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**CONFORMATIONAL-DEPENDENT REACTION MECHANISM:
CASE OF ACID HYDROLYSIS OF N-BENZOYL-9-
AZABICYCLO[6.1.0]NON-4-ENE**

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Abstract

Quantum chemical studies of the acid hydrolysis of *cis-cis*-N-benzoyl-9-azabicyclo[6.1.0]non-4-ene in gas phase and sulfuric acid solution have been carried out. Conformational analysis of reactant and intermediates were done at DFT level of calculations, using different basis sets. Transition states were identified and IRC calculations were done at the same level. In the first step of the reaction, the protonation occurs preferentially on the nitrogen atom. Three products are obtained. The type of mechanism: stepwise or concerted, depends on the stable conformers and the cleaved N-C bond. The main conclusion is that the products of the reaction depend on the nature of the stable conformer of reactant.

Key words: N-acylaziridine, conformational analysis, solvation, DFT, acid hydrolysis.

Draft

1. Introduction

The most important applications of aziridines are in organic synthesis¹⁻¹⁷. Indeed, the particular arrangement of two carbon atoms and a nitrogen atom in these smaller cycles makes them easily transformable chemical species. This arrangement gives electronic densities between nuclei rather different from those in the more stable arrangements and which can be cited to explain, the reactivity of aziridine. The smallest of actions of a disruptive element changes the electronic density in this arrangement weakens the cohesion of these three atoms that, after increasing its energy will be relaxed to non-cyclic species. This is the case of the aziridine protonation as shown by theoretical¹⁸⁻²³ and experimental²²⁻²⁷ published studies. It is well known that the aziridine ring opening is regioselective²⁸⁻³⁰. Berger shows that both frontier molecular orbital theory and Fukui function can be used to rationalize a experimentally observed regioselectivity in the nucleophilic ring opening of activated aziridine²¹. Baruah et al. used conceptual density functional theory based descriptors to strongly rationalize the experimentally observed activation and regioselectivity in the ring opening of non-activated aziridine¹⁹. In general it occurs on the side of the electron donor or less electron-withdrawing substituents. The following reaction therefore is a substitution of the detached arm from the ring by a nucleophile. It is also possible that the other carbon atom of the aziridine ring loses electrophilic substituents, thus providing opportunities for the formation of a double bond. The ring opening and the reaction that followed can happen sequentially or simultaneously. The stepwise mechanism requires a stable cationic intermediate. It is clear that this mechanism is enhanced by the carbocation stabilizing effects of solvent and aziridine structure. Sharing the C-C aziridine bond with another ring may also have effects on the protonation of nitrogen and the reactions that will follow³¹. It is well established that the effect of the protonation of an aziridine with hydrogen on the nitrogen atom and an N-substituted aziridine are different. The reaction following the protonation can be significantly different depending on the nature of the group linked to the nitrogen atom, which can bind to the carbon where the aziridine ring opening occurs in a ring expansion reaction. This is the case of N-acylaziridines which are classified as activated aziridine³¹⁻³⁵. Hori et al., using quantum calculations at different level of theory, shows that the acid-catalysed transformation of N-formylaziridines to the oxazoline isomer can be held in S_Ni or addition-elimination mechanisms³⁵. In both mechanisms the configurations of ring carbons are preserved³⁵. It should be noted that, the protonation occurs in competition between the aziridine nitrogen atom and the carbonyl oxygen atom³⁵⁻³⁸.

Scheme 1 shows the acid hydrolysis of the *cis-cis*-N-benzoyl-9-azabicyclo[6.1.0]non-4-ene **1** reaction equation³¹.

The Scheme 2 shows the experimentally proposed mechanism³¹. The oxazoline **2**, which is the result of the substitution of the nitrogen by the carbonyl oxygen is minority. The bicyclo[6.1.0] amidoalcohol **3**, which is majority, is the result of the substitution of the nitrogen by a carbon atom of the double bond of cyclooctene. The protonation followed by removal of the proton from the second carbon of aziridine ring leading to 1-benzamide cycloocta-1,5-diene **4** was not experimentally observed. In this paper, we present the results of theoretical investigations based on quantum calculations of the acid hydrolysis of the *cis-cis*-N-benzoyl-9-azabicyclo[6.1.0]non-4-ene **1** in gas phase and in sulfuric acid solution. In the last case the solvent was represented by a continuum model. The objective of these studies is to show how this reaction occurs in the gas phase and the effects of the continuum solvent model.

