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Substituent Effects on the Ring Opening of 2-Aziridinylmethyl Radicals

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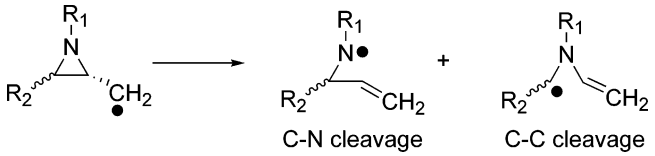


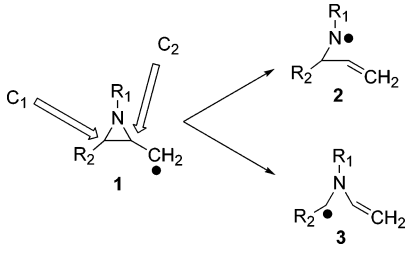
Substituent effects on the ring-opening reactions of 2-aziridinylmethyl radicals were studied systematically for the first time utilizing the ONIOM(QCISD(T)/6-311+G(2d,2p):B3LYP/6-311+G(3df,2p)) method. It was found that various substituents on the nitrogen atom had a relatively small effect on the ring opening of the 2-aziridinylmethyl radical. A π-acceptor substituent at the C_1 position reduced the energy barrier for C−C cleavage dramatically, but it increased the energy barrier for C−N cleavage significantly at the same time. When the C_1 substituent is alkyl, the ring opening should always strongly favor the C−N cleavage pathway, regardless of whether the N substituent is alkyl, aryl, or COR. When the C_1 substituent is CHO (or CO-alkyl, CO-aryl, or CO−OR but not CO−NR_2), the ring opening strongly favors the C−C cleavage pathway, regardless of whether the N substituent is alkyl, aryl, or COR. When the C_1 substituent is aryl (or alkenyl or alkynyl), the ring opening should favor the C−C cleavage pathway if the N substituent is alkyl or COR. If both the C_1 substituent and the N substituent are aryl, the ring opening should proceed via both the C−C and C−N cleavage pathways. The solvent effect on the regioselectivity of the ring opening of the 2-aziridinylmethyl radicals was found to be very small. The substituent effects on C−C cleavage could be explained successfully by the spin-delocalization mechanism. For the substituent effects on C−N cleavage, an extraordinary through-bond π-acceptor effect must be taken into account. Furthermore, studies on bicyclic 2-aziridinylmethyl radicals showed that the ring strain could also affect the regiochemistry of the ring-opening reactions.

1. Introduction

The ring opening of the 2-aziridinylmethyl radical (**1**) can result in the formation of either an allylaza radical (**2**) through C−N bond cleavage or a vinylazamethyl radical (**3**) via C−C bond homolysis (see Scheme 1).[1] This rearrangement reaction has drawn considerable attention in organic chemistry during the past several years because a variety of nitrogen-containing heterocycles including pyrrolidines and pyrrolizidines can be constructed efficiently by combining this ring opening with other radical reactions (see Scheme 2 for an example).[2]

Two dramatically different products (i.e., a nitrogen-centered radical vs a carbon-centered radical) can be generated in the rearrangement shown in Scheme 1. Therefore, the regioselectivity of the ring opening is an important and interesting subject. The early experimental studies by Murphy et al. showed that substituted 2-aziridinylmethyl radicals (R_1 = R_2 = alkyl) open exclusively to nitrogen-bearing radicals, with no evidence of any C−C bond breakage.[3] Recent theoretical studies by Pasto and Radom et al. on unsubstituted 2-aziridinylmethyl ($R_1 = R_2 = H$) revealed that the energy barrier for C−C bond cleavage is about 25 kJ/mol higher than that for C−N cleavage.[4]

SCHEME 1



(1) (a) Li, J. J. *Tetrahedron* **2001**, *57*, 1−24. (b) Gansauer, A.; Lauterbach, T.; Narayan, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5556−5573.

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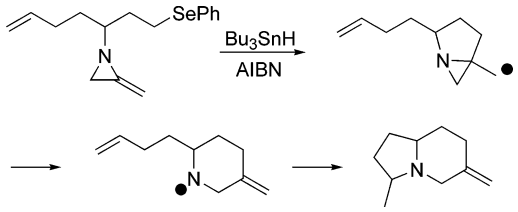
SCHEME 2. Synthesis of Octahydroindolizines by Shipman et al.[2i]



The above experimental and theoretical results let many researchers believe that C−N cleavage is always kinetically favored over C−C cleavage in the ring opening of 2-aziridinylmethyl radicals.[1b,2] Nonetheless, it was once reported by Schwan et al. that the ring opening of aryl-substituted (at the R_2 position) 2-aziridinylmethyl radicals produced some vinylazamethyl radicals through C−C bond homolysis.[5] Thus, certain substituents on the 2-aziridinylmethyl radicals may change the regioselectivity of their rearrangement reactions. Unfortunately, this particular finding by Schwan et al. has not received adequate attention. Few others have ever investigated the substituent effects on the ring-opening reactions of 2-aziridinylmethyl radicals.

Herein, we report the first systematic study about the substituent effects on the ring-opening reactions of 2-aziridinylmethyl radicals. Three types of substituents, (i.e., alkyl, aryl, and acyl groups) are interesting to us because the precursors of the 2-aziridinylmethyl radicals with these three types of substituents are well-defined species in synthetic organic chemistry, and they are relatively straightforward to synthesize. It is worth noting that few experimental chemists have examined the acylated 2-aziridinylmethyl radicals (at either the R_1 or R_2 position, see Figure 1). However, we envisage that these synthetically accessible 2-aziridinylmethyl radicals may have rich and unprecedented chemistry due to the presence of the acyl groups.

