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The Profound Effect of Fluorine Substitution on the Reactivity and Regioselectivity of Nucleophilic Substitution Reactions of Strained Heterocycles. A Study of Aziridine and Its Derivatives

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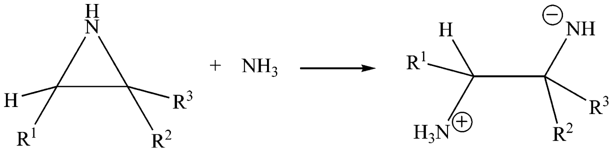
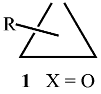


R^1, R^2, R^3 = F or H

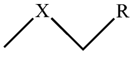
Unlike the synthetically exploited oxiranes and thiiranes, aziridines that lack electron-withdrawing substituents, such as acyl or sulfonyl functionalities at nitrogen, are rather unreactive. As expected, three-membered aziridine **6** was calculated to be significantly more reactive than azetidine **7** in nucleophilic cleavage by ammonia, a typical nucleophile. The reactivity of **7** was about the same as that of an acyclic model compound, **8**, when release of ring strain in the transition state was taken into account. Fluorine due to its similar size but vastly different electronegativity has been substituted for hydrogen as a means of modifying chemical properties for varied applications. In the present investigation, the effect of fluorine substitution at aziridine positions other than nitrogen was studied. Computations at the MP2(Full)/6-311++G(d,p)//MP2(Full)/6-31+G(d) level found a vast preference for attack by ammonia at the 3-position of 2-fluoroaziridine in the gas phase at 298 K. When release of ring strain was taken into account, this compound reacted more than 10^{11} times faster than **6**. The reaction rate with *trans*-2,3-difluoroaziridine was about twice that of 2-fluoroaziridine, while its diastereomer reacted with ammonia considerably slower. Acyclic fluorinated amine model compounds were employed to assess the generality of the effects produced by fluorine substitution. The results were rationalized by the energy contributions of strain energy releases, stabilization of the leaving group, and the relative electrostatic energies of the heterocycles in the transition states. The more reactive fluoroaziridines underwent nucleophilic attack at rates comparable to those of *N*-acetylaziridine.

Introduction

Strained ring heterocyclic compounds are exceedingly more reactive with nucleophiles than their acyclic analogues. Epoxides, **1**, and thiiranes, **2**, are widely used in synthesis, under conditions whereby the corresponding ethers, **4**, and thioethers, **5**, are essentially inert.



1 X = O
2 X = S
3 X = NH



4 X = O
5 X = S

Aziridines that are not substituted at nitrogen by electron-withdrawing substituents, **3**, however, are significantly less reactive. This fact may be illustrated by the fact that aziridine itself, **6**, can be synthesized by the cyclization of 2-chloro-1-aminoethane in water, a reasonably good nucleophilic solvent.[1] The strong basicity of the amide ion that renders the ring nitrogen a poor leaving group is largely responsible for the sluggish nucleophilic chemistry of **6**. Useful reactivity can be realized if the basicity of the displaced group is drastically decreased by conversion to its sulfonamide or amide, and indeed, this is a common synthetic strategy.[2] We have been interested in elucidating the factors responsible for the extraordinary reactivity of heterocyclic compounds in their reactions with nucleophiles in Menschutkin-type reactions.[3−5] In these reactions, both nucleophile and substrate are uncharged, leading to

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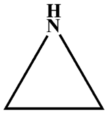
charge separation in the transition state. It has been demonstrated that, for the reactions of oxirane and thiirane with ammonia in the gas phase, relief of strain in the transition state is insufficient to explain the tremendous rate increases relative to unstrained model compounds. A *disjoined effect* that is related to the electrostatic energy calculated from the atomic charge of the carbon reaction center, the atomic charge of the heteroatom leaving group, and the distance separating these species at the transition state was used to explain the higher reactivity of the three-membered compounds relative to model compounds.[3]

In the present study, our calculations were first extended to aziridine (**6**), azetidine (**7**), and model compound, methylethylamine (**8**) to determine if the conclusions for the group VI heterocycles could be extended to their nitrogen analogues. The strain energy of each heterocycle was added to the calculated free energy of activation of its reaction with ammonia and the resulting sum compared to the free energy of activation of **8** in order to determine if a disjoined effect was operational in **6**.



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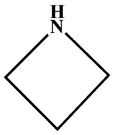

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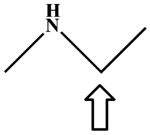

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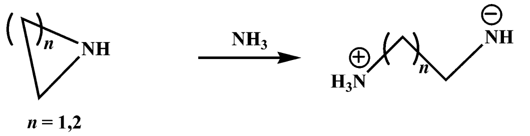
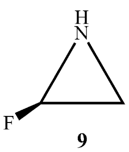


Fluorine substitution has been used extensively in organic chemistry studies to modify molecular properties[6] and to prepare analogues of medicinally important compounds.[7] Since fluorine is only somewhat larger than hydrogen, but vastly more electronegative, it can also be used as an effective mechanistic probe of electronic effects in the virtual absence of significant steric effects. To further probe the nucleophilic chemistry of aziridine, four fluoroaziridines were chosen for study of their relative rates of reaction with NH$_3$. Regioselectivity was examined by investigating **9** and **12**. Diastereoselectivity considerations were addressed by using *trans*- and *cis*-2,3-difluoroaziridine (**10** and **11**, respectively) as substrates.



