

Substituents Effect on Aziridine Chemistry: *N*-Inversion Energy, Reactivity and Regioselectivity of Nucleophilic Ring-opening

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The *N*-inversion energies and nucleophilic ring-opening reactions of *N*-substituted aziridine compounds are investigated using B3LYP/6-31+G* methods, where substituents (R) on the nitrogen atom has been H (**1**), Me (**2**), Ph (**3**), Bn (**4**), CHMePh (**5**), CO₂Me (**6**), COPh (**7**) and SO₂Ph (**8**). The *N*-inversion energy with X group are decreased as the following order: R = CHMePh (17.06 kcal/mol) > Me (16.97) > Bn (16.70) > H (16.64) > SO₂Ph (12.18) > Ph (8.91) > COPh (5.75) > CO₂Me (5.48). For reactivity of the ring opening toward cyanide ion, the aziridine **6** (R=CO₂Me) is shown to be the most reactive one. During the ring opening of aziridine **6** by CN[⊖], the torsional OCNC angle becomes near to 180°, where the geometry allows for the effective incorporation of electrons of the nitrogen atom to the C=O bond. It would be a possible driving force for nucleophilic ring opening reaction as well as decreasing the *N*-inversion energy barrier. Regarding to the regioselectivity, the orientation of nucleophile in ring opening reaction appears to be different in the case of **9** and **10**. The results are discussed in terms of steric/electronic effect of the C₂-substituents.

Key Words : Aziridine, *N*-Inversion energy, Nucleophilic ring-opening, *Ab initio*

Introduction

Aziridine functionality represents a valuable three-membered ring system in modern synthetic chemistry. It is well recognized as a significant building block for synthesizing many useful compounds. The nucleophilic ring-opening of the aziridine derivatives has been an important transformation to prepare numerous organic compounds.¹⁻³ Although the ring-opening of aziridines by nucleophiles is relatively facile due to the strain of three-membered ring, strong nucleophiles or acid catalysts are required in the case of non-activated group (*e.g.*, H, alkyl, or aryl) on the nitrogen atom in the aziridine ring. Thus, it becomes imperative to introduce *N*-substituents (*e.g.*, COR, CO₂R, or SO₂R), which can stabilize the negative charge on the nitrogen atom and increase the reactivity of aziridine rings towards nucleophiles.

The focus of the present work is to calculate optimized geometries of aziridine derivatives and to predict the

possible *N*-inversion energy barriers from planar-shaped transition states using B3LYP/6-31+G* methods.⁴ *N*-Substituents in aziridines considered are -H, -Me, -Ph, -Bn, -CHMePh, -CO₂Me, -COPh, and -SO₂Ph. We have also investigated the transition states of nucleophilic ring-opening reactions by cyanide anion. Here we wish to clarify; i) the effect of *N*-substituents on aziridine ring geometries and ii) their *N*-inversion energy barriers, iii) the influence of nucleophilic ring-opening reactions depending upon *N*-substituents, and iv) possible selectivity on ring-opening by nucleophiles.

Computational methods. *Ab initio* calculations and geometry optimizations were carried out for all the above mentioned aziridine compounds with the *gaussian*-98 program package⁵ using the standard 6-31+G* basis set with density functional (B3LYP) methods.⁶ For the planar-shaped transition state structure, only one imaginary frequency value was obtained. Also in the transition state structures⁷ of nucleophilic ring opening reactions of aziridines, one imaginary frequency value was accepted.

Results and Discussion

The equilibrium states and *N*-inversion energies of aziridines. Using density functional method B3LYP/6-31+G*, it has been determined the structural geometrical parameters of the equilibrium state and planar-shaped transition states of aziridines **1-8**. The results are summarized in Table 1. For the planar-shaped transition states, it is confirmed that the motion at the imaginary frequencies correspond to the *N*-inversion. In quasi-pyramidal aziridines, the total bond angles around the nitrogen atom vary with *N*-substituents (R). The order of relative flatness (*i.e.*, 360.0°