The focus of the present study is the substituent effect on the regiochemistry of the ring opening of 2-aziridinylmethyl radicals. Moreover, because few have ever investigated the relative rate of the ring opening of various 2-aziridinylmethyl radicals, the substituent effects on the velocity of the ring opening of 2-aziridinylmethyl radicals are also investigated here. It is worth noting that a number of studies of the substituent effects on the ring opening of cyclopropylcarbinyl radicals and oxiranylcarbinyl radicals have been performed.[6]

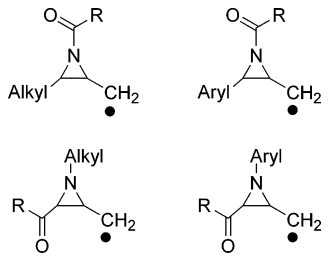


FIGURE 1. Acylated 2-aziridinylmethyl radicals.

2. Methods

Ab initio calculations were performed with the Gaussian 03 suite of programs.[7] Geometry optimizations were performed using the B3LYP/6-31G(d) method without any constraint. Frequency calculations were carried out at the B3LYP/6-31G-(d) level of theory and were performed on all of the species to confirm their convergence to appropriate local minima or saddle points on the energy surface. In all instances, transition-state structures gave one significant imaginary frequency, whereas no imaginary frequencies were observed for the minimum-energy species.

Single-point energies were determined using the ONIOM method[8] because pure QCISD(T) calculations for the substituted 2-aziridinylmethyl radicals were impractical for our computational resources. A two-layer ONIOM method was utilized, that is, ONIOM(QCISD(T)/6-311+G(2d,2p):B3LYP/6-311+G(3df,2p)). The inner layer treated at the "high" level (i.e., QCISD(T)/6-311+G(2d,2p) was comprised of four heavy atoms and their hydrogens, whereas the whole system was treated at the "low" level (i.e., B3LYP/6-311+G(3df,2p), see Chart 1). Corrections of the energy to 298 K were made from the frequency calculations, including zero-point energy corrections.

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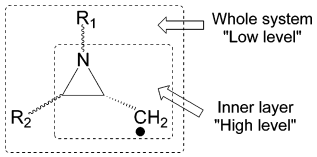
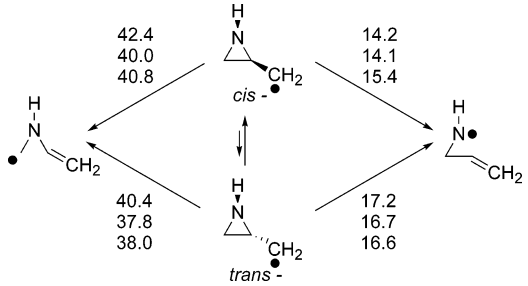
CHART 1



SCHEME 3. Activation Free Energies ($\Delta G^{\ddagger}$, kJ/mol) for the Ring-Opening Reactions of *cis*- and *trans*-2-Aziridinylmethyl Radicals[a]



[a] The values from the top to the bottom for each reaction pathway are obtained from the QCISD(T)/6-311+G(2d,2p) (298 K), CBS-QB3 (298 K), and CBS−RAD (0 K)[4b] methods, respectively.

3. Results and Discussion

3.1. Unsubstituted 2-Aziridinylmethyl Radical. Ring opening of the unsubstituted 2-aziridinylmethyl radical was studied previously by Radom et al. using the CBS−RAD method.[4b] Although the CBS−RAD method (or any other composite ab initio method) is probably able to provide very accurate results, we do not expect that this highly resource-demanding method is applicable to the substituted 2-aziridinylmethyl radicals. Therefore, in the present study, a two-layer ONIOM(QCISD(T)/6-311+G(2d,2p):B3LYP/6-311+G(3df,2p)) method is utilized to calculate the activation free energies of the ring-opening reactions.

The calculation results suggest that the unsubstituted 2-aziridinylmethyl radical has two possible geometrical isomers. The cis isomer is more stable than the trans isomer by 4.6 kJ/mol at the B3LYP/6-311+G(3df,2p) level. At the QCISD(T)/6-311+G(2d,2p) level, the activation free energies for C−C cleavage are 42.4 (cis) and 40.4 (trans) kJ/mol (see Scheme 3). These values are about 2 kJ/mol higher than those predicted by the CBS-QB3 method. The QCISD(T)/6-311+G(2d,2p) activation free energies for C−N cleavage are 14.2 (cis) and 17.2 (trans) kJ/mol. (For the transition states of the C−N and C−C cleavages, please see Figure 2.) These values are within 0.5 kJ/mol of the CBS-QB3 results. On the basis of these comparisons, it is concluded that the calculation results by the ONIOM(QCISD(T)/6-311+G(2d,2p):B3LYP/6-311+G(3df,2p)) method are of good quality (i.e., error $\approx$ 2 kJ/mol).

It is worth mentioning that the conformational change from the *cis*-2-aziridinylmethyl radical to the *trans*-2-aziridinylmethyl radical has an activation free energy of 79.6 kJ/mol. This activation free energy is much higher than the activation free energies of both the C−C (42.4 kJ/mol) and C−N (14.2 kJ/mol) cleavage reactions. Thus, both the C−C and C−N cleavage reactions are much faster than the conformational change of the 2-aziridinylmethyl radical. There is no need to consider the conformational change in the time scale of the ring-opening reaction. The overall ring-opening kinetics of the 2-aziridinylmethyl radical should be dominated by the more abundant isomer. Therefore, in the following sections, we will focus on the ring opening of the energetically favored isomers.

