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Theoretical Studies on the Mechanism of Acid-Promoted Hydrolysis of *N*-Formylaziridine in Comparison with Formamide

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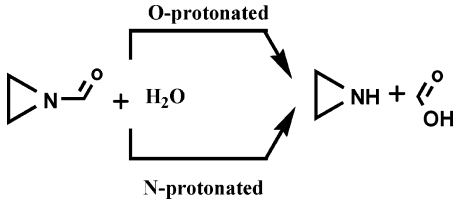

We present an ab initio study of the acid-promoted hydrolysis reaction mechanism of *N*-formylaziridine in comparison with formamide. Since the rate of amide hydrolysis reactions depends on the formation of the tetrahedral intermediate, we focused our attention mainly on the reactant complex, the tetrahedral intermediate, and the transition state connecting these two stationary points. Geometries were optimized using the density functional theory, and the energetics were refined using ab initio theory including electron correlation. Solvent effects were investigated by using polarizable continuum method calculations. The proton-transfer reaction between the O-protonated and N-protonated amides was investigated. In acidic media, despite that the N-protonated species is more stable than the O-protonated one, it is predicted that both N-protonated and O-protonated pathways compete in the hydrolysis reaction of *N*-formylaziridine.

Introduction

Amide hydrolysis is one of the most ubiquitous reaction found in biological systems[1,2] and has been intensively investigated by both experimental and theoretical methods.[3−5] The hydrolysis reactions of amides are often used as a model for studying the cleavage of peptide bonds. Many studies about the hydrolysis reactions of formamide and similar amides in neutral, acidic, and basic media have been reported.[6−8] In acidic media, there are two plausible protonation sites for amides, i.e., O-protonation and N-protonation; the amide hydrolysis reaction may proceed by either an O-protonated or N-protonated pathway. Kinetic studies on amide hydrolysis[9,10] suggest that the acid-catalyzed hydrolysis of amides proceed through a tetrahedral intermediate,

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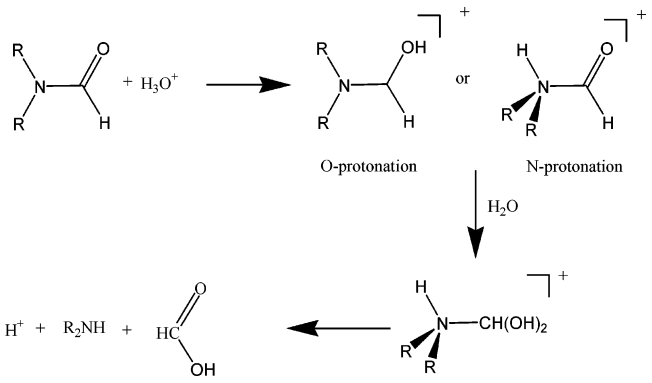

which is formed by nucleophilic attack of water molecules on the protonated amide (Scheme 1). The rate-determining step for the hydrolysis is believed to be the addition of water to the amides forming the tetrahedral intermediate.

Ordinary planar amides are expected to arise from H_2O attack on the O-protonated form (O-pathway).[11] Rivail and co-workers[12] studied the water-assisted hydrolysis of formamide for neutral and H_3O^+-promoted processes. They reported that assistance by water molecules lowers the energy barriers in the neutral and acid-promoted conditions. Calculations on protonated, neutral, and deprotonated forms of *N*-(*o*-carboxybenzoyl)glycine reveal that, in contrast to the mechanism for imide formation in which the solvent has little influence on the reaction barrier, the solvent effect plays a major role in the amide hydrolysis.[13] The solvent effect is also found to be important in the neutral and alkaline hydrolysis of β-lactum antibiotics.[14]

The general hydrolytic process of amides is presented in Scheme 1. The first step is the specific acid protonation of the amide to activate it in favor of attack by water molecules. The next step is the water addition to the carbonyl carbon of the protonated amide to form the tetrahedral intermediate, followed by the formation of caboxylic acid and ammonia by breaking the C−N bond of the tetrahedral intermediate. The rate-determining step is believed to be the formation of tetrahedral intermediate.

Studies on the protonation sites of strained *N*-formylaziridine indicated that N-protonation is favored over O-protonation in both aqueous and gas phases.[15,16] Ab initio study of the alkaline hydrolysis reaction of planar and pyramidal amides showed that twisting of the amide bond and nitrogen pyramidalization is found to be an effective way of accelerating the reaction.[17] The presence of polar solvents stabilizes N-protonation more than O-protonation. Our previous study revealed the thermodynamic features of protonation sites of some amides,[15] but details about the mechanism of the hydrolysis reaction of strained amides such as *N*-formylaziridine in acidic medium is not well understood. Although N-protonation is favored in highly strained *N*-formylaziridine thermodynamically, it is still a challenging problem whether the N-protonated form is more reactive than the O-protonated form toward the nucleophilic attack.

Recently many theoretical studies have been reported about the reactions of molecules bearing amide bonds.[18,19] To gain more insight into the mechanism of the hydrolysis of strained amides, we studied the acid-promoted water-assisted hydrolysis of *N*-formylaziridine in comparison with formamide, using computation. Both the O-pathway and the N-pathway were considered in detail, and the geometrical parameters and energies of the stationary points and transition states on the potential energy curves were investigated. We further studied the proton-transfer reaction between O-protonated and N-protonated formamide and that between O-protonated and N-protonated *N*-formylaziridine.

Calculation Method

All structures were fully optimized by density functional methods (Becke three parameters employing Lee−Yang−Parr functionals, B3LYP), and the energies were refined at the Moller−Plesset second-order perturbation method (MP2). For all calculations, we used the 6-311++G** basis set. Calculations were carried out with the Gaussian-98 suite of programs, and molecular structures were drawn using the POSMOL package.[20] Vibrational frequency analyses were performed to confirm the minima or transition states. The solvent effects were calculated using the polarizable continuum method (PCM) (dielectric constant $\epsilon = 80$).