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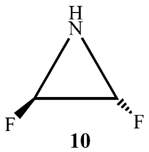

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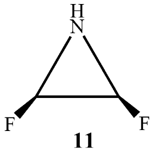

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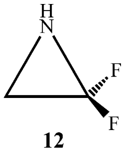

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Computational Methodology

Initial geometries for the ground and transition states were determined by means of semiempirical calculations using AM1 methodology as implemented by the Spartan 5.1.1 program.[8] The final ab initio calculations were performed by means of the Gaussian suite of programs[9] for reactions at 298.1 K in the gas phase at the MP2(Full)/6-311++G(d,p)//MP2(Full)/6-31+G(d) level. A method that incorporates electron correlation is required for these studies of nucleophilic displacement reactions. The 6-31+G(d) basis set that includes diffuse functions to accommodate the lone pairs and anionic species that typify these reactions was selected to calculate the geometries of the ground and transition states. Thermal energy corrections that include the consequences of translation, vibration, rotation, and translation at 298.1 K and the zero point energy were scaled[10] by 0.9646 and added to the energies of the ground state and transition states. Transition states possessed a unique imaginary frequency, while ground states had none. A transition state structure was further confirmed by animation of its imaginary frequency using GaussView 2.03[11] and intrinsic reaction coordinate (IRC) calculations to demonstrate that the calculated structure was found on the potential energy surface connecting the reactants and the product. Relative rates were computed by means of standard transition state theory.[12] Calculations using atoms in molecules were performed by means of the AIM 2000 program.[13]

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The attractive energies in the transition states due to the carbon and nitrogen reaction centers were compared using a simple, classical relationship for the electrostatic energy:[14]

$$E_{\text{elst}} = \frac{332(q_{\text{C}})(q_{\text{N}})}{d} \tag{1}$$

The charges of the carbon and nitrogen, q_{C} and q_{N}, respectively, are the sum of their atomic charges and attached hydrogens. Four procedures for calculating atomic charge that have seen wide application in the recent literature, NBO,[15] AIM,[16] CHELPG,[17] and Mulliken,[18] were utilized. Finally, d is the distance between carbon and the nitrogen atom leaving group. NBO, Mulliken, and CHELPG charges were obtained using the Gaussian suite of programs; AIM charges were derived from the AIM 2000 calculations.

TABLE 1. Calculation of Relative Rates of the Nitrogen Compounds with NH_3 [MP2(Full)/6-311++G(d,p)//MP2(Full)/6-31+G(d) at 298.1 K][a]

	ΔH_{act} kcal mol^{-1}	ΔS_{act} eu	ΔG_{act} kcal mol^{-1}	k_{rel}
6	63.4	−14.1	67.6	7.76E + 23
7	71.3	−17.6	76.5	2.30E + 17
8	97.4	−9.6	100.2	1.00E + 00

[a] See Supporting Information for the energies of the ground and transition states used for calculation of ΔH_{act}; 1 hartree = 627.5 kcal mol^{-1}. RT = 0.5928 kcal mol^{-1} at 298.1 K.

Results and Discussion

The most obvious explanation of differences in reactivity of small ring compounds in nucleophilic substitution reactions is variation in the ring strain energies of the substrate molecules. One can assume, to a first approximation, that all of the strain energy is released in the transition state. The strain energy of small ring heterocycles can be conveniently calculated using the method of Dudev and Lim.[19] Employing this method for **6** gives a strain energy of 27.3 kcal mol^{-1} in excellent agreement with the experimental value of 27.1 kcal mol^{-1}.[20] Although an experimental strain energy for **7** could not be found in the literature, the result with **6** and previous success with ring strain calculations on **1** and **2** provided confidence that the calculated value of 25.2 kcal mol^{-1} is reasonably accurate.

Table 1 presents the data required for the calculation of the relative rates of reaction of **6**−**8** with NH_3. It is not surprising that both **6** and **7** react at exceedingly fast rates with respect to acyclic model compound **8**. When the strain energies for the heterocycles calculated above are added to their ΔG_{act} values from Table 1, free energies of activation for **6** and **7** of 94.9 and 101.7 kcal mol^{-1}, respectively, are obtained corresponding to the expected values for the reaction with NH_3 in the absence of strain energy. The ΔG_{act} of the four-membered ring agrees with that of the strain-free molecule within 2.0 kcal mol^{-1}, while that of **6** corresponds to an enhancement of the reaction rate by a factor of 1.3 × 10^5. The inability of relief of ring strain alone to explain the large acceleration of three-membered heterocycles thus extends from oxygen and sulfur heterocycles to nitrogen.

The source of the disjoined effect for **6** was investigated as before[3] by recognizing that Menschutkin-type reactions involve charge separation in the transition state. Factors that are capable of diminishing this charge development will lower the energy

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[20] Cox, J. D.; Pilcher, G. *Thermochemistry of Organic and Organometallic Compounds*; Academic Press: London, 1970.

TABLE 2. Electrostatic Energies (in kcal mol^{-1}) of the Transition States of the Reactions of 6−8 with NH_3 Calculated by Different Methods

	distance (Å)	NBO	AIM	CHELPG	Mulliken
6	2.271	−22.4	−29.4	15.0	−37.2
7	2.328	−29.8	−41.8	−74.2	−45.4
8	2.390	−31.5	−51.6	−102.5	−48.3

TABLE 3. Atomic Charges of the Carbon Reaction Center for the Transition States and Leaving Group Using Different Methods with Hydrogens Summed into the Heavy Atoms

		NBO	AIM	CHELPG	Mulliken
6	C_r	0.21	0.23	−0.12	0.36
	N	−0.74	−0.87	−0.89	−0.71
7	C_r	0.28	0.33	0.53	0.42
	N	−0.76	−0.89	−0.99	−0.75
8	C_r	0.28	0.39	0.66	0.45
	N	−0.81	−0.93	−1.11	−0.78

TABLE 4. Calculated Free Energy of Activation (kcal mol^{-1}) in the Absence of Ring Strain Energy Release (ΔG_{act} + SE) and with Attractive Electrostatic Energies Included Relative to 8[a]

		ΔG_{act} + SE + Electrostatic Energy by Each Method			
	ΔG_{act} + SE	NBO	AIM	CHELPG	Mulliken
6	94.9	104.1	117.1	212.2	106.0
7	101.7	103.4	111.5	130.0	104.6
8	(100.2)	(100.2)	(100.2)	(100.2)	(100.2)

[a] The ΔG_{act} + SE value for **8** is given in parentheses.

of the transition state and make for a more facile reaction. The electrostatic energies were calculated using NBO, AIM, CHELPG, and Mulliken atomic charges. As with oxygen and sulfur heterocycles, it sufficed to consider only the carbon reaction center, q_C, and the nitrogen leaving group, q_N with hydrogens summed into the heavy atoms. The results are provided in Table 2; the appropriate atomic charges are listed in Table 3. The effective atomic charge at carbon, q_C, and the leaving group, q_N, was calculated as before[3] as the sum of the atomic charge of the appropriate heavy atom and its attached hydrogen atoms.

