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Cooperative effect of water molecules in the self-catalyzed neutral hydrolysis of isocyanic acid: a comprehensive theoretical study

Xi-Guang Wei · Xiao-Ming Sun · Xiao-Peng Wu · Song Geng · Yi Ren · Ning-Bew Wong · Wai-Kee Li

Abstract The detailed reaction mechanism for the water-assisted hydrolysis of isocyanic acid, $HNCO+(n+1) H_2O \rightarrow CO_2+NH_3+nH_2O$ (n=0−6), taking place in the gas phase, has been investigated. All structures were optimized and characterized at the MP2/6-31+G* level of theory, and then re-optimized at MP2/6-311++G**. The seven explicit water molecules participating in the hydrolysis can be divided into two groups, one directly involved in the proton relay, and the other located in the vicinity of the substrate playing the cooperative role by engaging in hydrogen-bonding to HN=C=O. Two possible reaction pathways, the addition of water molecule across the C=N bond or across the C=O bond, are discussed, and the former is proved to be more favorable energetically. Our calculations suggest that, in the most kinetically favorable pathway for the titled hydrolysis, three water molecules are directly participating in the hydrogen transfer via an eight-membered cyclic transition state, while the other four water molecules catalyze the hydrolysis of HN=C=O by forming three eight-membered cooperative loops near the substrate. This strain-free hydrogen-bond network leads to the best estimated rate-determining activation energy of 24.9 kJ mol^{-1} at 600 K, in excellent agreement with the gas-phase kinetic experimental result, 25.8 kJ mol^{-1}.

Keywords Cooperative effect · Isocyanic acid · Self-catalyzed neutral hydrolysis · Strain-free hydrogen-bond network

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Introduction

Isocyanic acid (NH=C=O) is an interesting molecule in many respects. It is the simplest stable chemical compound that contains carbon, hydrogen, nitrogen, and oxygen, the four most commonly-found elements in organic chemistry and biology, and it is also the simplest member of the isocyanic (RN=C=O) family. Since the discovery of HNCO by Liebig and Wöhler in 1830 [1], it has been exhaustively investigated experimentally and theoretically [2–23]. In particular, the hydrolysis reaction of isocyanic acid has been the subject of numerous studies [15–23]. This intense interest is likely due to the various roles HN=C=O plays in polymer industry, pharmaceutical industry, and agriculture [3], and also due to the controversial reaction mechanism of the hydrolysis [22, 23].

In the hydrolysis of HNCO, there are two possible reaction pathways (called path A and path B, see Scheme 1) [22]. In path A, the nucleophilic addition of the water molecule first occurs across the C=N bond, yielding intermediate carbamic acid, which breaks down to give the final products, ammonia and carbon dioxide, by intramolecular hydrogen shift. In path B, the same two products are formed by successive intramolecular hydrogen shifts, after the initial water addition across the C=O bond.

There are many studies on the hydrolysis of HN=C=O. Aigner et al. previously carried out the gas-phase kinetic experiment on this reaction [21], and determined the reaction order and the reaction constant, leading to an activation energy of 25.8 kJ mol^{-1}. Some authors reported the hydrolytic decomposition of HN=C=O on selective catalytic reduction (SCR) catalysts [15], over two different ion exchange zeolites in urea-SCR [17], or on the TiO$_2$-anatase (101) surface [19]. Raspoet et al. [22] made a kinetic and mechanistic study on the water-catalyzed hydrolysis of HN=C=O, and the reaction of isocyanic acid with up to three water molecules was modeled. Their study showed that the nucleophilic addition of water occurs concertedly, and addition across the C=N bond is preferred. Moreover, they also pointed out a third water molecule may be needed to facilitate the hydrolysis by forming a transition state (TS) with an eight-membered ring. More recently, Arroyo et al. [23] investigated the neutral hydrolysis of HN=C=O in solution phase by means of molecular dynamics simulation using a two-water hydrolysis model, and concluded that the water-assisted mechanism with attacking the C=N bond is preferred to the mechanism with three water molecules comprising a TS with an eight-membered ring, after taking the entropy contribution into account.

Generally speaking, there are two different schools of thought on the mechanism of this hydrolysis reaction. Some authors only consider the water self-catalysis, i.e., water directly participating in the proton transfer, via a six-membered or an eight-membered cycle [24–32], while other authors propose the idea of cooperative effect in the hydrolysis, i.e., the water molecule(s) can also catalyze the reaction by engaging in hydrogen bonding to the substrate, instead of directly participating in the proton transfer [33–

43]. In the study of the three-water hydrolysis of CO$_2$ [33] and NH=C=NH [34, 35], Lewis et al. suggested that the most favorable reaction pathway involves two water molecules forming a six-membered proton transfer ring, and the third water molecule is placed in the vicinity of the substrate catalyzing the hydrolysis. Our recent theoretical studies on the hydrolysis of COS [38], CS$_2$ [39], and CH$_2$=C=NH [42] also show that the hydrolysis mechanism of these cumulenes containing N, O, or S as the heteroatom can be better described by the model of Lewis et al., i.e., it is necessary to consider the cooperative effect. Moreover, it is found that the cooperative effect induced by a strain-free eight-membered hydrogen-binding ring is more favorable energetically. For example, the rate-determining activation barrier of the three-water hydrolysis of CH$_2$=C=NH is 148.3 kJ mol^{-1} via an eight-membered proton transfer cycle; this barrier is reduced to 95.1 kJ mol^{-1} if there is a water dimer in the non-reactive region, supplying cooperative effect via another eight-membered hydrogen-bond cycle [42].

In view of the importance of cooperative effect in the hydrolysis mechanism and no previous study has been reported about this effect for the hydrolysis of HN=C=O, the study on the hydrolysis mechanism of isocyanic acid is deemed as a desirable and timely project.

In the present work, a comprehensive theoretical investigation on the hydrolysis mechanism involving up to seven explicit water molecules is carried out. Seven water molecules are divided into two groups, some of which directly participate in the hydrolysis, while others act as cooperative water molecules.

$$HNCO + (n + 1)H_2O \rightarrow NH_3 + CO_2 + nH_2O(n = 0 - 6) \quad (1)$$

The main objectives of our study on the hydrolysis of HN=C=O include: (a) to determine how many water molecules are actively involved after considering the entropy contribution; (b) to assess the cooperative effect of water molecules in this process; (c) in particular, to compare the effect of cooperative water molecules located in different regions. The present research will help us to better understand the mechanism of hydrolysis and the influence of cooperative water molecules on the hydrolysis of HN=C=O in the gas-phase, and these findings may be

Scheme 1 Two possible reaction pathways for the neutral hydrolysis of HNCO, path A and path B
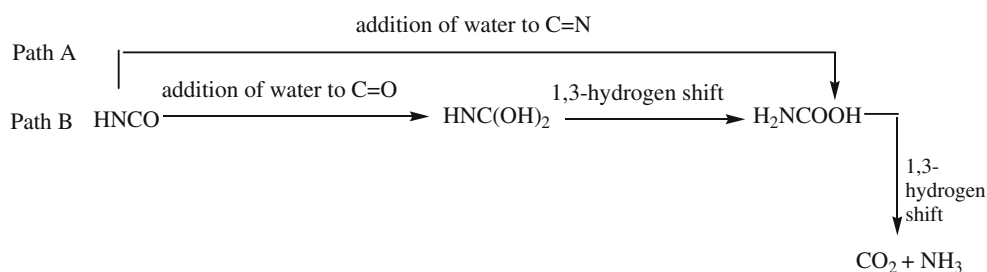
extended to the mechanistic study on the hydrolysis of cumulenes containing other heteroatom(s).

