N-Protonation vs O-Protonation in Strained Amides: *Ab Initio* Study

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Protonation plays an important catalytic role in amide bond hydrolysis. Although the protonation site of an amide is still debatable, O-protonation is generally preferred to N-protonation in ordinary amides. However, N-protonation can be favored in strained molecular systems. To investigate this strain effect systematically, we studied formamide, strained N-formylazetidine, and highly strained *N*-formylaziridine using *ab initio* calculations. The electron correlation effect is found to be important in determining the protonation sites of strained amides, since it contributes to stabilize N-protonation somewhat more than O-protonation. Although O-protonation is highly favored in *N*-formylazetidine as well as in formamide, N-protonation is favored in *N*-formylaziridine in both aqueous and gas phases. In case of O-protonation, the geometries become planar even for highly strained amides. The presence of polar solvents contributes to stabilize N-protonation more than O-protonation. The planarity found in O-protonated strained amides and the nonplanarity in N-protonated strained amides would have an important bearing in enzymatic reactions as well as in asymmetric syntheses.

I. Introduction

The amide bond has long attracted much attention since it is an essential building unit in proteins. Protonation plays an important catalytic role in amide bond hydrolysis.[1] There are two plausible protonation sites of the amide in the acid-catalyzed hydrolysis mechanism: i.e., protonation occurs on either the oxygen or nitrogen. Although O-protonation is known to be generally favored over N-protonation in ordinary amides,[2] there are cases when N-protonation seems to be favored by an inductive effect,[3] α-effect,[4] or strain effect. The strain effect was recently studied by Brown et al.[5−7] In strained anilides such as 3,4-dihydro-2-oxo-1,4-propanoquinoline, the amide bonds are distorted torsionally. The rapid hydrolysis of such compounds in acidic conditions seems to involve N-protonation.[6] This type of hydrolysis mechanism is common to a series of bridged anilides.[7] The rapid hydrolysis of these strained amides have been studied by kinetic methods. Here, we investigate how nitrogen pyramidalization and molecular strain affects the protonation site, using *ab initio* calculations. The amides calculated include the highly strained *N*-formylaziridine, which has been intensively studied for nitrogen inversion involving the characteristic nitrogen pyramidalization.[8] The geometry of *N*-formylaziridine is far from planarity due to the sp^3 hybridization of the nitrogen atom,[9] thereby indicating an enhanced basicity of the nitrogen.

To study the strain effect systematically, we have performed *ab initio* calculations of formamide **(1)**, somewhat strained *N*-formylazetidine **(2)**, and highly strained *N*-formylaziridine **(3)**, and their protonated tautomers (**1-O** through **3-N′**), as shown in Figure 1. It is likely that the unstrained formamide **1** would favor O-protonation, but it is not clear if the strained *N*-formylazetidine and *N*-formylaziridine would favor N-protonation.

II. Calculation Method

All the structures were fully optimized by Möller−Plesset second-order perturbation (MP2) theory using the 6-31G** and 6-31+G** basis sets without any constraint.[10] MP2/6-31G** vibrational frequency analyses were performed to confirm the minima or transition states of the structures. There were no significant differences in geometries and relative energies between the 6-31G** and 6-31+G** basis sets. Thus, only the MP2/6-31+G** geometries are reported. Relative energies with and without zero point energy (ZPE) correction are reported. In the case of ZPE correction, the unscaled MP2/6-