3.2. *N*-Substituted 2-Aziridinylmethyl Radicals. The ring opening of various *N*-substituted 2-aziridinylmethyl radicals is studied using the ONIOM(QCISD(T)/6-311+G(2d,2p):B3LYP/6-311+G(3df,2p)) method. Both the C−N cleavage and C−C cleavage pathways are considered. Although the *N* substituent causes two possible isomers, we report the activation free energies for only the energetically favored isomer for every species (see Table 1).

The results suggest that most of the *N*-substituted 2-aziridinylmethyl radicals prefer the trans isomer, except for the H and CHO substituents. Compared to the unsubstituted case, the CH_3 and CH_2CH_3 substituents on nitrogen increase the activation free energy of the C−N cleavage by ca. 3 kJ/mol. However, the CHO, $COCH_3$, $COOCH_3$, and Ph groups slightly reduce the activation free energy of C−N cleavage by 0.4−3.2 kJ/mol. The $CONH_2$ group reduces the activation free energy of C−N cleavage significantly by 5.2 kJ/mol.

For C−C cleavage, all of the substituents on nitrogen reduce the activation free energy. The most significant reduction (−10.6 kJ/mol) is seen for the CHO substituent. The slightest reduction (−3.0 kJ/mol) is seen for the $CONH_2$ group. Despite these reductions, all of the activation free energies of C−C cleavage in Table 1 are considerably higher than the activation free energies of C−N cleavage by ca. 20−30 kJ/mol. Therefore, these *N*-substituted 2-aziridinylmethyl radicals should open predominantly to nitrogen-bearing radicals.

3.3. C_1-Substituted 2-Aziridinylmethyl Radicals. The ring opening of various C_1-substituted 2-aziridinylmethyl radicals is also studied using the ONIOM(QCISD(T)/6-311+G(2d,2p):B3LYP/6-311+G(3df,2p)) method. Both the C−N cleavage and C−C cleavage pathways are considered. It is worth noting that each C_1-substituted 2-aziridinylmethyl radical has two diastereomeric isomers (i.e., *trans*-C_1 and *cis*-C_1), depending on the relative orientation between the C_1 substituent and the CH_2• center. Thus, both of these geometric isomers are considered in the present study. For each isomer, there are two possible isomers that rely on the orientation of the N−H group. Herein, we report the activation free energies for only the energetically favored isomer for each species (see Table 2).

The results show that the *cis*- and *trans*-CH_3 substituents at the C_1 position reduce the C−N cleavage activation free energy slightly by less than 0.1−1.1 kJ/mol. The *cis*- and *trans*-CH_3 substituents at the C_1 position also reduce the C−C cleavage activation free energy by less than 8 kJ/mol. Comparing the C−N and C−C cleavage activation free energies of the C_1−CH_3 case, we can predict that the C_1-alkylated 2-aziridinylmethyl radicals should open predominately to the N-centered radicals.

Strikingly, the π-acceptor groups, including CHO, $COCH_3$, and COOH, at the C_1 position increase the C−N cleavage activation free energy dramatically by 7.7−16.9 kJ/mol. Simultaneously, these groups decrease the C−C

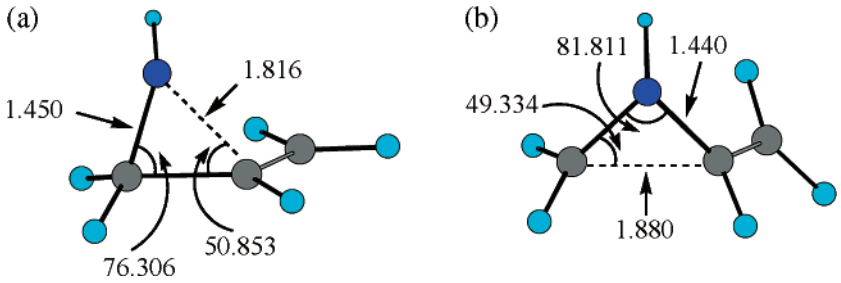
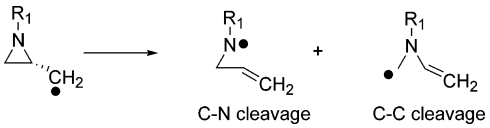


FIGURE 2. Transition states (B3LYP/6-31G(d)) for the C−N (a) and C−C (b) cleavages of the 2-aziridinylmethyl radical (unit for bond length, Å; unit for bond angle, deg).

TABLE 1. Activation Free Energies ($\Delta G^{\ddagger}$, kJ mol^{-1}) at 298 K for the Ring Opening of the N-Substituted 2-Aziridinylmethyl Radicals[a]



R_1	favored isomer[b]	C−N cleavage	C−C cleavage
H	*cis*-R_1	14.2	42.4
CH_3	*trans*-R_1	17.3	34.1
CH_2CH_3	*trans*-R_1	16.9	34.8
CHO	*cis*-R_1	13.7	31.8
$COCH_3$	*trans*-R_1	12.8	32.3
$CONH_2$	*trans*-R_1	9.0	39.4
$COOCH_3$	*trans*-R_1	13.8	34.8
Ph	*trans*-R_1	11.0	34.6

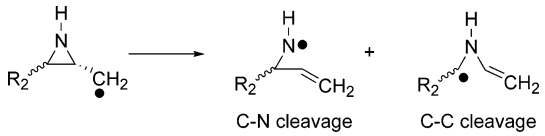
[a] $\Delta G^{\ddagger}$'s are calculated using the ONIOM(QCISD(T)/6-311+G(2d,2p):B3LYP/6-311+G(3df,2p)) method. [b] *cis*-R_1 or *trans*-R_1 depicts the orientation of the R_1 group on N relative to the $-CH_2^{\bullet}$ group. The most stable isomer is used in the calculation.

cleavage activation free energy considerably by 24.8−34.8 kJ/mol. Because of these remarkable effects, the C−N cleavage activation free energies of these radicals are much higher than those of C−C by 5.4−22.6 kJ/mol. Therefore, the C_1−CHO, C_1−$COCH_3$, and C_1−COOH 2-aziridinylmethyl radicals should open predominantly to the C-centered radicals.