Computational details

All calculations in this study were performed using GAUSSIAN 03 suite of programs [44]. The geometries of all species, including reactants, reactant complexes, transition states, intermediates and products were fully optimized and characterized by vibrational frequency analysis at the level of MP2/6-31+G*; then they were further optimized at MP2/6-311++G**. The relative energies were calculated by including MP2/6-31+G* zero-point vibrational energy corrections which were scaled by the empirical factor of 0.98 [45]. This procedure has been used previously [42] and appears to be reliable for the present system. Thermal and entropy corrections were computed by standard statistical methods. Charge distributions were obtained from the wave functions calculated at the MP2/6-311++G** level, employing natural population analysis (NPA) [46]. The catalytic effect of water molecules described in this study is explained by the geometric changes and electron re-organization among the species involved in the rate-determining step. Throughout this paper, all bond lengths are in angstroms (Å) and bond angles are in degrees (°). All energetics (in $kJ \cdot mol^{-1}$) are computed by the enthalpy and Gibbs free energy changes relative to separated reactants, $HN=C=O$ and water cluster, at 298 K, denoted as ΔH and ΔG at the level of MP2/6-311++G** including MP2/6-31+G* enthalpy and entropy corrections.

Results and discussion

For the convenience of discussions, reactant pre-complex, transition state, intermediate, and product complex are denoted as **M**, **TS, In**, and **P**, respectively. In order to distinguish the two possible reaction channels, path A and path B, as described in Scheme 1, the italic prefixes **a-** and **b-** are used to differentiate the species involved in the concerted nucleophilic addition of water molecules taking place across the $C=N$ bond or $C=O$ bond, respectively, of $HN=C=O$. These species names have subscripts i and j (i, j=0, 1, 2, and 3), connected by a hyphen, in which i refers to the number of water molecule(s) in the reactive region, where the proton relay occurs, and j refers to the number of water molecule(s) in the non-reactive region, where the water molecule(s) can catalyze the hydrolysis of $HN=C=O$ by taking part in hydrogen bonding with the substrate, i.e., cooperative effect.

In the hydrolysis of $HN=C=O$ involving several water molecules, the water cluster can act as nucleophilic reagent, as also seen in the theoretical studies for the hydrolysis of

metal-alkoxides [47], and the water-assisted solvolysis of N,N-dimethylformamide [48]. Due to the existence of many minimum-energy structures for the water cluster containing the same number of water molecules, the geometries of water cluster, $(H_2O)_n$, n=2−7, in the present work (Fig. 1), are the most stable ones from the previous studies [49–57].

Our discussion consists of three parts. We will first present the influence of the number of explicit water molecules on the potential energy surface (PES) in the presence of up to three water molecules directly participating in proton relay without explicit cooperative solvent molecule(s), i.e., i=0−3 and j=0. Then, we will add one water molecule at a time, until there is a total of four, into the reaction system to observe the cooperative catalysis effect. Finally, we will compare the catalytic effect of the two groups of explicit solvent molecules, and explore the origin of water self-catalysis in the hydrolysis of $HN=C=O$.

Hydrolysis reaction pathways of isocyanic acid without any cooperative water (i=0−3, j=0)

The hydrolysis of $HN=C=O$ without cooperative water molecules has been previously examined [22]. In this section, to facilitate comparisons at the same level of theory, we check these pathways again. Figures 2 and S1–S3 illustrate the important optimized geometries of the various species involved in the hydrolysis reaction of isocyanic acid. The relative energies in terms of enthalpy and Gibbs free energy are also presented.

Considering the similarity of one-, two-, three-, and four-water hydrolysis without explicit cooperative water molecule, in this part, we only make a simple comment on the mechanism of the one-water hydrolysis of isocyanic acid.

The extensive study for the interaction between a water monomer and $HN=C=O$ shows that there are two possible reactants pre-complexes, a-**M**$_{0-0}$ and b-**M**$_{0-0}$, related to the subsequent respective key TSs, corresponding to two different pathways. The neutral hydrolysis of $HN=C=O$ starts with the nucleophilic addition of a water molecule on the central carbon atom, accompanying a proton transfer from water to the nitrogen atom of $HN=C=O$ (path A), or the addition takes places across $C=O$ bond (path B). The final hydrolysis product, $H_3N \cdots CO_2$ complex, is formed by one or two intramolecular hydrogen shifts.

The activation barriers ($\Delta H^{\neq}$) of the three steps in the single water molecule hydrolysis of $HN=C=O$ across the $C=N$ bond (path A) imply that the first step is rate-determining. For the pathway of addition across the $C=O$ bond (path B), the first step is also found to be rate-determining and the energy barrier is as high as 202.6 $kJ \cdot mol^{-1}$. These results indicate that the hydrolysis of HN=

Fig. 1 The most stable
structures of water cluster
$(H_2O)_n$, n=2 − 7

Dimer

Trimer

Tetramer

Pentamer

Hexamer

Heptamer
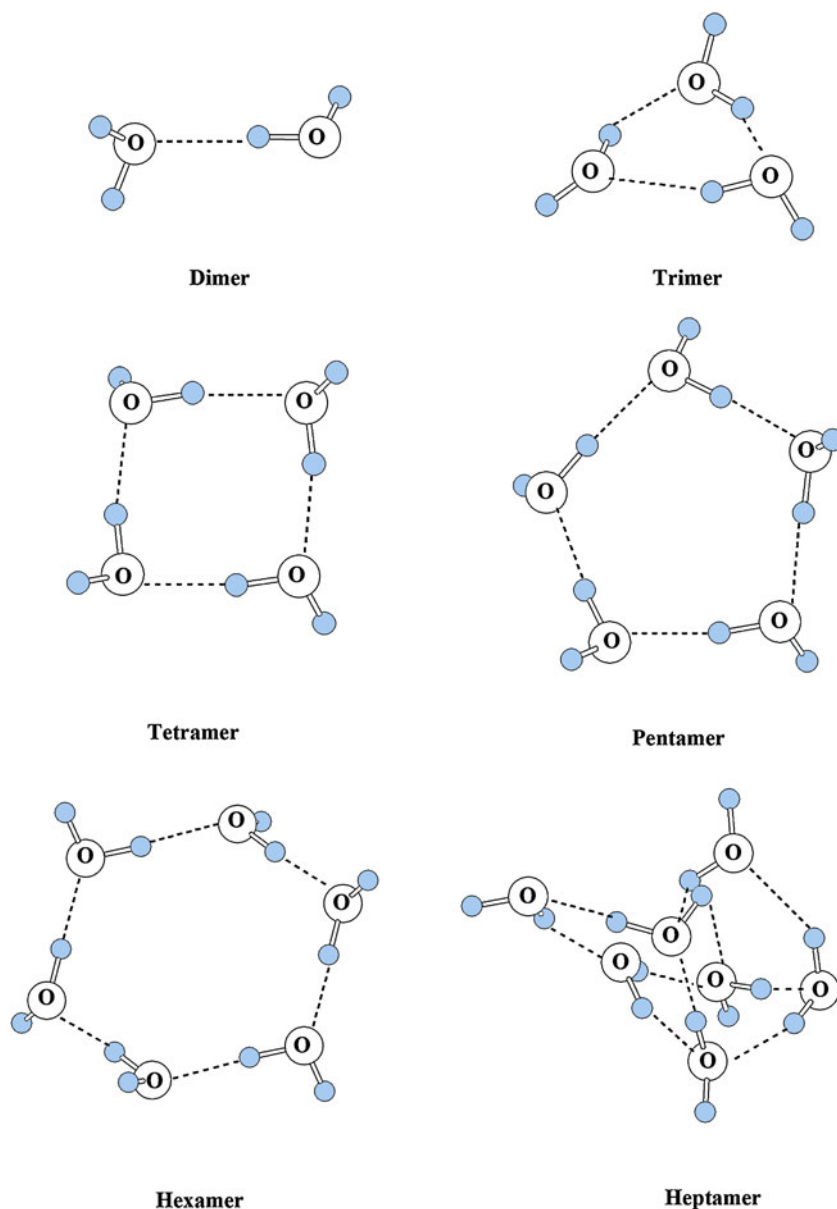
C=O involving one water molecule is difficult to occur. This difficulty can be attributed to that the formation of the four-center TS is orbital forbidden, and there is a very severe ring strain associated with the four-membered ring TS, suggesting that additional water molecules should be considered in the hydrolysis of isocyanic acid.