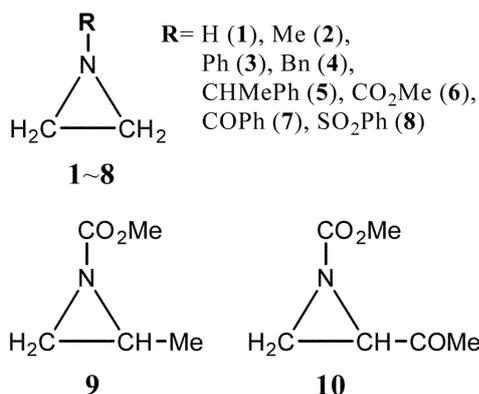
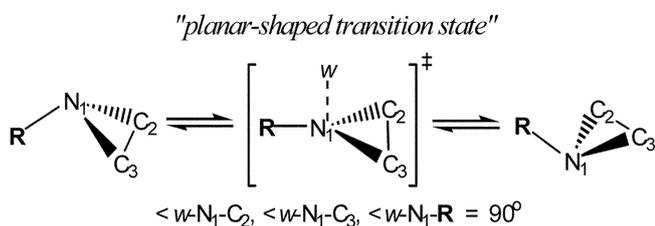


Table 1. The optimized equilibrium states and planar-shaped transition states of aziridines **1-8**^a

	R	E_{tot}^b	$N_1\text{-R}^c$	$N_1\text{-C}_2^c$	$N_1\text{-C}_3^c$	$R\text{-N}_1\text{-C}_2^d$	$R\text{-N}_1\text{-C}_3^d$	$C_2\text{-N}_1\text{-C}_3^d$	$C_2\text{-N}_1\text{-X-O}^e$	E_{inv}^f
1	H	-133.9265337 (-133.9000049)	1.019 (1.002)	1.474 (1.406)	1.474 (1.406)	110.750 (146.937)	110.750 (147.012)	60.623 (66.051)	–	16.647
2	Me	-173.2385754 (-173.2115217)	1.459 (1.427)	1.462 (1.402)	1.462 (1.402)	116.153 (146.794)	116.145 (146.862)	61.453 (66.343)	–	16.976
3	Ph	-364.9881875 (-364.9739807)	1.412 (1.368)	1.457 (1.408)	1.457 (1.408)	121.234 (147.025)	121.232 (147.061)	61.823 (65.914)	–	8.915
4	Bn	-404.2983206 (-404.2716955)	1.465 (1.428)	1.462 (1.404)	1.461 (1.405)	116.108 (147.831)	116.358 (145.950)	61.451 (66.218)	–	16.707
5	CHMePh	-443.6158852 (-443.5886913)	1.470 (1.436)	1.461 (1.406)	1.461 (1.404)	116.576 (147.988)	116.341 (145.850)	61.427 (66.162)	–	17.064
6	CO ₂ Me	-361.8180163 (-361.8092781)	1.388 (1.350)	1.456 (1.413)	1.449 (1.417)	122.222 (145.201)	124.379 (149.323)	62.308 (65.476)	46.106 (0.000)	5.483
7	COPh	-478.3364984 (-478.3273281)	1.402 (1.362)	1.448 (1.416)	1.463 (1.423)	123.659 (140.814)	121.077 (154.265)	62.029 (64.921)	32.510 (0.054)	5.754
8	SO ₂ Ph	-913.5670528 (-913.5476283)	1.723 (1.641)	1.478 (1.421)	1.477 (1.421)	117.731 (147.568)	115.539 (147.012)	60.421 (65.076)	17.494, 80.786 (22.256, 25.517)	12.189

^aThe values in parenthesis are for the planar-shaped transition states. ^bTotal energy (hartree). ^cBond lengths (angstrom, Å). ^dBond angle (degree, °). ^eTorsion angle (degree, °). $C_2\text{-N}_1\text{-C=O}$ for **6** and **7**, $C_2\text{-N}_1\text{-S=O}$ for **8**. ^f*N*-Inversion energy (kcal/mol), which are calculated from E_{tot} of the equilibrium states and planar-shaped transition states.

for complete planar geometry) with R group is shown by CO₂Me (308.9°) > COPh (306.8°) > Ph (304.3°) > CHMePh (294.3°) > Bn (293.9°) > Me (293.8°) > SO₂Ph (293.7°) > H (282.1°). Consequently aziridine **6** (R=CO₂Me) appears mostly near to planar ring geometry.