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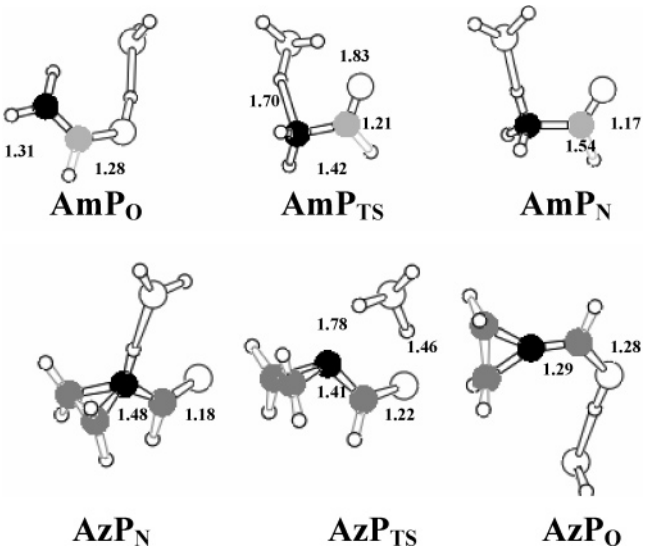

FIGURE 1. Geometries of stationary points and transition states (TS) in the proton-transfer reaction between N- and O-protonated isomers of formamide and *N*-formylaziridine. N, black; C, gray; O, white (big); H, white (small). The bond distances are given in Å.

Results and Discussion

A. Proton-Transfer Reactions. Before going into the details of amide hydrolysis, we start with the proton-transfer reactions for N- and O-protonated formamide and *N*-formylaziridine. Structures of stationary points and transition states of the proton-transfer reactions are shown in Figure 1, the geometrical parameters and relative energies are in Table 1; and the energy profiles are shown in Figure 2. The O-protonated complex is denoted as $\mathbf{XP_O}$, the N-protonated complex as $\mathbf{XP_N}$, and the transition state for the proton-transfer reaction as $\mathbf{XP_{TS}}$, where X stands for "**Am**" for formamide, and "**Az**" for *N*-formylaziridine.

We start with the protonation mechanism of formamide. Characterization of protonated formamide clusters by vibrational predissociation spectroscopy as well as theoretical predictions confirms that the O-protonation is favored over the N-protonation in formamide.[21] The length of C−O bond is 1.17 Å for $\mathbf{AmP_N}$ and 1.28 Å for $\mathbf{AmP_O}$, respectively. For $\mathbf{AmP_O}$, the C−N bond is shortened by 0.23 Å, and the C−O bond is lengthened by 0.10 Å relative to $\mathbf{AmP_N}$. Transition state $\mathbf{AmP_{TS}}$ has a six-membered ring structure, where the proton is bound to the water molecule, one of the hydrogen atom of H_3O^+ interacts with the carbonyl oxygen atom (the distance is 1.83 Å), and the other one with the amide nitrogen atom (the distance is 1.70 Å). The C−N and C−O distances of the formamide in $\mathbf{AmP_{TS}}$ are 1.20 and 1.42 Å, respectively. The energy barrier (in internal energy change ΔE at 0 K) for the forward reaction ($\mathbf{AmP_N} \rightarrow \mathbf{AmP_{TS}} \rightarrow \mathbf{AmP_O}$) is 12.9 kcal/mol (13.9 kcal/mol in free energy change ΔG at room temperature) and that of the reverse reaction ($\mathbf{AmP_O} \rightarrow \mathbf{AmP_{TS}} \rightarrow \mathbf{AmP_N}$) is 28.6 kcal/mol (30.1 kcal/mol in ΔG) at the MP2//B3LYP level. The corresponding energy barriers (in ΔE) at the MP2(PCM)//B3LYP level are 1.4 and 14.0 kcal/mol, respectively. Therefore, it can be concluded that the activation energy for converting the N-protonated formamide to the O-protonated form in polar solvent is very low. Although the energy barrier needs to be discussed in terms of ΔG instead of ΔE, the solvent effects were calculated only in ΔE, and so our discussion will be given in ΔE in solution, whereas the solvent effect in the gas phase will be discussed in terms of both ΔE and ΔG.

We studied the proton transfer between the N- and O-protonated *N*-formylaziridine. The neutral *N*-formylaziridine has a distorted structure that can be attributed to the strain of the three-membered amine ring, but the O-protonated form has a planar structure that can be rationalized by the resonance effect. The length of the C−O bond is 1.18 Å for $\mathbf{AzP_N}$, 1.28 Å for $\mathbf{AzP_O}$, and 1.22 Å for $\mathbf{AzP_{TS}}$. For $\mathbf{AzP_O}$, the C−N bond is shortened by 0.19 Å and the C−O bond is lengthened by 0.10 Å relative to $\mathbf{AzP_N}$ as a result of the disappearance of resonance effect caused by the protonation at the nitrogen atom.

