. In C_K-$6W_2$, it forms a three water chain, but in C_K-$6W_6$, the three water molecules form a side-water-chain structure. In C_E-$6W_3$, C_K-$6W_3$ and C_K-$6W_7$, four water molecules locate on one side of cyanuric acid and the other two locate on other two sides. In C_E-$6W_4$ and C_K-$6W_4$, five water molecules locate on one side of cyanuric acid while in C_E-$6W_5$ and C_K-$6W_5$, six water molecules locate on the same side of cyanuric acid.

3. 2. The Stability of C-mWn

Different coupling mode structures of C-mWn are designed. The number and arrangement of water molecules affect the stability and solubility of cyanuric acid. The corresponding binding energy (E_{bind}) and relative free energies (ΔG) obtained using B3LYP method in conjunction with 6-311++G** basis set are represented in Tables 3 and 4. The conclusion can be drawn from the E_{bind} and ΔG that the influence of water molecules to the stability of the system is strong because significant alterations of E_{bind} and ΔG are found between cyanuric acid and C-mWn. The stability of the system is enhanced after hydration. The tendency to form rosettes or one-dimensional tapes after combination with the melamine is decreased. Therefore, the toxicity of hydrated cyanuric is reduced. It can be seen from Table 3 that the binding energy of cyanuric acid and water molecules is not always increasing with the water molecules. The calculated binding energy of C_E-mWn is lower than that of C_K-mWn. In addition, the coupling modes with higher symmetry have lower binding energy. Take the binding energies of C-3W for example, C_E-$3W_2$ < C_E-$3W_1$ < C_E-$3W_3$ and C_K-$3W_2$< C_K-$3W_1$ < C_K-$3W_3$. Among these complexes, the binding energy of C_E-$6W_1$ is the lowest and that of C_K-1W is the highest. Reviewing the data represented in Table 3, it can be drawn that the influence of symmetry is significant to the solution of system. It can be seen from Table 4 that with the addition of water molecules, the stability of the system increases significantly. As a whole, C_K-mWn is more stable than C_E-mWn.

3.3. Tautomeric Process

3.3.1 Tautomeric Process from Isolated C_E to Tautomer C_K

Figure 2 shows the PT processes from isolated C_E to C_K. The calculated activation energies and the energy differences of two tautomers using different methods are listed in Table 5. The calculated energies using MP2 and B3LYP methods at the same basis set levels are in good agreement with each other. Therefore, it is reliable to employing the B3LYP/6-311++G** results for the following discussion.

Figure 2 shows that the isomerization of $C_E \rightarrow C_K$ can be fulfilled through the intermolecular proton (H_{10}, H_{11}, and H_{12}) transfer from O_7, O_8, and O_9 site to N_6, N_4, and N_5 site of C_E, respectively. Two different pathways can be found. One is that H_{10}, H_{11}, and H_{12} of C_E transfer to N_6, N_4, and N_5 simultaneously (Path1), the other is that the protons transfer separately (Path2). In Path1, optimizations show that the distances of O_8-H_{11} bonds are 0.968, 1.352, and 2.509Å in C_E, TS1 and C_K, respectively. During this process, the structure of cyanuric acid molecule changes significantly: C_1-O_8-H_{11}, C_2-O_9-H_{12}, C_3-O_7-H_{10} are 107.2° in C_E, 76.2° in TS1, and 54.2° in C_K, respectively. Therefore, C_E undergoes large structural changes and three OH bonds are broken simultaneously, which is

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energetically expensive. In Path2, the large structural changes maybe need a strong distorting power and this PT process is hard to achieve. In Path1, breaking out three O-H bonds of C_E at the same time needs a lot of energies, the activation energy is very high (99.7kcal/mol). The three O-H bonds of C_E are broken one by one in Path2, reducing the activation energy of Path2 significantly (34.8, 32.0, and 30.1kcal/mol, respectively) as compared with that of Path1. It can be seen in Path2 that the activation energy of these three steps ($C_E \rightarrow$ Int1, Int1 $\rightarrow$ Int2 and Int2 $\rightarrow C_K$) decreases gradually. In fact, Path2 is also very hard to achieve. Therefore, the synergic PT is difficult to occur in biology. In this work, we focus on the successive PT of cyanuric acid. In addition, the polarizable continuum model (PCM) has been employed to explore the solvent effect (Table 6). It is found that the results calculated in gas phase are in good agreement with those in water solvent. Therefore, the following discussions are carried out based on the results obtained in gas phase.