Furthermore, $CONH_2$, CH=CH_2, C≡CH, and Ph at the C_1 position also increase the C−N cleavage activation free energy significantly by 4.0−9.4 kJ/mol. Simultaneously, these groups reduce the C−C cleavage activation free energy by 15.6−27.8 kJ/mol. Because of these effects, the activation free energies for the C−N and C−C cleavages become close to each other. Therefore, we expect to see a mixture of C- and N-centered radicals as the ring-opening products for the C_1−$CONH_2$, C_1−CH=CH_2, C_1−C≡CH, and C_1−Ph 2-aziridinylmethyl radicals. This prediction is in agreement with Schwan's experimental findings because his group showed that the ring opening of C_1-arylated 2-aziridinylmethyl radicals produced both aminyl radicals by way of C−N bond cleavage and α-aminyl carbon radicals via C−C bond homolysis.[5]

Interestingly, the π-donor groups, including F, NH_2, and OCH_3, at the C_1 position slightly decrease the C−N cleavage activation free energy by 1.5−10.1 kJ/mol. Meanwhile, these groups slightly decrease the C−C cleavage activation free energy. The overall effect is that the C−N cleavage activation free energy is much lower than the C−C cleavage activation free energy. Thus, the

TABLE 2. Activation Free Energies ($\Delta G^{\ddagger}$, kJ mol^{-1}) at 298 K for the Ring Opening of the C_1-Substituted 2-Aziridinylmethyl Radicals[a]



R_2	favored conformation[b]	C−N cleavage	C−C cleavage
H	*cis*-H	14.2	42.4
cis-CH_3	*cis*-H	13.1	34.2
trans-CH_3	*cis*-H	14.1	39.1
cis-CHO	*cis*-H	24.3	7.6
trans-CHO	*trans*-H	31.1	8.5
cis-$COCH_3$	*cis*-H	23.1	9.5
trans-$COCH_3$	*trans*-H	29.7	11.7
cis-COOH	*cis*-H	21.9	16.5
trans-COOH	*trans*-H	27.6	17.6
cis-$CONH_2$	*cis*-H	20.3	20.6
trans-$CONH_2$	*cis*-H	18.2	26.8
cis-CH=CH_2	*cis*-H	18.8	16.5
trans-CH=CH_2	*cis*-H	20.0	14.6
cis-C≡CH	*cis*-H	18.9	17.7
trans-C≡CH	*trans*-H	23.6	14.9
cis-Ph	*trans*-H	20.5	15.3
trans-Ph	*cis*-H	19.4	16.4
cis-F	*cis*-H	4.1	42.4
trans-F	*cis*-H	9.0	42.3
cis-NH_2	*cis*-H	11.1	33.7
trans-NH_2	*cis*-H	12.7	24.4
cis-OCH_3	*cis*-H	8.0	28.9
trans-OCH_3	*cis*-H	11.8	33.6

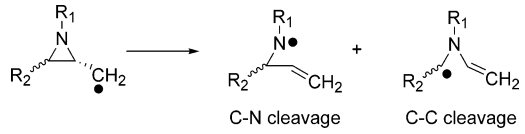
[a] $\Delta G^{\ddagger}$ values are calculated using the ONIOM(QCISD(T)/6-311+G(2d,2p):B3LYP/6-311+G(3df,2p)) method. [b] *cis*-H or *trans*-H depicts the orientation of the H group on N relative to the $-CH_2^{\bullet}$ group. The most stable isomer is used in the calculation.

C_1−F, C_1−NH_2, and C_1−OCH_3 2-aziridinylmethyl radicals should open predominantly to the N-centered radicals.

3.4. N- and C_1-Disubstituted 2-Aziridinylmethyl Radicals. Herein, the ring opening of the 2-aziridinylmethyl radicals with both N and C_1 substituents is studied. For the C_1 substituent, both the trans and cis isomers are considered. For the N substituent, only the energetically favored isomer is employed in the study (see Table 3).

The results in Table 3 show that when the C_1 substituent is alkyl, the ring opening should always strongly favor the C−N cleavage pathway, regardless of whether the N substituent is alkyl, aryl, or COR (see Figure 3). However, when the C_1 substituent is CHO (or CO-alkyl, CO-aryl, or CO−OR but not CO−NR_2), the ring opening

TABLE 3. Activation Free Energies ($\Delta G^{\ddagger}$) (C−N vs C−C, kJ mol^{-1}) at 298 K for the Ring Opening of the N- and C_1-Disubstituted 2-Aziridinylmethyl Radicals[a]



