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Dramatic Effects of Halogen Substitution and Solvent on the Rates and Mechanisms of Nucleophilic Substitution Reactions of Aziridines

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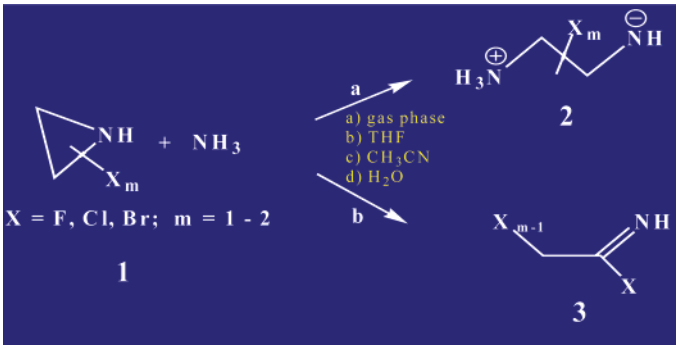

In a previous study we reported that fluorine substitution at the carbon positions of aziridine results in profound enhancements of the rate of reaction with ammonia, a typical nucleophile, in the gas phase. In this study the investigation is extended to include chloro- and bromoaziridines. Because syntheses are largely performed in the condensed phase, the present computational investigation [(MP2(Full)/6-311++G-(d,p)//MP2(Full)/6-31+G(d) level] was conducted with three typical solvents that cover a wide range of polarity: THF, CH_3CN, and H_2O. Nucleophiles can react with haloaziridines **1** by displacing a substituted amide ion by means of an S_N2 mechanism (pathway a), producing 1,2-diaminohaloethanes (from the initially formed dipolar species **2**). Alternatively, a rearrangement mechanism involving rate-determining departure of a halide ion (pathway b) to form an imidoyl halide, **3**, is possible. Transition-state theory was used to compute relative reaction rates of these mechanistic possibilities and to assess the role of the halogen substituents and the reaction solvent. Gas-phase results provided the basis of mechanistic insights that were more apparent in the absence of intermolecular interactions. Fluoroaziridines were found to react at accelerated rates relative to aziridine exclusively by means of the a Menshutkin-type mechanism (S_N2) in each solvent tested, while the reactions of the chloro- and bromoaziridines could be directed toward **2** in the highly nonpolar solvent, cyclohexane, or toward **3** in the more polar solvents. An assessment is made of the feasibility of using this chemistry of the haloazirdines in the synthetic laboratory.

Introduction

Aziridine chemistry continues to be an area of considerable interest synthetically and mechanistically.[1] A noteworthy bioorganic application to the preparation of irreversible inhibitors of cysteine protease has been reported by Engels and co-workers.[2]

Although oxirane and thiirane are widely used synthetically in nucleophilic substitution reactions to prepare 2-substituted alcohols and thiols, respectively, aziridine is a reluctant participant in these reactions due to the poor leaving group ability of its amide ion.[3−13] Amide and sulfonamide derivatives are typically prepared to increase its reactivity to synthetically useful levels. We recently reported that substitution of the carbon positions of the aziridine ring with fluorine led to spectacularly elevated rates of ring cleavage reactions with ammonia in the gas-phase calculations.[14] These findings have assumed increased significance with the subsequent report of De Kimpe and co-workers that fluoroaziridines can be prepared in good to fair yield.[15,16] It is anticipated that haloaziridines will prove to be useful synthetic intermediates.

Fluorine was an attractive substituent to probe this reaction since it is only slightly larger than hydrogen, yet vastly more

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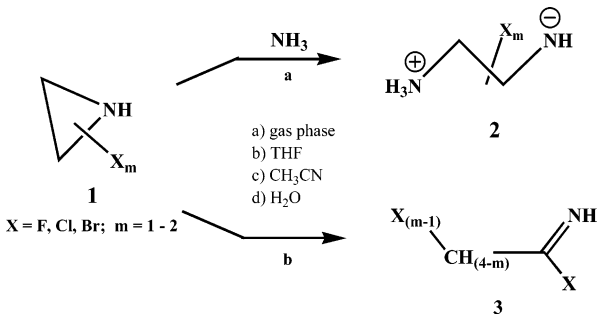
electronegative. Several reasons were provided for the rate accelerations.[14] Fluorine contributes to the disjoined effect.[14,17] Fluorine substitution makes the amide function a better leaving group. The electronegative fluorine can interact in an electrostatically stabilizing manner with the incoming partially positively charged ammonia moiety. Finally, fluorine substitution accelerates the reaction by increasing the ring strain of the ground state.