The geometrical parameters of $\mathbf{AzP_O}$, $\mathbf{AzP_{TS}}$, and $\mathbf{AzP_N}$ optimized at B3LYP(PCM) in aqueous media are shown in Table 1. In the gas phase and aqueous media, the geometrical parameters of $\mathbf{AzP_O}$ and $\mathbf{AzP_N}$ are similar. However, for $\mathbf{AzP_{TS}}$ the H_3O^+ in the aqueous phase is more separated from the formamide moiety than that in the gas phase. In the case of *N*-formylaziridine, the relative stability between N- and O-protonated forms varies with the level of theory. The energy difference between the two forms is in the range of a few kcal/mol. CCSD(T)/aug-cc-pVDZ energies of geometries optimized at MP2/aug-cc-pVDZ favor N-protonated *N*-formylaziridine over O-protonated form (∼1.9 kcal/mol), similar to the MP2 results. The energy barriers for the forward reaction ($\mathbf{AzP_O} \rightarrow \mathbf{AzP_{TS}} \rightarrow \mathbf{AzP_N}$) at the MP2 and MP2-(PCM) levels are 16.7 and 12.1 kcal/mol, respectively. The corresponding energy barriers at the gas and aqueous phases for the reverse reaction ($\mathbf{AzP_N} \rightarrow \mathbf{AzP_{TS}} \rightarrow \mathbf{AzP_O}$) are 17.5 and 16.2 kcal/mol, respectively.

B. Hydrolysis of Amides in Acidic Media. The acid-catalyzed hydrolysis of amides occurs via the formation of a tetrahedral intermediate. The formation of this intermediate by the attack of water molecules on protonated amides could occur in two different ways: N-pathway and O-pathway. We have inspected the potential energy surface of the amide hydrolysis reaction between protonated amides and water dimer, one of which is acting as a nucleophile to attack the carbonyl carbon and another as a general base as well as a proton donor. For the N-protonated form, one extra water molecule was added to keep the water dimer in an efficient position for the hydrolysis. The reactant complexes hereafter will be denoted as $\mathbf{XY_R}$, which is a direct precursor of TS and can be regarded as a hydrogen-bonded complex of the protonated amide with the water dimer. The transition states are denoted as $\mathbf{XY_{TS}}$, and the product-like intermediates are represented as $\mathbf{XY_P}$. In all of these cases we denote X = Am for formamide, X = Az for *N*-formylaziridine, Y = O for the O-protonated form, and Y = N for the N-protonated form. The geometries of the optimized structures are in Figure 3, the important geometrical parameters along with the energy barriers are in Table 2, and the energy profiles for the hydrolysis reaction are in Figure 4.

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TABLE 1. Bond Distances (Å) and Relative Energies (kcal/mol) of Stationary Points and Transition States in Proton Transfer Reactions between N- and O-Protonated Isomers of Formamide and *N*-Formylaziridine[a]

					relative energy (kcal/mol)			
system	C−N	C−O	N···H	O···H	B3LYP	MP2	MP2 (Δ*G*)	MP2-PCM
AmP_N	1.540	1.173	1.070		0.00	0.00	0.00	0.00
AmP_{TS}	1.423	1.208	1.698	1.828	11.53	12.91	13.90	1.38
AmP_O	1.306	1.275		1.012	−19.1	−15.65	−16.17	−12.57
AzP_O	1.290 (*1.288*)	1.284 (*1.288*)		1.012 (*1.031*)	0.00 (*0.00*)	0.00	0.00	(*0.00*)
AzP_{TS}	1.406 (*1.405*)	1.220 (*1.220*)	1.792 (*1.887*)	1.462 (*1.590*)	20.84 (*16.46*)	16.70	21.09	(*12.10*)
AzP_N	1.479 (*1.458*)	1.180 (*1.190*)	1.052 (*1.060*)		4.52 (*0.41*)	−0.75	3.69	(*−4.14*)

[a] Geometries and energies of systems optimized in the gas phase are shown in normal letters and those optimized in the aqueous medium (PCM) are shown in parentheses in italics. All energies are interaction energies except for the values Δ*G*, which are the MP2 free energies.

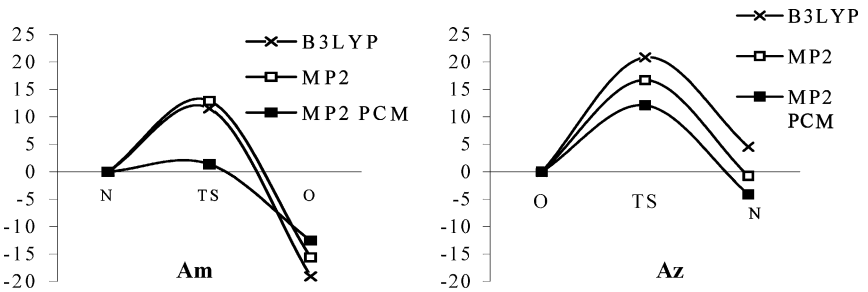

FIGURE 2. Energy profile of the proton-transfer reaction between N-protonated and O-protonated formamide (**Am**) and that between O-protonated and N-protonated *N*-formylaziridine (**Az**).

First we start with the hydrolysis of formamide. In the reactant complex $\mathbf{AmO_R}$, O-protonated formamide has a planar structure. The lengths of C−O and C−N bonds in $\mathbf{AmO_R}$ are 1.28 and 1.31 Å, respectively, whereas those in $\mathbf{AmN_R}$ are 1.18 and 1.52 Å, respectively. In $\mathbf{AmO_{TS}}$ the lengths of the C−O and C−N bonds are 1.35 and 1.45 Å, and the C−O_A distance is about 1.51 Å. The magnitude of the C−O_A distance in $\mathbf{AmO_{TS}}$ implies that the formation of the C−O_w bond proceeds significantly. In $\mathbf{AmO_{TS}}$ the distances of O_A−H_A and O_B−H_A are 1.27 and 1.15 Å, respectively (for labels of O and H atoms, refer to Figure 3). Compared to $\mathbf{AmO_R}$, in $\mathbf{AmO_{TS}}$ the C−O bond is lengthened by 0.07 Å due to the formation of the C−O_w bond, and the C−N bond is lengthened by 0.14 Å. In $\mathbf{AmO_{TS}}$ the nitrogen is pyramidal and forms a hydrogen bond with one of the hydrogen atom of the H_3O^+ ion. In $\mathbf{AmN_{TS}}$ the lengths of C−O, C−N, and C−O_x are 1.22, 1.67, and 1.66 Å, respectively. The O_x−O_y distance in AmN_{TS} is about 2.45 Å and the hydrogen atom which connects O_x and O_y transfers significantly from O_x to O_y (O_x−H 1.39 Å and O_y−H 1.08 Å). Structural parameters indicate that the proton transfer from the second water molecule to the carbonyl oxygen or the nitrogen atom has barely started for both $\mathbf{AmO_{TS}}$ and $\mathbf{AmN_{TS}}$.