R_1/R_2	H	CH_3	CHO	Ph
H	14.2 vs 42.4[b] (*cis*-R_1)	17.3 vs 34.1 (*trans*-R_1)	13.7 vs 31.8 (*cis*-R_1)	11.0 vs 34.6 (*trans*-R_1)
cis-CH_3	13.1 vs 34.2 (*cis*-R_1)	17.8 vs 27.7 (*trans*-R_1)	15.1 vs 25.0 (*trans*-R_1)	12.3vs 28.8 (*trans*-R_1)
trans-CH_3	14.2 vs 39.1 (*cis*-R_1)	9.0 vs 31.6 (*cis*-R_1)	14.7 vs 28.0 (*cis*-R_1)	6.0 vs 34.8 (*cis*-R_1)
cis-CHO	24.3 vs 7.6 (*cis*-R_1)	28.7 vs 10.3 (*trans*-R_1)	21.4 vs 9.6 (*trans*-R_1)	19.7 vs 10.3 (*trans*-R_1)
trans-CHO	31.1 vs 8.5 (*trans*-R_1)	19.0 vs 9.2 (*cis*-R_1)	21.0 vs 8.9 (*cis*-R_1)	13.6 vs 11.7 (*cis*-R_1)
cis-Ph	20.5 vs 15.3 (*trans*-R_1)	21.9 vs 10.7 (*trans*-R_1)	16.8 vs 9.8 (*trans*-R_1)	15.9 vs 11.4 (*trans*-R_1)
trans-Ph	19.4 vs 16.4 (*cis*-R_1)	15.3 vs 10.4 (*cis*-R_1)	18.4 vs 8.9 (*cis*-R_1)	10.5 vs 13.0 (*cis*-R_1)

[a] $\Delta G^{\ddagger}$ values are calculated using the ONIOM(QCISD(T)/6-311+G(2d,2p):B3LYP/6-311+G(3df,2p)) method. [b] *cis*-R_1 or *trans*-R_1 depicts the orientation of the R_1 group on N relative to the $-CH_2^{\bullet}$ group. The most stable isomer is used in the calculation.

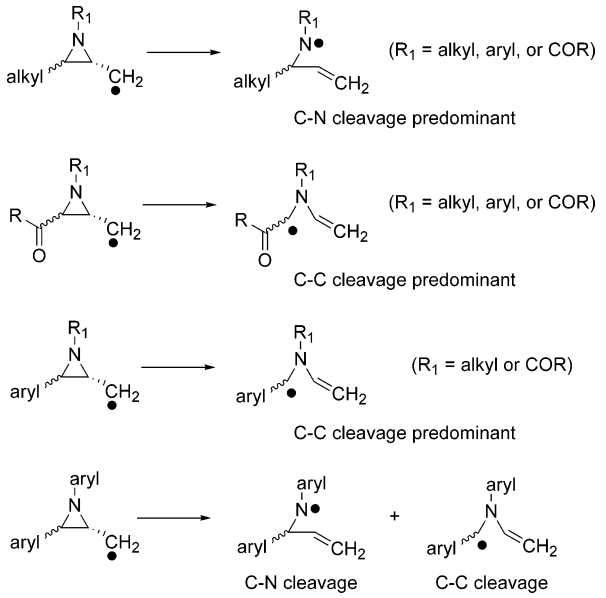
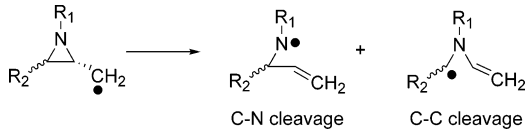


FIGURE 3. Predicted reaction pathways for the ring opening of various substituted 2-aziridinylmethyl radicals.

should strongly favor the C−C cleavage pathway, regardless of whether the N substituent is alkyl, aryl, or COR. Finally, when the C_1 substituent is aryl (or alkenyl or alkynyl), the ring opening should favor the C−C cleavage pathway if the N substituent is alkyl or COR. If both the C_1 substituent and the N substituent are aryl, the ring opening should proceed via both the C−C and C−N cleavage pathways. These results are summarized in Figure 3.

3.5. Solvent Effects. Experimentally, the ring opening of the 2-aziridinylmethyl radicals is performed in organic solutions. Thus, it is important to know the effects of solvents on the kinetics of the ring-opening reaction. Herein, we utilize the polarized continuum model (PCM)

TABLE 4. Activation Free Energies ($\Delta G^{\ddagger}$, kJ mol^{-1}) at 298 K for the Ring Opening of Some 2-Aziridinylmethyl Radicals in Vacuum and in Organic Solutions[a]



R_1	R_2	favored conformation[b]	solvent	C−N cleavage	C−C cleavage
CH_3	*cis*-CH_3	*trans*-R_1	vacuum	17.8	27.7
			C_6H_{12}	17.5	27.9
			THF	17.1	28.0
			MeCN	17.0	28.1
			DMSO	17.0	28.0
CHO	*cis*-CHO	*trans*-R_1	vacuum	21.4	9.6
			C_6H_{12}	21.5	9.3
			THF	21.9	9.0
			MeCN	22.0	8.8
			DMSO	22.0	8.8
Ph	*trans*-Ph	*cis*-R_1	vacuum	15.9	11.4
			C_6H_{12}	15.9	11.5
			THF	15.7	11.6
			MeCN	15.7	11.7
			DMSO	15.7	11.7

[a] $\Delta G^{\ddagger}$ values are calculated using the ONIOM(QCISD(T)/6-311+G(2d,2p):B3LYP/6-311+G(3df,2p))/PCM(UAHF) method. [b] *cis*-R_1 or *trans*-R_1 depicts the orientation of the R_1 group on N relative to the $-CH_2^{\bullet}$ group. The most stable isomer is used in the calculation.

with the cavity definition given by the UAHF of Tomasi and co-workers[9] to examine the solvent effects on the ring opening of a few 2-aziridinylmethyl radicals. For solvents, we select cyclohexane (C_6H_{12}, dielectric constant $\epsilon = 2.02$), tetrahydrofuran (THF, $\epsilon = 7.58$), acetonitrile (MeCN, $\epsilon = 36.64$), and dimethyl sulfoxide (DMSO, $\epsilon = 46.7$) (see Table 4).

