A Computational Study of the Reactions of Thiiranes with Ammonia and Amines

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The relative rates of reaction of thiirane and thiirane derivatives with NH_3, a series of secondary amines including aziridine, and trimethylamine were determined in the gas phase by means of B3LYP/6-31+G(d)//HF/6-31+G(d) computations and transition state theory. Convergence of the results was selectively tested using the 6-311++G(d,p) basis set. Comparison with MP2/6-31 + G(d)//MP2/6-31G(d) computations was made in model cases. These results are significant in that they supplement the only reported gas-phase experimental study of this type of reaction. The reaction rates of thiirane with secondary amines can best be rationalized by means of an interplay of steric and polarizability effects. While β-halo substituents retard S_N2 reactions in solution, both 2-fluorothiirane and its acyclic model react more than $l0^6$ times faster with NH_3 than the unsubstituted compounds in the gas phase. 2-Fluorothiirane was calculated to react with NH_3 at C_2 by a factor of 0.142 with respect to thiirane itself; attack at C_3 was found to be 3.42×10^6 times faster than the parent compound. 2-Methylthirane reacts with NH_3 at 0. 230 the rate of thiirane with a 12.8-fold regioselectivity for C_3. In the reaction of 2,2-dimethylthirane and NH_3, this preference for C_3 increases to a factor of 124. Ground-state destabilization of *cis*-2,3-dimethylthiirane is sufficient to account for its calculated rate acceleration with respect to the trans isomer.

Introduction

Few reactions are of greater synthetic and mechanistic importance than nucleophilic substitution.[1] When inherently poor leaving groups such as those found in amines, ethers, or thioethers are incorporated into a three-membered heterocyclic ring, an enormous increase in reactivity is observed. Such reactions are important synthetic routes to 2-substituted amines, alcohols, and thiols. While reactions with oxiranes and aziridines have received considerable attention in the literature, the chemistry of nucleophilic attack on thiiranes has been comparatively neglected.[2,3] This is surprising in view of the versatility of the thiol group and its derivatives as synthons for a variety of classes of compounds.[4]

Application of the Menschutkin reaction,[5] attack of an amine or ammonia on a suitable substrate, has proven to be a useful approach for synthesis of amines and quaternary ammonium salts under conditions that minimize polyalkylation. Examination of this reaction using thiiranes would permit exploration of this chemistry within the context of our interest in the chemistry of strained ring compounds (eq 1). Even though most synthetically important reactions are conducted in the condensed phase, a computational investigation in the gas phase appeared attractive.[6] Not only are such calculations considerably less costly than those using solution models, but since gas phase reactants are free of potentially complex interactions with the nearby molecules encountered in solution an assessment of the "intrinsic" factors critical in determining relative reaction rates is possible.

Those types of S_N2 reaction in which charge is dispersed in the transition state have been extensively studied in the gas phase by means of flowing afterglow, tandem mass spectrometry and ion cyclotron resonance

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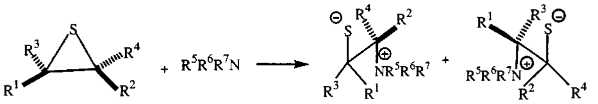

eq 1

spectrometry techniques.[7,8] There is, however, only one experimental gas-phase investigation of the Menschutkin reaction. Yen, Cross, and Saunders used the high translational energy of crossed-beam experiments to demonstrate that the reaction can occur in the gas phase.[9] Such reactions are difficult to study since oppositely charged product ions are required to separate, giving rise to high energy transition states.