To determine whether fluorine is unique among the halogens and to further elucidate the mechanism of the reaction, the present computational study was designed to study the larger, less electronegative halogen substituents, chloro and bromo, in a Menshutkin-type reaction proceeding via an S_N2 mechanism to form **2**; however, due to the superior leaving group ability of these halogens relative to fluorine, an additional mechanistic possibility encompassed expulsion of chloride or bromide via a rearrangement pathway to generate a carbocationic species followed by capture of halide ion, yielding an imidoyl halide, **3**. Indeed, heating mono- and dichloroaziridines in nonpolar solvents has been found to produce these compounds.[18,19]



Since most synthetic reactions are conducted in solution, relative rates were calculated with three typical solvents that span a wide range of dielectric constants:[20] relatively nonpolar THF ($\epsilon = 7.58$), polar, aprotic acetonitrile (AN; $\epsilon = 35.9$), and highly polar, protic H_2O ($\epsilon = 78.3$). In essence, it was of interest to determine whether these haloheterocycles are nothing more than theoretical curiosities or if they have potential as synthetic intermediates.

Computational Methodology

Ab initio calculations were performed at the MP2(Full)/6-311++G(d,p)//MP2(Full)/6-31+G(d) level by means of the Gaussian 03 suite of programs.[21] The solvation model utilized was SCI-PCM.[22,23] A scaling factor[24] of 0.9646 was used for the thermal correction to the computed energies at a reaction temperature of 298.1 K. Criteria for the transition state and ground state were calculation of one and zero imaginary frequencies, respectively. GaussView 3.09[25] was used for animation of the sole imaginary

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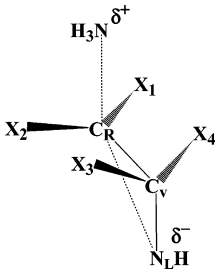


FIGURE 1. Transition state for the S_N2 reaction of an aziridine with ammonia.

frequency, and IRC calculations were used to confirm identification of the transition states. Rate differences between invertomers were found to be insignificant. Ring strain energies were estimated using the method of Dudev and Lim.[26] This technique provides a relatively simple method of estimating the strain energy of a cyclic molecule relative to a strain-free acyclic model compound. It consists of the following procedure. First, at the chosen level of theory, the energy of the acyclic model compound is computed. Since the energy of a cyclic compound differs from that of its acyclic model by the energy due to the removal of two C−H bonds and the formation of a C−C bond, terms for these energies must be included in the ring strain energy, E_{RS}. For monocyclic compounds

$$E_{RS} = E_{cyclo} - E_{acyclo} + E_{2H}$$

where E_{cyclo} and E_{acyclo} are the calculated energies of the cyclic compound and its acyclic model, respectively.

$$E_{2H} = 2E_{C-H} - E_{C-C}$$

$$E_{C-H} = E_{CH_3CH_3} - E_{CH_3CH_2\cdot}$$

$$E_{C-C} = E_{CH_3CH_3} - 2E_{CH_3\cdot}$$

Good to excellent agreement is achieved when the results of this method are compared to experimental values for small ring heterocycles.[27]

Relative reaction rates were obtained from transition-state theory.[28] The disappearance of **1** to form either **2** or **3** is effectively of the same kinetic order for each reaction since the reaction to form **2** would be conducted with a large excess of ammonia to minimize the formation of polyalkyated products, giving rise to pseudo-first-order kinetics.

The attractive energies (kcal/mol) in the transition state due to the carbon and nitrogen reaction centers were computed by means of a simple, classical relationship for the electrostatic energy:[29]

$$E_{elst} = \frac{332 q_{(C_R)eff} q_{(N_L)eff}}{d} \quad (1)$$

The effective charges of the carbon reaction center and nitrogen leaving group, $q_{(C_R)eff}$ and $q_{(N_L)eff}$, respectively, were computed (see Figure 1) using the NBO atomic charges as follows:

$$q_{(C_R)eff} = q_{C_R} + q_{X_1} + q_{X_2} + q_{(C_v)eff}$$

$$q_{(C_v)eff} = q_{C_v} + q_{X_3} + q_{X_4}$$

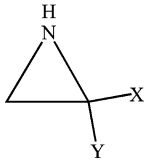
$$q_{(N_L)eff} = q_N + q_{H-N}$$

Finally, d is the distance between C_R and N_L.

The Laplacian plots of electron density of the transition for the rearrangement reaction were obtained by means of AIM 2000 calculations.[30]

Results and Discussion

S_N2 Reaction Pathway. Chloro and bromo compounds **7**−**10** were added to the previously studied[14] gas-phase calculations for **4**−**6**. The relative rates of the S_N2 reactions for these



	X	Y
4	H	H
5	F	H
6	F	F
7	Cl	H
8	Cl	Cl
9	Br	H
10	Br	Br

compounds were determined in the aforementioned solvents. The results are presented in Table 1. Extremely large acceleration of the rates of nucleophilic cleavage of the aziridine ring were calculated upon substitution of the ring by halogen substituents. The factors that contribute to these impressive rates of nucleophilic substitution will now be considered.

