Mechanistic insight into the tautomerization of histidine initiated by water-catalyzed N–H and C–H cleavages

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Abstract

The N–H and C–H activation is of great significance in organic chemistry and chemical industry fields, especially, in the utilization of petroleum raw materials. High NδH (tautomer of natural histidine) content would increase Alzheimer's disease risk. To inhibit this and improve the activation of N–H and C–H bonds, isomerization mechanism from NδH to NεH of histidine-containing dipeptide catalyzed by water cluster was explored. The results discovered that water cluster assists this reaction by reducing the activation energies from 68.20 to 9.60 kcal mol^{-1}, and its size not only affects the reaction rate but also determines reaction pathway in a degree. Moreover, water cluster, taken as potential green catalyst, is more effective on the reactions involving N–H and C–H bond cleavages than reported common toxic organometallic compounds and have different catalytic mechanisms. This work also provide some theoretical guidance for the modulation of Alzheimer's disease induced by histidine isomerization.

Introduction

The N–H and C–H bonds are the most common in organic molecules, due to high thermodynamic and kinetic stability, activation of the two bonds has become a challenging topic in the field of organic chemistry. In particular, on heterocyclic ring, the cleavage of N–H and C–H bonds would be useful in modification and functionalization of heterocyclic compound in the field of synthetic chemistry and life science, but with hu{López-Chávez, 2019 #1}ge energy consumption and harsh conditions. For example, the isomerization reaction of naphthalene (Fig. 1) needs high temperature≥1273 K.[1] To improve readability, the configuration of related organic compounds are shown in Fig. 1.

Histidine extensively involves in various biological fields, such as the growth of infants and animals, and it has been observed locating at the active sites for half of the enzymes,[2] and plays a pivotal role in the enzyme catalytic performance depending on its specific structure, two active nitrogen atoms with lone pair electron in imidazole ring.[3] Histidine can be used for adjusting pH of biological medium[4] due to its ability to accept or donate proton(s). Moreover, in different acidity solution it has various structural forms. At pH~6.5 in vivo, histidine has two tautomeric forms,[5] NδH and NεH, as shown in Scheme 1, where the hydrogen atom locates on either Nδ or Nε site with ~1:4 Nδ/Nε ratio.[6] More Nδ histidine isomers would generate more *β*-sheet contents for the *β*-amyloid (A*β*) monomers,[7] leading to the A*β* monomers more prone to aggregate into oligomers,[8] and subsequently more apt to induce the Alzheimer's disease. Therefore, promotion of NδH→NεH tautomerism recovery becomes the structural basis for design or modification of new *β*-amyloid inhibitors.

Water molecule can accelerate tautomerism of organic substances through directly participating in a chemical reaction and biological metabolism, as a catalyst does. For example, water solution decreases energy barrier from amide- to enol- form of formamide (Fig. 1),[9] and converts synchronous mechanism to asynchronous one for proton-transfer in guanine-cytosine base pair (Fig. 1),[10] and forms intermolecular H-bond to avail amino-imino tautomerism of adenine (Fig. 1)[11] and uracil (Fig. 1).[12] In this work, water molecule was designed as possible catalyst to isomerize NδH to NεH, and histidine-

containing dipeptide was capped with NME and ACE, in order to shield its terminal disturbances of COOH and NH_2. The current study aims to making clear two questions, (1) whether water molecules do assist tautomerism from NεH to NδH or not? and (2) how do they work?

Computational methods

Coulomb-attenuated hybrid exchange-correlation (CAM-B3LYP) functional[13] was employed as it has been shown to give very similar results to expensive complete-active-space plus second-order Møller-Plesset perturbation theory (CASPT2) and symmetry-adapted cluster configuration interaction (CAS-CI) calculations.[14] The 6-311++G (d,p) basis set[15] was used because it is known to be reliable, particularly for calculations of closed-shell stable molecules and H-bonding systems. After geometry optimization, the harmonic vibrational frequency was calculated to verify each stationary point or saddle point. To confirm every transition state (TS) connecting the two associated minima (reactant and product) on the potential energy surface (PES), intrinsic reaction coordinate (IRC) analyses[16] for each reaction pathway were performed. All TSs were confirmed by only one imaginary frequency. It is noted that various possible individual complexes were fully conformationally inspected at the CAM-B3LYP/6-31++G** level of theory to ensure that the global (rather than merely local) minima were obtained, and only the geometry with the lowest energy was discussed in this paper. All activation energies () are the Gibbs free-energy differences between the TS and the corresponding reactant. Frontier molecular orbital theory[17] was applied based on the optimized geometries at the same level of theory.

All calculations were performed with the Gaussian 09 program package.[18]

Results And Discussion

No-catalyst

To realize proton transfer from Nδ to Nε site, three pathways from reactant NδH to product NεH were proposed in Scheme 1, (1) a stepwise reaction pathway includes proton transfer first from Cε to Nε site, and then from Nδ to Cε in the plane of imidazole ring; (2) an elementary reaction one, in which the proton directly transfers from Nδ to Nε cross the plane of imidazole ring; and (3) a concerted reaction one, in which the proton transfers from Nδ via Cε to Nε in the plane of imidazole ring.

Result reveals that gas-phase NεH is energetically more stable by 3.61 kcal mol^{-1} than NδH, consistent with that~1:4 Nδ/Nε ratio from previous experimental and simulated estimate.[6-7, 19] For the isomerization reaction from NδH to NεH in the absence of water molecule, only the stepwise reaction rather than other two is obtained and displayed in Fig. 2, in which the most stable geometries of reactant (R) NδH, TSs, and product (P) NεH in absent (top panel) and in present of explicit water molecules (panels 2-7) are optimized and two-step reaction processes are predicted. Hydrogen on Cε is potential candidate for proton interchange between Nε and Nδ sites, as the proton transfer is more energetically favorable than hydrogen radical transfer.[20] Structural analysis shows that long space separation

between Nε to Nδ may explains why hydrogen cannot directly shifting from Nε to Nδ. Previous work[21] verified the higher activation energy of hydrogen-transfer than that of proton-transfer.

The PESs in Fig.2 establish the associations for various dipeptide states, reactant R (NδH), intermediate (IM), transition states (TS1 and TS2), product P (NεH) and the relative energies (in bracket), from which the transition between two different states can be clearly observed and compared. For the initial step in the absence of water, Cε–H cleavage is first triggered, and lengthened by 0.221 Å, with Nε···H(Cε) distance greatly shortened to 1.236 Å. The outcome of these changes results in the proton-migration from Cε to Nε, and the generation of IM. For the second step, Nδ–H bond is shortened by 0.008 Å due to formation of the new bond Nε–H in IM, indicating the increasing difficulty for the following Nδ–H cleavage and Nε–H formation. Activation energy shows that the transition from IM to TS2 is 37.97 kcal mol^{-1}, far smaller than that of first step (68.20 kcal mol^{-1}), indicating that the initial step is rate-determining. The high energy barriers of TS1 and TS2 imply this is not thermodynamically feasible for NδH→NεH conversion and explains why proton-transfer in heterocyclic ring is experimentally unavailable. The relative energies disclose three thermodynamics processes, first endothermic (first-step 28.34 kcal mol^{-1}), then exothermic (second-step 31.95 kcal mol^{-1}), and finally exothermic (total process 3.61 kcal mol^{-1}) for the NδH→NεH transition in the absence of water (top panel in Fig. 2).