Recent molecular dynamics calculations on amide hydrolysis in acidic media predict that during the process of addition of water molecule to the carbonyl carbon, one proton from the water molecule is transferred to the water phase. The nitrogen is protonated at a later stage.[7b] Based on the transition state geometry, it can be seen that although the C−O_w bond formation proceeds significantly in the TS structure, the protonation of the nitrogen atom barely started. Further calculations suggest that the proton transfer to the pyramidal nitrogen atom in formamide is almost barrierless. Therefore, the present results also suggest that the proton transfer from the hydronium ion to the nitrogen atom starts only at a later stage of addition of water to carbonyl carbon of the formamide.

The energy barriers for the O-pathway of the amide hydrolysis **[$\mathbf{AmO_R}$ → $\mathbf{AmO_{TS}}$ → $\mathbf{AmO_P}$]** at the B3LYP and MP2 levels are 24.5 and 21.8 (29.1 in Δ*G*) kcal/mol, respectively, and that at the MP2(PCM) level is 14.3 kcal/mol. Experimental studies show that the energy barrier for the acid-catalyzed hydrolysis of *N*-methylacetmide is 21.5 kcal/mol.[22] The results shown in Table 1 as well as earlier reports confirm that in acidic media formamide mainly exists as the O-protonated form. Therefore, the N-pathway for formamide hydrolysis would have two steps: the first is the conversion of O-protonated formamide to the N-protonated one [$\mathbf{AmP_O}$ → $\mathbf{AmP_{TS}}$ → $\mathbf{AmP_N}$], with the gas-phase energy barrier 30.6(g) kcal/mol at B3LYP and 28.6(g) (30.1 in Δ*G*) at MP2, and the aqueous media energy barrier 14.0(aq) kcal/mol at MP2-(PCM)], followed by hydrolysis [$\mathbf{AmN_R}$ → $\mathbf{AmN_{Ts}}$ → $\mathbf{AmN_P}$] with 19.9/21.9(g) kcal/mol at B3LYP, 24.0 kcal/mol (Δ*G*) at MP2, and 17.2(aq) kcal/mol at MP2(PCM). The bottleneck energy barrier for the N-pathway (in the slow reaction process) is the larger one between the two step barriers. Therefore, for the hydrolysis of formamide, the O-pathway is energetically more preferable over the N-pathway in both gas (by 5.1 at B3LYP and 6.8 and 1.0 (Δ*G*) kcal/mol at MP2) and aqueous phases (by 2.9 kcal/mol). Our results agree with the results of Rivail and coworkers; their calculations also predicted that formamide hydrolysis mainly proceeds through O-protonation.[12]

The selected geometrical parameters of the stationary points in the hydrolysis reaction of the *N*-formylaziridine in acidic media are in Table 2. The role of the water dimer in *N*-formylaziridine is similar to that in the case of formamide. The lengths of C−O and C−N bond for $\mathbf{AzO_R}$

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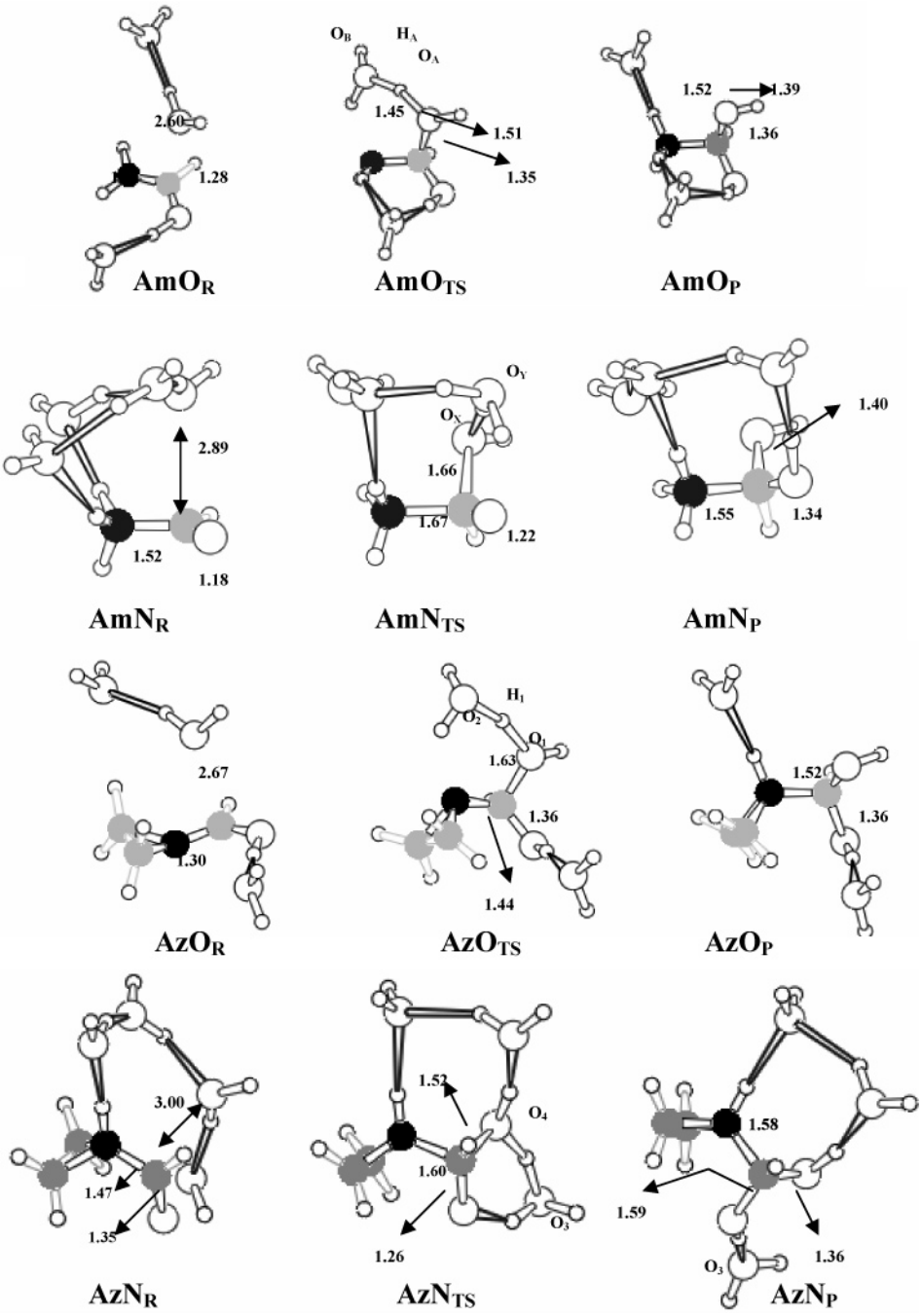