Computational Methodology

An SGI Octane or Indigo 2 workstation were used for all computations. Starting geometries for reactants and transition states were determined by means of semiempirical methodology (AM1) using Spartan 5.1.1.[10] The calculations were further refined by ab initio calculations by means of Gaussian 94[11] starting (vide infra) at the HF/6-31G(d) level using a zero point energy correction factor of 0.9135.[12] Thermochemical data were calculated from this program using a temperature of 298.15 K with the route section for a transition state calculation, opt = (ts,calcall,noeigentest), and for a ground state, opt = (freq,calcall.) Initial requirements for ground state and transition state structures were the presence of zero and one imaginary vibrational frequency, respectively. Geometries were determined using GaussView 2.03.[13] Identification of a transition state was further verified by animation of the sole imaginary frequency, and in representative cases (the reactions of thiirane with ammonia, and dimethylamine, and the reactions of ammonia with 2-methylthiirane, 2-fluorothiirane and 2,2-dimethylthiirane) by means of intrinsic reaction coordinate (IRC) calculations. This approach appeared reasonable in view of the high computational expense[14] of an exhaustive IRC analysis for each reaction. For example, for diethylamine, consideration of its four ground state conformations led to finding eleven transition states, each of which would have to have been subjected to an IRC calculation. A conservative estimate for each calculation on the available workstations was 24 h. Support for this approach was provided by the similarity of the geometries of the transition states for related groups of compounds (see Supporting Information.) These geometries were used for a single point energy calculation using the DFT hybrid functionals at the B3LYP level to incorporate electron correlation. Convergence of relative rates of reaction was tested by calculation at higher levels of theory, first at the HF/6-31+G(d) level and finally, for representative reactions, at the HF/6-311++G(d,p) level, with single point energy calculations at the B3LYP level. For a different approach to incorporation of electron correlation, MP2/6-31+G(d)//MP2/6-31G(d) calculations were performed for comparison. Since dipole−dipole complexes were not found for this system,[15] the activation energies were calculated as the difference between the transition state energy and the sum of the energies of the reactants.

When the amine lacked a C_3 axis, more than one approach to thiirane was possible, potentially resulting in more than one transition state. The initial approach was rotated along the forming C−N bond by 120° until no energetically unique approach was generated. The geometry of each such approach formed the starting point for calculation of a transition state energy. Not every approach resulted in locating a transition state.

In addition to modes of approach, amine conformations had to be considered. The majority of the amines studied were conformationally homogeneous. Diethyl and diisopropylamine, however, were found to have four and ten conformations, respectively, using MacroModel 6.0.[16] Consequently, a total of 12 and 30 approaches, respectively, were theoretically possible. Fortunately, taking Curtin−Hammett kinetics[17] into account, calculations were unnecessary on those conformations whose mole fractions were computed to be less than 0.004.

Results and Discussion

For each Gaussian 94 calculation that included a frequency calculation, thermochemical properties were predicted. This was done by separating the partition function into translational, rotational, and vibrational components.[18] The vibrational contribution to the partition function depends on the appropriateness of the harmonic oscilator approximation used in these calculations. Enthalpy and zero point energies are relatively unaffected by anharmonic behavior, while the entropy is considerably more sensitive. Entropy errors introduced in this manner affect the free energy calculation and represent a source of error in calculation of reaction rates. The entropy of activation was calculated as the difference of the entropy of the transition states and the sum of the entropies of the reactants. The enthalpy of activation was the difference of the energies of transition state and the sum of the energies of the reactants (after thermal correction) $-(1)RT$ (or −0.5925 kcal/mol at 298.15 K), since this reaction corresponds to a decrease in the number of moles by one. The free energy of activation was calculated,[19] and used to compute the absolute rate constant from which the relative rates were determined.

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(7) (a) For reactions in which an anion attacks a neutral species, see ref 1a and references therein. (b) For reactions in which a neutral nucleophile attacks a cationic substrate, see Uggerud, E., *J. Chem. Soc., Perkin Trans. 2* **1999**, 1459−1463 and references therein.

(8) Gas phase ab initio studies of thiirane formation by anionic intramolecular attack have been reported. (a) Gronert, S.; Lee, J. M., *J. Org. Chem*. **1995** , 60, 4488−4497. (b) Gronert, S.; Lee, J. M., *J. Org. Chem*. **1995**, *60*, 6731−6736. (c) Han, I.-S.; Kim, C. H.; Kim.; CK.; Lee, B.-S.; Lee, I., *J. Comput. Chem*. **1997**, *18*, 1773−1764.