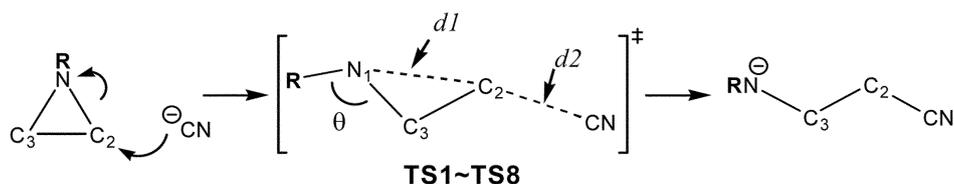


It shows further that, in the planar-shaped transition state, the increase in all bond angle values are accompanied by a decrease in bond lengths in general. In the case of **6**, for example, the N-R bond length changes from 1.388 Å to 1.350 Å, and the $C_2\text{-N}_1\text{-C}_3$ strained angle increases from 62.308° to 65.476°. It is noted that the variations of the strained angle ($\angle C_2\text{-N}_1\text{-C}_3$) are relatively small when nitrogen atom is directly substituted with a sp^2 -carbon compare to the case of being substituted with a sp^3 -carbon. For examples, the angle variations are 2.89° for **7** (R=COPh), 3.17° for **6** (R=CO₂Me), and 4.74° for **5** (R=CHMePh). In **6** and **7**, the C=O bonds and aziridine rings lie in same plane (torsion angles of $C_2\text{-N}_1\text{-C}_4\text{=O}$ are zero), which apparently the non-bonding electrons on the nitrogen are completely incorporated to the π -electrons of the C=O bonds by maintaining coplanarity with the ring. For **8** (R=SO₂Ph), the electrons on the nitrogen may not be able to exhibit complete incorporation (the torsion angle of $C_2\text{-N}_1\text{-S=O}$ are 22.25°, 25.51°). According to the above results, C=O functionality in R group effectively accommodate aziridine ring towards coplanarity than other substituents

such as S(=O)₂ group.

It has been known the energy barrier of *N*-inversion of non-cyclic trivalent amines is 6-7 kcal/mol at room temperature,⁸ and the strain of three-membered aziridine ring geometry causes the *N*-inversion energy to increase. *N*-Inversion energies of aziridines are calculated to be more than 16 kcal/mol (16.6-17.1 kcal/mol for **1**, **2**, **4**, and **5** in Table 1), which consistent with the literature values,^{8b} in the case that the steric effect of *N*-substituent does not seem significant. However, those values in **6** (R=CO₂Me) and **7** (R=COPh) are predicted to have 5.48 and 5.75 kcal/mol, which are even lower than those of non-cyclic trivalent amines. With a similar argument, *N*-substituent of carbonyl (C=O) group can decrease this energy barrier by a complete incorporation of the electrons on the *N* of ring into planar-shaped transition states. The order of *N*-inversion energy with R groups is predicted by CHMePh (17.06) > Me (16.97) > Bn (16.70) > H (16.64) > SO₂Ph (12.18) > Ph (8.91) > COPh (5.75) > CO₂Me (5.48) as shown in Table 2. Our results suggest that the energy barrier is decreased to about 5 kcal/mol by *N*-substituted carbonyl (C=O) group via complete incorporation of the electrons on aziridine ring-*N*. Compared with the alkyl group, the *N*-substituted carbonyl (C=O) group of aziridine ring may not allow us to isolate the resultant optically active chiral aziridine compounds. Note that *N*-substituent of an electronegative atom (*e.g.*, a halogen or an alkoxy group) increases this energy barrier. According to our calculation using B3LYP/6-31+G*, the *N*-inversion energy of *N*-chloroaziridine is predicted by 25.1 kcal/mol. The inversion energy of 24.4 kcal/mol was reported in *N*-chloro-2,2-diphenylaziridine,⁹ which may validate our calculation.

Nucleophilic ring opening of aziridine with the cyanide anion.^{10,11} The transition states of nucleophilic ring-opening by the cyanide ion have been optimized, and the results are

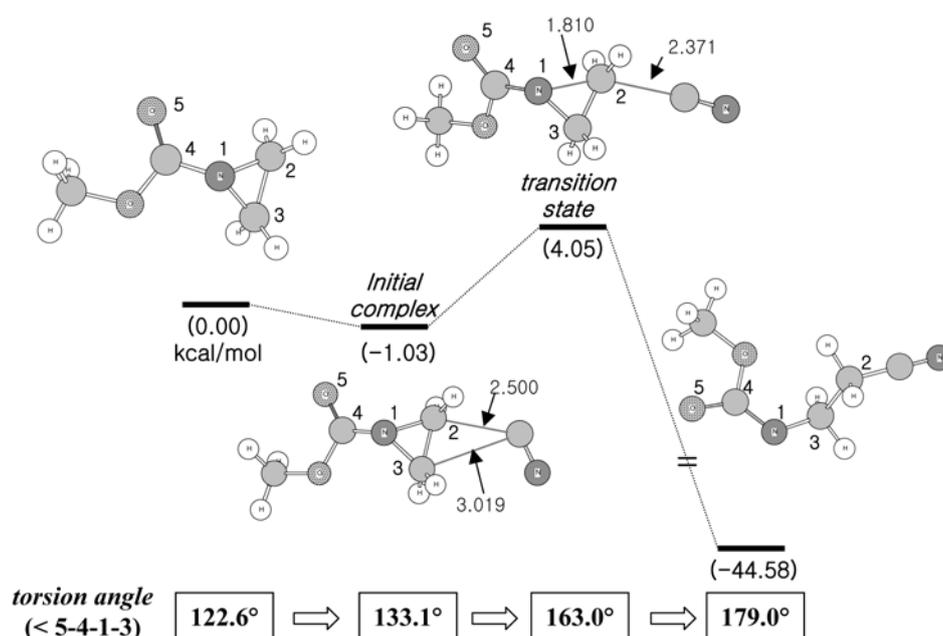
**Table 2.** The optimized transition state of nucleophilic ring-opening by CN^-