The results in Table 4 suggest that the solvent effects on the ring-opening reactions of 2-aziridinylmethyl radicals are very small. From vacuum to DMSO, the activation free energy varies maximally by 0.8 kJ/mol. Therefore, it is valid to use the gas-phase data to evaluate the reactivities of 2-aziridinylmethyl radicals in organic solutions.[10]

3.6. Mechanistic Considerations. At this point, we wish to gain some understanding about the mechanism of the ring opening of substituted 2-aziridinylmethyl radicals. First, the above results show that all of the N and C_1 substituents (i.e., alkyl, COR, aryl, alkenyl, alkynyl, F, NH_2, and OCH_3) decrease the C−C cleavage activation free energy. This observation is not surprising because these substituents are known to stabilize the carbon-centered radicals[11] through the spin-delocalization mechanism.[12]

To demonstrate the spin-delocalization effect on the C−C cleavage activation free energy, we calculate the

(9) (a) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027. (b) Barone, V.; Cossi, M.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3210.

(10) Small solvent effects on radical ring opening have also been observed for other radicals. See: Fu, Y.; Li, R.-Q.; Liu, L.; Guo, Q.-X. *Res. Chem. Intermed.* **2004**, *30*, 279.

(11) Henry, D. J.; Parkinson, C. J.; Mayer, P. M.; Radom, L. *J. Phys. Chem. A* **2001**, *105*, 6750.

(12) (a) Jiang, X.-K. *Acc. Chem. Res.* **1997**, *30*, 283. (b) Liu, L.; Cheng, Y.-H.; Fu, Y.; Chen, R.; Guo, Q.-X. *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 1164.

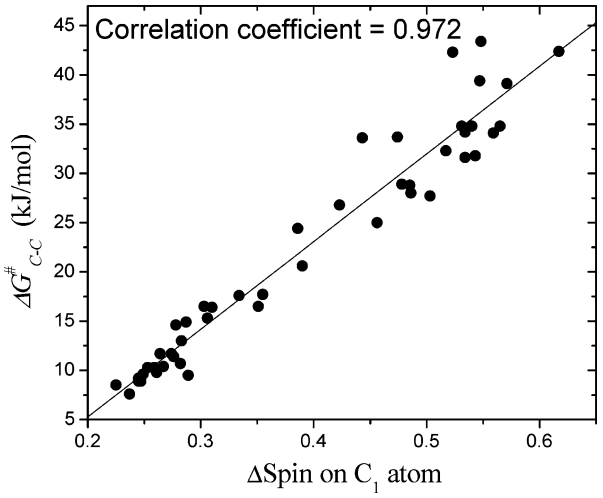


FIGURE 4. Correlation between the Δspin (C_1) values and the C−C cleavage activation free energies for all of the radicals shown in Tables 1−3.

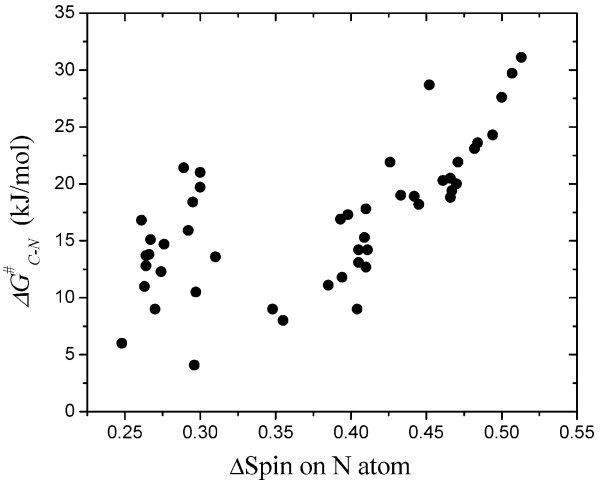


FIGURE 5. Correlation between the Δspin (N) values and the C−N cleavage activation free energies for all of the radicals shown in Tables 1−3.

spin carried by the C_1 carbon atom in the starting materials[13] and in the transition states for the C−C cleavage reactions. From these data, we can calculate the change of spin (Δspin) on C_1 from the starting material to the transition state (i.e., Δspin = spin(transition state) − spin(starting material), see the Supporting Information for details). Then the Δspin values are plotted against the C−C cleavage activation free energies for all of the radicals shown in Tables 1−3 (41 species in total, see Figure 4).

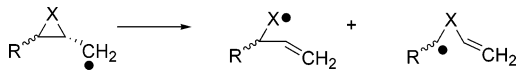
It is clear from Figure 4 that the Δspin (C_1) values correlate nicely with the C−C cleavage activation free energies for all of the 2-aziridinylmethyl radicals. The correlation coefficient is as high as 0.972. The slope of the correlation is positive, which indicates that less spin on C_1 should result in a lower activation free energy for C−C cleavage. Therefore, the substituent effect on the activation free energy of C−C cleavage is determined mainly by the ability of the substituent to delocalize the spin carried by the C_1 atom.

Having explained the substituent effects on C−C cleavage, we examine the substituent effects on C−N cleavage next. In the C−N cleavage pathway, the transition state leads to the formation of a nitrogen-centered radical. We wonder whether the spin-delocalization effect also plays an important role here. Therefore, we calculate the change of spin (Δspin) on N from the starting material to the transition state. These Δspin (N) values are plotted against the C−N cleavage activation free energies for all of the radicals shown in Tables 1−3 (see Figure 5). Unfortunately, it is found that the Δspin (N) values have only a loose correlation with the C−N cleavage activation free energies.

3.7. Extraordinary C_1 Effects of the π-Acceptor Groups. The above analysis indicates that the spin-delocalization effect cannot fully account for the C−N cleavage activation free energies. Further analysis reveals some intriguing effects of the substituents at the C_1 position. As shown in Table 2, the CH_3, F, NH_2, and OCH_3 substituents at the C_1 position reduce the C−N cleavage activation free energy by 0.1−10.1 kJ/mol. However, the π-acceptor groups, including CHO, $COCH_3$, and COOH, at the C_1 position dramatically *increase* the C−N cleavage activation free energy by 7.5−15.5 kJ/mol. In addition, groups with both π-acceptor and π-donor characters (i.e., CH═CH_2, C≡CH, and Ph) at the C_1 position also significantly *increase* the C−N cleavage activation free energy by 4.6−9.4 kJ/mol.