2. Computational details

Our approach is based on molecular electronic properties of stationary structures of the cited reaction. Geometries of stationary points were fully optimized using B3LYP/6-31G(d,p) method. Harmonic vibrational frequency calculations were realized to determine the nature of these points. Single point calculations of optimized structures are also performed using the extended basis 6-311G(df,pd). Cartesian coordinates of optimized geometries of stationary points of the reaction can be found in the supporting data. To estimate the solvation effect, we have done the DFT calculations at the same level in sulfuric acid, which is described by the continuum solvation model. No specific interaction solvent-solute is taken in the count. Only the electrostatic interaction is represented by a self-consistent reaction field (SCRF) model. We employed the integral equation formalism for polarizable continuum model (IEFPCM)³⁹. In this model the solute cavity is created via a set of overlapping spheres. We use for the sulfuric acid the dielectric constant is 110. As used in other studies⁴⁰. To investigate the dynamic of the chemical transformation, some intrinsic reaction coordinate (IRC) calculations are done. For the estimation of the relative populations of two conformers a and b we calculate their isomerization constant using the Van't Hoff equation 2 at room temperature. Q_{trans} refers to the translational partition function (three-dimensional particle in a box model), Q_{rot} is the rotational partition function (rigid rotor model), and Q_{vib} is the vibrational partition function (harmonic oscillator model). The values of vibrational partition function computed with the zero of energy being the first vibrational level are used in these studies. These values are labeled by (V=0) in Gaussian⁴¹ output files.

$$Q_{\text{tot}} = Q_{\text{trans}} * Q_{\text{rot}} * Q_{\text{vib}}$$

Eq. 1

$$K_{a \rightarrow b} = \frac{[a]}{[b]} = \frac{Q_a}{Q_b} * \exp\left(\frac{-E_a + E_b}{RT}\right) \quad \text{Eq. 2}$$

All quantum chemistry calculations were carried out using Gaussian 09 package ⁴¹.

3. Results and Discussion

Reactant conformational analysis

In many molecules the atomic groups can freely rotate around single bonds and allows these ones to interconvert between different conformations. In these cases, when it exists, the energy barrier is low. Even though rotation occurs rapidly at room temperature, the product selectivity of some reaction has been explained by conformational-dependent reaction mechanisms ⁴²⁻⁴⁴. The yield of each product can be related, in statistical thermodynamic, to the partition function. When the energy barriers of interconversion process of reactant are high, some products do not appear under some thermodynamic conditions. So, a conformational analysis of reactants is the first step of the studies of a reaction pathway ⁴⁵.

As presented in Figure 1, the structure of N-benzoyl-9-azabicyclo[6.1.0]non-4-ene contain two substructures which determine its configurational space. They are the aziridine ring and the double bond at his α position. According to the distribution of substituents around these two substructures, there are the *cis* or *trans* configurations. Four configurations are then possible: *cis-cis*, *cis-trans*, *trans-cis* and *trans-trans*. In this paper we are concerned with the *cis-cis* configuration which is the configuration of the experimentally used compound ³¹. The conformational variety of *cis-cis*-N-benzoyl-9-azabicyclo[6.1.0]non-4-ene **1** is due to the limited rotation around cyclooctene single bonds C-C, the inversion of the aziridine nitrogen atom, rotations of the benzoyl group around C-N bond, and the phenyl group around C-C bond. In effect, the benzoyl group conformations only depend on the rotation of the phenyl. The most stable one, is that allows the delocalization of π electrons and thus a better resonance between the carbonyl and phenyl groups. The stability of the conformations due to the rotation of the benzoyl group depends on the interactions between the benzoyl group and the two carbon atoms of aziridine ring. The nitrogen inversion, in the case of unsubstituted aziridine, gives two limit invertomers of equal energy. In the case of substituted aziridines, this equivalence is lost because of the interactions that can occur between different substituents. The aziridine nitrogen atom inversion process passes through a transition state. The Table 1 presents the activation energy of inversion of different aziridines obtained at different levels of theory.