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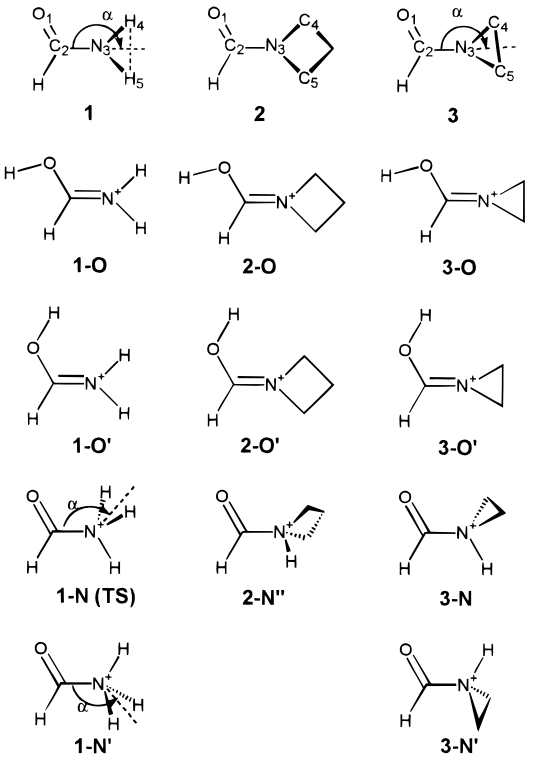

Figure 1. Structures of formamide, *N*-formylazetidine, and *N*-formylaziridine and their protonated species.

31G** frequencies were used, as we were interested in relative[11] rather than absolute energies which are better described by scaled frequencies. It is because lower frequencies, which are most susceptible to conformational changes and thus most responsible for the relative energy changes, should not be scaled much unlike higher frequencies.[12] Since molecular strain tends to affect the entropies, the free energies at 298 K and 1 atm (G_{298}^{rel}) are also reported on the basis of harmonic vibrational frequency approximation (by neglecting anharmonic correction)[13] using unscaled frequencies, since in this case lower frequencies are much more important than higher frequencies. To consider the solvent effect, the self-consistent reaction field (SCRF) method was employed; SCRF-(MP2)/6-31+G** calculations at the MP2/6-31+G** geometries were performed using a dielectric constant $\epsilon = 80$. The solute-occupied cavity was defined as the volume inside a contour of 0.001 electron/bohr^3 density, and the SCRF energies were calculated using the Onsager model.[14] We have also performed single-point Möller−Plesset fourth-order perturbation (MP4) calculations using frozen core (FC) orbitals at the MP2/6-31+G** optimized geometries in the case of protonated *N*-formylaziridine for which the protonation site predicted by MP2 is different from that predicted by Hartree−Fock (HF) calculations.

III. Results

The predicted geometries and relative energies of the unprotonated and protonated species shown in Figure 1 are listed in Table 1. All structures in Figure 1 are at the local minima except for **1-N** which is a transition state (TS) with respect to **1-N′**. All protonated tautomers have C_s symmetry except for N-protonated *N*-formylazetidine **(2-N″)**, which has no symmetry. For all the O-protonated tautomers *trans* and *cis* forms of H−O−C−N are denoted as ***n*-O** and ***n*-O′**, respectively, where $n = 1$, 2, 3, and for all the N-protonated species *trans* and *cis* forms of O−C−N−H are denoted as ***n*-N** and ***n*-N′**, respectively, where $n = 1$ and 3. In the case of N-protonated *N*-formylazetidine, the minimum energy conformer is **2-N″**. As shown in Table 1 and Figure 2, in all cases O-protonation lengthens the C−O bond (by 0.07−0.09 Å) and shortens the C−N bond (by 0.06−0.11 Å). In contrast, N-protonation shortens the C−O bond (by 0.02−0.04 Å) and lengthens the C−N bond (by 0.10−0.21 Å). In cases of O-protonation, the C−O bond lengths show a single bond character, while the C−N bond lengths show a double bond character.