Inspection of Figs. 2 and S1–S3 shows that the rate-determining barriers in terms of relative Gibbs free energy vary with the increment of water molecules. For path A, the calculated $\Delta G^{\neq}$ values for the first step are 202.6, 142.0, 134.6, and 157.1 kJ·mol^{-1} for i=0 − 3, respectively. In path B, the corresponding barriers are 248.4, 191.4, and 182.9 kJ·mol^{-1} for i=0 − 2, respectively, while, unfortunately, the b-TS$_{3-0}$ was not located after numerous tries. These calculations indicate that the nucleophilic addition of water

always prefers to attack across the C=N bond rather than across the C=O bond of the isocyanic acid, and the hydrolysis via an eight-membered proton transfer loop (i=2) is the most favorable energetically, which is consistent with the findings by Raspoet et al. [22]. The favorable addition of water across the C=N bond can be explained by electrostatic surface potential (ESP) analysis of HN=C=O (see Fig. S4), where the ESP value in the region around nitrogen atom is more negative, implying the nitrogen atom is the preferred site for electrophilic attack. Additionally, applying the condensed Fukui functions f introduced by Yang et al. [58] will also arrive at the same conclusion. Depending on the attacking mode, the most reactive site in HN=C=O, has the largest f value. Based on the f values calculated by a finite difference approximation at the level

Fig. 2 MP2 optimized structures of the stationary points along the hydrolysis path of HN=C=O with one water molecule across the C=N bond (path A) or C=O bond (path B). The values in brackets are the enthalpies (ΔH, in *normal font*) and Gibbs free energies (ΔG, in *bold font*) in kJ·mol^{-1} relative to the separated reactants, HN=C=O and H$_2$O
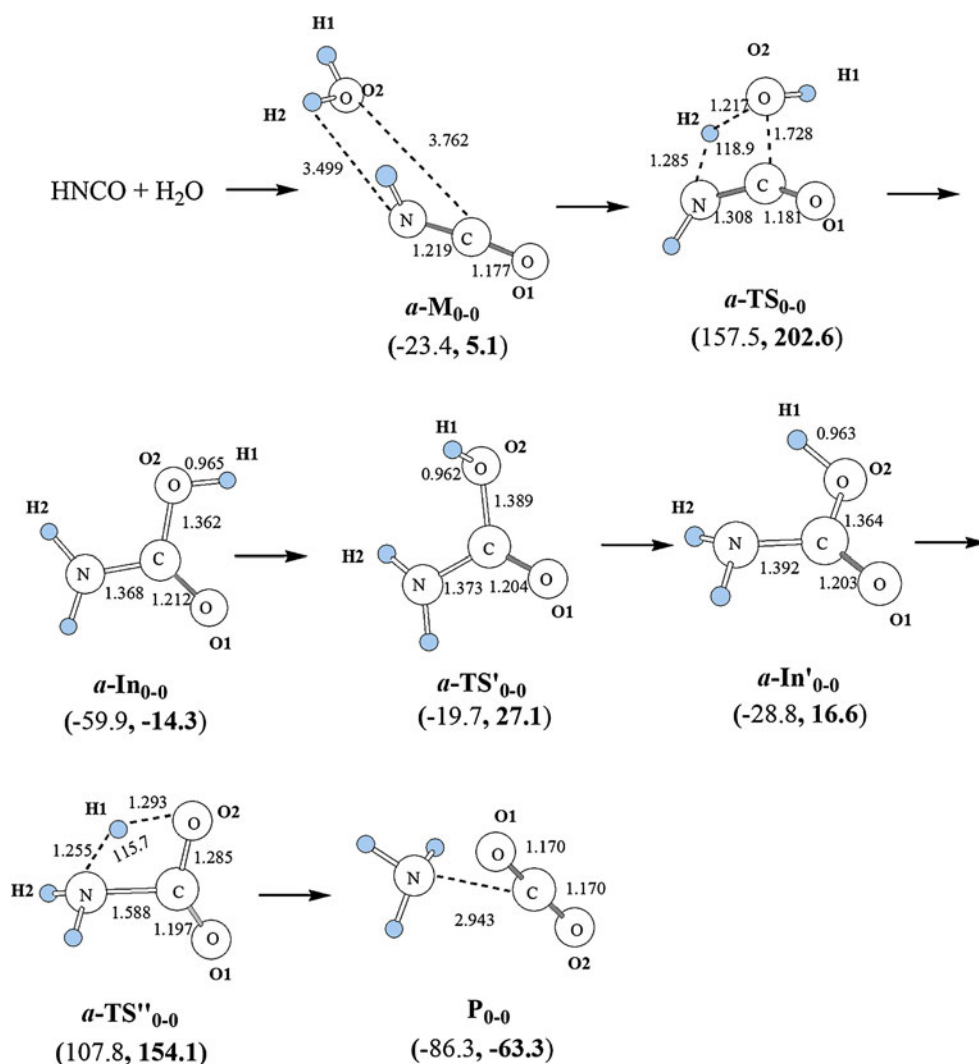
of MP2/6-311++G**, the distinct mechanism of hydrolysis of HN=C=O illustrates: the preferred addition proceeds via a nucleophilic attacking of the O-atom on water at the C-atom of HN=C=O (the largest f^+ for C, $f_C^+=0.590$, $f_O^+=0.066$, $f_N^+=0.273$, $f_H^+=0.068$), while an electrophilic attack occurs by proton at the N-atom (the largest f^- for N, $f_C^-=0.103$, $f_O^-=0.481$, $f_N^-=0.575$, $f_H^-=0.047$). These results indicate that the ability of the N-atom on HN=C=O to accept and distribute positive charge is important: electrophilic attack on N-atom is preferred over attack on O-atom in NH=C=O.

It is worth noting that the rate-determining barrier does not always decrease with the enlargement of proton transfer ring. In fact, the hydrolysis that proceeds via an eight-membered proton transfer loop ($i=2$) is more favorable than via the ten-membered proton transfer loop, and the former barrier is lower than the latter by about 19 kJ mol^{-1}. This can be rationalized by comparing the geometric relaxation of O–H bond, and the average geometric relaxation of the O–H bonds in the rate-determining TSs: in the ten-membered proton transfer loop, quite a large number of hydrogen atoms must be moved from their more stable positions in the reactant, i.e., water cluster, to a somewhat distorted geometry in the rate-determining TS to accompany the elongation of O–H bonds, implying a higher distortion energy and a higher barrier. A detailed account can be found in ref [59].