Use of this simple equation to calculate the attractive electrostatic energies dictates that only relative and not the absolute values are meaningful. For the NBO charges, the electrostatic energies for **7** and **8** are essentially equal within the limits of computational error. This finding is reasonable since these compounds have virtually identical reactivity with NH_3 after the strain energy of **7** has been considered. A significantly diminished attractive energy of −22.4 kcal mol^{-1} calculated for **6** is ca. 8 kcal mol^{-1} lower than the average value of **7** and **8** and is quite close to its lower ΔG_{act} of ca. 7 kcal mol^{-1} with respect the strain-free model compound, after strain energy release in the transition state has been considered. Since work has to be supplied to overcome attractive energy, the lower the attractive energy, the lower the energy of the transition state relative to the ground state. This indicates that the three-membered ring has a unique stabilization that is unavailable for the other compounds.

The remaining three methods of calculation of atomic charge evidenced the same qualitative trends in attractive electrostatic energy. Each procedure necessarily incorporates its particular assumptions and has varying virtues depending on the application.[21] None of these methods for calculating atomic charge is a perfect choice for application of a classical electrostatic equation that requires a spherical charge distribution centered at each nucleus. Mulliken charges have been found to be dependent on the basis set used.[22] NBO charges and AIM charges are not centered at the nucleus.[21] AIM atomic charges have been characterized as too large; however, when atomic multipole moments are incorporated into AIM atomic charges, reasonable electronic distributions are obtained using this methodology.[23] The assumption made here was that qualitatively satisfactory atomic charges would be derived from this closely related group of compounds, and that similar trends in calculated electrostatic energies using these four diverse methods would be indicative of actual changes in this contribution to the energy of the transition state. The results presented in Table 2 show that the electrostatic energy of **6** is lower than those of the other members of this series, consistent with its higher reactivity; Table 2 demonstrates that electrostatic energy, when added to ΔG_{act} + SE, is more than enough to explain the reactivity of **6** relative to **8**. Given the nature of the methods described above, the NBO, Mulliken, and AIM results are consistent with a decrease in electrostatic energy in the transition state of **6** relative to **8**, making a contribution to its increased rate of reaction with NH_3. The CHELPG charges led to electrostatic energy calculations that differed most from those expected on the basis of rate differences.[24]

An alternative method of analyzing the data is addition of the electrostatic energies calculated by each method, relative to the model acyclic compound **8**, to the calculated free energy of activation if ring strain release did not participate in the transition state. The results of this procedure are provided in Table 4. Ideally, the sums of the energies for **6** and **7** should be identical to that of **8**. The results for the NBO and Mulliken methods are close to this expectation, while those for the AIM method are somewhat high; the CHELPG results are again exaggerated. It is important to remember, however, that given the assumptions inherent in the use of a classical equation for calculation of electrostatic energies combined with departures of the methods for deriving atomic charge from rendering point charges centered at the nuclei, only qualitative agreement is reasonable. In all cases, the energy due to electrostatic energy is of a magnitude more than enough to explain the increased acceleration of **6** relative to **8** when the effect of release of ring strain has been taken into account.

An attractive explanation of the disjoined effect for nitrogen heterocycle **6** is derived from the work of Wiberg.[25] It is reasonable that the partially negatively charged nitrogen leaving group repels electron density of the back lobe of the adjacent carbon atom, leading to a diminution of positive charge at the carbon reaction center, lowering the electrostatic attractive

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(21) Excellent discussions of different procedures for obtaining atomic charges are available. (a) Wiberg, K. B.; Rablen, P. R. *J. Comput. Chem.* **1993**, *14*, 1504. (b) Bailey, W. F.; Beak, P.; Kerrick, S. T.; Ma, S.; Wiberg, K. B. *J. Am. Chem. Soc.* **2002**, *124*, 1889.

(22) Jensen, F. *Introduction to Computational Chemistry*; John Wiley & Sons: New York, 1999; pp 218−220.

(23) For leading references and a discussion of the utility of AIM charges, see: (a) Bader, R. F. W.; Matta, C. F. *J. Phys. Chem. A* **2004**, *108*, 8385. (b) Parr, R. G.; Ayers, P. W.; Nalewajski, R. F. *J. Phys. Chem. A* **2005**, *109*, 3957. (c) Matta, C. F.; Bader, R. F. W. *J. Phys. Chem. A* **2006**, *110*, 6365. (d) See also ref 14, pp 317−318.

(24) This is perhaps not surprising since CHELPG charges have found utility under very different conditions, such as, nonbonding interactions at long distances. Petryk, M. W. P.; Henry, B. R.; Sage, M. L. *J. Phys. Chem. A* **2005**, *109*, 9969.

(25) Wiberg, K. B. *J. Am. Chem. Soc.* **1990**, *112*, 3379.