FIGURE 3. Geometries of stationary points in the hydrolysis reactions of N- and O-protonated isomers of formamide and *N*-formylaziridine. N, black; C, gray; O, white (big); H, white (small).

are 1.28 and 1.30 Å, respectively, and the corresponding values in **AzN$_R$** are 1.19 and 1.47 Å. In **AzO$_{TS}$** the lengths of C−O, C−N, and C−O$_1$ are 1.34, 1.45, and 1.53 Å, respectively. The magnitude of C−O$_1$ distance for **AzO$_{TS}$** implies that the formation of C−O$_1$ bond proceeds significantly. In **AzN$_{TS}$** the lengths of C−O, C−N, and C−O$_4$ are 1.26, 1.60 ,and 1.52 Å, respectively. Structural parameters indicate that the proton transfer from the second water molecule to the carbonyl oxygen or nitrogen atom has barely started for both **AzO$_{TS}$** and **AzN$_{TS}$** as in the case of formamide. In **AzO$_{TS}$**, the O$_1$−O$_2$ distance (atoms labels are depicted in Figure 3) are computed to be 2.37 Å (O$_1$−H and O$_2$−H are in the range of 1.2 Å). The O$_3$−O$_4$ distance in AzN$_{TS}$ is ∼2.36 Å; O$_3$−H is 1.18 Å, and O$_4$−H is 1.24 Å.

The relative energies of N- and O-protonated *N*-formylaziridine are in the range of only a few kcal/mol. It is expected that both N-protonated and O-protonated conformers compete. In the gas phase, O-protonated conformers are more stable by 4.5 kcal/mol at B3LYP but less stable by 0.7 kcal/mol (but more stable by 3.7 kcal/mol in ΔG) at MP2. At the MP2 level, the N-protonated form is only slightly more stable in ΔE but less stable in ΔG, and so the temperature effect would make the O-conformer more stable. On the other hand, in the aqueous phase, O-protonated conformers are only slightly

TABLE 2. Bond Distances (Å) and Relative Energies (kcal/mol) for Stationary Points and Transition States in the Hydrolysis of N- and O-Protonated Formamide and *N*-Formylaziridine[a]

						relative energy (kcal/mol)			
system	C−N	C−O	C−O_w	N−H	O−H	B3LYP	MP2	MP2 (Δ*G*)	MP2-PCM
AmO_R	1.306	1.281	2.595		1.000	0.00	0.00	0.00	0.00
AmO_{TS}	1.448	1.351	1.512	1.925	0.982	24.50	21.76	29.11	14.32
AmO_P	1.525	1.364	1.390	1.048	0.975	3.28	−0.72	8.85	−10.75
AzO_R	1.297 (*1.296*)	1.284 (*1.285*)	2.672 (*2.749*)		1.005 (*1.027*)	0.00 (*0.00*)	0.00	0.00	(*0.00*)
AzO_{TS}	1.449 (*1.428*)	1.363 (*1.358*)	1.630 (*1.527*)	1.887 (*3.220*)	0.988 (*0.991*)	21.53 (*11.3*)	17.35	25.20	(*6.65*)
AzO_P	1.521 (*1.514*)	1.359 (*1.370*)	1.391 (*1.389*)	1.037 (*1.044*)	0.956 (*0.991*)	−4.84 (*−9.38*)	−9.88	−0.56	(*−14.84*)
AmN_R	1.524	1.176	2.891			0.00	0.00	0.00	0.00
AmN_{TS}	1.667	1.219	1.655		2.037	19.87	21.89	24.04	17.21
AmN_P	1.547	1.344	1.399		0.99	−6.48	−6.84	−0.52	−14.01
AzN_R	1.468 (*1.463*)	1.187 (*1.192*)	3.000 (*2.832*)	1.057 (*1.063*)		0.00 (*0.00*)	0.00	0.00	(*0.00*)
AzN_{TS}	1.597 (*1.591*)	1.263 (*1.279*)	1.523 (*1.481*)	1.025 (*1.031*)	1.067 (*1.831*)	20.88 (*15.08*)	23.25	23.05	(*18.66*)
AzN_P	1.589 (*1.556*)	1.350 (*1.360*)	1.362 (*1.372*)	1.027 (*1.036*)	0.989 (*0.0992*)	−2.79 (*−5.00*)	−2.19	−0.34	(*−5.62*)

[a] See the footnote of Table 1.