1W-system (1WR®1WP)

Water molecules usually bind together to form water clusters (nW, n=1,2,3….). This can be rationalized that lone pair of oxygen atom in one water molecule easily enters s-orbital of hydrogen atom from another adjacent water molecule to form strong H-bond. To consider the size effect of water cluster on the NδH→NεH isomerization reaction, up to 6W (n=1,2,3,…., 6) involved cases (1WR, 2WR,…, 6WR) were studied. Due to the presence of water molecule, elementary pathway (Scheme 1 and Fig. 3) was also obtained, besides of the stepwise one.

The stepwise pathway shown in Fig. 2 was firstly discussed. In reactant 1WR, H-bond distance of H(W)···Nε is 1.978 Å, indicating the strong binding affinity of the water molecule with NδH. With the addition of the water molecule, the structure of 1WTS1 has great changes. Five atoms O(W), H(W), Nε, Cε, and H(Cε) make up a planar five-membered ring with the dihedral angles $D_{Cε\text{-}Nε\text{-}H\text{-}O}$ of 1^o. The large dihedral $D_{Nδ\text{-}Cε\text{-}Nε\text{-}O}$ of 176^o indicates that the five-membered ring is almost coplanar with the imidazole ring. For the initial step, Nε···H(Cε) distance in 1WTS1 decreases by 0.783 Å and Cε–H bond increases by 0.265 Å, compared to the counterparts in reactant 1WR, indicating one proton migration from Cε to Nε. Meanwhile, the extended O–H(W) distance (0.314 Å) and shortened O(W)···H(Cε) (1.376 Å) imply that water plays a participator role, who accept a proton from Cε site and donate one of itself to the Nε site with an activation energy of 38.36 kcal mol^{-1}, far lower than that(68.20 kcal mol^{-1}) of TS1. Moreover, once the proton-transfer process of Cε®Nε is completed in the step, the water molecule will gain reconversion, characterizing a catalyst. In the second step, there is also a planar Cε–H–O–H–Nδ five-membered ring formed in 1WTS2. The small dihedral angle $D_{Nδ\text{-}Nε\text{-}H(W)\text{-}O(W)}$ of 1.4^o indicates that the ring is almost

coplanar to imidazole ring. The lower activation energy of 24.66 kcal mol^{-1} in the step than that in the first one indicates the first step rate-determining.

There is another potential pathway-elementary pathway once a water molecule is involved because the water can bridge Nδ and Nε sites by crossing the imidazole ring. The reactant and product in such a pathway are defined as nWR1 and nWP1 (Fig. 3), respectively, to differentiate them from their counterpart in the two-step pathways. Different from stepwise (two-step) pathway, the reaction is triggered first by the breaking of Nδ–H instead of Cε–H bond. Then H(Nδ) will bind the water and meanwhile a proton of the water itself will denote to the adjacent Nε site, confirmed by the distance changes and the formation of transition state 1WTS in the Fig. 3 (top panel). In 1WTS, dihedral angle $D_{Nδ\text{-}H\text{-}O\text{-}Nε}$ of 94° indicates that Nδ–H–O(W)–H(W)–Nε five-membered ring is perpendicular instead of coplanar to imidazole ring, and the water molecule does cross the imidazole ring and bridge Nδ and Nε sites. Cε–H bond does not participate this reaction as there is no large change observed during the whole reaction. The activation energy in such an elementary pathway is 46.75 kcal mol^{-1}, lower by 21.45 kcal mol^{-1} than that of rate-determining step in no-water system but higher by 8.39 kcal mol^{-1} than that of the stepwise pathway, respectively. Therefore, the stepwise pathway is the top priority for 1W-system in energy. Structurally, the activation for elementary pathway is mainly triggered from the cleavage of Nδ–H bond, while that of stepwise one is from the cleavage of Cε–H bond.

2W-system

For the keto → enol tautomerization of α- and *β*-cyclodiones (in Scheme 2),[22] 2W cluster shows a higher catalytic effect than 1W. Inspired by the result, the second water molecule is added to the 1W-system. After calculation, the most stable position of second water is determined close to Nε. As 1W-system does, 2W-system can be obtained from either stepwise or elementary pathway.

For the stepwise pathway shown Fig. 2, there is strong H-bond interaction between two water molecules with the short H···O distance of 1.811 Å in reactant 2WR. Shortened H(W)···Nε distance of 0.149 Å, in comparison with the counterpart in 1WR, implies stronger binding affinity of NδH with water. Structural analysis shows Cε–H and Nε are closer to water with shortened Cε–H···O(W) and Nε···H(W) distances of 0.523 and 0.149 Å. As a result, Cε–H bond, which can trigger the reaction, is apt to break with lengthened 0.007 Å. 2W forms planar seven-member ring with the responding reactant in both 2WTS1 and 2WTS2. The little dihedral angles of 1° for $D_{Cε\text{-}O\text{-}O\text{-}Nε}$ and $D_{Cε\text{-}O\text{-}O\text{-}Nδ}$ reveal the seven-member rings being coplanar to imidazole ring. For the initial step, Nε···H(Cε) distance decreases by 0.699 Å and Cε–H bond increases by 0.180 Å in 2WTS1 relative to that in 2WR, indicating one proton migration from Cε to Nε site. Meanwhile, shortened O(W)···H(Cε) and H(W)···Nε distances (0.793 and 0.699 Å) imply that 2W accepts a proton from Cε site and donates its proton to the Nε site with an activation energy of 23.53 kcal mol^{-1}, being lower by 14.83 kcal mol^{-1} than that (38.36 kcal mol^{-1}) of 1W-system (1WTS1). Moreover, the shortened O···O and H···O distances of 0.334 and 0.682 Å and the extended O–H bond length of 0.346 Å in 2W, reveal proton-transfer from one oxygen atom to another. In the transition from 2WIM to 2WTS2, the

activation energy is only 3.45 kcal mol^{-1}, 9.86 kcal mol^{-1} lower than that in 1W-system. Obviously, 2W is a more effective than 1W to catalyze the isomerization reaction, which is in line with the result of Liang.[9b]

In the elementary pathway, 2W forms H-bonds with H(Nδ) and Nε sites by cross the imidazole ring. In reactant 2WR1, one strong H-bond with H···O distance of 1.825 Å forms between the two water molecules. The reaction of 2WR1→2WTS is triggered first by Nδ–H cleavage, then H(Nδ) binds the near water molecule and one proton from another water transfers to the neighboring Nε site. Compared with reactant 1WR1, the shortened H(Nδ)···O(W) distance of 0.024 Å shows greater interaction of water with NδH. Extended Nδ–H and Nε–Cε distances of 0.004 and 0.002 Å and shortened Nδ–Cε bond of 0.002 Å reveal a trend that H(Nδ) more easily transfers to Nε site through water. In 2WTS, one coplanar seven-member ring formed by 2W cluster and NδH is almost perpendicular to imidazolium ring, proved by dihedral angles $D_{Nδ\text{-}O\text{-}O\text{-}Nε}$ of -1° and $D_{O\text{-}Nε\text{-}Cε\text{-}Nδ}$ of 94°. Contrast to that of 1W-system, the activation energy in the elementary pathway is greatly lower by 22.41 kcal mol^{-1} and slightly higher 0.81 kcal mol^{-1} than that of rate-determining step in the stepwise pathway, indicating a competitive effect between the elementary and stepwise pathways.