Hydrolysis reaction of isocyanic acid with cooperative water molecule(s)

In this section, we explore the role, if any, played by the cooperative water molecule(s) in the hydrolysis of iso-cyanic acid. Initially, we place one and two water molecules in the non-reactive region as cooperative agents. Then more cooperative water molecules are considered. Building on the aforementioned discussions on the $A_{i,0}$, and $B_{i,0}$ ($i=0 - 3$), it is clear that single-water hydrolysis is energetically unfavorable. Therefore the hydrolysis pathway involving

$HNCO + H_2O \longrightarrow$

b-M$_{0-0}$
(-5.0, 13.5)

b-TS$_{0-0}$
(201.9, 248.4)

b-In$_{0-0}$
(44.5, 89.6)

b-TS'$_{0-0}$
(148.5, 194.8)

b-In'$_{0-0}$
(-61.3, -14.5)

b-TS''$_{0-0}$
(-19.7, 27.1)

b-In''$_{0-0}$
(-28.8, 16.6)

b-TS'''$_{0-0}$
(107.8, 154.1)
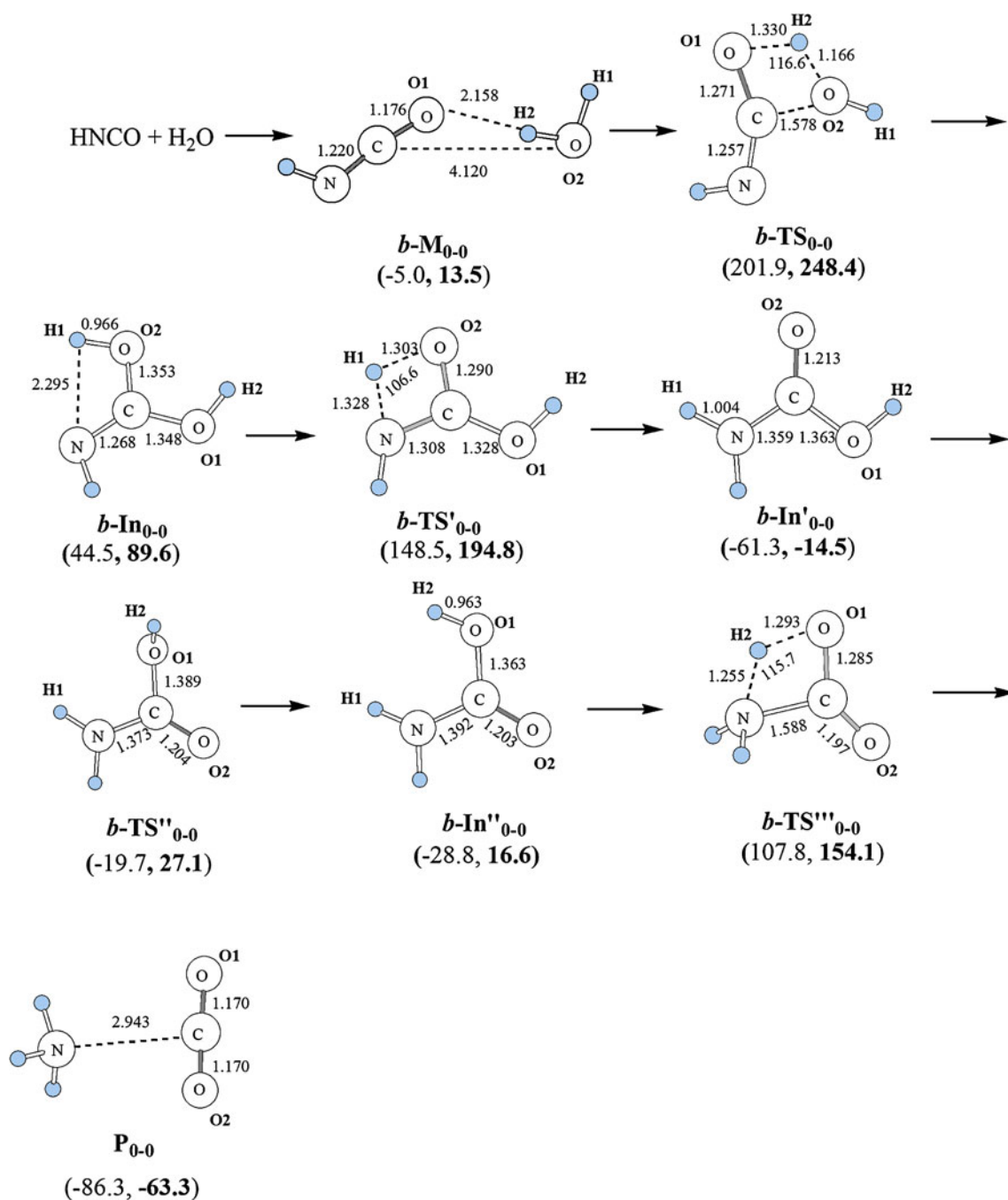
P$_{0-0}$
(-86.3, -63.3)

Fig. 2 (continued)

four-membered cyclic TS is not considered in the following presentation. Only the rate-determining step of hydrolysis pathways $A_{i,j}$ and $B_{i,j}$, $i=1 - 3$ and $j=1 - 3$, will be discussed in this part.

In the hydrolysis of HN=C=O involving one cooperative water, the rate-determining Gibbs free energies of activation are: for additions across the C=N bond, 133.1, 131.8, and 148.9 kJ mol^{-1} for paths A_{1-1}, A_{2-1}, and A_{3-1}, respectively; for additions across the C=O bond the barriers become 150.9, 144.8, and 153.1 kJ mol^{-1} for paths B_{1-1}, B_{2-1}, and B_{3-1}, respectively, lower than the corresponding barriers without cooperative water molecule by 8.9, 2.8, and 8.2 kJ mol^{-1} for paths A_{1-0}, A_{2-0}, and A_{3-0}, respectively; by 40.5 and 38.1 kJ mol^{-1} for paths B_{1-0} and B_{2-0}, respectively. These results show that one cooperative water molecule can reduce the rate-determining barriers. Moreover, as in earlier discussions, we again have the confirmation that addition across the C=N bond with an eight-

membered proton transfer loop is energetically favorable. The geometrical advantage of these TSs will be analyzed later.

Similar to the cases where there are no cooperative water molecules, the barrier of $a\text{-}TS_{2\text{-}1}$ or $b\text{-}TS_{2\text{-}1}$ is still lower than that in $a\text{-}TS_{3\text{-}1}$ or $b\text{-}TS_{3\text{-}1}$.

The aforementioned results show that one cooperative water molecule can significantly reduce the barrier, and an eight-membered proton transfer loop is more favorable for the hydrolysis of isocyanic acid. The ensuing discussions will focus on what happens when more cooperative water molecules are added in the hydrolysis of HN=C=O. If a water dimer is placed in the non-reactive region acting as cooperative reagent, and an eight-membered ring hydrogen bond network will