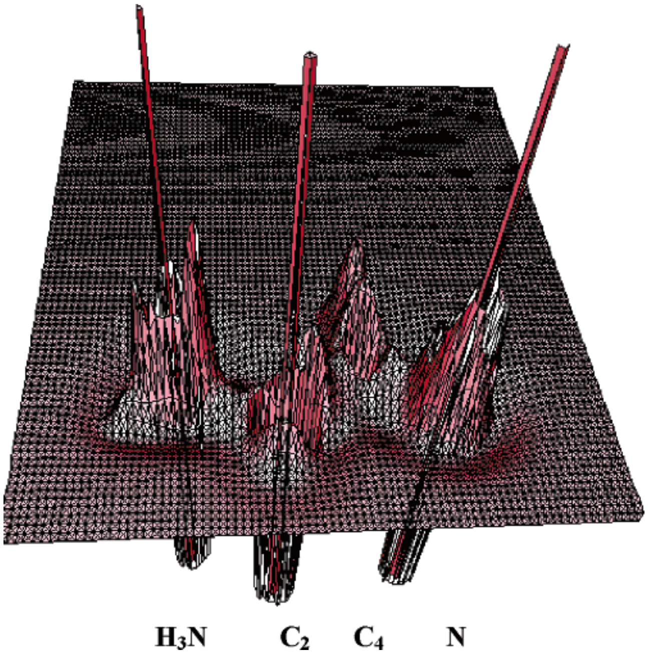


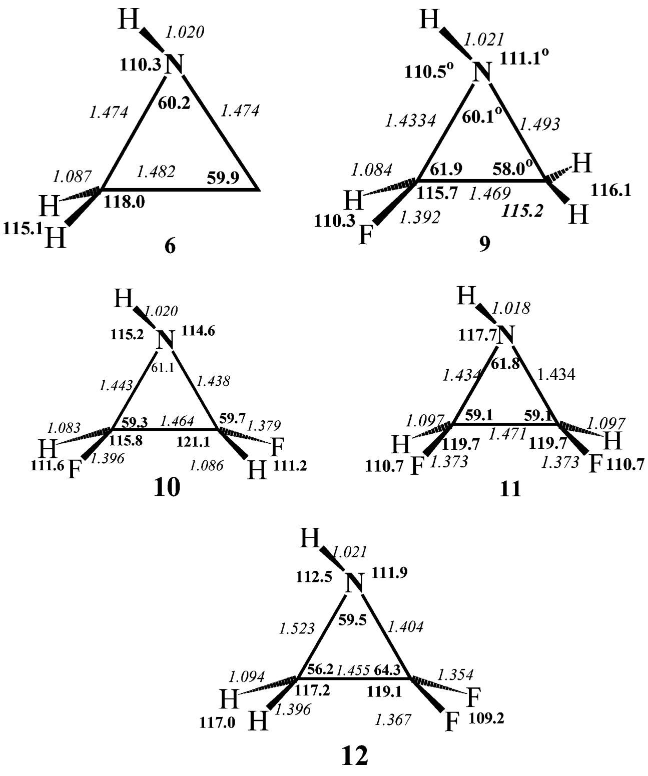
FIGURE 1. Laplacian of the electron density of the transition state for **6** + NH_3. The atomic centers are indicated below.

energy in the transition state. As the leaving group moves further from the reaction center as in **7** or **8**, such stabilization of the transition state is no longer possible.

In a classical S_N2 mechanism, little charge is developed on the central carbon atom. In Menschutkin-type reactions, it is presumed that as the reaction proceeds positive charge development is the province of the originally neutral nucleophile, while negative charge forms on the leaving group. Bader presented results that indicate that this charge distribution is incorrect, and in fact, the carbon reaction center has a partial positive charge.[26] The carbon reaction centers in this study (with the exception of the CHELPG charge for **6**) were all found to have partial positive charges. Inspection of a typical Laplacian of the transition state for the reaction of **6** with NH_3 (Figure 1) demonstrates that, with relatively little bond formation to the incoming nucleophile, the heterocyclic ring has been completely cleaved as evidenced by the virtual absence of electron density between C_2 and the departing amide group. The behavior of the nitrogen heterocycles, thus, closely parallels that of oxygen and sulfur heterocycles.[27]

In a study of the nucleophilic chemistry of thiirane, it was observed that fluorine substitution had a pronounced accelerating influence on the reaction rate as well as the regiochemistry.[4] It was of interest to determine if this effect would extend to aziridines. Fluoroaziridines have been prepared by the reactions of carbenes with imines.[28] The presence of a carbon in 2-fluoroaziridine at a formal oxidation state of an aldehyde, for example, provides potential for synthetic exploitation.

TABLE 5. Calculated Structures. Interatomic Distances (in italics) in Angstroms and Bond Angles in Degrees



The geometries of the fluoroaziridines chosen for this study are presented in Table 5. Only data for the *syn* invertomers of **9** and **11** are given since computations demonstrated that their *anti* stereoisomers were virtually equivalent in energy (different by less than 0.1 kcal mol^{-1}) and geometry. The highly electronegative fluorine prefers to be bonded to a carbon of low electronegativity; the electronegativity of 2s orbitals is greater than that of 2p orbitals.[29] Fluorine thus demands attachment to a hybridized orbital with high p character, while the carbons also require orbitals with similar characteristics in order to accommodate the demands of their small internal ring angles. The tension between these opposing requirements creates additional ring strain. When aziridine is unsymmetrically substituted as in **9** and **12**, the C−N bonds opposite to the carbon bearing fluorine(s) are lengthened with respect to **6**,[30] generating increased ring strain. Since these bonds opposite the site of fluorine substitution are somewhat longer and weakened in the ground state, it might be assumed that this is partially responsible for the regioselectivity of this reaction. These reactions are highly endothermic, however, and application of the Leffler−Hammond Postulate[31] requires that the transition state structure in these reactions assume strong product-like character, invalidating rationalizations based on weakened ground state bonds.

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[26] Bader, R. F. W.; Duke, A. J.; Messer, R. R. *J. Am. Chem. Soc.* **1973**, *95*, 7715.

[27] Recently Hoz and co-workers (Wolk, J. L.; Sprecher, M.; Basch, H.; Hoz, S. *Org. Biomol. Chem.* **2004**, *2*, 1065) computationally studied reactions of three- and four-membered rings of anions, cations, and radicals at the B3LYP/6-31G* level. They found that charge effects were absent. This observation is hardly surprising. Our use of electrostatic energy to rationalize the high reactivity of three-membered heterocycles, after release of ring strain energy had been considered, was applied only to Menschutkin-type reactions, reactions in which charge separation developed in the transition state. For the reactions studied by Hoz, for example, in the S_N2 reaction of $(CH_3)_2N^-$ with *N*-methylaziridine, the negative charge is *dispersed* in the transition state. One would expect the electrostatic energy contribution here to be absent or considerably attenuated.

[28] Yamanaka, H.; Kikui, J.; Teramura, K. *J. Org. Chem.* **1976**, *41*, 3795.

[29] For a discussion of the effects of fluoro substituents on cyclopropane, see ref 7b.

[30] The average $C(sp^3)-N$ bond length is 1.47 Å. March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; p 21.