3.3.2 Tautomeric Process between Hydrated Systems

During the past years, many experimental and theoretical studies have been performed to study the role of water in the tautomeric process [错误!未定义书签。] It is found that water can assist the PT process for the similar central molecules to some extent, however, it is worth studying how water molecules affect the tautomerization process from C_E-mWn to C_K-mWn, finding out the optimal number, and determining the arrangement of water molecules.

Figures 3 - 6 list the C_E-mWn $\rightarrow$ C_K-mWn tautomeric processes. Obviously, if the water is located between H_{12} and N_5 atom of C_E, the hydration will affect the tautomeric process of $C_E \rightarrow C_K$ distinctly. In the tautomeric processes of C_E-mWn $\rightarrow$ C_K-mWn, a significant change is observed compared with the nonhydrated case. Figure 3 shows the monohydrated PT process. The water molecule first accepts the H_{12} from O_9 of C_E and then donates its hydrogen to the N_5 atom of C_E to complete the PT process of $H_{12} \rightarrow N_5$. In this process, water molecule plays the role of the "bridge" for the PT. This bridge compresses the $C_2O_9H_{12}$ angle by only 3.4° in PT process (it is 31.0° for Path1 of $C_E \rightarrow C_K$). It reduces the angle distorting power and favors PT. In addition, the attachment of water molecule increases the negative charge on N_5 significantly and makes N_5 susceptible to accept a proton. Hence, compared with the isolated $C_E \rightarrow C_K$ tautomeric process, it is not surprising that monohydration can greatly reduce the activation energy of the tautomeric process (from 34.8 kcal/mol to 10.4 kcal/mol). Recently, the water-assisted PT reaction of pterin in aqueous environment has been carried out.[错误!未定义书签。] The activation energy of water-assisted process for monohydrated pterin could be reduced from 34.2 to ~10.0 kcal/mol. But how does this water molecule affect the second and the third PT processes of cyanuric acid? Must H_{12} that is connected with the water molecule transfer first? To solve these problems, we studied other three pathways: 1W-Path1, 1W-Path2 and 1W-Path3 (Figure 3). In 1W-Path1, H_{12} is the first proton transferring to N atom (10.4 kcal/mol); in 1W-Path2, H_{12} transfers to N atom in the intermediate step of the whole PT process and in 1W-Path3 (7.1 kcal/mol), H_{12} is the last proton transferring to N (5.7 kcal/mol). Obviously, the PT through a water molecule is distinctly favored no matter which proton transfers first. From the above analysis, the following conclusion can be drawn: first, a water molecule favors the PT process significantly; second, all the three different pathways may be possible, no matter which proton transfers first.

For dihydrated cyanuric acid, the activation energy of this PT is further decreased by 1.9 kcal/mol than that of the monohydrated system. That is to say, the second bridging water molecule has no significant effect on the activation energy for PT process compared with that of monohydrated tautomeric process. It is similar to the results of PT in 2-Pyridone [错误!未定义书签。] that two water molecules favor the protons transfer. It is similar to the process of C_E-1W $\rightarrow$

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Int11-1W. Obviously, the activation energy of C_E-$2W_2$ → Int11-$2W_2$ is less than that of C_E-1W → Int11-1W but more than that of C_E-$2W_1$ → Int11-$2W_1$. This phenomenon illustrates that the water molecule localized in other zone affect the PT slightly. As a whole, the PT process of $2W_2$ is easier to achieve than that of $2W_1$. In summary, the hydration of the second water molecule further reinforces the assisting effect on the tautomeric process. When more water molecules are added, can they favor the PT furthermore?