In a recent study published by Neuenschwander et al.⁴⁵ sixteen among the most stable conformations of *cis*-cyclooctene were identified. The rotation of carbon atoms around the double bond being prohibited, at least four atoms belong to the same plane, while the maximum number of coplanar carbon atoms is five. Thus the conformations were separated into two classes. In the first class, the conformations have four coplanar carbon atoms. They are denoted **A** or **C** (Figure 2). The **A** conformation have the lowest energy. Those of the second class have five coplanar carbon atoms. They are denoted **B** or **D** (Figure 2).

It was noted that the transition from one conformation to another always requires crossing an energy barrier.⁴⁵ In our conformational analysis of *cis-cis*-N-benzoyl-bicyclo-9-aza[6.1.0]non-4-ene we built its conformers by steps. Only two more stable conformers of *cis-cis*-bicyclo-9-aza[6.1.0]non-4-ene **1** were obtained. Presented in Figure 3, the first one has four coplanar carbon atoms, and is denoted **E**, when the second one has five coplanar carbon atoms, and is denoted **F**. The conformational space was then reduced because the rotation of carbon atoms located out of the plane is prohibited.

The main difference between these two conformers is the number of coplanar carbon atoms, which can be quantified by the values of $\angle C_6C_3C_7C_2$ dihedral angle. In the conformer **E** this angle is about 180° , while it is about 289° in the conformer **F**. The interconvert process between the conformers **E** and **F** can be obtained by the variation of this dihedral angle. The transition state of this interconvert process was identified to be where the named dihedral angle is about -165.82° .

As shown in Table 2, the two conformers **E** and **F** have equivalent energies, in gas phase and sulfuric acid solution. We note negligible solvent effect on the electronic energies. The solvent effect is more pronounced on the conformer population. In gas phase the two conformers have nearly the same populations, but the **F** conformer is majority in sulfuric acid solution. The interconvert process energy barrier is about 8 Kcal/mol. This result indicates that this conformational change can be stopped at a low temperature. It's noted that the most stable structures are when the hydrogen atom linked to nitrogen atom and cyclooctene ring are on opposite sides of aziridine ring.

As shown in Table 1, the energy barrier is sufficiently high that the nitrogen inversion cannot occur at low temperature. It is well known that, because of the cyclic structure, the energy barrier of the nitrogen inversion is

higher in aziridines than in amines. The energy barrier of simple aziridine inversion is about 18-20 kcal-mol⁻¹.⁴⁶ These experimental values are in good agreement with calculated ones at MP2/6-311G(df,pd)// B3LYP/6-31G(d,p) level. It is noted that the basis set extension, DFT level of theory using B3LYP functional didn't improve the nitrogen inversion energy barrier, while a best representation of electronic correlation in MP2 method give the best agreement with experimental value. So, the values obtained at this last level of theory are good approximation and can be used to rationalize the ring substitution on the nitrogen inversion in aziridine derivatives. A neglected effect of the substitution by methyl groups on ring carbon is observed while the substitution by methyl group on the nitrogen decrease the energy barrier by 1,51 Kcal-mol⁻¹. The cyclooctene substitution on ring carbons increases the energy barriers of nitrogen inversion in the conformers **E** and **F**. At the DFT level, the conformer **E** present a small nitrogen inversion energy barrier in comparison with the conformer **F**, while the tow conformers presents slightly the same value at the MP2 level.

Two more stable conformers of *cis-cis*-N-benzoyl-9-azabicyclo[6.1.0]non-4-ene **1** were obtained. Presented in Figure 4 they are denoted **1E** and **1F**. Due to steric effect, the conformers where the cyclooctene fragment and the benzoyl group are on the same side of aziridine ring are unstable.

From the results presented in the Table 3, it's appears that the two conformers have slightly the same energy. These results reveal that the barrier energy of the interconversion between the two conformers is about 8 Kcal-mol⁻¹. All calculated relative populations indicate that the conformer **1F** is majority. The difference between the populations of the two conformers is more important in the sulfuric acid solution.

The protonation

In the Scheme 2, it is mentioned that the reaction began by the protonation of the aziridine nitrogen atom but it can be held on the carbonyl oxygen atom. H NMR studies of N-acylaziridines indicated that the O-protonated species are in equilibrium with N-protonated ones³⁶. In the opposite, theoretical studies have showed that the preferential protonation site is the nitrogen atom of N-acylaziridines^{35,37-38}. Our results of partial charges, Fukui index and local electrophilicity index calculations performed at various levels of theory for the two conformers **1E** and **1F** did not clearly designate the preferred protonation site. These results are exposed in the supporting data.