It is worth noting that the C_1 substituent is separated from the C_2−N bond by one sp^3 carbon (i.e., C_1). Thus, the C_1 substituent cannot increase or decrease the spin carried by the nitrogen atom in the transition state via the spin-delocalization mechanism. There must be some other unusual reason that is responsible for the dramatic increase in the C−N cleavage activation free energy in

TABLE 5. Activation Free Energies ($\Delta G^{\ddagger}$, kJ mol^{-1}) at 298 K for the Ring Openings of the C_1-substituted Cyclopropylcarbinyl, Aziridinylmethyl, and Oxiranylcarbinyl Radicals[a]

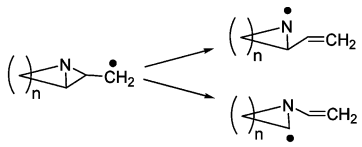


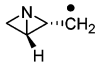
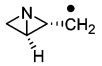
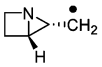
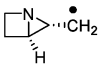
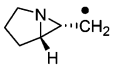
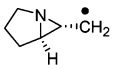
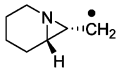
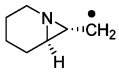
X	R	C−X cleavage	C−C cleavage
CH_2	H	37.4	37.4
	cis-CHO	50.6	7.1
	trans-CHO	52.2	7.7
	cis-Ph	41.3	14.2
	trans-Ph	40.7	11.7
NH	H	14.2	42.4
	cis-CHO	24.3	7.6
	trans-CHO	31.1	8.5
	cis-Ph	20.5	15.3
	trans-Ph	19.2	16.4
O	H	17.3	51.7
	cis-CHO	23.3	22.3
	trans-CHO	23.5	23.6
	cis-Ph	18.3	24.4
	trans-Ph	21.3	24.3

[a] $\Delta G^{\ddagger}$ values are calculated using the ONIOM(QCISD(T)/6-311+G(2d,2p):B3LYP/6-311+G(3df,2p)) method.

(13) Because of the orbital overlap, the C_1 carbon atom carries some spin in the 2-aziridinylmethyl radicals in spite of the fact that the C_1 carbon is not the radical center. For more discussions about this, please see section 3.7.

TABLE 6. Activation Free Energies ($\Delta G^{\ddagger}$) at 298 K for the Ring Opening of the Bicyclic 2-Aziridinylmethyl Radicals[a]



N	Structure	C-N cleavage	C-C cleavage
1-*trans*		8.4	59.9
1-*cis*		17.0	66.8
2-*trans*		8.4	40.8
2-*cis*		16.2	44.8
3-*trans*		6.4	32.2
3-*cis*		14.2	36.0
4-*trans*		8.7	30.1
4-*cis*		8.5	18.1

[a] $\Delta G^{\ddagger}$ values are calculated using the ONIOM(QCISD(T)/6-311+G(2d,2p):B3LYP/6-311+G(3df,2p)) method.

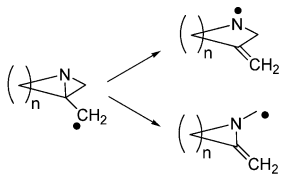
the presence of the π-acceptor C_1 substituents (including the groups with both π-acceptor and π-donor characters). To find out this unusual reason, we performed some natural bond orbital (NBO) analyses[14] for the C_1-CHO and $C_1-CH=CH_2$ 2-aziridinylmethyl radicals.

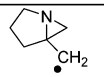
The NBO analyses reveal significant hyperconjugative interactions of the antibonding $\pi^*(CH=O)$ or $\pi^*(CH=CH_2)$ orbital with the $\sigma(C_1-C_2)$ and $\sigma(C_1-N)$ orbitals, and these hyperconjugative interactions lower the energies of the $\sigma(C_1-C_2)$ and $\sigma(C_1-N)$ orbitals (for details, please read the Supporting Information). At the same time, both the $\sigma(C_1-C_2)$ and $\sigma(C_1-N)$ orbitals have hyperconjugative interactions with the $\sigma^*(C_2-N)$ antibond, which weakens the C_2-N bonding strength. Because lowering the energies of the $\sigma(C_1-C_2)$ and $\sigma(C_1-N)$ orbitals will bring about weaker $\sigma(C_1-C_2)-\sigma^*(C_2-N)$ and $\sigma(C_1-N)-\sigma^*(C_2-N)$ hyperconjugative interactions, the presence of an antibonding $\pi^*(CH=O)$ or $\pi^*(CH=CH_2)$ orbital may increase the C_2-N bonding strength via a through-bond relay mechanism. Thus, all of the C_1 substituents that have a π^* orbital may increase the energy barrier for C_2-N cleavage.

It is worth noting that the above mechanism is validated by the NBO analysis. However, the NBO analysis provides only relatively low hyperconjugative interaction energies. Thus, the proposed mechanism may not be adequate for explaining the extraordinary C_1 substituent effect on C−N cleavage. Nevertheless, at this point, we should point out that the extraordinary C_1 substituent effect is not limited to the 2-aziridinylmethyl radicals. In Table 5, the activation free energies for the ring opening of the C_1-substituted cyclopropylcarbinyl, aziridinylmethyl, and oxiranylcarbinyl radicals are shown. It is clear that the C_1-CHO and C_1-Ph substituents reduce the C−C cleavage activation free energies dramatically, but at the same time they significantly increase the C−X cleavage activation free energies. Therefore, the special π-acceptor effect is also applicable to the C_1-substituted cyclopropylcarbinyl and oxiranylcarbinyl radicals.