3W-system

Encouraged by the ongoing decrease of activation energy during isomerization of NδH→NεH from 1W to 2W system, the third water molecule was tried on various possible positions of 2WR, and only the structures with optimal position between two water was shown on the PESs for the elementary (Fig. 3) and stepwise pathways (Fig. 2).

In reactant 3WR, the H-bond interactions between the water molecules become stronger, confirmed by the shortened H(W)···O(W) distances of 0.099 and 0.071 Å with the intervened third water. Shortened Nε···H(3W) and O(W)···H(Cε) distances of 0.058 and 0.085 Å show stronger interaction of H(Nδ), meanwhile, weakened Cε–H bond is found with its shortened bond distance by 0.003 Å. Three water molecules in 3WTS1 have a chain-like structure and ∠O-O-O is 104°. All the three water molecules participate the proton-transfer process from Cε to Nε. The activation energy of 20.56 kcal mol^{-1} is lower by 2.97 kcal mol^{-1} than that (23.53 kcal mol^{-1}) of 2W-system. During the transition from 3WIM to 3WTS2, the activation energy is 2.73 kcal mol^{-1}, lower by 0.62 kcal mol^{-1} than that from 2WIM to 2WTS2 in 2W-system, indicating that the participation of the third water molecule does facilitate proton-transfer.

The 3WR1→3WP1 process in the elementary pathway involves the breaking of Nδ–H bond and the formation of Nε–H bond, verified by the distance changes. In reactant 3WR1, the third water increases length of the water-chain and another H-bond forms between water and Nε site, so the Nδ–H bond continually weakens with the extended bond distance by 0.002 Å. The activation energy is 16.84 kcal mol^{-1}, less by 7.50 kcal mol^{-1} than that of the 2W-system. To be surprising, the activation energy is lowered by 3.72 kcal mol^{-1} than that of the rate-determining step in the stepwise pathway. Therefore, the unexpected result indicates that the dominant reaction pathway is dependent on the size of water cluster and interchangeable.

4W-system

Urged by up-to-up catalytic effect of water, the fourth water molecule was designed to various possible positions of 3WR, but only one site between two water near Nδ was ultimately obtained. Due to more water molecules, concerted pathway (Fig. 4) was also discovered, besides of the stepwise and elementary ones.

On the PES of stepwise pathway, the shortened H-bond distances of Cε-H···O(4W) and Nε···H(4W) of 0.018 and 0.008 Å in 4WR indicate that the interaction further enlarges between NδH and water cluster. The structural analysis of 4WR and 4WTS1 reveals that a proton emigrates from Cε to the 4W cluster and the activation energy of 20.03 kcal mol^{-1} is required, slightly lower by 0.53 kcal mol^{-1} than that of 3W-system (from 4WR to 4WTS1), while a proton from the 4W donates to the Nε site. In the elementary pathway, the activation energy becomes 14.65 kcal mol^{-1}, lower by 5.38 kcal mol^{-1} than that in stepwise pathway (20.03 kcal mol^{-1}), indicating the elementary pathway to be more preferential one.

There is third potential pathway-concerted pathway, where one proton emigrates from Nδ via Cε to Nε, and 4W can bridge Nδ and Nε sites and simultaneously interact with Cε−H in the plane of imidazole ring. The reactant and product in such a pathway are defined as nWR2 and nWP2 (Fig. 4), respectively, to differentiate them from their counterparts in the elementary pathways. Compared with elementary pathway, the reaction is triggered by the breaking of Cε−H and Nδ−H instead of only Nδ−H bond. Meanwhile, the proton binding Cε transfers via two water of 4W to Nε site, and the proton at Nδ site emigrates to Cε via three water of 4W, instead of H(Nδ) transferring directly to Nε site via 4W, confirmed by the distance changes and the formation of transition state 4WTS3 in the Fig. 4 (top panel). Vibrational frequency analyses for 4WTS3 show that only one imaginary frequency (638 cm^{-1}) is observed, mainly composed of three stretching vibrations, Nδ−H, Cε−H, and O−H (near Nε) sites; whereas the imaginary frequency of 4WTS on elementary pathway includes only two stretching vibrations, Nδ−H and O−H without Cε−H. On PES of the concerted pathway, IRC analyses show that it can be completed from reactant 4WR2 to product 4WP2 in one step, which is different from the stepwise pathway, where two steps are required. Surprisingly, the activation energy in such a concerted pathway is 13.54 kcal mol^{-1}, lower by 1.11 and 6.49 kcal mol^{-1} than that in elementary pathway and stepwise one, respectively. Obviously, the concerted pathway is the most favorable to the NδH→NεH isomerization. Structurally, the concerted pathway characterizes the cleavages of both Cε−H and Nδ−H bonds, different from that of elementary and stepwise pathways, in which only cleavage of either Nδ−H or Cε−H bond is featured.

5W-system

The fifth water molecule was continually added in most probable positions, and the most stable structures in various states on PESs of potential stepwise, elementary, and concerted pathways were shown.

For the stepwise pathway, the activation energy is 19.75 kcal mol^{-1} from 5WR to 5WTS1 in the initial step, slightly lower by 0.28 kcal mol^{-1} than that for 4W-system (from 4WTS1 to 4WR). The proton-transfer from Cε to Nε is via four not all five water molecules of the 5W cluster, different from the second step. In the second step, i.e., from 5WIM to 5WTS2, a very low activation energy is 1.52 kcal mol^{-1}, lower by 0.82 kcal mol^{-1} than that of 4W-system.

On the PES of elementary pathway, all the five water molecules also participate in the reaction of 5WR1→ 5WP1 via 5WTS, and the activation energy (10.39 kcal mol^{-1}) is lowered by 4.26 kcal mol^{-1} because of the participation of one more water.

On concerted pathway, the activation energy (9.65 kcal mol^{-1}) reduces by 2.52 kcal mol^{-1} with the fifth water. This energy in such a concerted pathway is lower by 0.74 and 10.10 kcal mol^{-1} than that of elementary and stepwise ones, respectively. Therefore, the concerted pathway is optimal in terms of the energy. In 5WTS3, all water molecules in 5W cluster participate the proton-transfer process, in which five oxygen atoms of 5W are arranged in chain-like conformation instead of cyclic, due to the long distance between Nδ and Nε and the H-bond between water and Cε.

6W-system

To obtain the optimal cluster of water, the sixth water molecule was added and 6W cluster was designed through potential stepwise, elementary and concerted pathways, respectively.

On the PES of stepwise pathway, the activation energy (19.60 kcal mol^{-1}) from 6WR to 6WTS1 slightly decreases by 0.15 kcal mol^{-1} in the initial step. By contrast, the activation energy (1.59 kcal mol^{-1}) increases by 0.07 kcal mol^{-1} in the second step. So does in the elementary pathway, where the activation energy (10.94 kcal mol^{-1}) increases by 0.55 kcal mol^{-1}.