The differences of energies presented in Table 4 shows that, for all the used methods, the N-protonated conformers are more stable than the O-protonated ones. These relative stabilities are more pronounced in sulfuric acid media. From Table 5 we note that the calculated relative populations indicate that between the N-protonated conformers the **1F(NH⁺)** (Figure 5) is the majority. The energy differences between the two protonated species are more important in sulfuric acid solution. The dihedral angles $\angle \text{N}$ of **1E(OH⁺)** et **1F(OH⁺)**, and $\angle \text{OCNH}$ of **1E(NH⁺)** et **1F(NH⁺)** are about 180° (Figure 5). The same results were obtained from quantum calculations on N-formylaziridine by Cho et al.³⁷. So the proton-transfer between nitrogen and oxygen atoms needs to be assisted by acid and/or solvent molecules. The calculations at MP2 level of theory show an energy barrier of 16,7 and 12,1 Kcal·mol⁻¹ in gas and aqueous phases respectively in the tautomerism process from O-protonated to N-protonated N-formylaziridine, while it's of 17,5 and 16,2 Kcal·mol⁻¹ respectively³⁸. Due to the strained caused by cyclootène and the resonance in the benzoyl moiety we expected a higher energy barrier in the case of the understudy molecule **1**.

Valence angle and bond length of aziridinic ring of the optimized structures of neutral, N-protonated and O-protonated of the two conformers **1E** and **1F** are presented in Table 6 and Table 7 respectively. It appears that the N-protonated species have the longest N-C bonds in the both phases. A similar result was obtained by Hori and co-workers, in the case of N-formylaziridine³⁵. No effect of the solvent on the geometric parameters is observed. So, we can deduce that the ring opening by N-C bond cleavage is energetically favored in N-protonated conformer in comparison to O-protonated one in gas phase and sulfuric acid solution.

Aziridine ring opening

After protonation, the opening of aziridinic cycle happened by breaking one of the two N-C bonds. As we mentioned above, the ring opening of the aziridine is regioselective and occurs on the most substituted carbon. However, for the four conformers **1E(NH⁺)**, **1F(NH⁺)**, **1E(OH⁺)** and **1F(OH⁺)** (Figure 5) the two N-linked carbon atoms have the same environment. The two N-C bond distances are nearly equal. So, there is no reason to favor the ring opening by one or the other of the two bond cleavage. Then, we studied the breaking process of the two bonds N-C₁ and N-C₈ (Figure 5) and their consequences. The various transition states have been identified and characterized by frequency calculations at the B3LYP/6-31G(d,p) level of theory.

As expected, the calculated activation energy of N-C bond cleavage in gas phase and sulfuric acid media presented in Table 8 confirms that the aziridine ring opening occurs preferentially in the N-protonated conformers. The solvent reduces the activation energy in all cases. We note that the O-protonated **1E** conformer **1E(OH⁺)** presents the largest values. Then we conclude that the ring opening did not occur in these species. The cleavage of N-C₈ of the **1F(OH⁺)** produces N-(octahydropentalen-1-yl)benzimidic acid ion **5'** (Figure 6). The hydrolysis of this carbocation conducts to N-(4-hydroxy-octahydropentalen-1-yl)benzimidic acid **5** (Figure 6) which is the iminol tautomer of N-(4-hydroxy-octahydropentalene)benzamide **3**. The compound **5** wasn't experimentally observed. It can be supposed that it is converted to the experimentally obtained compound **3**. But, as noted by Tavakol the energy barrier of the conversion between iminol and amide forms is high⁴⁷. The cleavage of N-C₁ of the same conformer gives 3-(cyclopent-2-enyl)-N-(1-hydroxy ethylidene) propan-1-iminium **6** (Figure 6) which is largely different from the experimentally obtained ones. The optimal structures of **5** and **6** compounds can be obtained from supporting data.

The Figures 7, 8, 9, and 10, show the energetic profiles of N-C₁ and N-C₈ bonds breaking obtained by DFT calculations in the both phases. In the case of **1E(NH⁺)** conformer, the breaking of one or the other C-N bond gives the same product: the oxazolinium **2'** with the same energetic profile and following a concerted mechanism. Oxazoline **2** is obtained by deprotonation of the oxazolinium **2'** (Scheme 2 route a).