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(10) Spartan Version 5.5.1: Wave function Inc., 18401 Von Karman Avenue, Suite 370, Irvine, CA 92612.

(11) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A, *Gaussian 94*, Gaussian, Inc., Pittsburgh, PA, 1995.

(12) Foresman, J. B.; Frisch, A. E. *Exploring Chemistry with Electronic Structure Methods*, 2nd ed.; Gaussian, Inc., Pittsburgh, PA, 1996; p 64.

(13) Gaussian, Inc., Carnegie Office Park, Building 6, Suite 230, Carnegie, PA 15106.

(14) For example, for diethylamine, consideration of its four ground state conformations led to discovery of eleven transition states, each of which would have to have been subjected to an IRC calculation. A conservative estimate for each IRC calculation on the available workstations was 24 h.

(15) This is not the case for the reaction of NH_3 with the more polar CH_3Cl where the dipole−dipole complex lies slightly below the energy of the reactants.[6a,b] In a recent ab initio study of the reaction of NH_3 and CH_3Cl, dipole−dipole complexes were neglected: Hori, K.; Aboud, J.-L. M.; Lim, C.; Fujio, M.; Tsuno, Y. *J. Org. Chem*. **1998**, *63*, 4228−4234.

(16) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caulfield, C.; Chang, F., Hendrickson, T.; Still, W. C., *J. Comput. Chem*. **1990**, *11*, 440−467.

(17) (a) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; pp 629−634. (b) Seeman, J. I. *Chem. Rev*. **1983**, *83*, 84−134

(18) See for example, Janz, G. J. *Thermodynamic Properties of Organic Compounds: Estimation Methods, Principles and Practice*; Academic Press: New York, 1967

(19) Lowry, T. H.; Richardson, K. S., *Mechanism and Theory in Organic Chemistry*, 2nd ed.; Harper & Row Publishers: New York, 1981; p 188.

Table 1. Relative Rates of Reaction of Nucleophiles with Thiirane at 298.15 K from B3LYP/6-31+G(d)//HF/6-31+G(d) Calculations

NH_3	1.00
CH_3NH_2	2.04×10^3
$(CH_3)_2NH$	9.61×10^3
$(CH_3CH_2)_2NH$	79.0
$[(CH_3)_2CH]_2NH$	0.367
$[(CH_3)_3C]_2NH$	1.28×10^{-5}
	562
$(CH_3)_3N$	818

Reactions with Thiirane. The most cost-efficient method of calculation was determined to be B3LYP/6-31+G(d)//HF/6-31+G(d) (vide infra.) Although computational time is a function of how far the starting geometry differs from that of the final structure, this approach consistently produced acceptable results in a fraction of the time required for MP2/6-31+G(d)//MP2/6-31G(d) computations. The time required to perform the MP2 transition state calculation for the reaction of ammonia and thiirane, for example, was more than eight times that of the chosen method.

Table 1 compares the rates of reaction of a series of secondary amines with that of ammonia.[20] The reaction rates span a range of 10^9. As alkyl substitution of an amine increases, so does its nucleophilicity as reflected in its ability to contribute to stabilization of the transition state by its greater polarizability. Increasing as well, but providing a rate retarding influence, is steric bulk. Alkyl substitution of the parent compound, ammonia, greatly increases nucleophilicity. Dimethylamine is ca. 10^4 times more reactive. The relative reactivity of the remaining dialkylamines is consistent with relative rate being largely determined by the steric bulk of the attached substituents. The lowest energy transition state for each secondary amine was found to be that in which the N−H bond was directed toward the thiirane framework as the electron pair of nitrogen approaches to form the new C−N bond. When this approach is structurally precluded in the example of trimethylamine, the rate exceeds that of diethylamine, demonstrating that amine nucleophilicity can be more important than nonbonded interactions. In accord with this observation, even though steric retardation is significant for the two largest members of Table 1, considerable nucleophilicity is expressed; the reaction rate of diisopropylamine was diminished to only about one-third that of ammonia. Aziridine was calculated to react about 17 times slower than an acyclic analogue, dimethylamine. Aziridine should encounter diminished nonbonded interactions upon approach to thiirane relative to dimethylamine since the groups attached to nitrogen are pinned back with respect to dimethylamine. On the basis of steric effects, aziridine would be expected to react faster. Its decreased relative reactivity may be ascribed to the lowered nucleophilicity of the heterocyclic base due to more s character in the orbital bearing the electron pair relative to its acyclic analogue.