For the concerted pathway, six corresponding TSs were obtained, where the sixth water molecule can forms two H-bonds with two near water molecules or one H-bond with the terminal water molecules in 5W cluster. The optimal reaction pathway including transition state 6WTS3 was shown in Fig. 4 and the other potential TSs (6WTSa-e) in Fig. 5. The activation energy (9.60 kcal mol^{-1}) is lower by 10.00 and 1.34 kcal mol^{-1} than that for stepwise and elementary pathways, and by 0.05 kcal mol^{-1} than that of 5W-system, consistent with the comparable activation energy of 5W- and 6W-systems (5WTS3 vs 6WTS3). It is worth mentioning that for all TSs in these three pathways expect 6WTSe, five water molecules are present in the first water shell, and the sixth one is present in the second water shell. So 5W would be the minimum cluster but the most potent catalyst for NdH→NεH isomerization.

A comparison for three pathways

Fig. 6 shows that the introduction of water cluster (nW) greatly reduces the activation energy and the value is becoming smaller and smaller along with the increase of water cluster size from n=1 to 5, up to

6. The added water molecule induces extended Cε—H or Nδ—H bond to varying degrees, which can trigger the isomerization reaction. Furthermore, the choice of reaction pathway would depend on the number of water in cluster. In detail, stepwise pathway is more favorable than elementary one when n=1. That is to say, the cleavage of Cε—H bond is easier than Nδ—H. When n=2, stepwise and elementary pathways are competitive; when n=3, elementary pathway takes priority over the stepwise one, indicating Nδ—H bond would prefer to breaking instead of Cε—H bond. While n=4, the concerted pathway becomes available and competitive with elementary one and superior to the stepwise one. When n=5 and 6, concerted pathway is the best candidate, implying that the simultaneous breaking of Nd—H and Cε—H is superior to the successive one, and 5W cluster in such pathway would be the potential optimal catalyst and minimum cluster size for NδH→NεH isomerization. The extended and comparable either Nd—H or Cε—H distance in 5W-system and 6W-system further validates this point (Fig. 8).

Table 1 Computed frontier molecular orbital energies (in a.u) of the reactants for stepwise (nWR), elementary (nWR1), and concerted (nWR2) pathways.

	n	HOMO	LOMO	HOMO-LUMO gap
stepwise	1	-0.292	0.080	0.372
	2	-0.259	0.046	0.315
	3	-0.244	0.034	0.278
	4	-0.233	0.027	0.260
	5	-0.226	0.008	0.234
	6	-0.218	0.001	0.219
elementary	1	-0.290	0.077	0.367
	2	-0.257	0.053	0.310
	3	-0.237	0.037	0.274
	4	-0.231	0.026	0.257
	5	-0.202	0.013	0.215
	6	-0.210	0.015	0.225
concerted	4	-0.231	0.030	0.261
	5	-0.224	0.027	0.251
	6	-0.220	0.028	0.248

The frontier molecular orbital theory was used at the same theory level. High HOMO and low LUMO energies severally suggest strong electron-donor and electron-acceptation capability, and small HOMO-LUMO gap indicates the transmission being easy to do.[23] These molecular orbital energies of reactants

on each of three pathways were shown in Table 1, from which one can find that with increasing size of water cluster, the HOMO and HOMO-LUMO gap show a decreasing tendency, while LUMO energies are the opposite. Thus, electron-donor, electron-acceptor and electron-transfer capability of reactant NδH-nW all enhance, that is in consistent with the decreasing trend of energy barrier for nW-systems as *n* grows from 1 to 6.

A comparison to theoretical and experimental results

For amino-imino tautomers of formamide,[9] nW (n=1-3)-systems were considered, only one water participates the proton-transfer process, while we studied the 3W-system of formamide of Liang[9b] and obtained new TS (Fig. 7), in which all three water take part in the process, and its energy is lowered by 12.88 kcal mol^{-1} than the reported results. The nW (n=1-5)-systems were also studied for intramolecular proton-transfer of uracil,[12] where only three water participate this process in the 5W-system, different from present mutual participation of 5W. For these systems, although only one elementary pathway was obtained, catalytic mechanism is same to our result that water accepts a proton from one atom on the active site and denotes its proton to other atom on the active site. While water helps catalyze proton-transfer in guanine-cytosine base pair,[10] water does not directly interact with the atoms on the active sites, but with the atoms in the vicinity of active sites, indicating an assistant catalytic mechanism.

Organic transition metal can activate C—H or N—H bonds by combining N—Heterocyclic carbene, would help to synthesize various ring-fused cationic N—Heterocyclic structural motifs. For example, Ir,[24] Rh,[25] and palladium complexes can catalyze C2—H alkylation in imidazole ring of indole (in Fig. 1),[26] and palladium complex also activates N—H bond of phthalimide (Fig. 1).[27] The mechanism of metal-catalyzed was predicted[27-28] as that the electrophilicity metal cation attacks five-member ring of indole, due to this ring with N having more electron than fix-member benzene ring, and then bonds with C or N atom. This mechanism is different from present water-assisted C—H breaking reaction. It is worth mentioning that ruthenium complex could improve the terminal C_{sp2}—H bond cleavage in phenyl vinyl (Fig. 1) with a energy barrier of 27.3 kcal mol^{-1},[29] although this bond is more prone to breakage than C_{sp2}—H at the active site in our system according to the values of bond dissociation energy,[30] the energy barrier is higher than that of present 6W-system (9.60 kcal mol^{-1}), indicating the catalytic activity of water is better that the metallorganics. Moreover, it is well known transition metal ruthenium is biologically toxic, and could bring serious environmental pollution of water and soil. Moreover, these metal-catalyzed reactions need many substances harmful to the environment, such as organic ligand triphenylphosphine derivatives, organic solvent, halide and some base compound. To sum up, water cluster is more effective, safe and green than metal-containing catalyst for N—H and C—H cleavages.

Conclusion

Herein isomerization reaction mechanism from NδH to NεH of histidine-containing dipeptide was systematically analyzed. Potential elementary, stepwise, and concerted reaction pathways were obtained for nW-catalyzed systems (n=0, 1 to 6). Water cluster exhibits proton-delivery effect in proton-transfer

process of all the three pathways. It participates in the isomerization and form proton-transfer chain, leading to C–H and N–H bonds breaking easily. Calculated results revealed that this reaction would not possibly take place in the absence of water because of very high energy barrier (68.20 kcal mol^{-1}), whereas growing water cluster size nW (n from 1 to 6) can greatly catalyze this reaction. The activation energy for rate-determining step on stepwise pathway greatly reduces from 38.36 to 19.60 kcal mol^{-1} as n is from 1 to 6. The energies on elementary pathway become 46.75 to 10.39 kcal mol^{-1}. Whereas on concerted one it is from 13.54 to 9.60 kcal mol^{-1} along with n from 4 to 6. It is clearly that the size of water cluster determines reaction pathway in a degree. When 1W is present, the stepwise pathway is more favorable than the elementary one, indicating the breaking of C–H bond takes priority over that of N–H bond. The participation of 2W makes these two pathways to be competitive; while 3W leads the cleavage of N–H bond to be first. Concerted pathway in 4W-system is slightly dominant among these three ones and has an increasing advantage for 5W- and 6W-systems. By contrast, 5W cluster is determined the minimum cluster size as the most potent catalyst for NδH→NεH isomerization in the concerted and elementary pathways. Compared with toxic organometal catalysts, water cluster is potential green and more efficient catalyst for N–H and C–H bonds cleavage with different catalytic mechanisms.

This work was hoped to provide some theoretical guidance and basis for the activation and cleavage of N–H and C–H bonds in other molecules with such kind of cyclic structure and for the treatment measures of Alzheimer's disease induced by histidine isomerization.