Because solvent effects can play a significant role in the relative rates, the gas-phase reaction rates were used in seeking explanations of relative reactivity. Since release of ring strain in the transition state plays a prominent role in the overall rate, the relative rate constants, k'_{rel}, were also determined in the absence of the strain energy contributions so that the importance of other factors on the transition-state energy could be evaluated. The strain energies were calculated using the method of Dudev and Lim.[26]

Substituent effects were determined to be most pronounced in the gas phase. This finding is not unexpected since there is no other available mechanism to stabilize the developing dipolar transition state. The more polar the solvent, the less important the substituent effect, emphasizing the likelihood that the intramolecular energetics of halogen substituents can effectively compete with the favorable intermolecular stabilization offered by polar solvents.

Dichloro compound **8** has the largest substituent effects. Additionally, while substitution of a second bromo substituent produces a rate increase of about 2 orders of magnitude, a similar transformation for the chloro derivative gives rise to a rate factor in excess of 10^5. Chlorine thus emerges as the most potent accelerating substituent. Fluorine substitution, giving rise to the impressive rate increases reported previously, was found in this study to be the least effective halogen studied for increasing reactivity when ring strain release in the transition state was considered.

A useful model to explain the differences in reactivity is depicted in Figure 2. This concept, the disjoined effect, is derived in part from the work of Wiberg.[31] It is postulated that the unshared pairs of electrons on the developing amide ion repel the electron pair of the C−C bond toward the reaction

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TABLE 1. Substituent and Solvent Effects on the Relative Rates of Reaction of Aziridines with NH_3 with and without Ring Strain Energy Corrections

	solvent	4	5	6	7	8	9	10
$\Delta H^{\ddagger}$ [a]	none	63.4	40.6	32.0	40.2	33.0	38.1	31.5
	THF	44.3	30.0	21.4	31.6	24.7	28.7	23.5
	AN	40.8	30.5	20.4	30.8	23.3	27.9	23.1
	H_2O	40.4	28.2	20.2	30.7	23.1	27.8	23.0
$\Delta G^{\ddagger}$ [a]	none	67.6	43.4	34.1	42.1	34.8	40.0	33.4
	THF	54.1	39.6	30.8	41.2	33.5	38.3	33.4
	AN	50.6	40.1	29.9	40.3	33.9	37.5	32.8
	H_2O	48.4	37.8	29.7	40.2	33.7	37.3	32.8
k_{rel}	none	1.00	5.17E+17	3.65E+24	4.50E+18	1.12E+24	1.62E+20	1.11E+25
	THF	1.00	4.51E+10	1.21E+17	3.35E+09	1.44E+15	4.53E+11	1.68E+15
	AN	1.00	4.91E+07	1.58E+15	3.35E+07	1.60E+12	4.29E+09	1.02E+13
	H_2O	1.00	5.99E+07	5.08E+13	4.03E+07	5.49E+10	1.32E+08	2.90E+11
SE[a,b]		27.3	35.6	42.9	33.1	33.5	36.1	39.9
k'_{rel} [c]	none	1.00	4.11E+11	1.23E+13	2.47E+14	3.22E+19	5.76E+13	6.65E+15
	THF	1.00	3.59E+04	4.08E+05	1.84E+05	4.14E+10	1.61E+05	1.01E+06
	AN	1.00	3.91E+01	5.34E+03	1.84E+03	4.61E+07	1.52E+03	6.12E+03
	H_2O	1.00	4.77E+01	1.72E+02	5.47E+01	1.58E+06	4.71E+01	1.73E+02

[a] In kilocalories per mole. [b] Strain energy calculated by means of ref 26. [c] Relative rate with the ring strain energy included in the calculation.

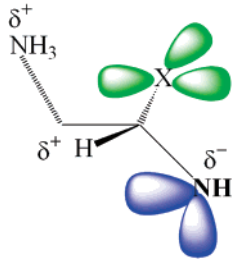

FIGURE 2. Transition-state model for the reaction of haloaziridines with NH_3.

center, decreasing its positive charge and introducing a stabilizing effect by decreasing the electrostatic attraction of the reaction center and the leaving group. The presence of an electronegative fluorine at the vicinal position can supplement the stabilization due to nitrogen alone as was the case for aziridine itself by using its unpaired electrons to repel the electron density of the C−C bond toward the reaction center.

This explanation does not apply fully to the high reaction rates of the chloro- and bromoaziridines. Clearly, since the nonbonded electron pairs on chlorine and bromine are found in $3sp^3$ and $4sp^3$ orbitals, respectively, direct interactions leading to repulsion of the electrons of the bonding orbital between the carbon reaction center (C_R) and the vicinal carbon comprised of $2sp^3$ orbitals giving rise to a lowering of positive charge at C_R are not operative. Interaction of the electron pairs of the departing nitrogen of these compounds with C_R should still, as is the case for the parent compound **4**, occur. Support for this idea is provided by calculation of the effective charge at the carbon reaction center, $q_{(C_R)eff}$, by means of the NBO atomic charges (Table 2), found useful previously.[14] It should be noted that atomic charges are not physical observables, but are defined by the computational method employed. They are not necessarily centered at the nuclei.[32] It is expected that at best only qualitative results will be obtained. With this in mind it is noted that while the fluoroaziridines all have less positive values of $q_{(C_R)eff}$, these quantities for **7**−**10** and the dichloro diastereomers **17** and **18** are all rather close to that of **4**, indicating that the disjoined