(14) Glendening, E. D.; Badenhoop, J. K.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *NBO*, Version 3.1; Theoretical Chemistry Institute, University of Wisconsin, Madison.

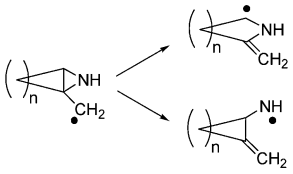
TABLE 7. Activation Free Energies ($\Delta G^{\ddagger}$) at 298 K for the Ring Opening of the Bicyclic 2-Aziridinylmethyl Radicals[a]



N	Structure	C-N cleavage	C-C cleavage
3		8.2	42.0
4		0.8	33.0

[a] $\Delta G^{\ddagger}$ values are calculated using the ONIOM(QCISD(T)/6-311+G(2d,2p):B3LYP/6-311+G(3df,2p)) method.

TABLE 8. Activation Free Energies ($\Delta G^{\ddagger}$) at 298 K for the Ring Opening of the Bicyclic 2-Aziridinylmethyl Radicals[a]



N	Structure	C-N cleavage	C-C cleavage
2		1.3	29.0
3		33.0	12.5
4		21.5	4.5

[a] $\Delta G^{\ddagger}$ values are calculated using the ONIOM(QCISD(T)/6-311+G(2d,2p):B3LYP/6-311+G(3df,2p)) method.

3.8. Bicyclic 2-Aziridinylmethyl Radicals. In the above sections, we have studied the ring opening of monocyclic 2-aziridinylmethyl radicals. Herein, we extend our research to the ring opening of bicyclic 2-aziridinylmethyl radicals. We envisage that the bicyclic 2-aziridinylmethyl radicals will be very interesting precursors for synthetic organic chemists. The ring opening of bicylic 2-aziridinylmethyl radicals, when combined with further radical reactions, may be employed to construct sophis-

ticated nitrogen-containing heterocycles in a highly intelligent and efficient way.

In the first class of bicyclic 2-aziridinylmethyl radicals, the aziridine nitrogen and the C_1 carbon are at the bridge-head position (see Table 6). Thus, the ring opening of the aziridine ring does not change the size of the other ring system. The calculation results suggest that C−N cleavage is strongly favored over C−C cleavage.

In the second class of bicyclic 2-aziridinylmethyl radicals, the aziridine nitrogen and the C_2 carbon are at the bridge-head position (see Table 7). C−N cleavage will increase the size of the other ring, but C−C cleavage will not do so. It is found that under this condition C−N cleavage is favored much more over C−C cleavage.

Finally, in the third class of bicyclic 2-aziridinylmethyl radicals, the C_1 and C_2 carbons are at the bridge-head position (see Table 8). C−C cleavage will increase the size of the other ring, but C−N cleavage will not do so. It is found that C−N cleavage is still favored over C−C cleavage when the other ring is four-membered. Strikingly, when the other ring is five- or six-membered, C−C cleavage is strongly favored over C−N cleavage.

The above results demonstrate that the ring strains may also affect the regiochemistry of the ring opening of bicyclic or multicyclic 2-aziridinylmethyl radicals significantly. By tuning the size of the rings and the position of the C and N atoms, one can deliberately select the C−N or C−C cleavage pathway. It is worth noting that we have not considered the substituent effects in the bicyclic 2-aziridinylmethyl radicals. By taking both the ring size and the substituent effects into consideration, one will have great opportunities to accomplish highly creative and elegant syntheses of sophisticated heterocycles on the basis of the 2-aziridinylmethyl radical chemistry.

4. Conclusions

In the present study, we investigate the substituent effects on the ring-opening reactions of 2-aziridinylmethyl radicals systematically for the first time. The following major findings were obtained.

1. The ONIOM(QCISD(T)/6-311+G(2d,2p):B3LYP/6-311+G(3df,2p)) method is found to be a good compromise between accuracy and efficiency for the study of substituted 2-aziridinylmethyl radicals.

2. Various substituents on the nitrogen atom have little effect on the ring opening of the 2-aziridinylmethyl radical. A π-acceptor substituent at the C_1 position decreases the energy barrier dramatically for C−C cleavage, but it increases the energy barrier significantly for C−N cleavage.

3. When the C_1 substituent is alkyl, the ring opening always strongly favors the C−N cleavage pathway, regardless of whether the N substituent is alkyl, aryl, or COR. When the C_1 substituent is CHO (or CO-alkyl, CO-aryl, or CO−OR but not CO−NR_2), the ring opening strongly favors the C−C cleavage pathway, regardless of whether the N substituent is alkyl, aryl, or COR. When the C_1 substituent is aryl (or alkenyl or alkynyl), the ring opening favors the C−C cleavage pathway if the N substituent is alkyl or COR. If both the C_1 substituent and the N substituent are aryl, the ring opening proceeds via both the C−C and C−N cleavage pathways.

4. The solvent effect on the regioselectivity of the ring opening of the 2-aziridinylmethyl radicals is very small.

5. The substituent effects on C−C cleavage can be explained successfully by the spin-delocalization mechanism. For the substituent effects on C−N cleavage, an extraordinary through-bond π-acceptor effect must be taken into account.

6. Studies on bicyclic 2-aziridinylmethyl radicals show that the ring strain can also affect the regiochemistry of the ring-opening reactions.

Acknowledgment. We thank the NSFC (no. 20332020) for financial support.

Supporting Information Available: Detailed optimized geometries, spins, and free energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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