Indeed, in this conformer, the cyclization is facilitated by the short distance between C₁ carbon atom and oxygen atom of the carbonyl (2.682 Å). In the **1F(NH⁺)** conformer, this distance is about 3.641 Å, so it should not allow strong attractive interaction between the two atoms leading to the cyclization. In the case of the later conformer, the cleavage of the bond N-C₈ gave the benzamide cycloocta-1,5-diene ion **4'** (Scheme 2 route b). There is a migration of hydrogen atom to oxygen atom at the same time of the aziridine ring opening. Then we observe the formation of the double bond between carbon atoms of the aziridine ring. After deprotonation, the benzamide cycloocta-1,5-diene **4** is obtained. The N-C₁ bond breaking gives the N-(octahydropentalen-1-yl)benzamide ion **3'** which by hydrolysis and deprotonation gives the N-(4-hydroxy-octahydropentalene)benzamide **3** (Scheme 2 route c). We noted only light solvent effects on the energy values but the mechanisms are the same in the phases.

4. Conclusion

Quantum studies of the acid hydrolysis of N-benzoyl-9-azabicyclo [6.1.0] non-4-ene **1** in gas phase and sulfuric acid solution, allowed us to show that the reaction mechanism and the reaction products depend on the stable conformations of the reactant and various intermediates. It is noted that the solvent don't change the

mechanisms. The first step of the reaction is a protonation. From our results, the protonation of the nitrogen atom seem to be favored in comparison to that of the oxygen atom. The three products mentioned in Scheme 2 are obtained. The type of mechanism: stepwise or concerted, depends on the stable conformers and which N-C bond is broken. Depending on the conformation of the protonated species, the aziridine ring opening occurs in the same time with either the formation of a new O-C bond and a new cycle leading to oxazoline **2**, or the elimination of the proton from the second aziridine ring carbon atom, leading to the benzamide cycloocta-1,5-diene **4**. This compound wasn't experimentally obtained. The low relative population of the conformer responsible in its formation can be evoked to explain this experimental result. We identified one case where the mechanism occurs in two steps. Like the experimentally proposed mechanism, the first step lead to a carbocation before going to the bicyclic amidoalcohol **3** which was mainly experimentally obtained. From the populations and relative stability of conformations, it appears that, in this type of reaction, a competition between a concerted mechanism and the stepwise one can happen. We pointed out that the conformational analysis of *cis-cis* N-benzoyl-9-azabicyclo [6.1.0] non-4-ene **1** was necessary to explain and interpret the resulting products of his acidic hydrolysis.

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Supporting Information

Cartesian coordinates of optimized structure of some species cited in this paper and some electronic properties of the conformers **1E** and **1F** are provided in supporting data file. This file is available free of charge.

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Table 1. Nitrogen inversion energy barriers of some aziridines in kcal·mol⁻¹

Compounds		B3LYP/6-31G(d,p)	B3LYP/6-311G(df,pd)/B3LYP/6-31G(d,p)	MP2/6-311G(df,pd)//B3LYP/6-31G(d,p)	IEFPCM B3LYP/6-311G(df,pd)//B3LYP/6-31G(d,p)
Aziridine		17.20	16.68	19.72	-
2-methylaziridine		17.31	16.82	19.86	-
2,2-dimethylaziridine		17.44	16.75	19.84	-
N-methyl-2,2-dimethylaziridine		14.81	14.35	18.33	-
<i>cis-cis</i> -9-aza-bicyclo[6.1.0]non-4-ene	Conformer E	14.68	17.72	20.93	18.23
	Conformer F	17.94	17.60	20.78	18.40

Table 2: Differences between the energies and relative partition function of conformers **E** and **F** and conformational isomerism energy barrier of **E** to **F** in gas phase and sulfuric acid solution

Methods	Conformers	proportion of coexistence	$\Delta E = E_E - E_F$ (kcal-mol ⁻¹)	Energy barrier (kcal-mol ⁻¹)
B3LYP/6-31G(d,p)	E	47.65%	- 0.23	7.99
	F	52.35%		
IEFPCM B3LYP/6-31G(d,p)	E	31.03%	- 0.10	7.73
	F	68.97%		
B3LYP/6-311G (df,pd)//B3LYP/6-31G(d,p)	E	44.99%	- 0.18	7.73
	F	55.01%		
IEFPCM B3LYP/6-311G (df,pd)//B3LYP/6-31G(d,p)	E	29.08%	- 0.15	7.48
	F	70.92%		