TABLE 2. Effective Charges of the Transition States in the Gas Phase at the Carbon Reaction Center and Electrostatic Energies Using NBO Atomic Charges[a,b]

	NBO charges			NBO charges	
	$q_{(C_R)eff}$	E_{elst}		$q_{(C_R)eff}$	E_{elst}
4	0.237	−25.6	**11**	0.492	−25.2
5	0.141	−10.1	**13**	0.370	−40.1
6	0.132	−9.7	**15**	0.138	−9.5
7	0.273	−22.6	**16**	0.164	−11.7
8	0.286	−26.1	**17**	0.248	−20.0
9	0.265	−20.8	**18**	0.287	−24.5
10	0.284	−24.2			

[a] $q_{(C_R)eff}$, the effective atomic charge at the reaction center, is defined as the sum of the atomic charges of C_R, X_1, X_2, C_v, X_3, and X_4. The effective charge at the nitrogen leaving group is the sum of the atomic charges of nitrogen and that of its attached hydrogen atom. [b] See Figure 1 and the Supporting Information.

effect is of similar magnitude for this group of compounds. When the electrostatic energies are calculated (eq 1), the results are again similar to that of **4**.

Table 3 provides the critical carbon−halogen and carbon−nitrogen transition-state bond distances and their differences with respect to the appropriate average distances.[33] It is noteworthy that increases for the carbon−halogen bond distances are all within 12% of their average values and that the shortenings of C−N bonds are less than 9%. The changes for the gas phase are greater than those in the various solvents. In the absence of solvent the incipient amide ion can be stabilized by stretching the carbon−halogen bond to impart imine character to this species. This intramolecular effect is responsible for stabilization in the vapor phase. This finding is rather remarkable since, especially in the case of the good chloro and bromo leaving groups, one might expect negative charge to be transferred to these groups by complete cleavage of the carbon−halogen bond, certainly in the case of the more polar solvents as presented in Scheme 1. The absence of this behavior indicates that the aziridine intermediate is quite a stable species indeed.

One rationalization of the exceptional reactivity of **7**−**10** results from considering the relative electronegativities[34] and

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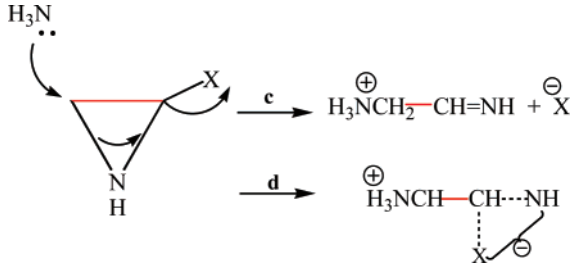
TABLE 3. Haloaziridine Transition-State Bond Distances (Å) [Percent Difference with Respect to Average Bond Distances]

	C−X bond distance (Å)				C−N bond distance (Å)			
	gas	THF	CH_3CN	H_2O	gas	THF	CH_3CN	H_2O
5	1.525	1.472	1.468	1.467	1.363	1.385	1.389	1.390
	[8.93]	[5.14]	[4.86]	[4.79]	[−7.28]	[−5.78]	[−5.51]	[−5.44]
6	1.435	1.408	1.398	1.484	1.342	1.362	1.365	1.365
	[2.50]	[0.57]	[0.14]	[6.00]	[−8.71]	[−7.35]	[−7.14]	[−7.14]
	1.414	1.399	1.406	1.495				
	[1.00]	[−0.07]	[0.43]	[6.79]				
7	2.002	1.896	1.880	1.878	1.361	1.387	1.393	1.394
	[11.84]	[5.92]	[5.03]	[4.92]	[−7.41]	[−5.65]	[−5.24]	[−5.17]
8	1.916	1.824	1.821	1.878	1.344	1.368	1.374	1.375
	[7.04]	[1.90]	[1.73]	[1.68]	[−8.57]	[−6.94]	[−6.53]	[−6.46]
	1.819	1.837	1.825	1.825				
	[1.62]	[2.63]	[1.96]	[1.96]				
9	2.177	2.103	2.091	2.089	1.361	1.378	1.439	1.382
	[1.051]	[6.75]	[6.14]	[6.04]	[−7.41]	[−6.26]	[−2.11]	[−5.99]
10	1.983	1.978	1.975	1.975	1.341	1.352	1.354	1.355
	[0.66]	[0.41]	[0.25]	[0.25]	[−8.78]	[−8.03]	[−7.89]	[−7.82]
	2.094	2.063	2.058	2.056				
	[6.29]	[4.72]	[4.47]	[4.37]				