induce the TS to be tighter than the corresponding TS with only one cooperative water molecule. Comparisons between Figs. 3 and S5 with Figs. 4 and 5 show that the barrier for $a\text{-}TS_{1\text{-}2}$ or $a\text{-}TS_{2\text{-}2}$ is lower than that in $a\text{-}TS_{1\text{-}1}$ or $a\text{-}TS_{2\text{-}1}$ by 5.5 or 6.3 kJ mol^{-1}, respectively, for the addition across the C=N bond, and the barrier for $b\text{-}TS_{1\text{-}2}$ or $b\text{-}TS_{2\text{-}2}$ is lower than that in $b\text{-}TS_{1\text{-}1}$ or $b\text{-}TS_{2\text{-}1}$ by 5.9 or 5.6 kJ mol^{-1}, respectively, for the addition across the C=O bond. These results further confirm the existence of the cooperative effect; also the cooperative effect induced by a water dimer is more pronounced than by water monomer. This can be explained by the existence of less strained hydrogen bonds in an eight-membered cyclic structure and a shorter C−O2 distance in $a\text{-}TS_{2\text{-}2}$ or $b\text{-}TS_{2\text{-}2}$.
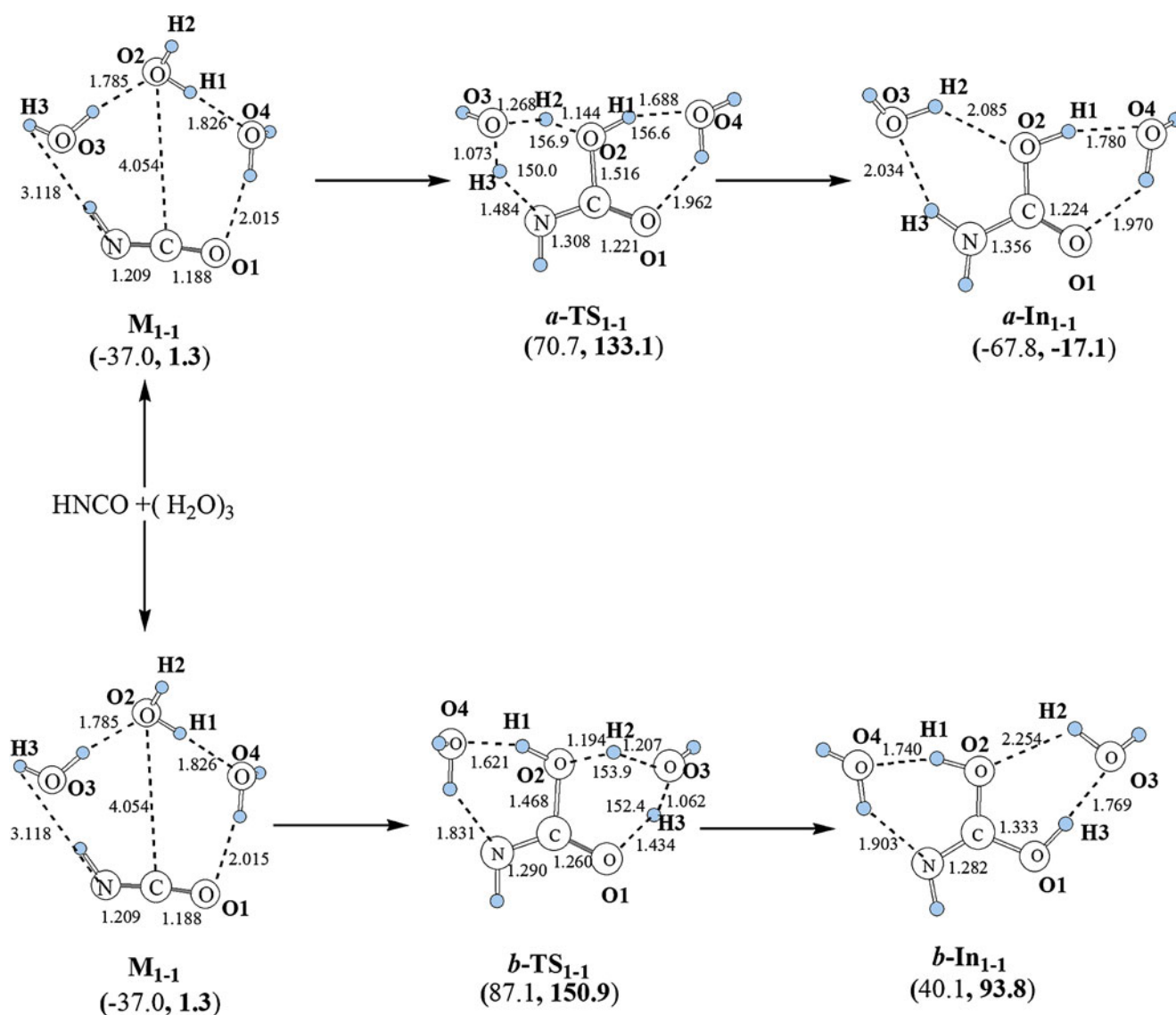

Fig. 3 MP2/6-311++G** optimized structures of the key stationary points along the three-water hydrolysis of HN=C=O with one cooperative molecule across the C=N or C=O bond, where pre-complex $M_{1\text{-}1}$ is same as $M_{2\text{-}0}$. The values in brackets are the enthalpies (*normal font*) and Gibbs free energies (*bond font*) in kJ·mol^{-1} relative to the separated reactants, HNCO and water trimer

Fig. 4 MP2/6-311++G** optimized structures of the key stationary points along the four-water hydrolysis of HN=C=O with two cooperative molecules across the C=N or C=O bond. The values in brackets are the enthalpies (*normal font*) and Gibbs free energies (*bold font*) in kJ·mol^{-1} relative to the separated reactants, HN=C=O and water tetramer
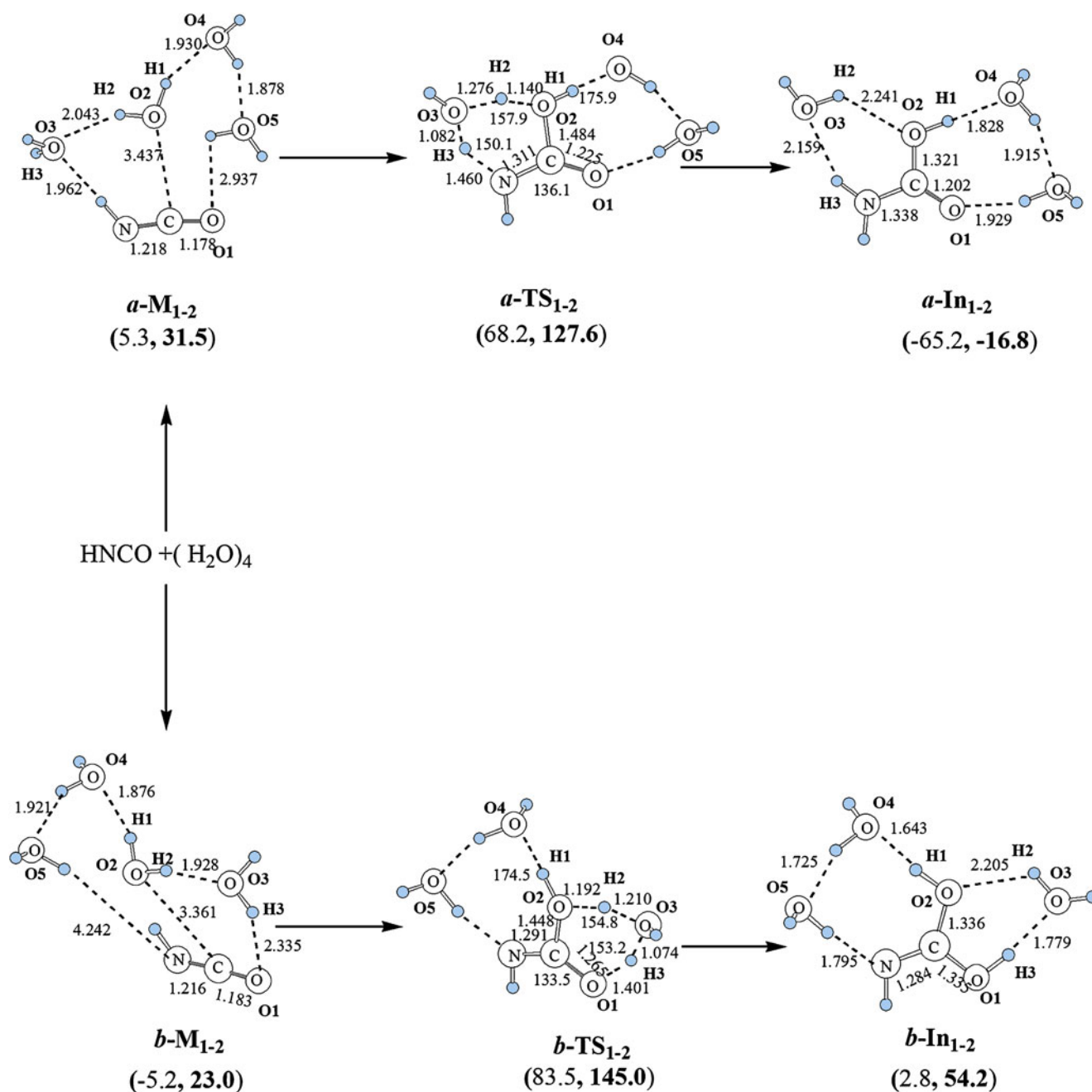
In a recent theoretical study of hydrolysis of CO_2 by Nguyen et al. [37], it is found that a water molecule located in the upside of an eight-membered cycle can reduce the reaction barrier by microsolvation. Following this idea, two new rate-determining TSs are derived from the aforementioned favorable *a*-TS$_{2-2}$ with one cooperative water molecule in the upside of eight-membered proton transfer loop (Fig. 6, *a*-TS$_{3-2}$) or adding another cooperative water molecule in the downside of eight-membered hydrogen