[31] Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper and Row: New York; pp 197−199.

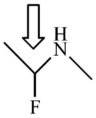
TABLE 6. Calculated[19] Strain Energies of Fluoroaziridines (kcal mol^{-1}) [MP2(Full)/6-31+G(d)]

6	9	10	11	12
27.3	35.6	35.4	39.2	42.9

Clearly a major contributor to the rates of the fluoroheterocycles is relief of ring strain. It has previously been demonstrated that the experimental values for the strain energies of unsubstituted heterocycles can be acceptably reproduced using the method of calculation of Dudev and Lim.[19] To validate this method for fluoro derivatives, a calculation was performed for 1,1-difluorocyclopropane. The value of ring strain energy obtained, 41.9 kcal mol^{-1}, is quite close to the value (42.4 kcal mol^{-1}) obtained using an alternative approach.[32−34]

As expected, the calculated strain energies of the fluoroaziridines provided in Table 6 were higher than that of **6**. Monosubstitution of the aziridine ring causes an increase in ring strain of ca. 8 kcal mol^{-1}. An additional 7 kcal mol^{-1} of ring strain is introduced when an additional fluorine is added to C_2. The energy increase of **12** is partially revealed in the stretched $N-C_3$ and the compressed $N-C_2$ bonds relative to **6**. No additional ring strain is calculated for **10** with respect to **9**, while **11** is less than 4 kcal mol^{-1} more strained.

Table 7 furnishes the free energies of activation, corresponding rates of reaction, and rates relative to acyclic model compound **8** as well as **6**. Attack at C_2 of **9** occurred about four times more rapidly than the reaction of **6**. This observation is consonant with conventional wisdom[5c] that fluorine bonded to a positively charged carbon provides stabilization by means of p−p interactions. This apparent rate acceleration relative to the unsubstituted compound was actually determined to be a significant deceleration when the increased ring strain of **9** relative to **6** is taken into account. In fact, reaction $\mathbf{9_g}$ (attack at C_2 or geminal attack with respect to fluorine), corrected for strain energy, occurred about 35 times slower than that of **8** and some 280 000 times slower than that of **6**.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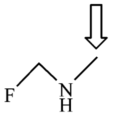
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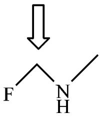
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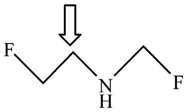
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The importance of differences in attractive electrostatic energies was first investigated. The simplified procedure of summing attached hydrogens into heavy atoms worked acceptably well for unsubstituted amines **6**−**8**. It might be expected that the introduction of fluorine into the molecular framework would result in a significant perturbation of the electrostatics relative to the parent compounds. When computing the energy of separating the developing negative charge of the ring nitrogen from the carbon undergoing attack, the same procedure of incorporating only the attached hydrogen(s) into the charge of the heavy atom was judged unsuitable for use with the fluorinated aziridines since, in addition to the effect of fluorine, the number of hydrogens at C_r (the carbon reaction center) varied from substrate to substrate. It was decided, therefore, to perform a more complete analysis in which the charge at C_r was computed as the sum of the atomic charges of each of its attached atoms, including the effective charge of the neighboring carbon, that is, the sum of its atomic charge and those of attached hydrogens and/or fluorines. To avoid redundancy, the charge of the leaving nitrogen group was computed as before. The results of these calculations are provided in Table 8. Using this method of calculation, the attractive electrostatic energy of the transition state for $\mathbf{9_g}$ attack was greater than those of the other fluoroaziridines, in qualitative accord with the calculations. It was also apparent that, with the exception of some anomalously low values for the electrostatic attractive energy of the transition state of $\mathbf{9_v}$ from AIM and CHELPG calculations, there was little variation of the electrostatic energies of the reactive group of compounds ($\mathbf{9_v}$, **10**, **11**, and **12**) within each method. Fluorine has a leveling effect on the electrostatic attractive energies when positioned at the neighboring carbon.

Fluorine attached to the vicinal position of a carbocation has a destabilizing effect attributed to its powerful electron-withdrawing inductive effect.[6f,35] Our calculations demonstrate that when correction is made for the strain energy of **9**, reaction at C_3 occurs very much faster than with **6** despite partial positive charge at the reaction center. The most reactive aziridine derivative studied was **12**. It was attacked exclusively at C_3. Attack at C_2 of **12** resulted in a change of mechanism and extrusion of a carbenoid species. The rate of this reaction was insignificant relative to the substitution reaction at C_3. The most evident reason for the accelerated rates for reactions $\mathbf{9_v}$ (with attack at C_3 or **v**icinal attack with respect to fluorine), **10**, **11**, and **12** with NH_3 is that the amide leaving group contains at least one fluorine that can provide considerable stabilization by virtue of its powerful electron-withdrawing effect.

When the geometries of the transition states of $\mathbf{9_v}$, **10**, **11**, and **12** were examined, clues as to the accelerations of the reactions relative to that of **6** emerge. First, the atoms other than fluorine attached to the departing nitrogen approached planarity. Second, the C_3-N bond distances were unusually short.[30] Third, the C_3-F bonds were unusually long. A typical example is given in Figure 2 for reaction of $\mathbf{9_v}$. The C_3-N and C_3-F distances are 1.363 and 1.525 Å, respectively. This suggests a transition state structure possessing imine character promulgated by negative fluorine hyperconjugation.[36]

In all cases for the reactive group of compounds, the transition state conformation positions a fluorine (or two in the case of **12**) close to one of the hydrogens of the incoming partially positively charged ammonia moiety. In the transition state geometry for $\mathbf{9_v}$ (Figure 2), these atoms are separated by only 2.080 Å (arrow.) The corresponding distances for **10** and **11** are 2.142 and 2.155 Å, respectively, and for **12**, 2.406 and 2.805 Å. In addition, the C−F bonds are unusually long: $\mathbf{9_v}$ (1.525 Å), **10** (1.525 Å), **11** (1.512 Å), and **12** (1.435 and 1.414 Å (Figure 3). These observations suggest that at least one additional stabilizing effect is at work. While formal H-bonding between N−H and F−C is rare,[37] these calculations strongly suggest that strong dipole−dipole interactions contribute to stabilization of the transitions state.[38]

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(32) Zeiger, D. N.; Liebman, J. F. *J. Mol. Struct.* **2000**, *556*, 83.