R	ETS ^a	N ₁ -R ^b	N ₁ -C ₃ ^b	N ₁ ⋯C ₂ ^b (<i>d1</i>)	C ₂ ⋯CN ^b (<i>d2</i>)	C ₃ -N ₁ -R ^c (θ)	C ₃ -N ₁ -X=O ^d	ΔE^d (E _a)
TS-1	H	-226.7604567	1.028	1.452	2.019	2.166	106.633	19.770 (30.843)
TS-2	Me	-266.0699095	1.447	1.452	1.986	2.150	111.691	21.395 (15.292)
TS-3	Ph	-457.8400841	1.382	1.444	1.862	2.320	119.698	8.492 (7.354)
TS-4	Bn	-497.1357149	1.443	1.451	1.957	2.181	112.540	17.592 (12.565)
TS-5	CHMePh	-536.4534739	1.447	1.451	1.956	2.185	112.831	17.470 (8.208)
TS-6	CO ₂ Me	-454.6769873	1.358	1.447	1.810	2.371	120.088	163.021 (4.053)
TS-7	COPh	-571.1914058	1.358	1.459	1.813	2.298	123.086	141.543 (6.602 (7.793))
TS-8	SO ₂ Ph	-1006.435897	1.652	1.450	1.788	2.418	116.748	160.969 & 27.130 (-2.143 (9.057))

^aTotal energy of transition state (hartree). ^bBond lengths (angstrom, Å). ^cBond angle θ (degree, °). ^dTorsion angle (degree, °). C₃-N₁-C=O for **TS-6** and **TS-7**, C₃-N₁-S=O for **TS-8**. ^e ΔE (kcal/mol) is obtained from the total energy of aziridine (in table 1) and CN to the transition state energy ETS, where CN-energy is -92.865429287. The values in parenthesis are obtained from the initial complex energies of aziridine and CN, which are denoted by 'E_a's. The initial complex energies of **1-8** are -226.8096082, -266.0942799, -457.8518035, -497.1557388, -536.4665538, -454.6850826, -571.2038246, -1006.450331, respectively.

summarized in Table 2. It shows that the distances of N₁⋯C₂ (*d1*) and C₂⋯CN (*d2*) (R=H) appear at 2.019 Å and 2.166 Å in **TS-1**, respectively. Also the corresponding

values for **TS-4** (R=Bn) are 1.957 Å and 2.182 Å, respectively, where *d1* is decreased and *d2* is increased. In the case of **TS-6** (R=CO₂Me), the structure becomes more