bond cycle (Fig. 6, *a*-TS$_{3-3}$). Our calculations show that the hydrolysis barrier is significantly reduced by 27.5 kJ mol^{-1} via *a*-TS$_{3-2}$ or by 29.5 kJ mol^{-1} via *a*-TS$_{3-3}$, yielding an activation enthalpy of 32.7 or 30.7 kJ mol^{-1}, respectively. Moreover, the theoretical predicted hydrolysis barrier via *a*-TS$_{3-3}$ is 24.9 kJ mol^{-1} at 600 K. The latter value is very close to the gas-phase kinetic experimental result of 25.8 kJ·mol^{-1}, as measured by Aigner et al. for the temperature range of 553 to 613 K [21].
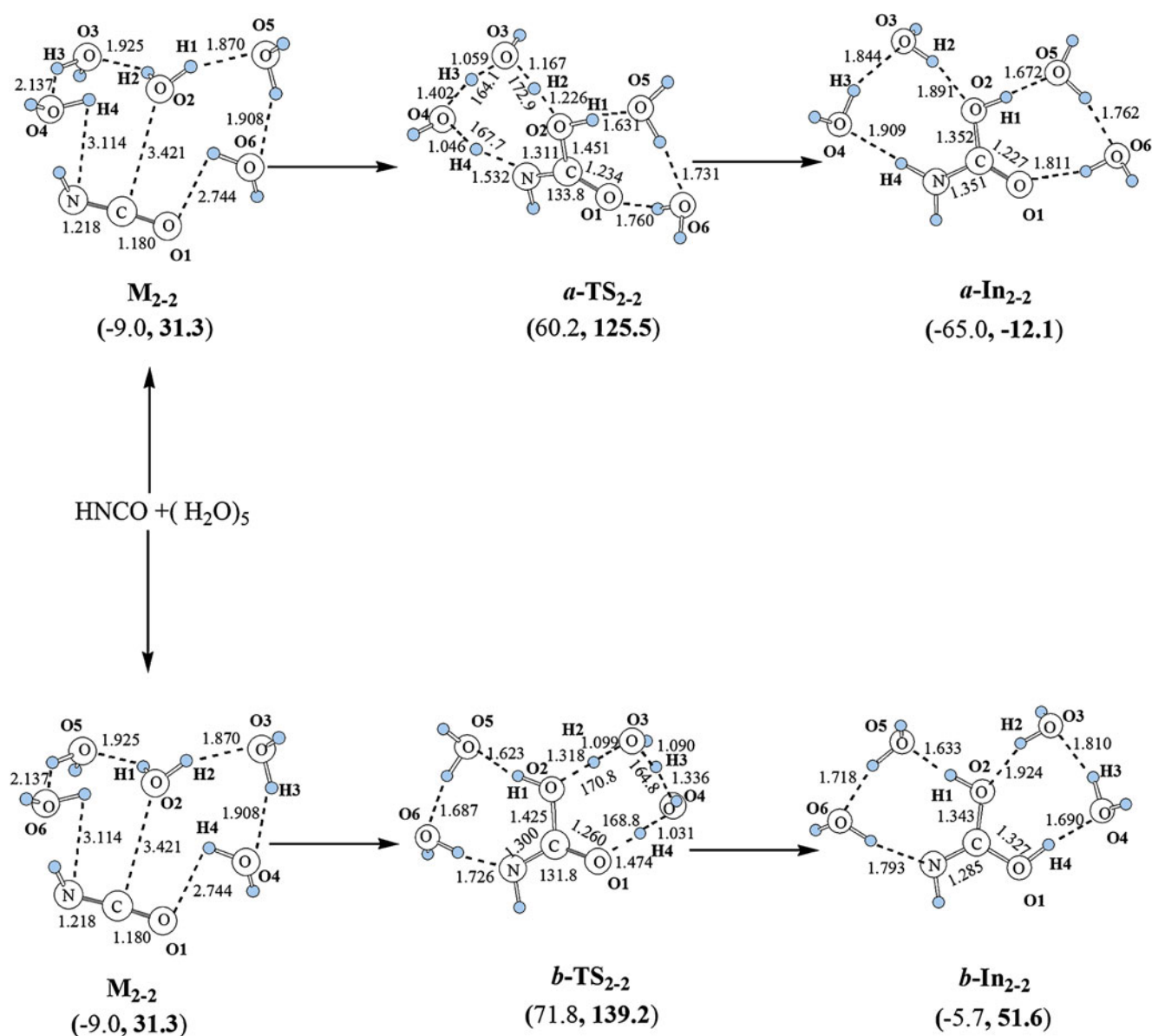
Fig. 5 MP2/6-311++G** optimized structures of the key stationary points along the five-water hydrolysis of HN=C=O with two cooperative molecules across the C=N or C=O bond. The values in brackets are the enthalpies (*normal font*) and Gibbs free energies (*bold font*) in kJ·mol^{-1} relative to the separated reactants, HN=C=O and pentamer

Exploring the essence of water self-catalysis in the hydrolysis of isocyanic acid

In the concerted mechanism of hydrolysis of HN=C=O, a water molecule acting as nucleophile or Lewis base would attack the positively charged central carbon atom. Meanwhile, the N- or O-atom bearing lone pair electrons in HN=C=O will accept the proton from the water molecule. Stronger nucleophilicity for the attacking O-atom or the stronger basicity of the proton acceptor will facilitate the hydrolysis of HN=C=O.

The preceding discussions show that the addition of water molecule across the C=N bond is more favorable than across the C=O bond. This result can be attributed to the stronger basicity of the N-atom, as measured by the negative of Gibbs free energy change, defined as gas basicity (GB), associated with the reaction HNCO+H$^+$ → H$_2$N$^+$CO (GB=697.7 kJ mol^{-1}), whereas the corresponding GB value for the O-atom is 624.2 kJ mol^{-1}, evaluated with the protonation reaction HNCO+H$^+$ → HNCO$^+$H.