In order to answer the above question, we studied the trihydrated and hexadhydrated cases. In $3W_3$-Path1, the hydration occurs in the same region like the dihydrated case. The changes of O_9-H_{12} bond in C_E-$3W_3$ is inappreciable compared with C_E-$2W_1$ (1.001 Å in C_E-$2W_1$ and 1.001 Å in C_E-$3W_3$, depicted in Table S1). Therefore, the assistant effect of three water molecules on PT should be similar to that of the dihydrated system. But the activation energy of the C_E-$3W_3$ → Int11-$3W_3$ is higher than that of C_E-$2W_1$→ Int11-$2W_1$ by 1.7 kcal/mol. This may be due to the higher energy cost of H_{12} transfer in a long chain. Similar results have been found for the intramolecular PT of Uracil.[错误！未定义书签。] Figure 8 demonstrates that the vibrational frequency of the O_9-H_{12}…O_{13} stretching mode is red-shifted when the second water molecule attaches to C_E-1W. That is to say, the electron density between O_9 and O_{13} decreases, leading to the decrease of the electrostatic interaction of this O-H…O H-bond. Therefore, H_{12} prefers to depart from O_9. But the vibrational frequency of O_9-H_{12}…O_{13} stretching mode is blue-shifted upon adding the third water molecule. This implies that the dihydrate is favorable than trihydrate. So it is not the case that the longer the water molecule chain is, the easier the proton transfers. Comparing C_E-$3W_1$ with C_E-$2W_1$, only fewer changes of the O_9-H_{12} is observed, so the assistant effect of water molecules on these two tautomeric processes are similar. The activation energy of the tautomeric process C_E-$3W_1$ → Int11-$3W_1$ (8.16kcal/mol) is a little lower than that of C_E-$2W_1$ → Int11-$2W_1$ (8.48kcal/mol). This means that the water molecule that is located in other zone can also favor H_{12} transfer process slightly. Int11-$3W_1$ → Int12-$3W_1$ is easier to achieve than C_E-$3W_1$ → Int11-$3W_1$, although the former one is assisted by only one water molecule. $3W_2$ is the easiest to achieve as these three molecules distribute symmetrically in three sides of cyanuric acid molecule. So the protons (H_{10}, H_{11}, H_{12}) transfer are all assisted by one water molecule. The activation energies of the whole tautomeric process are all very low (9.5kcal/mol for C_E-$3W_2$ → Int11-$3W_2$, 7.1kcal/mol for Int11-$3W_2$ → Int21-$3W_2$, 6.1kcal/mol for Int31-$3W_2$ → C_K-$3W_2$) and the activation energies of the three PT steps decrease gradually as discussed before. Further optimization for the trihydrated cyanuric acid molecule determines a special structure, C_K-$3W_4$. It forms a side-water-chain structure, so the tautomeric process of C_E-$3W_3$ may undergo two different pathways ($3W_3$-Path1 and $3W_3$-Path2). In $3W_3$-Path2, H_{12} transfer should be mainly assisted by two inside water molecules like the dihydrated case discussed above. But the activation of C_E-$3W_3$ → Int21-$3W_3$ (9.5 kcal/mol) is lower than that of C_E-$3W_3$ → Int11-$3W_3$ (10.2 kcal/mol) by 0.7 kcal/mol. As indicates that this kind of side-water-chain structure is favorable for PT. Comparing the tautomeric process of $2W_1$ with $3W_3$-Path2, it can be seen that the activation energy of C_E-$2W_1$ → Int11-$2W_1$ is lower than that of C_E-$3W_3$ → Int21-$3W_3$ by 1.0 kcal/mol. This indicates that the effect of side chain on the intermolecular PT is weak in this case. The activation energies of PT are not always reduced with the increasing of water molecule number and the long-range PT assisted by three water molecules is not optimal.

From the above analysis, the following three conclusions can be drawn: First, in the tautomeric process of cyanuric acid, the proton prefers to transfer step by step; second, the activation energies of these three steps decrease gradually when the protons are in similar situations; third, two water molecules are optimal in the PT process.