SCHEME 1. Alternative Pathways for Attack of NH_3 on Aziridine and Its Acyclic Model Compounds



leaving group ability. The departure of nitrogen is promoted by the stabilization afforded by development of partial double bond character with the vicinal carbon, forming a species having imide character. A good leaving group at the vicinal carbon is clearly advantageous; however, additional stabilization can be provided by a bonded atom of reasonably high electronegativity. Brauman[35] reported in a classical paper studying the *anionic* S_N2 reaction that gas-phase leaving group ability is not absolute and depends on the hardness/softness of the nucleophile and leaving group. To the best of our knowledge, gas-phase leaving group ability has not been studied for S_N2 reactions between neutral substrates. From the k'_{rel} values for **7** and **9**, leaving group ability appears to make a minor contribution since the former only reacts about 4 times faster. This observation is strengthened by the relatively minor increases in the C_v−halogen bonds in the transition states (Table 3). Stabilization of the developing negative charge afforded by the considerably higher electronegativity of the second chlorine relative to bromine at C_v is proposed to be the major contributor to the higher reactivity of **8** as opposed to **10**.

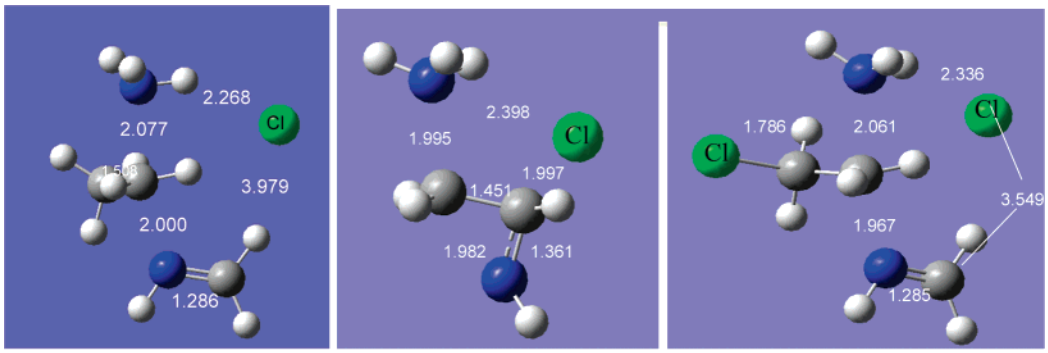
By analogy with the acyclic model compound previously employed for C_3 attack on **5**, $ClCH_2CH_2NHCH_2Cl$ (**11**) was selected for **7**. Attack on C_1 of the 2-chloroethyl group simulates an environment in which the vicinal carbon bears a chlorine and the departing amino group has a chloroalkyl attachment. When steric strain considerations were included, this compound was calculated to react at a relative rate of 2.37×10^{28} with respect to the rate of aziridine in the gas phase. Unlike the case for the fluoro compounds where the acyclic model reacted about 10^2 times slower, the relative acceleration of **11** is ca. 10^{14}.

It is likely that two factors are at work to give rise to this remarkable difference. First, chloride is a considerably superior leaving group relative to fluoride. Second, the distance of chlorine from the reaction center makes it difficult for it to interact with the incoming nucleophile at an early stage along the reaction coordinate. The path of lowest energy is formation of a chloride ion that migrates close to the incipient ammonium ion with the concurrent genesis of the corresponding neutral imine. The importance of having a chloro substituent at the vicinal position was explored by studying the reactivity of $CH_3CH_2NHCH_2Cl$ (**12**); the relative reaction rate of 1.16×10^{28} and geometry (Figure 3) were virtually identical to those of the dichloro model compound, demonstrating that the second chloro group has a trivial effect.

A radically different result was obtained when a similar transformation was made for the acyclic fluoro model compound. Replacement of the vicinal fluorine by hydrogen led to a rate increase of 9.20×10^7. Unlike the transition state for difluoroamine $FCH_2CH_2NHCH_2F$ (**13**) (Figure 4) that has a C−N bond length of 1.356 Å, the bond distance for the monosubstituted $CH_3CH_2NHCH_2F$ (**14**) is 1.287 Å, closely resembling that of an imine bond. The carbon−fluorine bond is completely broken, and fluoride ion has migrated close to a hydrogen of the incipient ammonium ion. In the difluoro compound, strong electrostatic interactions between the ammonia hydrogens and the fluorine of the 2-fluoroethyl group decrease the ability of the developing ammonium ion to assist in formation of a fluoride ion. In the absence of this fluoro group, fluoride ion formation proceeds unimpeded.