Table 2. Regiospecificity and Relative Rates of Reactions with 2-Methylthiirane at 298.15 K from B3LYP/6-31+G(d)//HF/6-31+G(d) Calculations.

nucleophile	C_3/C_2 substitution	relative total rate
NH_3	12.79	1.00
CH_3NH_2	69.68	1.58×10^3
$(CH_3)_2NH$	19.09	932
$(CH_3)_3N$	268.2	3.87

Regioselectivity. Over 50 years ago Snyder and coworkers[21] studied the reaction of acyclic secondary amines and piperidine derivatives with 2-methyl- and 2,2-dimethylthiirane in the condensed phase. They concluded, based on a color reaction and the high yield formation of sulfenyl iodides, that attack occurred predominantly, if not exclusively, at the less-hindered position of the thiirane. Acceptance of this mode of attack was not universal; Turk,[22] however, demonstrated by ^1H NMR that the product isolated from the reaction of dimethylamine and 2-methylthiirane corresponded to attack at C_3.. Recently Dong[3a] obtained good yields of the products of substitution at C_3 when 2,2-dimethylthiirane and 2,2-dicyclohexylidenethiirane were heated with several heterocyclic amines without solvent.

Table 2 presents the results of computations of the regioselectivity of an increasingly bulky series of amines on 2-methylthiirane in the gas phase at the B3LYP//6-31+G(d)//HF/6-31+G(d) level at 298.15 K. Each amine was found to react considerably faster at C_3. The monotonic progression of selectivity with increasing bulk is broken by dimethylamine. Inspection of the transition state geometries for the approaches of dimethylamine to C_2 shows that they are relatively unhindered. Examination of the individual rates for reaction of methylamine and dimethylamine at C_2 demonstrates that the reaction of the latter is calculated to be 2.08 times faster presumably due to its higher nucleophilicity. On the other hand, methylamine is somewhat more reactive (a factor of 1.76) than dimethylamine at C_3. This is an instance of rate retardation due to a substituent at the vicinal position, behavior previously observed in the condensed phase for S_N2 reactions in which anions react with neutral substrates.[1d] This effect is expressed even with the small nucleophile, ammonia, whose calculated rate of reaction of ammonia with thiirane is 4.69 times faster than its reaction with 2-methylthiirane at C_3. The seemingly anomolous regioselectivity of dimethylamine is the result of the subtle interplay of two rather small regiochemical effects working in opposition. Considering its bulk and inability to present a more favorable side for approach to the reaction center due to its C_{3v} symmetry, trimethylamine was calculated to react with 2,2-dimethylthiirane 270 times faster at C_3 than C_2.

The effect of the presence of methyl groups at the neighboring position may be assessed by comparison of the relative reaction rates for a given amine with thiirane as opposed to 2-methylthiirane. Ammonia, methylamine, dimethylamine, and trimethylamine are calculated to react 4.69, 5.72, 47.2, and 1.08×10^4 times faster with thiirane, respectively, than with 2-methylthiirane at C_3. For reaction at C_2, this series of nucleophiles, the respective calculated rate ratios are 60.0, 399, 902, and

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[20] Reactions with primary amines have been previously reported: Banks, H. D.; White, W. E. *Arkivoc (Online Ed.)* **2000**, *1*, 153−158.