(33) Recently the results of calculations at the B3LYP/6-31G(d) level have become available: Khoury, P. R.; Goddard, J. D.; Tam, W. *Tetrahedron* **2004**, *60*, 8103.

(34) For a discussion of the strain energies of geminally substituted fluorocyclopropanes, see: Dolbier, W. R., Jr.; Battiste, M. A. *Chem. Rev.* **2003**, *103*, 1071−1098 and references therein.

(35) Olah, G. A. *Carbocations and Electrophilic Reactions*; Wiley: New York, 1974; pp 55−59.

(36) Rahman, M. M.; Lemal, D. M.; Dailey, W. P. *J. Am. Chem. Soc.* **1988**, *110*, 1964 and references therein.

TABLE 7. Calculation[a] of Relative Rates of Reaction of Substituted Aziridines and Acyclic Amines with Ammonia Including Strain Energy [MP2(Full)/6-31+G(d)//MP2(Full)/6-311++G(d,p)]

	$\Delta H^{\ddagger}$ kcal mol^{-1}	$\Delta S^{\ddagger}$ eu	$\Delta G^{\ddagger}$ kcal mol^{-1}	k_{rel}	$\Delta G^{\ddagger}$ + SE^{b} kcal mol^{-1}	k_{rel} w/ SE^{c}
6	63.4	−14.1	67.6	1.00E + 00	94.9	1.00E + 00
7	71.3	−17.6	76.5	2.97E − 07	101.7	9.75E − 06
8	97.4	−9.6	100.2	1.29E − 24	100.2	1.24E − 04
9 @ C$_2$	63.7	−10.0	66.7	4.44E + 00	102.3	3.54E − 06
9 @ C$_3$	40.6	−9.3	43.4	5.14E + 17	79.0	4.10E + 11
10	40.8	−7.9	43.1	8.76E + 17	78.5	1.02E + 12
11	46.6	−12.3	50.3	4.87E + 12	89.4	9.65E + 03
12 @ C$_2$^{d}	64.1	8.8	61.5	2.94E + 04	104.4	9.94E − 08
12 @ C$_3$	32.0	−7.0	34.1	3.63E + 24	77.0	1.23E + 13
13 @ *C*HFCH$_3$	108.6	8.1	106.2	5.65E − 29	106.2	5.45E − 09
14 @ CH$_3$	85.3	−4.7	86.7	9.76E − 15	86.7	9.41E + 05
15 @ CH$_2$F	109.2	−5.9	111.0	1.70E − 32	111.0	1.64E − 12
16 @ *C*H$_2$CH$_2$F	71.3	−35.1	81.7	4.30E − 11	81.7	4.15E + 09
17	32.1	−34.6	42.4	3.04E + 18	80.2	6.04E + 10

[a] See Supporting Information. [b] SE is the calculated strain energy. [c] The relative rate with respect to **6** when ring strain energy is considered. [d] A change in mechanism occurs (see text.)

TABLE 8. Electrostatic Energies Using Different Methods (kcal mol^{-1}) with All[a] Attached Atoms Summed into the Heavy Atoms

	NBO	AIM	CHELPG	Mulliken
6	−25.6	−68.2	−39.5	−34.2
9$_g$	−22.1	−54.0	−66.8	−28.2
9$_v$	−10.1	−24.1	−5.1	−17.8
10	−9.5	−42.9	−32.6	−24.5
11	−11.7	−42.7	−26.0	−26.9
12	−9.7	−41.9	−28.5	−23.7

[a] The charge on the neighboring carbon after summing its attached hydrogens and fluorines was included in the charge for the carbon reaction center but not for the nitrogen of the leaving group.

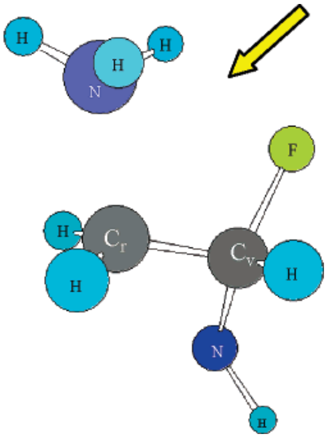

FIGURE 2. Transition state for **9$_v$** with NH$_3$. Selected distances (Å): C$_v$−F, 1.525; C$_v$−NH, 1.363; C$_r$−NH, 2.026; H$_3$N−C$_r$, 1.955; C−C, 1.455.

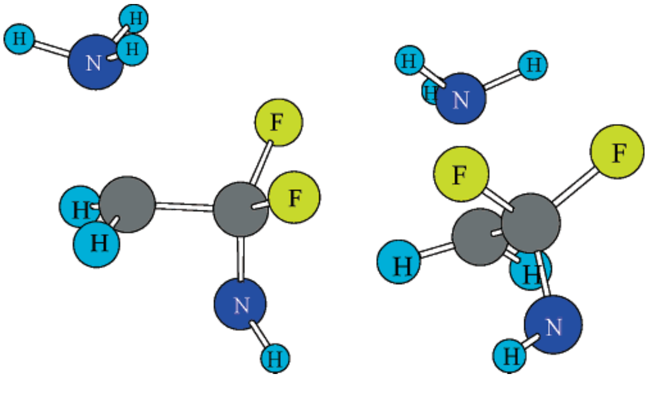

FIGURE 3. Two views of the transition state for the reaction of **12** with NH$_3$. Selected distances (Å): C$_v$−F, 1.435, 1.414; C$_v$−NH, 1.342; C$_r$−NH, 2.072; H$_3$N−C$_r$, 1.928; C−C, 1.455.

The presence to two fluorines at the position neighboring C$_r$ might have been predicted to exert a more profound effect on the reaction rate.[39] The data suggest that the second fluorine competes with the first. With regard to imine formation, the C− N bond distance was the longest of the reactive series of compounds, 1.455 Å, while the C−F distances, 1.435 and 1.414 Å, were the shortest; in order for each fluorine to interact with one of the hydrogens of the forming ammonium ion, the distances of separation from these hydrogens are the longest of the series.