In all the O-protonated tautomers, *trans* conformers **(*n*-O)** are 2−4 kcal/mol more stable than the corresponding *cis* conformers **(*n*-O′)**. For ***n*-O**, there is an electrostatic repulsion between two H atoms in H−O−C−H, resulting in a stretched O−C single bond. On the other hand, for ***n*-O′**, there is an electrostatic repulsion between two H atoms in either H−O−C−N−H ($n = 1$) or H−O−C−N−CH ($n = 2$ and 3), resulting in the stretching of the C=N double bond. Therefore, ***n*-O′** would lose more energy than ***n*-O** because the stretching of the C=N double bond requires more energy than that of the C−O single bond, which may explain why the ***n*-O** conformers are more stable than ***n*-O′** conformers. The lowest-energy N-protonated tautomers for $n = 1$, 2, and 3 are **1-N′**, **2-N″**, and **3-N**, respectively. Their conformational energetics may be governed by competing forces between electrostatic interactions and stereoelectronic effects. In terms of electrostatic interactions, **1-N** has two O···H attractions and one H···H repulsion, while **1-N′** has one O···H attraction and two H···H repulsions. Since the corresponding charges and interatomic distances do not significantly differ from each other, **1-N** is electrostatically more stabilized than **1-N′**. Owing to interatomic electrostatic interactions, the CN bond length of **1-N** would be slightly shorter than that in **1-N′**. On the other hand, the stereoelectronic effect which are $\sigma_{CH}-\sigma_{NH}^*$ and $\sigma_{NH}-\sigma_{CH}^*$ interactions[15] are present in **1-N′**, while $\pi_{CO}-\sigma_{CH}^*$ and $\sigma_{CH}-\pi_{CO}^*$ interactions do not work in **1-N** due to the orthogonality of orbitals. This will shorten the CN bond length in **1-N′** greatly. Indeed, the CN distance of **1-N′** is 0.009 Å shorter than that of **1-N**, which indicates that the stereoelectronic effect is somewhat greater than the electrostatic interaction in this system. On the other hand, in the case of **3** the aziridine ring is found to be positively charged by an inductive effect, as a result of transfer of charge from N. This positive charge tends to interact strongly with the negative charge of the O atom, which provides **3-N** with a large stabilizing energy. In **3-N′**, the stereoelectronic effect plays an important role in stabilizing it as a local minimum; however the large electrostatic interactions are more important than the stereoelectronic effect, since the CN bond length in **3-N′** is only 0.002 Å shorter than that in **3-N**. Thus, the N-protonated species for *N*-formylaziridine favors the

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Table 1. MP2 Geometries and MP2, MP4(FC), and SCRF(MP2) Energies Using the 6-31+G Basis Set[a]**

	r_{CN}	r_{CO}	α	E_e^{rel} MP2	E_e^{rel} MP4	E_e^{rel} SCRF	E_0^{rel} MP2	G_{298}^{rel} MP2
1	1.361	1.227	173.2	205.0		201.5	195.7	188.9
1O	1.296	1.297	180.0	0.0		0.0	0.0	0.0
1O′	1.301	1.293	180.0	3.6		2.4	3.6	3.6
1N	1.569	1.187	123.3	16.0		8.0	14.8	14.7
1N′	1.560	1.188	128.7	15.4		7.4	14.4	13.9
2	1.357	1.233	154.7	220.2		218.4	211.7	205.9
2O	1.287	1.316	180.0	0.0		0.0	0.0	0.0
2O′	1.291	1.310	180.0	3.0		4.4	3.1	3.1
2N″	1.512	1.197	123.7	11.7		10.4	11.6	12.2
3	1.392	1.225	126.6	212.8		214.4	204.4	198.2
3O	1.280	1.312	180.0	1.9	2.9	4.8	2.0	1.8
3O′	1.285	1.307	180.0	3.8	4.7	7.1	3.9	3.7
3N	1.494	1.197	122.8	0.0	0.0	0.0	0.0	0.0
3N′	1.492	1.195	126.0	1.9	1.9	2.1	1.7	1.6

[a] r_{CN} is the distance between carbon C_2 and nitrogen N_3; r_{CO} is the distance between carbon C_2 and oxygen O_1 in amide. α is the angle between the C_2-N_3 bond and the $N_3-C_4-C_5$ (or NH_2) plane. E_e^{rel} and E_0^{rel} are the relative binding energies of the protonated species at 0 K without and with ZPE calculation, respectively, and G_{298}^{rel} is the corresponding relative free energy (298 K and 1 atm) for which the entropies were calculated using the MP2/6-31G** frequencies. MP4 (FC) and SCRF (MP2) calculation were performed at the MP2/6-31+G**-optimized geometries. In SCRF(MP2) calculations, ϵ was set to 80. Distances are in angstroms, angles in degrees, and energies in kcal/mol.