Table 3. Differences between the energies and relative partition function of conformers **1E** and **1F** and conformational isomerism energy barrier of **1E** to **1F** in gas phase and sulfuric acid solution

Methods	Conformers	proportion of coexistence	$\Delta E = E_{1E} - E_{1F}$ (kcal-mol ⁻¹)	Energy barrier (kcal-mol ⁻¹)
B3LYP/6-31G(d,p)	1E	42.33%	- 0.22	8.09
	1F	57.67%		
IEFPCM B3LYP/6-31G(d,p)	1E	35.06%	- 0.008	7.95
	1F	64.94%		
B3LYP/6-311G (df,pd)//B3LYP/6-31G(d,p)	1E	40.52%	- 0.18	7.90
	1F	59.48 %		
IEFPCM B3LYP/6-311G (df,pd)//B3LYP/6-31G(d,p)	1E	33.78%	- 0.04	7.74
	1F	66.22%		

Table 4. Differences between the energies of N-protonated and O-protonated conformers of *cis-cis*-N-benzoyl-9-azabicyclo[6.1.0]non-4-ene **1** in gas phase and sulfuric acid solution

Methods	$\Delta E = E_{1E(NH^+)} - E_{1E(OH^+)}$	$\Delta E = E_{1F(NH^+)} - E_{1F(OH^+)}$
	(kcal·mol ⁻¹)	(kcal·mol ⁻¹)
B3LYP/6-31G(d,p)	- 3.73	- 3.35
IEFPCM B3LYP/6-31G(d,p)	- 4.47	- 4.59
B3LYP/6-311G(df,pd) //B3LYP/6-31G(d,p)	- 3.18	- 2.82
IEFPCM B3LYP/6-311G(df,pd) //B3LYP/6-31G(d,p)	- 4.01	- 4.12

Table 5. Differences between the energies and relative partition function of conformers **1E(NH⁺)** and **1F(NH⁺)** and conformational isomerism energy barrier of **1E(NH⁺)** to **1F(NH⁺)**.

Methods	Conformers	proportion of coexistence	$\Delta E = E_{1E(NH^+)} - E_{1F(NH^+)}$ (kcal-mol ⁻¹)	Energy barrier (kcal-mol ⁻¹)
B3LYP/6-31G(d,p)	1E(NH⁺)	36.23%	0.23	7.18
	1F(NH⁺)	63.77%		
IEFPCM B3LYP/6-31G(d,p)	1E(NH⁺)	14.53%	0.63	2.69
	1F(NH⁺)	85.47%		
B3LYP/6-311G (df,pd)//B3LYP/6-31G(d,p)	1E(NH⁺)	41.86%	0.37	7.14
	1F(NH⁺)	58.14%		
IEFPCM B3LYP /6-311G (df,pd)//B3LYP/6-31G(d,p)	1E(NH⁺)	13.05%	0.72	2.68
	1F(NH⁺)	86.95%		

Table 6: Some structural parameters: bond lengths in Å and valence angles in degrees of neutral, N-protonated and O-protonated **1E** conformer carried out at B3LYP/6-31G(d,p) level*.

Geometric parameters	In gas phase			In sulfuric acid		
	1E	1E(NH⁺)	1E(OH⁺)	1E	1E(NH⁺)	1E(OH⁺)
N-C ₁	1.472	1.534	1.470	1.473	1.534	1.468
N-C ₈	1.453	1.531	1.462	1.454	1.532	1.460
C ₁ -C ₈	1.513	1.486	1.525	1.514	1.485	1.526
∠C ₁ NC ₈	62.27	58.01	62.71	62.28	57.92	62.83
∠C ₁ C ₈ N	59.49	60.88	58.90	59.47	61.12	58.82
∠NC ₁ C ₈	58.24	61.11	58.39	58.25	60.96	58.36

*The atom labels are indicated in Figure 5.