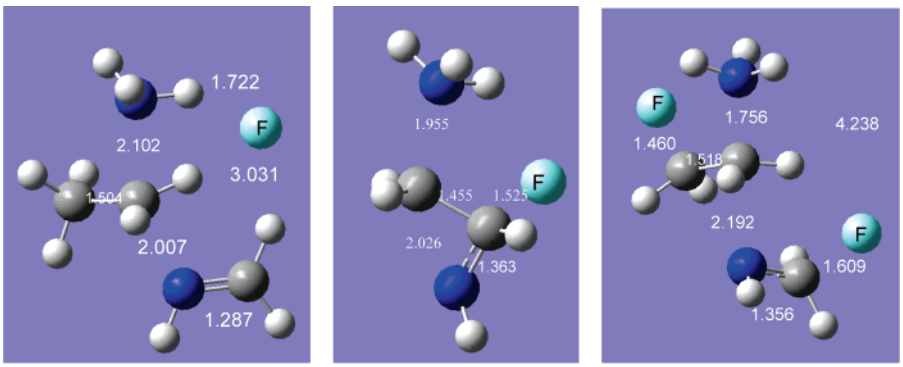
No model compound can perfectly capture every structural detail of the compound it is intended to mimic. Aziridines have the leaving group tethered to the carbon reaction center (red bond, Scheme 1) with pathway d the lowest energy pathway because the developing negative charge can be dispersed in the transition state over three atoms with electron density fed into the developing partially positively charged carbon reaction center by means of the disjoined effect without the necessity of breaking a carbon−halogen bond. In the absence of this tether, as is the case for the acyclic model compounds, pathway d would be expected to be followed since the energy required

(34) See, for example: Pritchard, H.; Skinner, H. A. *Chem. Rev.* **1955**, *55*, 745−786.
(35) Olmstead, W. N.; Brauman, J. I. *J. Am. Chem. Soc.* **1977**, *99*, 4219.



12‡ **7‡** **11‡**

FIGURE 3. Transition-state geometries of **7** and two model compounds in the gas phase (distances are in angstroms).



14‡ **5‡** **13‡**

FIGURE 4. Transition-state geometries of **2** and two model compounds in the gas phase (distances are in angstroms).

TABLE 4. Regiochemical Studies for the S_N2 Reaction of the Haloaziridines

	solvent	$\Delta G^{\ddagger}$ at C_2 (kcal/mol)	$\Delta G^{\ddagger}$ at C_3 (kcal/mol)	$k_{rel}(C_2$ vs $C_3)$
5	H_2O	52.3	37.8	2.37E−11
6	THF	55.8	30.8	5.46E−19
7	none	63.9	42.1	1.17E−16
8	H_2O	57.9	33.7	1.92E−18
8	none	67.6	34.8	9.80E−25
9	none	67.1	40.0	1.36E−20
10	none	68.6	33.4	1.66E−26

to cleave the C−X bond is partially compensated for by formation of a relatively strong carbon−nitrogen double bond. This analysis suggests that since the hybridization of the carbon possessing imide character approaches sp^2, the C−N bond will be shortened. This prediction is confirmed by the fact that the acyclic model compounds have C−C bond lengths of ca. 1.29 Å, while that of the aziridine derivative is ca. 1.36 Å (Figure 3).

The regiochemical consequences of the reaction are presented in Table 4. From these results it is reasonable to conclude that for synthetic purposes attack will invariably occur exclusively at the less substituted position.

Comparing **5** to its model **13** and **7** to **11** (Table 2), it is noted that the acyclic model compounds develop considerably more positive charge at C_R than the heterocycles in accord with the disjoined effect. In the case of **11**, the rupture of the carbon−chlorine bond permits advanced imine character for the leaving group and greatly accelerates this reaction.

Diasteroselectivity in this reaction was explored using *cis*- and *trans*-2,3-dichloroaziridine (**17** and **18**, respectively). In the gas phase, the rates relative to that of aziridine after correction for strain energy release in the transition state are 1.15×10^5 and 3.80×10^9. With the disastereomers of 2,3-difluoroaziridine, the *trans* isomer **15** reacted ca. 10^8 times faster.[14] This difference was ascribed in part to the greater stability of the dipolar complex of the *cis* isomer **16** and to interactions of the vicinal fluorine with the hydrogen of the imine-like leaving group. Although the dipolar complex of **18** was found to be more stable than **17** by 2.2 kcal/mol at the MP2(Full)/6-31+G(d) level, the dipolar interactions between the imine hydrogen and chlorine are expected to be minimal. This is consistent with the fact that the relative rate of the dichloroaziridines has dropped to 3×10^4 from the considerably higher value for their fluoro analogues.

Both stereoisomers react faster than aziridine, demonstrating that the presence of a chloro group at C_R does not hinder the reaction; however, these compounds both react slower than **7**. The more reactive **17** is 6.5×10^4 slower than **7**. The $q_{(C_R)eff}$ values (Table 2) are quite similar and close to that of **4**; however, it is somewhat surprising that the chlorine atoms bonded to C_R in the transition states of **17** and **18** bear virtually no charge; the NBO atomic charges (Supporting Information) are 0.033 and 0.080, respectively. This suggests an energy requirement is engendered by the relatively electronegative chlorine atom at the reaction site in donating electron density to stabilize the transition state.