Reactions of **10** and **11** must occur at positions that possess both a fluorine at the reaction center and a fluorine located on the neighboring carbon. An increase in rate was calculated for **10** relative to **9**, although one might have expected the presence of fluorine at the reaction center to make a rate-retarding contribution as was the case for **9$_g$**. The orientation of the fluoro groups is of the utmost importance since **11** is vastly more reactive than **9$_g$**, but considerably less reactive than **9$_v$**. A key difference is that the distance between fluorines in **10** is 3.593 Å, while that for **11** is 2.920 Å. Using NBO atomic charges and dielectric constants of 1.0 and 2.0[40] for **11** and **10**, respectively, an energy difference estimate of about 10 kcal mol^{-1} may be calculated for these transition states using eq 1. Examination of the transition state geometries of **10** and **11**

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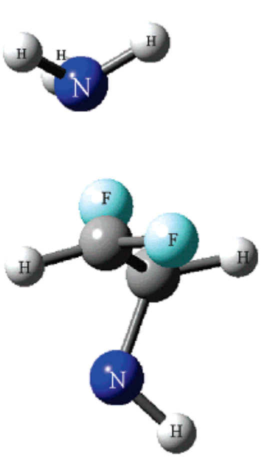
(37) (a) Allen, F. H.; Taylor, R. *Chem. Soc. Rev.* **2004**, *33*, 463. (b) Caminati, W.; Melandri, S.; Rossi, I.; Favero, P. G. *J. Am. Chem. Soc.* **1999**, *121*, 10098. (c) Parsch, J.; Engels, J. W. *J. Am. Chem. Soc*. **2002**, *124*, 5664. (d) Mountford, A. J.; Lancaster, S. J.; Coles, S. J.; Horton, P. N.; Hughes, D. L.; Hursthouse, M. B.; Light, M. E. *Inorg. Chem*. **2005**, *44*, 5921. Most evidence for this type of bonding is negative.

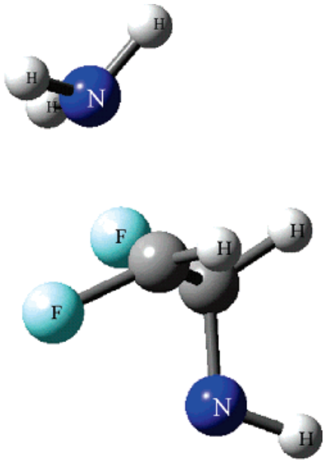
(38) (a) Shimoni, L.; Glusker, J. P.; Bock, C. W. *J. Phys. Chem*. **1995**, *99*, 1194. Ab initio calculations determined the dissociation energy of the CH$_3$F···HNH$_3^+$ to be 13.5 kcal mol^{-1}. This result represents an upper limit for our studies since the transition states in the present study depart from the linear geometry attained in this intermolecular complex. (b) Briggs, C. R. S.; Allen, M. J.; O'Hagan, D.; Tozer, D. J.; Slawin, A. M. Z.; Goeta, A. E.; Howard, J. A. K. *Org. Biomol. Chem*. **2004**, *2*, 732. (c) Snyder, J. P.; Chandrakumar, N. S.; Sato, H.; Lankin, D. C. *J. Am. Chem. Soc*. **2000**, *122*, 544.

(39) One would expect the basicity of the of the amide ions to reflect that of the neutral species for which NH$_3$ > NFH$_2$ > NF$_2$H > NF$_3$. Catalán, J. *J. Org. Chem*. **1999**, *64*, 1908.

reveals a difference between these species in the imine-like moiety. The stereochemistry is such that fluorine and the imine hydrogen are considerably closer in **10** than in **11**. For model compound, $FCH_2CH{=}NH$, the calculated relative stability of the **10**-like orientation was 2.3 kcal mol^{-1} at the MP2(Full)/6-311++G(d,p) level. An additional consideration was the relative stability of the reactant molecules. Uncomplexed **10** was calculated to be 2.5 kcal mol^{-1} more stable than **11**; however, when the actual reactants, dipolar complexes, were compared, the *cis* was found to be about 1.6 kcal mol^{-1} more stable; this observation was consistent with the calculated higher dipole moment of the *cis* compound (4.92 as opposed to 1.55 D). The sum of these contributions to $\Delta\Delta G_{act}$ of these diastereomers gives an estimate of about 14 kcal mol^{-1}, in qualitative agreement with the calculated results.



Transition State for **10**



Transition State for **11**

To gain further insight into the nature of these Menschutkin-type reactions with heterocyclic compounds, acyclic model compounds containing fluorine were studied (Table 7). Relative to nonfluorinated **8**, attack on **13** at the fluorine bearing carbon was calculated to occur at a relative rate of 4.4 × 10^{-5}, again demonstrating that a geminal fluorine has a significant rate-retarding effect. The fact that **13** was calculated to be about 650 times less reactive than $\mathbf{9_g}$ may be indicative of the operation of a steric effect since the alkyl groups are partially pinned back in the transition state of the heterocycle, making nucleophilic attack less obstructed. The profound rate-enhancing effect of a $FCH_2NH^{\ominus}$ leaving group was demonstrated by **14**; relative to **8**, it was found to react almost 10^{10} times faster. When rate acceleration due to ring strain energy release has been removed, $\mathbf{9_v}$, **10**, and **12** are more than 10^5 times more reactive than **14**. Inspection of the transition state geometry of **14** further reinforces our rationalization of transition state stabilization by fluorine. The carbon−fluorine distance is especially long (2.004 Å), and when combined with virtual planarity of the remaining atoms of the leaving group, and the short nitrogen−carbon bond distance of 1.3091 Å, the molecule $HN{=}CH_2$ is approximated (Figure 4).