In the hydrolysis of HN=C=O, the performance of self-catalysis of water molecule(s) can be evaluated by the magnitude of negative charge, or nucleophilic ability, of the attacking O-atom. The O-atom bearing a more negative charge in the water cluster will transfer more electronic charge from the water molecule(s) to the HN=C=O moiety.
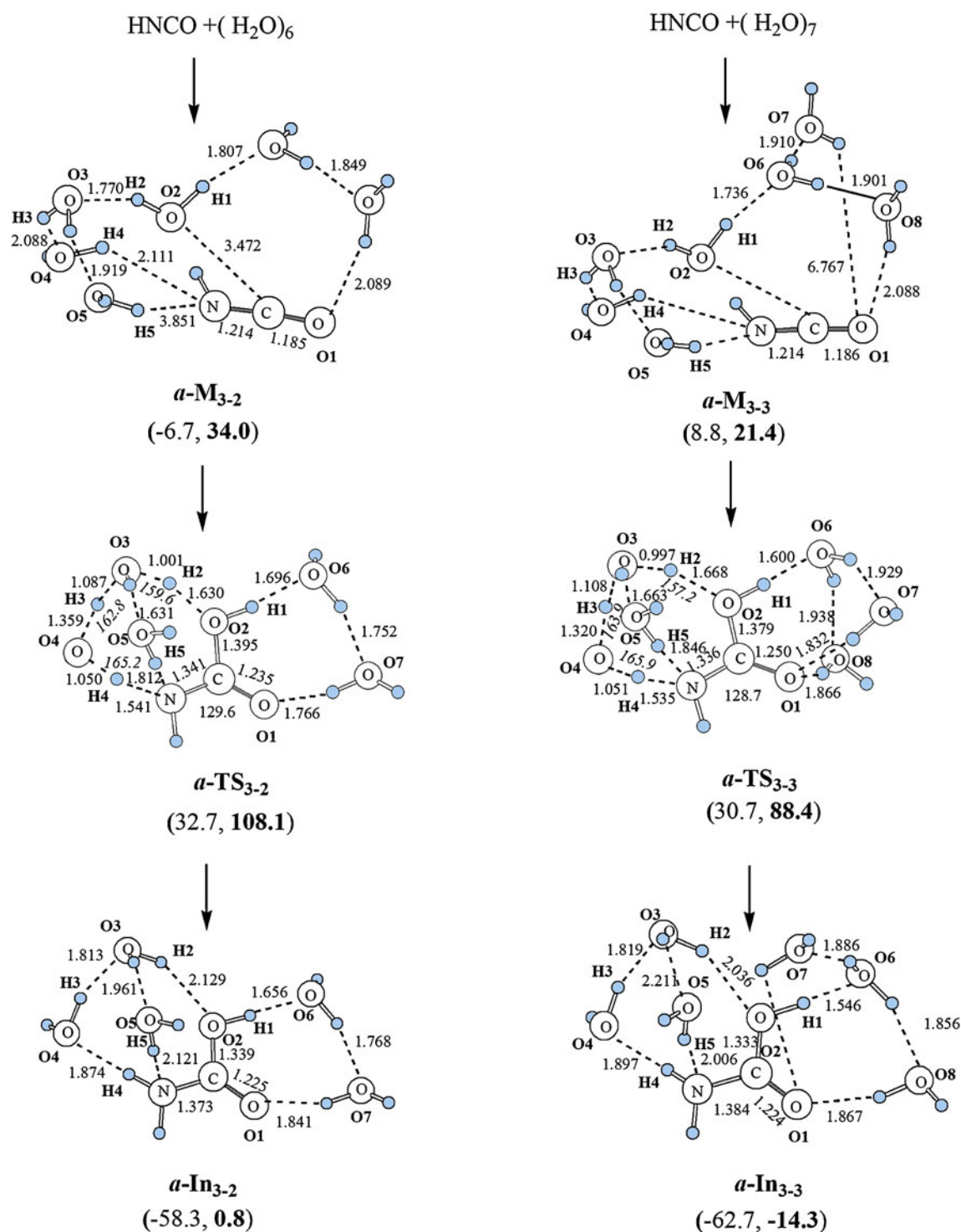
Fig. 6 MP2 optimized structures of the key stationary points along the six-water or seven-water hydrolysis of HN=C=O across the C=N bond with three, or four cooperative water molecules. The values in brackets are the enthalpies (*normal font*) and Gibbs free energies (*bold font*) in kJ·mol^{-1} relative to the separated reactants, HN=C=O and water cluster

The magnitude of electron transfer can be measured by the Δq value, defined as q (HNCO in TS$_{i-j}$) − q (HNCO in reactant). A more negative Δq value implies that more electronic charge is transferred from the water cluster to

HN=C=O moiety in the rate-determining step, and the electron reorganization will stabilize the TS, leading to a lower activation barrier. This rationalization was supported by the selective NPA results for the addition across the

C=N bond, as summarized in Table 1, where $q(O2)$ and Δq values generally become more negative as we go from a one-water to a seven-water hydrolysis.

In order to obtain additional support for the above rationalization, we carried out a study on the base-catalyzed hydrolysis of HN=C=O, where one cooperative water in process A_{2-2} is replaced with one NH_3 molecule, denoted as A'_{2-2} (see Fig. S7). The incorporation of an NH_3 molecule increases the nucleophilicity of the attacking O-atom, and hence facilitates the hydrolysis reaction. This supposition is validated by the more negatively charged attacking oxygen atom, $q(O2) = -1.008$, in $(H_2O)_4$-NH_3 cluster, and lower activation enthalpy, $\Delta H^{\neq} = 47.0$ kJ mol^{-1}, or Gibbs free energy of activation, $\Delta G^{\neq} = 111.6$ kJ mol^{-1} for the process HN=C=O+$(H_2O)_4$+$NH_3 \rightarrow a$-TS'$_{2-2}$, as shown in Fig. S7, than the corresponding values, $q(O2) = -0.994$, for the attacking O-atom in $(H_2O)_5$, $\Delta H^{\neq} = 60.2$ kJ mol^{-1} or $\Delta G^{\neq} = 125.5$ kJ mol^{-1} for the process HNCO+$(H_2O)_5 \rightarrow a$-TS$_{2-2}$.

A closer inspection of the rate-determining activation energies listed in Table 2 reveals that the hydrolysis of HN=C=O can be catalyzed in two ways, one by directly participating proton transfer via a six-, eight-, or ten-membered cyclic TS, or by the formation of hydrogen bonds involving water cluster and terminal nitrogen or oxygen atom on HN=C=O. It will be interesting to compare the relative merits of these two effects when the same number of water molecules are involved in the hydrolysis: which effect is more important, or are they comparable? For the three-water hydrolysis of HN=C=O, there are four possible reaction pathways. The third water molecule could be added to the proton transfer ring to form an eight-membered cyclic a-TS$_{2-0}$, or b-TS$_{2-0}$. Alternatively, the water-assisted hydrolysis of HN=C=O involves a TS with a six-membered proton transfer ring, and the third water molecule is located near the nonreactive region to engage in hydrogen-bonding with the terminal oxygen atom (a-TS$_{1-1}$), or to the terminal nitrogen atom (b-TS$_{1-1}$). It is found that the rate-determining barrier for A$_{1-1}$ is slightly lower than that for A$_{2-0}$ by 1.5 kJ mol^{-1}, but the barrier for

B$_{1-1}$ is significantly lower than that for B$_{2-0}$ by 32.0 kJ mol^{-1} (path B), showing that cooperative catalysis effect induced by single water molecule in the non-reactive region is stronger than that from the directly catalyzing through the water chain. Moreover, this cooperative effect is enhanced in the reaction pathway across the C=O bond, indicating that the six-membered cyclic TS with hydrogen bonding involving a dimeric water chain and the terminal nitrogen atom is more effective because the N-atom on HN=C=O is a stronger proton-acceptor. These results can also be discerned in the variation of rate-determining barriers with the increment of cooperative water molecules for different reaction pathways. The results in Table 2 show that, if we fix two water molecules in the reactive region, i.e., $i=2$, the rate-determining barriers will decrease in the following order: 134.6 (A$_{2-0}$)>131.8 (A$_{2-1}$) > 125.5 (A$_{2-2}$) kJ mol^{-1}, or 182.9 (B$_{2-0}$) > 144.8 (B$_{2-1}$) > 139.2 (B$_{2-2}$) kJ mol^{-1}, indicating that the barrier for the addition across the C=O bond will be significantly reduced by 43.7 kJ mol^{-1} due to the cooperative effect, much larger than the corresponding reduction (9.1 kJ mol^{-1}) for the addition across the C=N bond. Figure 7 illustrates the trend of the rate-determining Gibbs free energies of activation along the increase of the explicit water molecule(s) in the one-water to five-water hydrolysis reactions of isocyanic acid, showing that the difference between two mechanisms, across the C=N bond and C=O bond, becomes smaller. This is mainly due to the enhanced cooperative effect in the latter case.