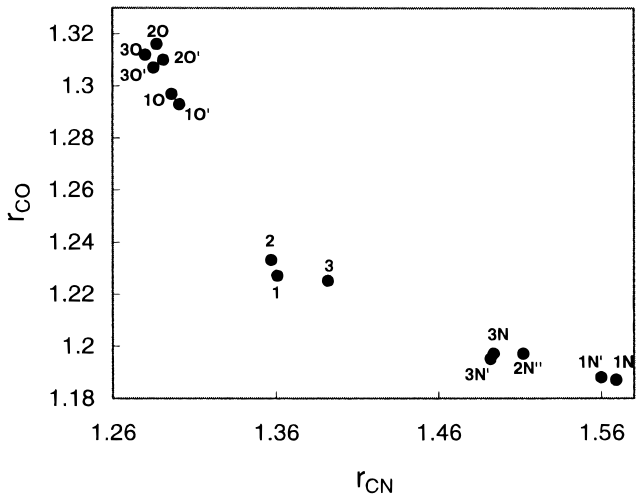

Figure 2. Plots of CN vs CO bond lengths for structures **1**−**3** and their O- and N-protonated tautomers.

s-trans conformation over the *s-cis* conformation (i.e., **3-N** is 2 kcal/mol more stable than **3-N′**). In the case of **2**, it is likely that the competition between the electrostatic interactions and stereoelectronic effects results in no minima for structures with C_s symmetry but a minimum for the twisted structure **2-N″**.

Comparing O-protonated and N-protonated tautomers, the lowest energy conformers for the protonated species of **1**, **2**, and **3** are **1-O**, **2-O**, ad **3-N**, respectively. For formamide, **1-O** is much more stable than **1-N′** by 15 kcal/mol. For *N*-formylazetidine, **2-O** is more stable than **2-N″** by 12 kcal/mol. On the other hand, for *N*-formylaziridine, **3-N** is more stable than **3-O** by 2 kcal/mol. This migration of the protonation site from O to N in *N*-formylaziridine can be rationalized by nitrogen pyramidalization (due to sp^3 hybridization), which should be responsible for the enhanced basicity of the nitrogen atom in *N*-formylaziridine. Although sp^2 hybridization of N is most suitable for **1-O**, it would not be so for **3-O** because of the small bond angle of C−N−C in the aziridine ring. *N*-Formylaziridine favors a pyramidalized N atom to minimize the strain of the 3-membered ring. Upon protonation, the strong π-conjugation between the carbonyl carbon and nitrogen in **3-O** constrains the 3-membered ring to be coplanar with the remaining moiety, resulting in a highly strained structure. On the other hand, the nitrogen in **3-N** is able to possess a pyramidalized character akin to the corresponding neutral species **3**, so that the 3-membered ring is less strained in **3-N**. As a result, **3-N** is more stable than **3-O**.

For the C=O bond rotation along the C−N bond, the rotational energy barriers for **1**, **2**, and **3** are 16, 14, and 4 kcal/mol, respectively. This indicates that **1** and **2** are somewhat highly conjugated, whereas **3** is hardly conjugated due to the highly pyramidalized N atom. The degree of the pyramidalization can also be signified by the angle (α) between C−N bond and N−C−C plane. As the geometrical structures become more pyramidalized (**1**, α = 173°; **2**, α = 155°; **3**, α = 127°), the stability of the N-protonated tautomer increases. The relative stabilities of the tautomers do not change significantly even if the entropy effects as well as the ZPEs are taken into account, as seen from ΔG_{298}^{rel}. To take into account the solvent effects, the SCRF(MP2)/6-31+G** calculations were performed. In this case, for formamide, **1-O** is 7 kcal/mol more stable than **1-N′**, and for N-formylazetidine, **2-O** is 10 kcal/mol more stable than **2-N″**, whereas for *N*-formylaziridine, **3-N** is 5 kcal/mol more stable than **3-O**.