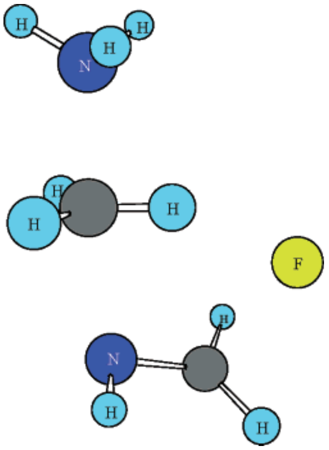


FIGURE 4. Transition state for the reaction of **14** with NH_3.

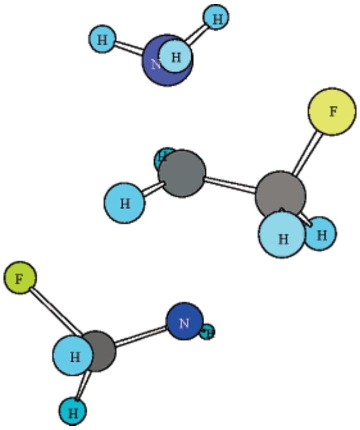


FIGURE 5. Transition state for **16**.

Attack at a fluorine-bearing carbon with the poor $CH_3NH^{\ominus}$ leaving group resulted in a very slow reaction rate for **15**. When the reaction rates of **13** and **15** were compared, the secondary fluoride was found to be over 3 × 10^3 times more reactive, contrary to expectations in conventional S_N2 reactions based on steric arguments. This reactivity difference may be the result of the ability of the additional methyl group of **13** to stabilize the partial positive charge on the carbon reaction center.

Inspection of the topography of the reaction with $\mathbf{9_v}$ reveals that attack occurs at a position that, in addition to possessing an excellent leaving group due to the presence of fluorine at the position next to nitrogen, also presents this vicinal fluorine to the incoming nucleophile. This combined effect was modeled with acyclic compound **16**. Not surprisingly, **16** was found to be extremely reactive, although not quite as reactive as $\mathbf{9_v}$ with acceleration due to ring strain removed. The transition state geometry of **16** is shown in Figure 5. Its leaving group is similar to that of **14**, with a long carbon−fluorine distance (1.610 Å) and a shortened carbon−nitrogen distance of 1.356 Å. It can be hypothesized that stabilization provided by attractive interactions between the remaining fluorine and the two closest hydrogens of ammonia (average distance = 2.338 Å) provides a driving force for the reaction that is supplemented by partial formation of $HN{=}CH_2$ in the transition state. It can be noted that the fluoromethyl moiety of the leaving group is oriented far removed from the remaining fluorine-bearing moiety, probably due to both electronic and steric factors. Comparison of **14** and **16** suggests that the acceleration due to a neighboring

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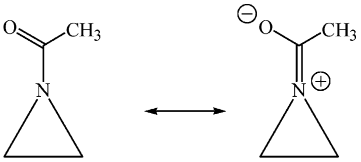
(40) (a) The effective dielectric constant of the molecular framework is assumed to be 2.0. Wiberg, K. B. *J. Org. Chem.* **1999**, *64*, 6387. (b) The gauche conformation of 1,2-difluoroethane is slightly stabilized by less than 1 kcal mol^{-1}. Goodman, L.; Gu, H.; Pophristic, V. *J. Phys. Chem. A* **2005**, *109*, 1223 and references therein. Charge distributions in the transition states differ considerably from that of this ground state molecule.

fluorine group when the effect of the $FCH_2NH^{\ominus}$ leaving group is decoupled is about 4 × 10^3.

As stated previously, aziridines are rather poor substrates for nucleophilic substitution reactions; however, they can be converted into useful synthetic intermediates by means of derivatization in the form of amides or sulfonamides. Such substitution has a profound effect on reactivity; for example, the free energy of activation for **6** was calculated to be lowered from 67.6 to 42.4 kcal mol^{-1} when converted to its *N*-acetyl derivative, a computationally reasonable model compound for derivatives of this general type. This corresponds to a rate acceleration of 3.0 × 10^{18}. Clearly a significant component of this stabilization is the electron-withdrawing ability of the acetyl functionality, lowering the basicity of the departing amide ion. In addition, however, an increase in ring strain for the three-membered heterocyclic amide relative to **6** would be anticipated to increase reactivity. This may be calculated[12] to be 37.8 kcal mol^{-1} compared to 27.3 kcal mol^{-1} for **6**. Thus, strain energy release and stabilization of the leaving group are, on the basis of this calculation, approximately equally important in the rate increase of the amide relative to the amine **6** in this nucleophilic substitution reaction. The additional strain partially eventuates from sp^2 character of the nitrogen of the amide functionality:



17

When compared to the activated aziridine substrate **17**, **9** and **10** reacted with NH_3 somewhat faster; the difluoro compound **12** was even more reactive (Table 7). On the basis of these calculations, fluorination of the aziridine ring appears to be an approach to consider for activation to potentially useful synthetic rates.

Conclusions

As was the case for oxygen and sulfur heterocycles, three-membered nitrogen heterocycle **6** was calculated to be the most reactive unsubstituted compound with ammonia. When ring strain release contributions to the transition state were removed, a reasonable explanation of the residual stabilization of its transition state is its lowered attractive electrostatic energy relative to acyclic model compound **8**.

Substitution of fluorine(s) on the aziridine ring had profound effects on reactivity, regioselectivity, and diastereoselectivity. For **9**, attack occurred exclusively at C_3. The rate of this reaction was 5 × 10^{17} times that of **6**. Geminally disubstituted **12** also reacted exclusively at C_3 with of a rate of 4 × 10^{24} times that of **6**. These regioselective reactions occur in the opposite manner predicted on the basis of carbocation stabilization. The *trans* and *cis* diastereomers of 2,3-difluoroaziridine have vastly different reactivities, although each is considerably more reactive than unsubstituted **6**. The effects of fluorine extend to acyclic systems as well. The major importance of the imine-like leaving group was illustrated with **14** and **16**. Additionally, model compound **16** demonstrated that dipole−dipole interactions between the hydrogen of incoming ammonia and the fluorine vicinal to the position of attack make an important contribution to stabilization of the transition state.

Supporting Information Available: The energies of the reactants, transition states, their Cartesian coordinates as well as the NBO, AIM, CHELPG, and Mulliken atomic charges of the transition states for **9**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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