Declarations

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Consent for publication All authors agree for the publication of the manuscript.

Conflict of interest The authors declare no competing interests.

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Scheme

Scheme 1 is available in supplementary section.

Figures

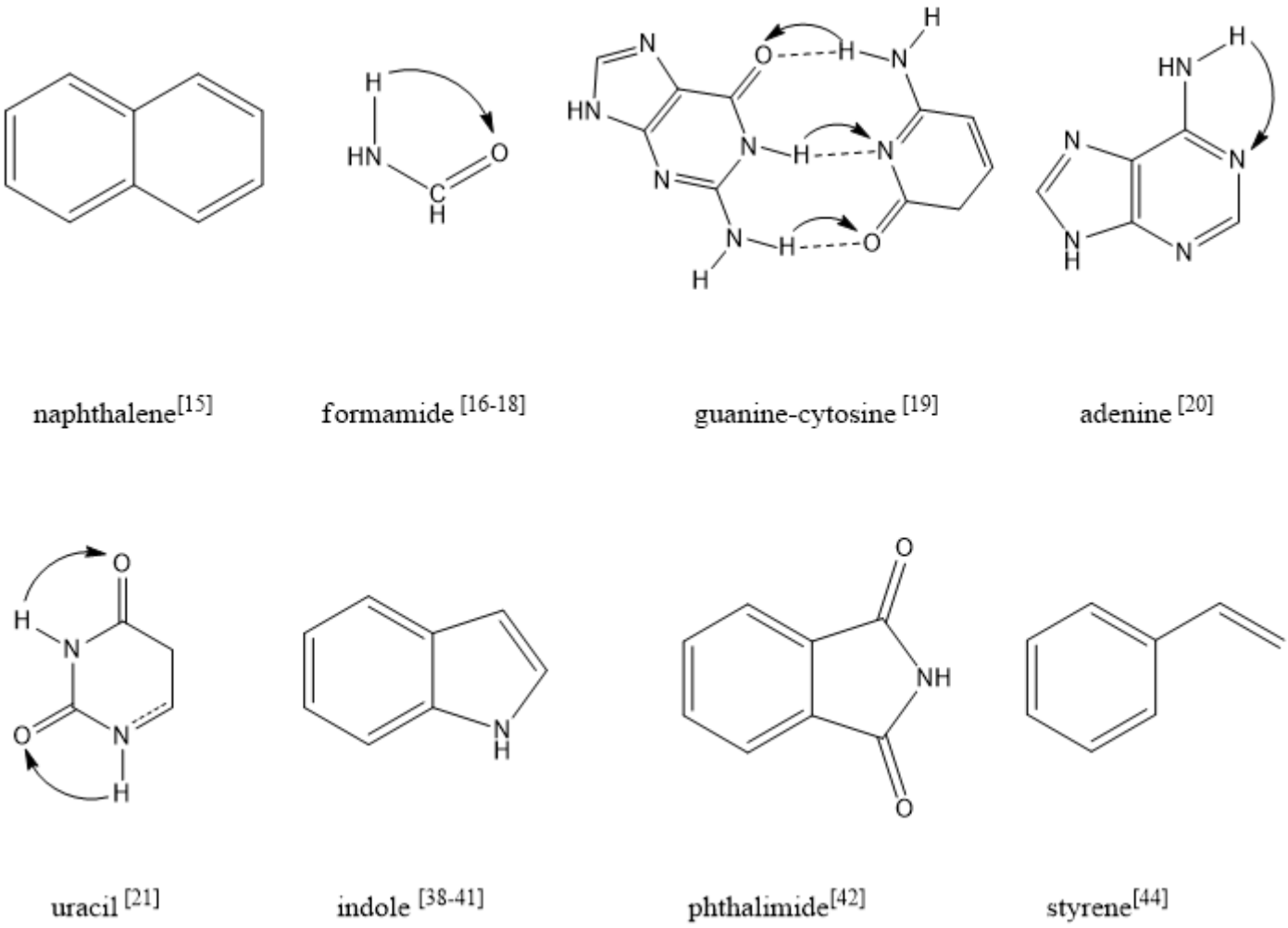


Figure 1

2D structures of eight compounds.

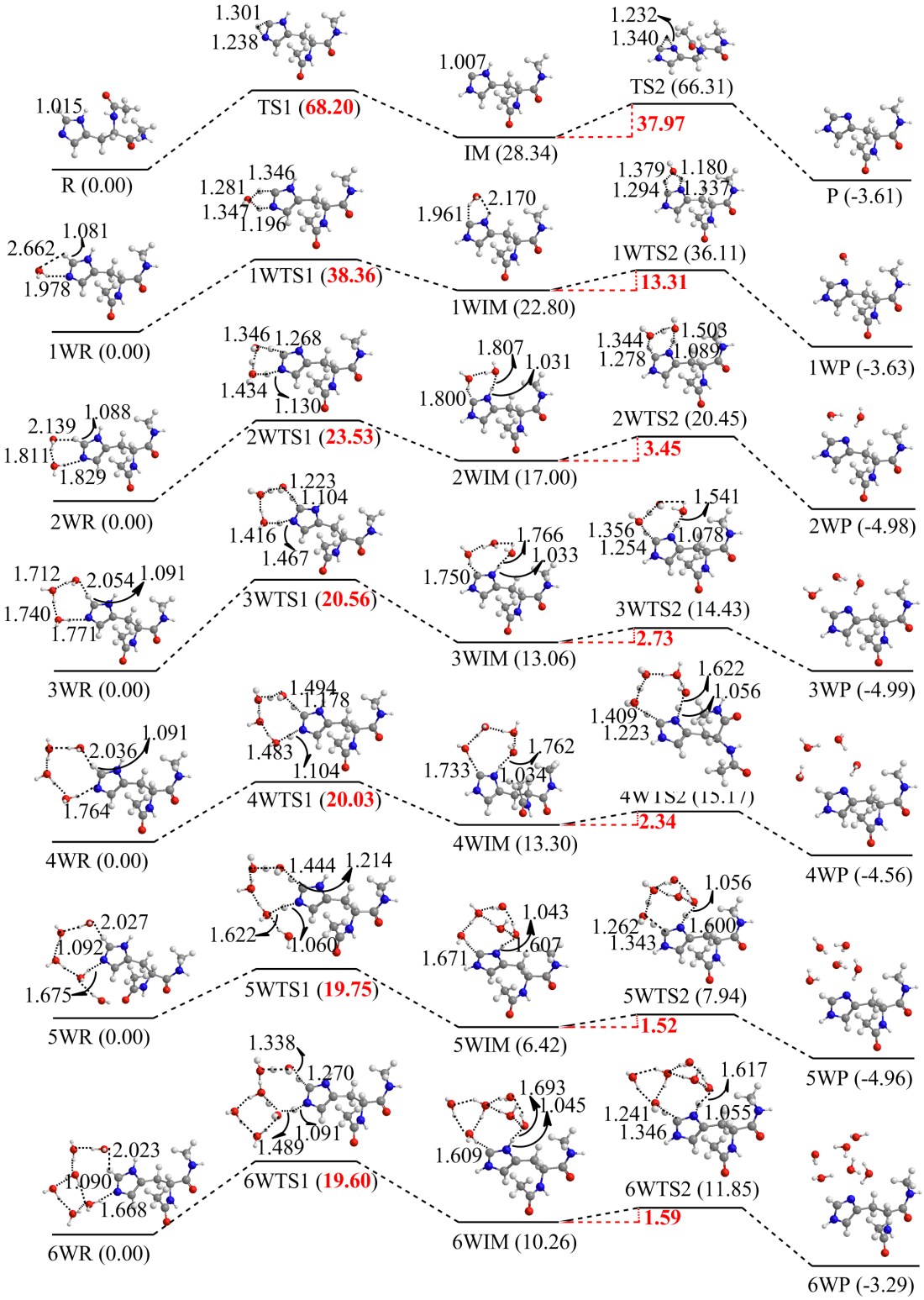


Figure 2

PESs of stepwise pathway for no/one/double/triple/quadruple/quintuple/sextuple-water -catalyzed isomerization from NδH to NεH of histidine-containing dipeptide. Distances in Å and relative energies (in bracket) in kcal mol^{-1}.