How about the activation energy changes (increase or decrease furthermore) when more

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water molecules are added to the system? How the water molecules in side chain affect the PT process? The hexadhydrated cases are taken into account to investigate the multihydrated effect (the tautomeric processes are depicted in Figure 6). C_E-$6W_1$ is similar to the dihydrated tautomeric process, but it is much easier than the PT process of C_E-$2W_1$. The activation energies of these three steps decrease gradually (8.2 kcal/mol, 5.2 kcal/mol and 4.6 kcal/mol). For C_E-$6W_2$, C_E-$6W_3$, C_E-$6W_4$, C_E-$6W_5$, everyone has been divided into two different cases to analysis. In Path1 of C_E-$6W_{2\text{-}5}$, the protons transfer through a long-water-chain, while in Path2 of C_E-$6W_{2\text{-}5}$, they undergo a side-water-chain structure. The PT process of C_E-$6W_2$ is similar to that of C_E-$3W_3$. The activation energy of C_E-$6W_2$ → Int11-$6W_2$ (9.4 kcal/mol) is a little higher than that of C_E-$6W_1$ → Int11-$6W_1$ (8.2 kcal/mol). In Path2 of C_E-$6W_2$, the side water chain plays a subordinate role in the PT process. Contrary to two paths of C_E-$3W_3$, the activation energy of C_E-$6W_2$ → Int21-$6W_2$ (9.9 kcal/mol) is a little higher than that of C_E-$6W_2$ → Int11-$6W_2$ (9.4 kcal/mol). But the activation energy of Int21-$6W_2$ → Int22-$6W_2$ (7.6 kcal/mol) is lower than that of Int11-$6W_2$ → Int12-$6W_2$ (8.8 kcal/mol). Compared with Path1 of $6W_{3\text{-}4}$ and $6W_2$, it can be found that the activation energy of C_E-$6W_{3\text{-}4}$ → Int11-$6W_{3\text{-}4}$ is increased. We also try to find out the TS11 of C_E-$6W_5$, where a six-water-chain is formed in one plane, but failed. It is proposed that its activation energy be higher because of its long hydrated chain. It can be concluded that the Path1 of $6W_{3\text{-}5}$ is much easier to achieve than the Path2 of $6W_{3\text{-}5}$. The results illuminate that the structure containing side-water-chain favors the PT significantly. The structure with two water molecules in the side chain (the structure like TS21-$6W_3$) is optimal. Figure 8 obviously shows that in Path1, the activation energy of C_E-$6W_n$→ Int11-$6W_n$ process increases gradually and the long-range PT assisted by three or even more water molecules is not favorable. This is due to the higher energy cost of PT in a long water-chain. Additionally, in the first step of tautomeric process except $6W_2$, the activation energy of Path2 is much lower than that of Path1. That is to say, the side-water-chain structure is more favorable for the PT and the structure with two water molecules in the side chain is optimal for the tautomeric process.

4. Conclusions:

The reliable B3LYP/6-311++G** method was employed to investigate the water-assisted PT processes of hydrated cyanuric acid. The following conclusions were drawn on the basis of DFT calculations and discussions.

First, the coupling modes of hydrated cyanuric acid are determined (C-mWn). As a whole, hydration stabilizes the system. C_K-mWn is more stable than C_E-mWn. The solubility of the system is related not only to the number of water molecules but also with the arrangement of water molecules. The one with higher symmetry is more soluble. Contrary to their stabilities, C_E-mWn is more soluble than C_K-mWn.

Second, in the tautomeric process of cyanuric acid, the protons transfer step by step and the activation energies decrease gradually. Water molecule assists the PT process of C_E → C_K. The optimal water molecule number to assist the PT is two. With the number of water molecules increasing, PT need go through a longer pathway and the extra energy consumption, so the activation energy increases. The PCM model is not as good as the explicit solvent model to describe the isomerization of the enolic form and the keto form.

At last, the structure containing side-water-chain is more efficient to reduce the activation energy of long-ring PT process. The cluster with two water molecules in the side chain is the most favorable for PT process. In all, hydration can induce the mutation of C_E to its keto isomer.

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