**Figure 1.** Reaction profile of nucleophilic ring-opening of aziridine **6**.

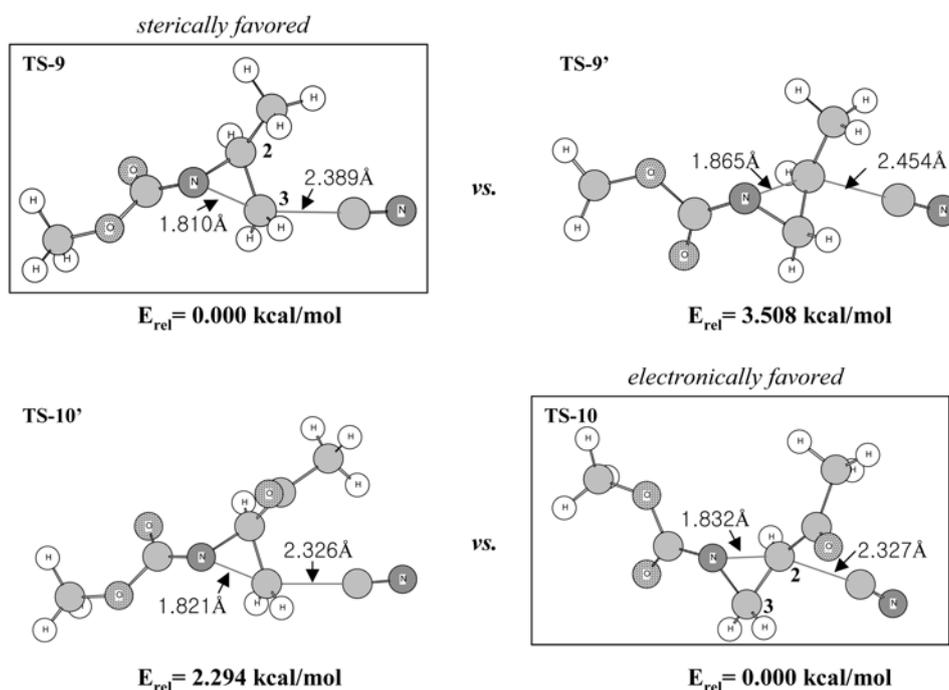


Figure 2. The structures and relative energies of TS-9 and TS-10.

similar (*i.e.*, $d1=1.810$ Å and $d2=2.371$ Å) to that of the starting point of the reaction. The energy variations (denoted by “ E_a ”), between energy of the initial complex and the corresponding E_{TS} , are 30.84 kcal/mol for TS-1 and 5.08 kcal/mol for TS-6. The order of E_a (in kcal/mol) with *N*-substituents R group is predicted by H (30.84) > Me (15.29) > Bn (12.56) > SO₂Ph (9.05) > CHMePh (8.20) > CPh (7.79) > Ph (7.35) > CO₂Me (5.08) as shown in Table 2. Although the E_a values in this investigation may not represent the practical ones, the relative trend should be reliable. Thus it implies that CPh and CO₂Me behaves as activating groups to cause facile ring opening.

Figure 1 shows reaction profile for the ring opening reaction of aziridine **6** with CN[⊖]. The overall reaction appears exothermic, with the E_a predicted by 5.08 kcal/mol. It should be noted the torsional angles ($\angle 5-4-1-3$) are changed during the reaction. From the starting aziridine to the ring opening product, the torsional angle was varied by $122.6^\circ \rightarrow 133.1^\circ \rightarrow 163.0^\circ \rightarrow 179.0^\circ$. Coplanarity has become maintained between C=O and N₁-C₃ bonds for achieving a complete incorporation of electrons on N and C=O bond. Apparently, it suggests the geometrical allowance for this complete incorporation may be a possible driving force of the ring opening reaction, which accords with the trend of the *N*-inversion energy of **6** or **7**.

For the investigation of the regio-selectivities on ring-opening (*i.e.*, C₂ vs. C₃), the possible transition states, which corresponds to the reaction of CN[⊖] attack to aziridine **9** and **10**, have been optimized. Figure 2 shows the structures and relative energies of TS-9 and TS-10. For the reaction of **9**, CN[⊖] nucleophile prefers to attack less hindered center C₃ (*i.e.*, TS-9 energy is lower than TS-9' by 3.51 kcal/mol as

shown in Figure 2) due to the steric effect of C₂-Me group. In the case of TS-10, C₂-attack is favored (the energy of TS-10 predicted is lower than TS-10' by 2.29 kcal/mol). It might due to a possible electron-withdrawing effect of the C₂-COMe group. Similar rationale has been reported.³ This calculation method may provide an excellent example for the prediction of regioselectivity of nucleophilic ring-opening of *N*-substituted aziridines.

Conclusions

The structure of the above mentioned aziridines (**1-8**) in equilibrium state and planar-shaped transition state were determined using DFT method (B3LYP/6-31+G*) as shown in Table 1. The *N*-inversion energy barrier of **6** is predicted to be 5.08 kcal/mol, which is even lower than non-cyclic trivalent amines. Using the same method above, the transition states of ring opening reaction with cyanide ion have been optimized, and relative activation energies are calculated as shown in Table 2. During the reaction of **6** with CN[⊖], it also has been noted that the torsion angle maintains coplanar geometry between C=O and N₁-C₃ bond. These results can be understood by an incorporation between the electrons on the ring-N and the π -electrons of C=O bond. Although those values in Table 2 are somewhat semi-quantitative, they provide relative reactivity of aziridines depending on *N*-substituents and suggests that E_a and E_{inv} are decreased with C=O functionality on the ring-N. In addition, the transition states **9** and **10** have been optimized. The regio-selective ring-opening (C₂ vs. C₃) is proven to be influenced by steric/electronic effect of C₂-substituents. The regioselectivity is efficiently predicted by this calculation

and all the results provide excellent informations for understanding of the chemical nature of aziridines.

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