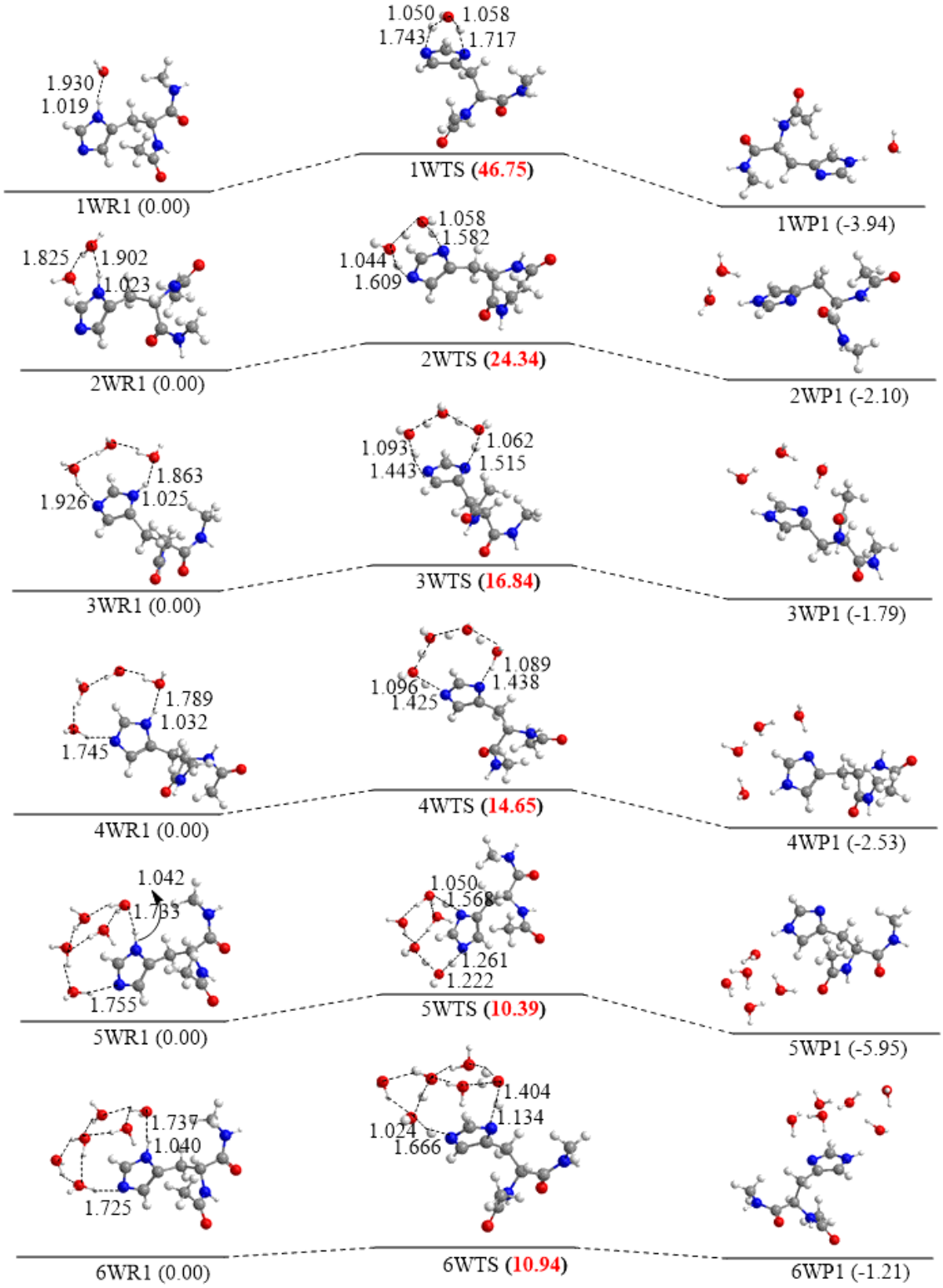


Figure 3

PESs of elementary pathway for one/double/triple/quadruple/quintuple/sextuple-water -catalyzed isomerization from NδH to NεH of histidine-containing dipeptide. Distances in Å and relative energies (in bracket) in kcal mol^{-1}.