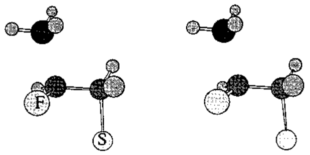
[21] Snyder, H. R.; Stewart, J. M.; Ziegler, J. B. *J. Am. Chem. Soc.* **1947**, *69*, 2672−2674.

[22] Turk, S. D.; Louthan, R. P.; Cobb, R. I.; Bresson, C. R. *J. Org. Chem.* **1964**, *29*, 974−975.

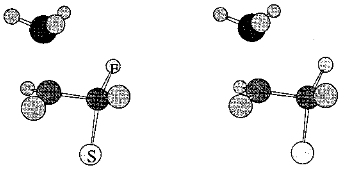
2.47 × 10^5. Unfavorable nonbonding interactions have larger rate retarding effect at the reaction center, but are clearly important at the vicinal position, especially in the case of large nucleophiles.[23] This effect is augmented when an additional methyl group is found at this position. The overall reaction rate for thiirane is more than 900 times that of the C_3 position of 2,2-dimethylthiirane.[24a]

Because hydrogen and fluorine are often assumed to be isosteric (the van der Waals radii are 1.20 and 1.35 Å, respectively), the effects of the significant differences in electron distribution due to replacement of hydrogen by fluorine can be studied directly.[25] Perhaps the most stunning result of this investigation was the finding that 2-fluorothiirane reacts with ammonia at C_3 at 3.420 × 10^6 times the rate of the reaction with thiirane. The rate at C_2 is 0.142 that of thiirane, indicating a huge regioselectivity of more than 10^7. Calculations for the acyclic analogues, diethyl sulfide, and its mono α-fluoro derivative show the latter to have an acceleration of ca. 10^6 when attack occurs at the position analogous to C_3 of 2-fluorothiirane· There are no reported experimental examples of reactions of this type.[26] Given the geometric requirements of the S_N2 reaction, the thiirane derivative necessarily has the C−F bond in a gauche-like orientation with respect to the forming bond between C_2 and NH_3. This requires the nitrogen of the positive dipole and fluorine to be 2.90 Å (2.76 Å from the MP2 calculation) apart. This relatively close distance gives rise to favorable dipole−dipole interactions on the way to the transition state, and probably formation of a hydrogen bond in the transition state.[27] It is noteworthy that the dihedral angle formed by the acyclic analogue approaches the optimal 0° (8.03°), but the N−F distance is considerably greater. Unlike the acyclic compound, the heterocycle has the leaving group bonded to the moiety that is undergoing attack; thus some of the energy required for separation of oppositely charged species is already built into the bonding scheme. To obtain a qualitative description of the nature of this reaction, Mullikan charges, the default atomic charge calculations, for each regiotopic transition state were examined. The incautious use of Mullikan charges can lead to difficulty. For example, several years ago, Tidwell[28] performed ab initio calculations that allowed comparison of Mullikan, Natural Bond Order (NBO) and Bader charges for substituted ketenes, allenes, diazomethanes, diazirines and cyclopropenes; at the HF/6-31G(d)+ZPE//HF/6-31G(d) level the NBO charges were determined to be most reasonable in terms of the electronegativity of the substituents, with the Mullikan charges correlating well, considerably better than the Bader charges. More recently, Bruns and co-workers[29] found that GAPT carbon charges obtained from MP2/6-311++G(3d,3p) calculations provided better agreement with the experimental mean dipole moment derivatives for CO, CO_2, COS, and CS_2, with a correlation coefficient of 0.9990, than the Mulliken, Bader, or CHELPG charges, with correlation coefficients of 0.9778, 0.9841, and 0.8443, respectively.