Table 7. Some structural parameters: bond lengths in Å and valence angles in degrees of neutral, N-protonated and O-protonated **1F** conformer carried out at B3LYP/6-31G(d,p) level*.

Geometric parameters	In gas phase			In sulfuric acid		
	1F	1F (NH⁺)	1F (OH⁺)	1F	1F (NH⁺)	1F (OH⁺)
N-C ₁	1.468	1.527	1.461	1.469	1.527	1.459
N-C ₈	1.454	1.536	1.460	1.456	1.536	1.458
C ₁ -C ₈	1.511	1.479	1.523	1.512	1.480	1.524
∠C ₁ NC ₈	62.24	57.76	62.83	62.27	57.79	62.99
∠C ₁ C ₈ N	58.42	61.43	58.56	59.30	60.80	58.54
∠NC ₁ C ₈	59.34	60.81	58.61	59.44	61.42	58.47

*The atom labels are indicated in Figure 5.

Table 8. Activation energy in kcal·mol⁻¹ of aziridine ring opening by the two N-C bonds cleavage in the O-protonated and N-protonated **1E** and **1F** conformers*.

Cleaved bond	Methods	1E(NH⁺)	1E(OH⁺)	1F(NH⁺)	1F(OH⁺)
N-C ₁	B3LYP/6-31G(d,p)	24.46	26.00	15.51	21.04
	IEFPCM B3LYP/6-31G(d,p)	19.17	25.70	14.71	30.58
	B3LYP/6-311G(df,pd) //B3LYP/6-31G(d,p)	19.55	25.86	15.98	22.21
	IEFPCM B3LYP /6-311G (df,pd)//B3LYP/6-31G(d,p)	18.44	25.58	15.06	32.11
N-C ₈	B3LYP/6-31G(d,p)	20.22	34.27	20.71	26.53
	IEFPCM B3LYP/6-31G(d,p)	19.17	25.90	19.04	26.41
	B3LYP/6-311G(df,pd) //B3LYP/6-31G(d,p)	19.55	34.64	19.96	27.78
	IEFPCM B3LYP /6-311G (df,pd)//B3LYP/6-31G(d,p)	18.44	27.04	18.09	27.26

*The atom labels are indicated in Figure 5.

Scheme 1. Acid hydrolysis of *cis-cis*-N-benzoyl-9-azabicyclo [6.1.0] non-4-ene **1**

Draft

Scheme 2. The proposed mechanism of acid hydrolysis of *cis-cis*-N-benzoyl-9-azabicyclo [6.1.0]non-4-ene **1**

Figure 1. Structure of the *cis-cis*N-benzoyl-9-azabicyclo[6.1.0]non-4-ene **1**

Draft

Figure 2. Structures of some stable *cis*-cyclooctene conformers

Figure 3. B3LYP/6-31G(d,p) optimized structures of **E** and **F** conformers of *cis-cis*-9-aza-bicyclo[6.1.0]non-4-ene

Figure 4: Optimized structures of the conformers **1E** and **1F** of N-benzoyl-9-azabicyclo[6.1.0]non-4-ene **1** obtained at B3LYP/6-31G(d,p) level.

Figure 5: Optimized structures of N-protonated and O-protonated conformers of N-benzoyl-9-azabicyclo[6.1.0]non-4-ene **1** carried out at B3LYP/6-31G(d,p) level.

Figure 6: Products of 1F(OH⁺) aziridine ring opening

Figure 7: Energetic profile of N-C₁ bond rupture in N-protonated conformers of reactant **1** carried out by B3LYP/6-31G(d,p)// B3LYP/6-311G(df,pd) in gas phase (activation energy is between brackets)

Figure 8: Energetic profile of N-C₁ bond rupture in N-protonated conformers of reactant **1** carried out at B3LYP/6-31G(d,p)// B3LYP/6-311G(df,pd) in sulfuric acid (activation energy is between brackets)

Figure 9. Energetic profile of N-C₈ bond rupture of reactant 1 N-protonated conformers carried out by B3LYP/6-31G(d,p)// B3LYP/6-311G(df,pd) in gas phase (activation energy is between brackets)

Figure 10. Energetic profile of N-C₈ bond rupture of reactant 1 N-protonated conformers carried out by B3LYP/6-31G(d,p)// B3LYP/6-311G(df,pd) in sulfuric acid (activation energy is between brackets)

Graphical Abstract

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