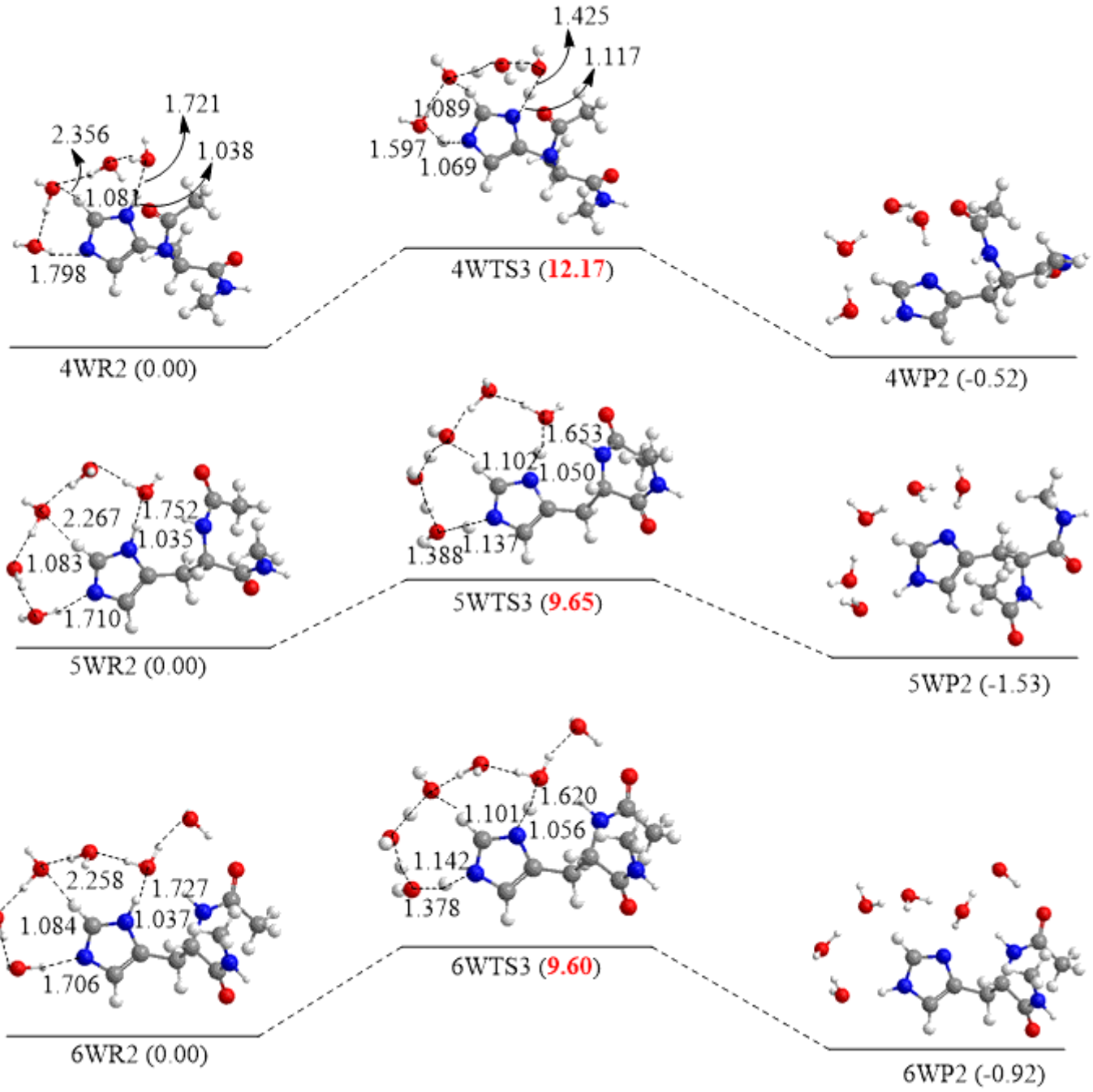


Figure 4

PESs of concerted pathway for quadruple/quintuple/sexruple-water-catalyzed isomerization from NδH to NεH of histidine-containing dipeptide. Distances in Å and relative energies(in bracket) in kcal mol^{-1}.

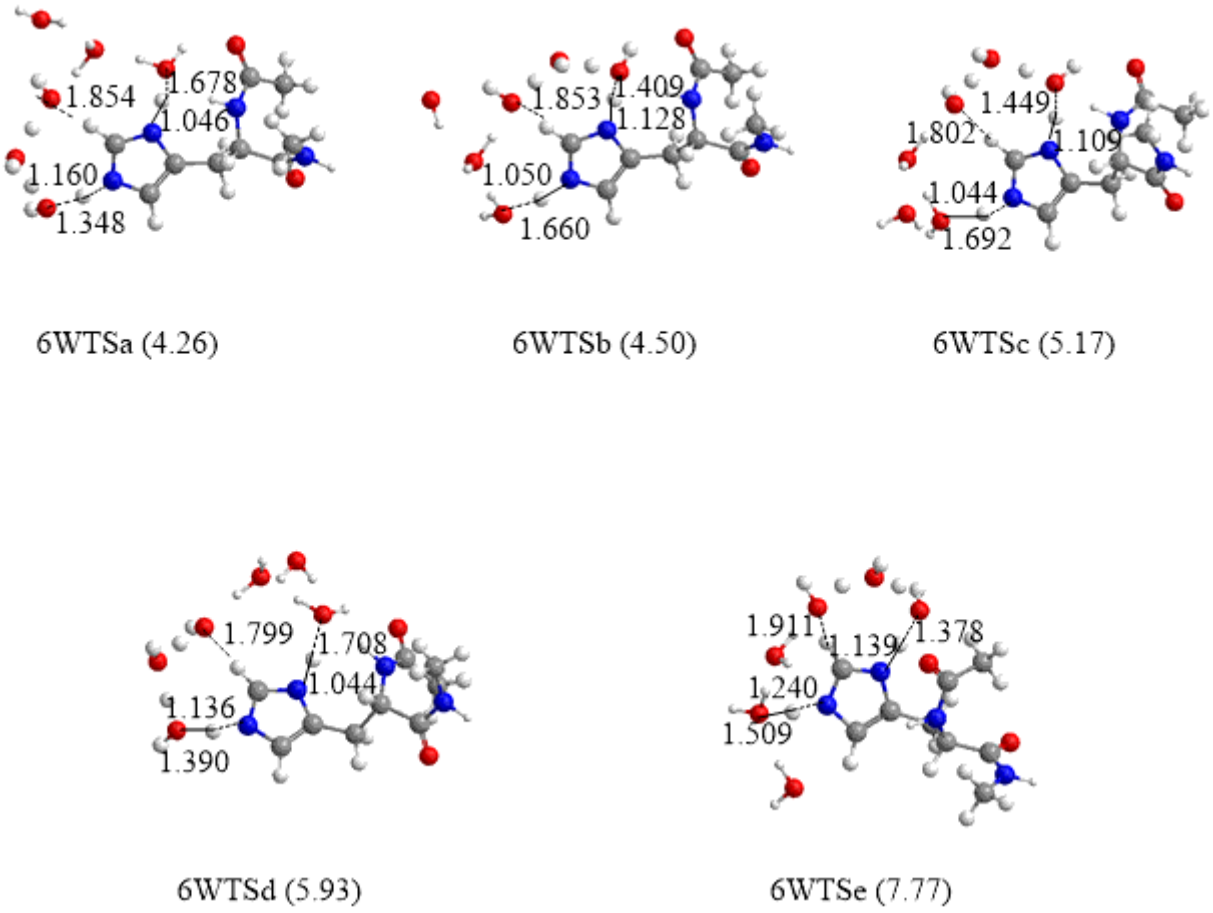


Figure 5

Five possible TSs 6WTSa-e of 6W-system on concerted pathway. Distances in Å and the relative energies(in bracket) of each to 6WTS3 in kcal mol^{-1}.