Concluding remarks

In the present work, a comprehensive study on the hydrolysis mechanism of isocyanic acid with up to seven water molecules has been performed by *ab initio* methods. In each of the studied reaction pathway, the first step is rate-determining, and nucleophilic addition across the C=N bond is favored. The hydrolysis of NH=C=O can be

Table 1 Selected NPA charge on the O2 atom of water cluster, $q(O2)$, charge changes of the HN=C=O moiety from reactant to the rate-determining TSs, $\Delta q(HNCO)$, Gibbs free energies of activation, $\Delta G^{\neq}$ (kJ mol^{-1}), of the rate-determining steps for the hydrolysis of H=N=C=O by addition across the C=N bond in the gas phase at the MP2/6-311++G** level

Pathway A$_{i\text{-}j}$	Reactants→a-TS $_{i\text{-}j}$	$q(O2)$	$\Delta q(HNCO)$	$\Delta G^{\neq}$
$i=0, j=0$	HNCO+H_2O→a-TS$_{0-0}$	−0.912	−0.125	202.6
$i=1, j=0$	HNCO+$(H_2O)_2$→a-TS$_{1-0}$	−0.948	−0.263	142.0
$i=1, j=1$	HNCO+$(H_2O)_3$→a-TS$_{1-1}$	−0.975	−0.352	133.1
$i=1, j=2$	HNCO+$(H_2O)_4$→a-TS$_{1-2}$	−0.989	−0.370	127.6
$i=2, j=2$	HNCO+$(H_2O)_5$→a-TS$_{2-2}$	−0.994	−0.431	125.5
$i=2, j=3$	HNCO+$(H_2O)_6$→a-TS$_{3-2}$	−0.996	−0.485	108.1
$i=2, j=4$	HNCO+$(H_2O)_7$→a-TS$_{3-3}$	−1.034	−0.509	88.4

Table 2 Rate-determining activation enthalpies, $\Delta H^{\neq}$ (kJ mol^{-1}, in *normal font*), and Gibbs free energies of activation, $\Delta G^{\neq}$ (kJ mol^{-1}, in **bold font**), for the hydrolysis of isocyanic acid in the gas phase

	Pathway	C=N addition		Pathway	C=O addition	
HNCO+H$_2$O	A$_{0-0}$	157.5 [a]	**202.6 [a]**	B$_{0-0}$	202.6 [a]	**248.4 [a]**
HNCO+2H$_2$O	A$_{1-0}$	77.7 [b]	**142.0 [b]**	B$_{1-0}$	128.2 [b]	**191.4 [b]**
HNCO+3H$_2$O	A$_{1-1}$	70.7 [b]	**133.1 [b]**	B$_{1-1}$	87.1[b]	**150.9 [b]**
	A$_{2-0}$	73.2 [c]	**134.6 [c]**	B$_{2-0}$	123.0 [c]	**182.9 [c]**
HNCO+4H$_2$O	A$_{1-2}$	68.2 [b]	**127.6 [b]**	B$_{1-2}$	83.5 [b]	**145.0 [b]**
	A$_{2-1}$	69.7 [c]	**131.8 [c]**	B$_{2-1}$	80.0 [c]	**144.8 [c]**
	A$_{3-0}$	96.6 [d]	**157.1 [d]**			
HNCO+5H$_2$O	A$_{2-2}$	60.2 [c]	**125.5 [c]**	B$_{2-2}$	71.8 [c]	**139.2 [c]**
	A$_{3-1}$	80.6 [d]	**148.9 [d]**	B$_{3-1}$	85.7 [d]	**153.1 [d]**
HNCO+6H$_2$O	A$_{3-2}$	32.7 [e]	**108.1 [e]**			
HNCO+7H$_2$O	A$_{3-3}$	30.7 [f]	**88.4 [f]**			

[a] Four-membered cyclic TS

[b] Six-membered cyclic TS

[c] Eight-membered cyclic TS

[d] Ten-membered cyclic TS

[e] Eight-membered cyclic TS with a cooperative water in the reactive region, and a dimeric water in the non-reactive region

[f] Eight-membered cyclic TS with four cooperative waters.

facilitated by the direct participation of water molecule(s) via proton relay or by cooperative effect. Both of these two effects are important and neither one can be ignored. However, it should be noted that the cooperative effect is particularly important for the addition across C=N bond, as revealed by the results listed in Table 2. Moreover, the cooperative effect is significantly enhanced by placing water molecules in the upside of proton transfer cycle or in the downside of eight-membered hydrogen-bonded cycle. The calculations for the hydrolysis of HN=C=O in the gas phase show that, in both the reactive or non-reactive region, the TS with an eight-membered ring is most favorable, likely due to the lack of strain in these hydrogen bonded cycles. Accordingly, our best reaction pathway involves an eight-membered cyclic TS, with two three-water chains

located in the vicinity of non-reactive region to catalyze the hydrolysis by cooperative effect, and yet another cooperative water molecule is in the reactive region. This strain-free hydrogen bond network leads to the best estimated rate-determining activation energy of about 25 kJ mol^{-1} at 600 K, in very good agreement with the gas-phase kinetic experimental result. Our calculations further confirm the crucial cooperative role of water molecule(s) in the hydrolysis process. The origin of water self-catalysis in the hydrolysis is analyzed by the electron reorganization in the formation of the rate-determining TS. If the O-atom on the attacking water molecule bears more negative charge, its nucleophilicity will become stronger, and more electrons will transfer from the water cluster to the substrate HN=C=O, leading to a short O–C2 distance and a lower activation barrier.

Fig. 7 The trend of the rate-determining Gibbs activation free energies along the increase of the water molecule(s) in the hydrolysis of isocyanic acid. The *red line* is for addition across the C=N bond, and the *blue* one is for the addition across the C=O bond
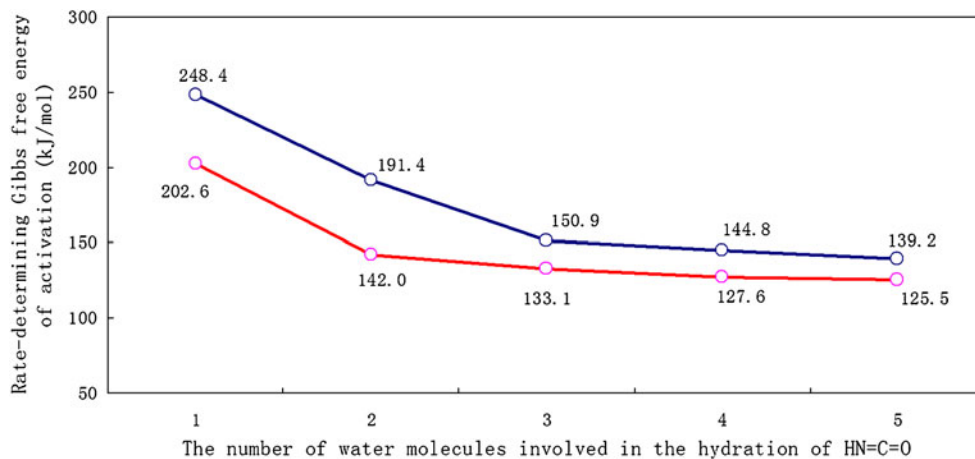
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