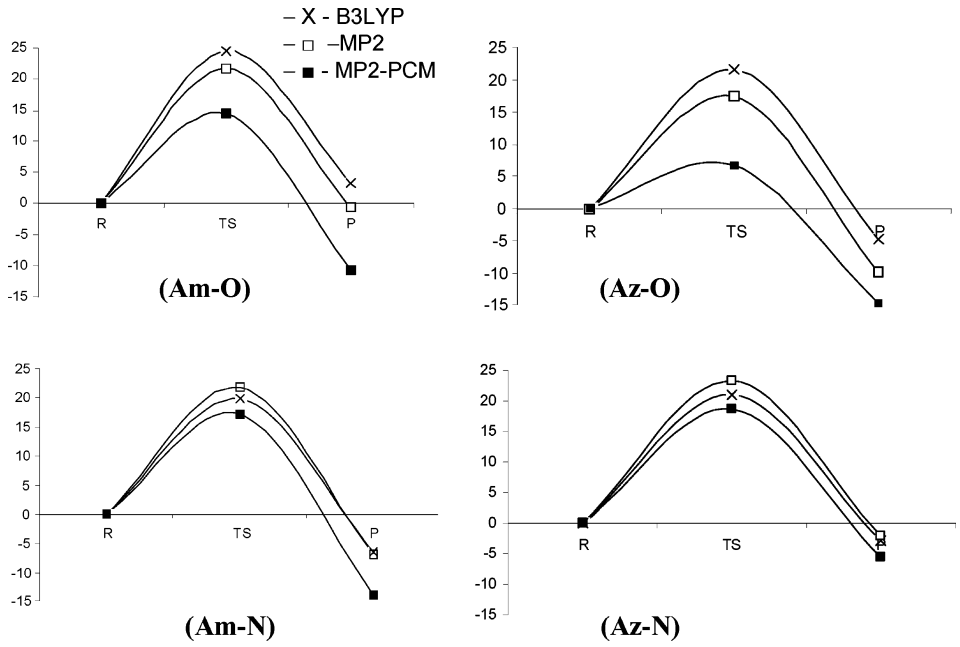

FIGURE 4. Energy profiles of the hydrolysis reaction of O-protonated formamide (**Am-O**), O-protonated *N*-formylaziridine (**Az-O**), N-protonated formamide (**Am-N**), and N-protonated *N*-formylaziridine (**Az-N**).

more stable by 0.4 kcal/mol at B3LYP but less stable by 4.1 kcal/mol at MP2. Coupled-cluster theory with singles, doubles, and perturbative triplet excitations [CCSD(T)] are consistent with the MP2 results. We expect that in the gas phase the O-protonated form is more stable, while in the aqueous phase, the N-protonated form is more stable.

In the gas phase, the O-conformer is more stable, and so the O-pathway is a single step process, while the N-pathway would have two steps: isomerisation of O-protonated *N*-formylaziridine to N-protonated form ($\mathbf{AzP_O} \rightarrow \mathbf{AzP_{TS}} \rightarrow \mathbf{AzP_N}$) by proton-transfer reaction followed by hydrolysis ($\mathbf{AzN_R} \rightarrow \mathbf{AzN_{Ts}} \rightarrow \mathbf{AzN_P}$). The former and latter energy barriers are 20.8(g) and 20.9-(g) kcal/mol at B3LYP and 21.1(g) and 23.1(g) (Δ*G*) kcal/mol at MP2. Thus, the effective energy barrier for the N-pathway would be 20.9−25.4 at B3LYP and 23.1−26.8 (Δ*G*) kcal/mol at MP2. The energy barrier for the single step O-pathway ($\mathbf{AzO_R} \rightarrow \mathbf{AzO_{TS}} \rightarrow \mathbf{AzO_P}$) is 21.5(g) kcal/mol at B3LYP and 17.4 (25.2 in Δ*G*) kcal/mol at MP2. Therefore, both N-pathway and O-pathway would compete.

In the aqueous phase, at the B3LYP level, both O-protonated and N-protonated forms are almost isoenergertic (within 0.4 kcal/mol). Thus, the hydrolysis of *N*-formylaziridine by both pathways can be considered as one-step processes with the energy barriers 11.3 and 15.1 (or 15.5 including 0.4) kcal/mol, respectively. Thus, the O-protonated pathway would be favored. At the MP2 level, the N-protonated form is more stable (by 4.1 kcal/mol). Thus, the N-protonated pathway is a one-step process with the energy barrier 18.7 kcal/mol, while the O-protonated pathway is a two-step process with one energy barrier 16.2 kcal/mol for ($\mathbf{AzP_N} \rightarrow \mathbf{AzP_{TS}} \rightarrow \mathbf{AzP_O}$) by proton-transfer reaction and the other energy barrier 6.7 kcal/mol (or 10.8 kcal/mol with respect to $\mathbf{AzP_N}$) for the hydrolysis ($\mathbf{AzO_R} \rightarrow \mathbf{AzO_{TS}} \rightarrow \mathbf{AzO_P}$). The effective energy barrier of the O-protonated reaction requires the effective activation barrier of 16.2 kcal/mol. Thus, the O-protonated pathway would be slightly more favored,