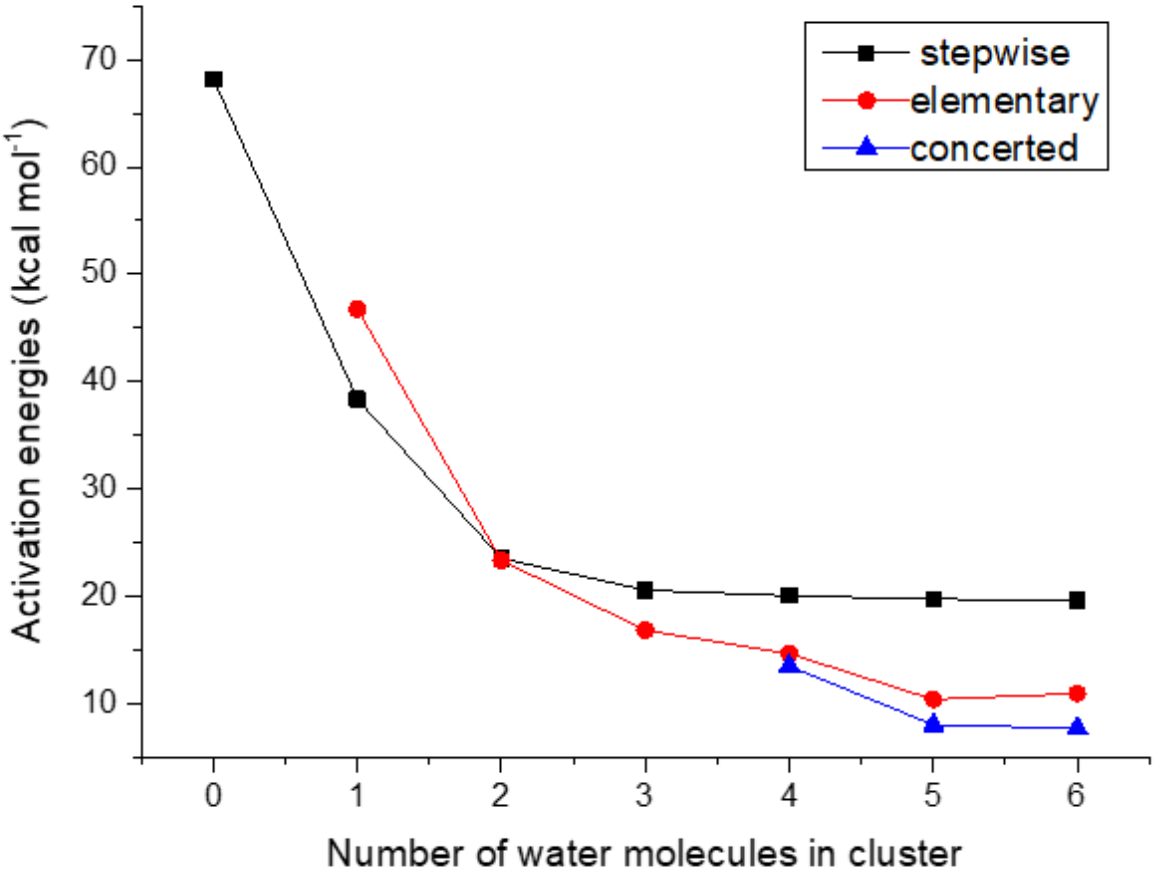
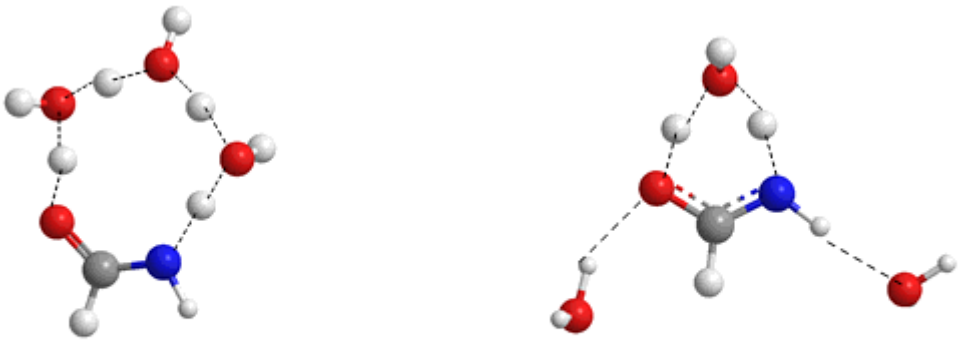


Figure 6

The activation energy changes with the size of water cluster in the complexes of reactant histidine-containing dipeptide and water cluster (nW, n=1-6).



TS^1 (0.00)

TS^2 (12.88)

Figure 7

TSs for the isomerization from amino- to imino- form of formamide. TS^1 is our result and TS^2 show the report of Liang.[12b] The relative energies (in bracket) in kcal mol^{-1}.

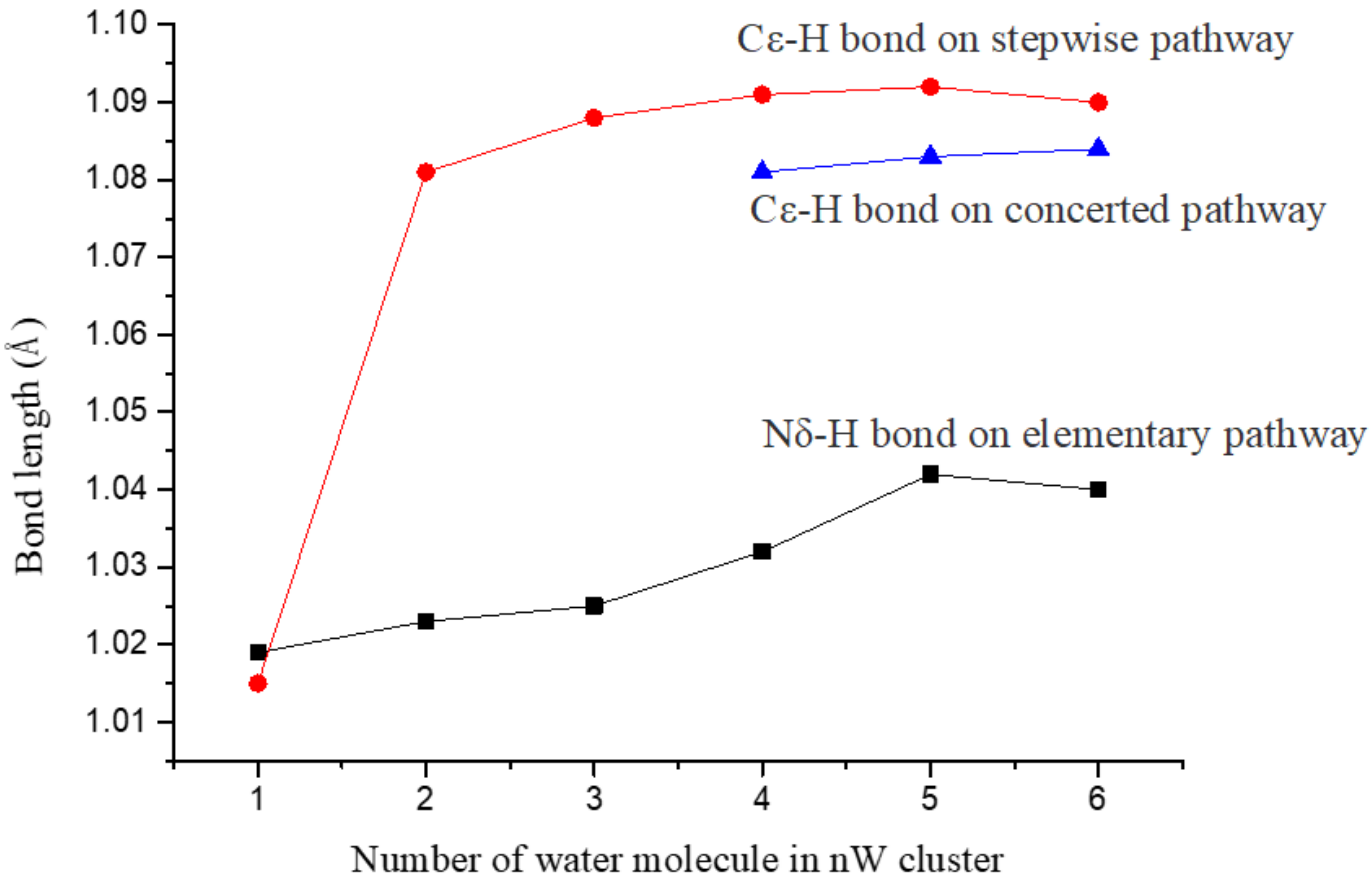


Figure 8

Bond length changes with the size of water cluster for the complexes of reactant histidine-containing dipeptide and water cluster (nW, n=1-6).

Supplementary Files

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