Although for the protonated *N*-formylaziridine MP2 theory favors **3-N** more than **3-O** by 2 kcal/mol, HF theory favors **3-O** more by 1 kcal/mol. In case of formamide, *N*-formylazetidine, and *N*-formylaziridine, N-protonated tautomers are much less stabilized at the HF level than at the MP2 level by 8, 5, and 4 kcal/mol, respectively. This may be correlated with the difference in their electronic structures, i.e., the $C=N^+$ double bond character in the O-protonated tautomer vs the C=O double bond character of the N-protonated tautomer. Since the latter has more electrons in a bonding region of high electron density, we may conjecture that it has a larger electron correlation effect than the former, resulting in more stabilized energy for the N-protonated tautomer. Because of the importance of the electron correlation effect, we have carried out MP4 energy calculations at the MP2/6-31+G**-optimized geometries. According to MP4(FC) results, the relative stabilities of **3-O** over **3-O′** and **3-N** over **3-N′** are 1.9 kcal/mol, which are the same as those obtained from the MP2 results.

The MP4(FC) relative stability of **3-N** over **3-O** is 2.9 kcal/mol, which is 1 kcal/mol larger than the MP2 values.

Olah and collaborators[16] studied the acylation of aziridine and protonation of *N*-acylaziridine and characterized N-protonated N-acylaziridinium ion by NMR. They found that when aziridine was acylated with alkyl- or aryloxocarbonium hexafluoroantimonate ($RCO^+SbF_6^-$, where R = Me, Et, and Ph) at −60 °C, N-protonated *N*-acylaziridinium was formed. When protonating *N*-acetyl-, *N*-propionyl-, *N*-butyryl-, *N*-benzoyl-, and *N*-naphthoylaziridine in $FSO_3H-SbF_5-SO_2$ solution at −60 °C, they obtained O-protonated *N*-acylaziridinium ions. Although both N-protonated and O-protonated tautomers for the same species were characterized by NMR spectra at −60 °C in different chemical reaction conditions, the transfer from one conformer to another did not occur. The different experimental results seem to have a kinetic origin. According to our MP2 and MP4 results, *N*-formylaziridine favors N-protonation over O-protonation thermodynamically. However, the energy difference is not so large that the steric and electronic effects of substituents in either acyl group or aziridine ring might change the order of the stability between the N- and O-protonations.

Structures **1**−**3** are not planar. However, the local minimum energy structures of all the O-protonated tautomers are planar regardless of the direction of O−H bond. The complete planarity found in such highly strained molecules is surprising. Such a geometrical change is important for hydrolysis of strained amide bonds, especially in enzymatic reactions where a certain portion of the exothermicity of substrate binding is utilized to activate amide bonds.[6,17] The lone pair effect of nitrogen may be utilized in asymmetric syntheses.[18] The stereoselectivity of systems containing a nitrogen lone pair may originate mainly from the electrostatic and stereoelectronic effects.[18−20]

IV. Conclusion

We have studied the protonation sites of formamide, strained *N*-formylazetidine, and highly strained *N*-formylaziridine using HF, MP2, and SCRF(MP2) calculations. The inclusion of electron correlation was found to be important in the study of strained amide systems, since it contributes to stabilize the N-protonation somewhat more than O-protonation. Therefore, MP4(FC) calculations were also carried out on protonated *N*-formylaziridines. Our calculational results indicate that all *N*-formyl *n*-membered rings for $n \geq 4$ would have the O-protonation in aqueous solution as well as in the gas phase. In these cases, the molecular structure undergoes significant geometrical change to become planar. On the other hand, in the case of highly strained *N*-formylaziridine, the strong pyramidalization of the nitrogen atom thermodynamically favors N-protonation over O-protonation slightly. Therefore, in this case it may be possible that the protonation sites change if substituents and chemical environments are changed. The presence of polar solvents contributes to stabilize N-protonation more than O-protonation. Considering the importance of ligand rigidity and geometrical distortion in enzymatic reactions,[21] the nonplanarity in N-protonated strained amides as well as the planarity found in O-protonated strained amides may play an important role in enzymatic reactions as well as in asymmetric syntheses.

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Supporting Information Available: MP2/6-31+G**-optimized structures and energies of all species in Figure 1 (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS; see any current masthead page for ordering information.

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