Table 3. Comparison of the Transition States for Attack at the Regiotopic Positions of 2-Fluorothiirane



Mulliken charges		Distances		Angles	
C_3	-0.419	N-C_2	1.91 A	NC_2S	153 °
C_2	0.304	C_2-S	2.47	C_2C_3S	97.0
S	-0.540	C_3-S	1.83	FC_2C_3	118
F	-0.256	N-S	4.27	HC_2C_3	120
N	-1.18	N-C_3	2.73		
		C_2 F	1.31		



Mulliken charges		Distances		Angles	
C_3	0.236	N-C_3	1.96 A	NC_2S	153 °
C_2	0.394	C_3-S	2.38	C_3C_2S	93.8
S	-0.464	C_2-S	1.78	HC_2C_3	109
F	-0.367	N-S	4.22	HC_2C_3	115
N	-1.17	N-C_2	2.74		
		C_2F	1.38		

If one examines the Mullikan charges in the transition states for the regiotopic processes (Table 3), there are several features that suggest significant energy differences. In the case of attack at C_2, positive charge is concentrated on the reaction center and nitrogen, while fluorine, which has a Mullikan charge of −0.352 in a reasonable model compound, 1-fluoro-1-(ethylthio)ethane, has become more positive, assuming a value of −0.256 in the transition state. Since this electron density release from fluorine to the reaction site must take place by means of the sigma framework, this requirement necessarily entails a significant energy investment since fluorine is the most electronegative element. The situation is quite different when attack occurs at C_3. The presence of the fluoro group in this case causes the positive charge of the transition state to be distributed not only at nitrogen and the carbon under attack, but also on the vicinal carbon. Delocalization of positive charge is clearly a significant contributor to overall

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(23) Reference 18, pp 343−345.

(24) A referee suggests that (a) the great reactivity of fluorothiirane at C_3 can also be explained in VBCM terms as resulting from stabilization of the excited state of the reactants by the fluorine dipole; the slower attack at C_2 was partially attributed to filled orbital repulsions involving F_{2p} lone pairs and (b) that the rate reduction of the reaction of ammonia with thiirane upon geminal disubstitution was partially rationalized by the observation that steric hindrance should increase as the CH_3−C−CH_3 angle decreases upon ring opening with the accompanying diminution of s-character in the bond.

(25) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1991.

(26) (a) Hine, J.; Brader, W. H. *J. Am. Chem. Soc.* **1953**, *75*, 3964. While not directly comparable to the present results, the rates of S_N2 reactions of sodium phenoxide with bromoethane in methanol decreased somewhat with β-substitution by a fluoro, chloro, or bromo substituent. (b) Lim, C.; Kim, S.-H.; Yaoh, S.-D.; Fujio, M.; Tsuno, Y. *Tetrahedron Lett.* **1997**, *38*, 3243−3246. Separation of the reactions of 1-aryl-1-bromoethanes with pyridine in acetonitrile into S_N1 and S_N2 contributions demonstrated that the S_N2 reaction was retarded by electron-withdrawing substituents.

(27) Hudlický, M., *Chemistry of Organofluorine Compounds*; Ellis Harwood Ltd.: Chichester, UK., 1976; p 546.

(28) McAllister, M. A.; Tidwell, T. T. *J. Org. Chem.* **1994**, *59*, 4506−4515.

(29) de Oliveira, A. E.; Guadagnini, P. H.; Haiduke, R. L. A.; Bruns, R. E., *J. Phys. Chem. A* **1999**, *103*, 4918−4924.