TABLE 3. Bond Distances (Å) and Relative Energies (kcal/mol) of Stationary Points and Transition States in Ring-Opening Reactions of N- and O-Protonated *N*-Formylaziridine[a]

					relative energy (kcal/mol)		
system	C_e-N	C_e-C_r	$N-C_o$	C_e-O_w	B3LYP	MP2	MP2(PCM)
$AzNR_R$	1.516 (*1.509*)	1.465 (*1.465*)	1.468 (*1.463*)	3.500 (*3.407*)	0.0	0.0	(*0.0*)
$AzNR_{TS}$	2.177 (*2.147*)	1.463 (*1.461*)	1.374 (*1.372*)	2.465 (*1.525*)	26.90	39.96	(*38.41*)
$AzNR_P$	2.529 (*2.530*)	1.538 (*1.537*)	1.300 (*1.296*)	1.431 (*1.428*)	−27.74	21.11	(*−23.37*)
$AzOR_R$	1.441 (*1.438*)	1.514 (*1.515*)	1.293 (*1.290*)	5.322 (*5.267*)	0.0	0.0	(*0.0*)
$AzOR_{TS}$	2.152 (*2.124*)	1.469 (*1.469*)	1.294 (*1.292*)	2.314 (*2.343*)	43.86	49.06	(*42.39*)
$AzOR_P$	2.442 (*2.489*)	1.523 (*1.519*)	1.298 (*1.300*)	1.425 (*1.425*)	−21.46	22.49	(*−28.34*)

[a] Geometries and energies of systems optimized in the gas phase are shown in normal letters and those optimized in aqueous medium (PCM) are shown in parentheses in italics. Refer to Figure 5 for the atom labeling.

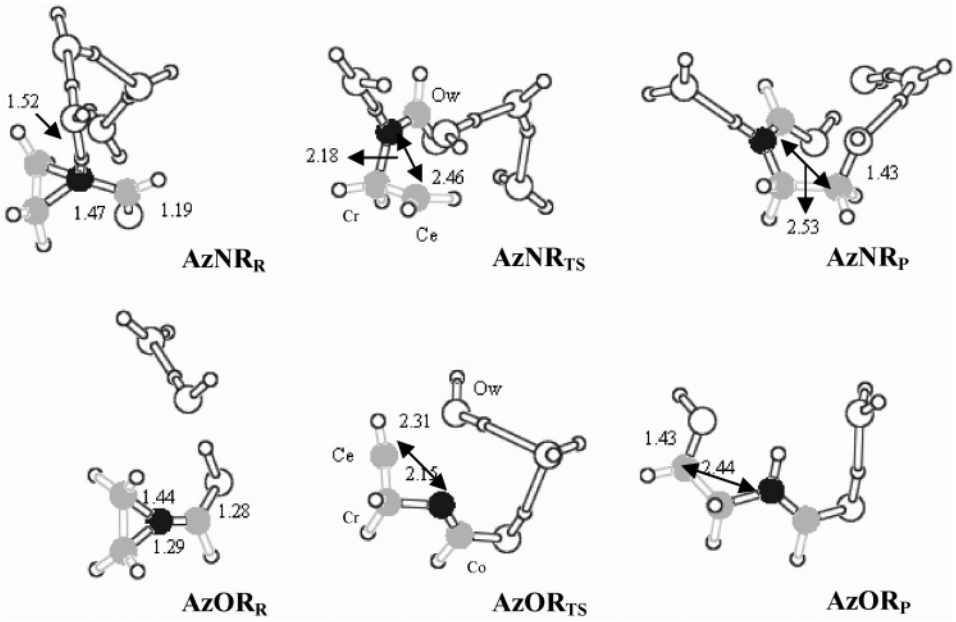

FIGURE 5. Geometries of stationary points and transition states in the ring-opening reaction between N- and O-protonated *N*-formylaziridines. N, black; C, gray; O, white (big); H, white (small).

while competing with the N-protonated pathway. Given the possible inaccuracy of the calculations with the range of a few kcal/mol, the energy barrier difference between the N-protonation and O-protonation is small, and so the two pathways would compete. However, the entropy effect in aqueous solution is not considered. It should be noted that in the *N*-formylaziridine the O-protonation is favored at 0 K, whereas the N-protonation is favored at room temperature. Thus, the entropy effect could make the N-pathway more favorable than the O-pathway, and it is likely that both N-protonated and O-protonated pathways would compete. More accurate prediction should be made at the CCSD(T) level, which is still beyond the current computational capacity.

Brown and co-workers showed that in acidic media *N*-benzoylaziridine undergoes ring-opening reaction and gives benzoyl amides of ethanolamines.[23] Hori et al. addressed the isomerization of 1-acylaziridine in acidic media.[24] Here we discuss about the water-assisted ring-opening reaction of N- and O-protonated *N*-formylaziridine. In this case we also optimized the geometries at the B3LYP level and the energies were refined at the MP2 level. Frequency calculations were performed to confirm whether the geometries are minima or transition states. All geometries were further optimized at the B3LYP(PCM) level ($\epsilon = 80$), and the energies were refined at the MP2(PCM) level. The results are summarized in Table 3 and Figures 5 and 6.