Rearrangement Pathway. The good halide leaving groups of the chloro and bromo derivatives introduce the possibility of a reaction that proceeds with a different chemoselectivity. Instead of concerted attack by the nucleophile with displacement

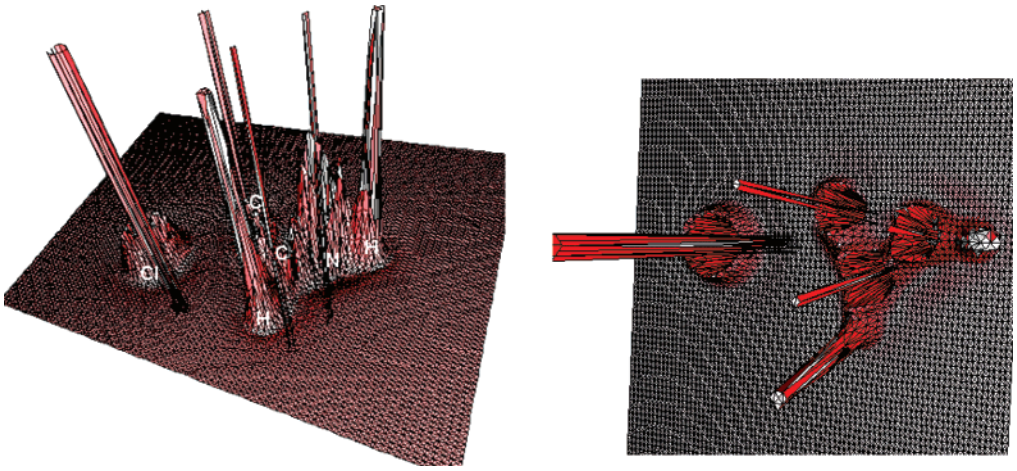
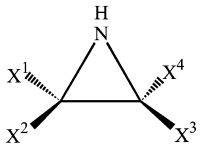


FIGURE 5. Two views of the Laplacian for the transition state in the reaction of **7** with NH_3.

of a substituted amide leaving group considered above, departure of a halide ion could occur by means of an isomerization mechanism, producing **3**. As mentioned above, this reaction, the formation of α-chloroimidoyl chlorides from 2-chloro- and 2,2-dichloroaziridines, respectively, has been observed.[17,18] A logical intermediate in this reaction is illustrated below. A typical

$ClCH_2CH_2NHCH_2Cl$ **11**

$FCH_2CH_2NHCH_2F$ **13**



15 $X^1 = X^3 = F; X^2 = X^4 = H$

16 $X^1 = X^4 = F; X^2 = X^3 = H$

17 $X^1 = X^3 = Cl; X^2 = X^4 = H$

18 $X^1 = X^4 = Cl; X^2 = X^3 = H$

Laplacian for the transition state leading to this competing reaction in the case of **7** and NH_3 is provided in Figure 5 as viewed from two planes passing through the atoms indicated. It is clear that considerable electron density has accumulated in the C_v-N bond, while both the C_R-N and C_v-Cl bonds are essentially ruptured. To evaluate the chemoselectivity of each haloaziridine, the free energies of activation of these compounds via the rearrangement mechanism were determined in the chosen solvents and compared to the values for the S_N2 process (Table 5). As expected, given the less polar nature of its transition state, all haloaziridines chose the S_N2 mechanism in the gas phase.

It was discovered that dichloro derivative **8** could follow either mechanistic course depending on the solvent. Using the values of Table 5, the rate constant for the rearrangement reaction in water at 25 °C was about 67 times that of the Menschutkin-type mechanism; this result could be reversed by changing the solvent to THF (rate factor ca. 63). Consistent with these findings is the observation that the 1,3-diphenyl derivative of **8** yields products resulting from a carbocationic intermediate in refluxing toluene[36]($\epsilon_{25} = 2.4$).[20] The stability of the carbocation formed from this compound is undoubtedly augmented by the exceptional stability conferred by the aromatic rings.

TABLE 5. Effects of Solvent on the Free Energies of Activation and Relative Rates of the Chemoselective Reactions

compd	solvent	$\Delta G^{\ddagger}_a$	$\Delta G^{\ddagger}_b$	k_a/k_b
5	none	43.4	68.5	2.50E+18
	THF	39.6	60.5	1.86E+15
	AN	40.1	62.4	2.28E+16
	H_2O	37.8	42.7	3.89E+03
6	none	34.1		1.077E−25
	THF	30.8		2.501E−23
	AN	29.8		1.344E−22
	H_2O	29.7	48.7	9.02E+13
7	none	42.1	68.5	2.21E+19
	THF	41.2	38.6	1.30E−02
	AN	40.3	34.9	1.13E−04
	H_2O	40.2	34.6	7.16E−05
	C_6H_{12}	43.4	51.1	4.48E+05
8	none	34.8	60.3	5.29E+18
	THF	33.5	35.9	6.33E+01
	AN	33.9	31.9	3.12E−02
	H_2O	33.7	31.3	1.501E−02
9	none	40.0	45.8	1.75E+04
	THF	38.3	31.8	1.87E−05
	AN	37.4	28.2	1.60E−07
	H_2O	37.3	27.7	8.79E−08
	C_6H_{12}	36.8	44.1	2.16E+05
10	none	33.4	45.8	1.13E+09
	THF	33.4	30.2	4.95E−03
	AN	32.8	26.5	2.63E−05
	H_2O	33.4	25.8	2.84E−06
	C_6H_{12}	31.0	45.3	3.03E+10

Since **6** was found to vigorously shun the rearrangement process, even in the extremely polar medium H_2O, presumably the solvent most likely to promote this reaction, calculations were not performed for **6** in THF and AN. The most reactive haloaziridines by means of the rearrangement pathway are the bromo derivatives. The isomerization pathway was determined to be favored by **7**, **9**, and **10** in the solvents selected for this study. To determine whether synthetic versatility could be conferred on these reactions by further solvent change, calculations with cyclohexane as solvent were conducted. Due to its very low dielectic constant ($\epsilon_{25} = 2.02$), cyclohexane should be essentially incapable of meaningful dipolar interactions with the highly polar carbocationic transition state of the rearrangement reaction. Reactions for which calculations were performed in cyclohexane solution resulted in a reversal of the relative

(36) Meilahn, M. K.; Olsen, D. K.; Brittain, W. J.; Anders, R. T. *J. Org. Chem.* **1978**, *43*, 1346.

TABLE 6. Calculated Relative Rates of S_N2 Reaction of Haloaziridines in Various Media with Respect to the Rate of Oxirane in THF at 25 °C

	C_6H_{12}	THF	AN	H_2O
5		5.09E−03	2.28E−03	1.12E−01
6		1.36E+04	7.34E+04	9.53E+04
7	9.36E−06	3.78E−04	1.56E−03	1.87E−03
8		1.62E+02	7.41E+01	1.03E+02
9	5.60E−01	5.12E−02	1.99E−01	2.48E−01
10	1.05E+04	1.90E+02	4.75E+02	5.43E+02

reactivities of **7**, **9**, and **10**, and **2** was found to be the overwhelmingly favored product. This transformation for **10**, the most reactive in the rearrangement reaction in the other solvents explored, is strikingly gratifying.

As noted previously, aziridine reacts with ammonia by means of the S_N2 mechanism at an unacceptably slow rate for synthetic purposes at 25 °C. Choosing THF as the reaction medium, its free energy of activation for cleavage by ammonia is 54.2 kcal/mol compared to values of 36.5 and 34.8 kcal/mol for the synthetically useful oxirane and thiirane. To access the likelihood that a given haloaziridine would react at a synthetically useful rate, the bimolecular reaction of ammonia with oxirane in THF was chosen for comparison. Table 6 provides the relative rates of reaction of the haloaziridines with ammonia at 25 °C in the various solvents. Using this criterion, dihalo compounds **8** and **10** are sufficiently reactive; however, the calculations show that, for the S_N2 reaction to predominate, while THF may be chosen for **8**, cyclohexane is necessary for **10**. The S_N2 reaction occurs rapidly in the three chosen solvents for difluoro compound **6**, while **5** and **7** are too slow in these solvents. Borderline reactivity in C_6H_{12} is calculated for **9**. It should be noted that although ammonia is a relatively good nucleophile, more potent nucleophiles may well elevate the monosubstituted derivatives to useful reaction rates under these relatively mild reaction conditions.

In a similar manner, it can be shown that, for the isomerization reaction, the chloro- and bromoaziridines proceed with acceptable reaction rates in AN and H_2O.

Conclusions

In addition to that of fluorine, chlorine and bromine substitution in aziridines produces dramatic rate accelerations in S_N2 nucleophilic substitution reactions with ammonia. As expected, increasing the polarity of the solvent increased the reaction rate, although much larger solvent effects were observed for aziridine itself than for its halo derivatives. The chloro- and bromoaziridines are considerably more reactive in the gas phase than the fluoroaziridines when strain energy release in the transition state is considered.

For the chloro- and bromoaziridines, different chemoselectivity that followed a rearrangement mechanism with displacement of halide was favored in most solvents; however, these results could be reversed in cyclohexane solution. It is not surprising that increasing the solvent polarity increases the rate of this reaction; however, since both reaction pathways involve charge separation, it would be difficult to make predictions of the favored reaction course in a chosen solvent. The power of the computational chemistry exemplified herein is that it allows one to choose those solvents that are likely to be most effective in the laboratory to effect the desired outcome. As the haloaziridine family becomes more readily available to researchers, it will be worthwhile to experimentally test their utility as synthetic intermediates.

Supporting Information Available: Energies and Cartesian coordinates of the reactants and transition states, unique imaginary transition-state frequencies in the various reaction media, and gas-phase NBO atomic charges of the transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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