First, we discuss the ring-opening reaction of N-protonated *N*-formylaziridine. One water molecule acts as a nucleophile. The ring opening of the three-membered ring as well as the formation of a bond between the C atom of the ring and the oxygen atom of the water molecule (C_e-O_w bond) occurs almost simultaneously (Table 3, Figure 5). In the reactant C_e-O_w and C_e-N distances are 3.50 Å and 1.52 Å, respectively. The C_e-O_w distance shortened by ~1.46 Å, whereas that of C_e-N is increased by 0.67 Å in the transition state, which indicates partial breaking of the C_e-N bond and partial formation of a C_e-O_w bond in the transiton state. The activation energy for the ring opening of N-protonated formylaziridine assisted by water molecules is 40.0 kcal/mol in the gas phase and 38.4 kcal/mol in the aqueous medium (Figure 6). The activation energy for the ring-opening reaction of O-protonated form is 49.1 kcal/mol in gas phase and 42.4 kcal/mol in the solvent media. The ring opening (elongation of Ce−N) as well as the formation of the C_e-O_w bond occurs almost simultaneously,

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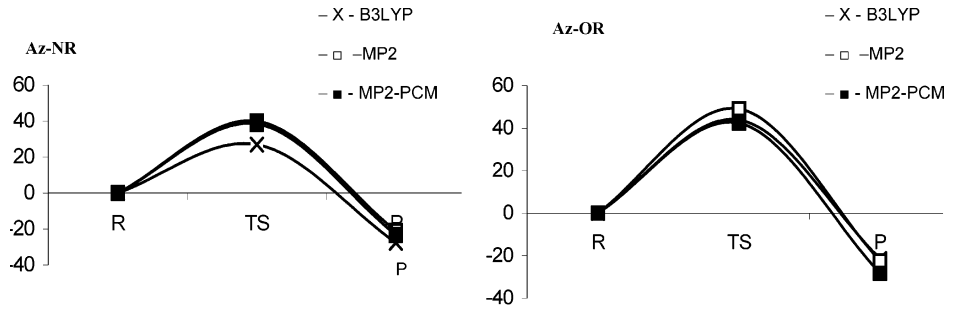

FIGURE 6. Energy profiles of the ring-opening reaction of N-protonated formylaziridine (**AzNR**) and O-protonated *N*-formylaziridine (**AzOR**).

which can be rationalized from the bond distances. The C_e-O_w and C_e-N distances in the transition states are 2.31 Å and 2.15 Å, respectively, which indicates partial formation of C_e-O_w and partial bond breaking of C_e-N in the transition states. The geometries of the reactants, transition states, and products are shown in Figure 5; the corresponding energy profiles are shown in Figure 6. Thus, it is interesting to note that the ring-opening process occurs via N-protonation. Since these energy barriers are much higher than those of the hydrolysis, chances of ring-opening reaction are much less compared with the hydrolysis. However, our study is based on *N*-formylaziridine. Since the charge of N in the aziridine moiety of *N*-benzoylaziridine is very different from that of *N*-formylaziridine due to the large difference in charge between H and C bonded to the carbonyl carbon, the present calculation does not correspond to the *N*-benzoylaziridine case. Thus, although the ring-opening process is not favored in the *N*-formylaziridine case, we do not exclude the possibility that the ring-opening process would occur in the *N*-benzoylaziridine case, since a significant change in charge of N in the aziridine moiety could significantly lower the energy barrier for the ring-opening process.

Our calculations indicate that in all transition states (for both formamide and *N*-formylaziridine) the distance between oxygen atoms of the water dimer is in the range of 2.4 Å. This indicates that these hydrogen bonds are short strong hydrogen bonds (SSHB),[25] which are stronger than strong hydrogen bonds,[26] which in turn stronger than normal hydrogen bonds.[27] Recent calculations by Boyd and co-workers found that this type of low barrier hydrogen bonds exists in the case of reaction mechanisms of the imide formation in *N*-(*o*-carboxybenzoyl)-L-amino acid.[13] To explore the effect of the short strong hydrogen bond, we performed calculations with a single water monomer reacting with the O-protonated formamide, thereby eliminating the chances of forming short strong hydrogen bonds (SSHB) in the transition state. By using the water monomer[12] instead of the water dimer in $\mathbf{AmO_R}$, the activation energy increased by 15 kcal/mol, which can be partially attributed to the lack of SSHB between two water molecule in the transition state for the case of water monomer.

The calculations predict that in all reactants and to some extent in the transition state the charged H-bond[28] exists between the catalyst proton and water molecule. For O-protonated species, the distance between the carbonyl oxygen and the oxygen atom of complexing water molecule is in the range of 2.55−2.60 Å, and for N-protonated species the distance between N and O atom complexing the water molecule is in the range of 2.60−2.65 Å. The charged H-bonds stabilize the reactant over the product and transition state, which implies that the formation of a charged H-bond will increase the energy barrier for the reaction. Experimental evidence shows that the dipolar aprotic and non-hydrogen bond donor solvents have a rate-enhancing effect on formamide hydrolysis, while protic solvents that can act as both hydrogen bond donor and acceptor exert a rate-decreasing effect.[29] To estimate the effect of the charged hydrogen bond, we performed a calculation on O-protonated formamide without water molecule interaction with the catalyst proton. The activation energy barrier of the reaction is lowered by 5.8 kcal/mol.

Conclusion

We studied the acid-promoted and water-assisted hydrolysis mechanism of *N*-formylaziridine in comparison with formamide. Both the O-pathway and the N-pathway were considered in detail. The electron correlation effect seems to stabilize N-protonated *N*-formylaziridine more than the O-protonated one. In acidic media, the hydrolysis reaction of formamide would proceed mainly by the O-pathway because the transition state of the O-pathway is much more stable than that of the N-pathway. In acidic media *N*-formylaziridine exists mainly in the N-protonated form, and the studies on the transition state structure and energies indicate that the hydrolysis reaction of the *N*-formylaziridine would proceed by two

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competing processes of both the N- and O-pathways. In all transition states of the hydrolysis reaction for both formamide and *N*-formylaziridine, short strong hydrogen bonds were identified.

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Supporting Information Available: Fully optimized geometries of all the reactants, transition states, and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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