Table 4. Relative Rates of Reaction of NH_3 and Amines with Thiiranes at 298.15 K

reaction	relative rate from B3LYP/6-31+G(d)// HF/6-31+G(d) calculations	relative rate from B3LYP/6-311++G(d,p)// HF/6-311++G(d,p) calculations	relative rate from MP2/6-31+G(d)// MP2/6-31G(d) calculations
thiirane + NH_3	1.00	1.00	1.00
2-methylthiirane at C_2 + NH_3	0.0167	0.0293	1.15×10^{-5}
2-methylthiirane at C_3 + NH_3	0.213	0.215	1.06×10^{-3}
2,2-dimethylthiirane at C_2 + NH_3	0.000581		
2,2-dimethylthiirane at C_3 + NH_3	0.0723		
cis-2,3-dimethylthiirane + NH_3	0.00703		1.35×10^{-4}
trans-2,3-dimethylthiirane + NH_3	0.00126		1.29×10^{-5}
2-fluorothiirane at C_2 + NH_3	0.142	0.120	1.88×10^{-4}
2-fluorothiirane at C_3 + NH_3	3.42×10^{6}	2.72×10^{6}	1.14×10^{8}
thiirane + Me_2NH	9.61×10^{3}	2.56×10^{4}	1.82×10^{7}

stabilization for reactions run in an environment in which those dipolar interactions from the neighboring molecules that would be found in the condensed phase are nonexistent. The transition state for the more reactive position is also stabilized by the fact that the negative charge developed on sulfur is palpably diminished relative to that produced in the regiotopic attack. Charge separation in the transition state which represents the most costly energy requirement of the Menschutkin reaction is considerably reduced when the positive and negative charge is dispersed in this manner during attack at C_3. Similar conclusions are reached if the Natural Population Analysis (NPA) or CHELPG methods are used to calculate the atomic charge. The absolute values of charge on sulfur differ; however, in all cases, sulfur is consistently less negatively charged in the transition state resulting from attack at C_3 as opposed to that at C_2 [(−0.429 compared to −0.527 (NPA) and −0.610 compared to −0.686 (CHELPG).] [24a]

Reactions with Ammonia. The relative rates of several substituted thiiranes are compared in Table 4. Both positions of 2-methylthiirane are less reactive than thiirane itself, although as stated above, C_3 is preferentially attacked. Geminal disubstitution results in a significant rate reduction relative to thiirane, although it is interesting to note that reaction at the substituted position is about four times faster than for the analogous position of 2-methylthiirane. This result is inconsistent with an interpretation using steric effects although the distance between the nitrogen and the reacting carbon is somewhat longer, 2.02 Å for 2,2-dimethylthiirane as opposed to 1.95 Å for 2-methylthiirane. When steric effects are considered, this rate ratio would be expected to increase considerably. Examination of the respective Mullikan charges indicates that in attack at C_2 for the dimethyl compound the methyl groups are able to assume considerably more of the developing positive charge than the smaller homolog; each methyl has a charge of +0.203 while the sole methyl group in the latter case has assumed a charge of only 0.112. The ability to minimize charge separation is clearly an important factor in stabilizing the transition state in the gas phase.[24b]

The relative rates for the diastereomers of 2,3-dimethylthiirane may be considered to be the result of a contribution from an attack at a position bearing a methyl group, derived from 2-methylthiirane with attack at C_2, and a contribution from attack at a position in which there is a vicinal methyl group, 2-methylthiirane with attack at C_3. The product of these two relative rates is 0.00355 which is about the average of the calculated rate constants for the diasteromeric pair. Of the 2,3-dimethylthiirane diastereomers, the cis isomer is found to react with ammonia 5.60 times faster than the trans and 0.00703 times the rate of thiirane. The difference in rate between the cis and trans isomers was calculated to be due to ground-state destabilization of the former.

Computational Method Selection. The goal of this investigation was to calculate reasonable relative rate constants for the reaction of thiianes with ammonia and amines in the gas phase using the most cost-efficient computational methodology. Accordingly, a relatively low level basis set, 6-31G(d), was utilized for a restricted Hartree−Fock calculation. The B3LYP method was used to incorporate electron correlation into these transition state structures.[30] For a given thiirane, the relative rates of reaction with a series of nucleophiles appeared reasonable; however, when the rates of reaction of substituted thiiranes for a given nucleophile were compared with those for the parent compound, methyl substitution produced unreasonably high rate retardations. This observation prompted calculations using larger basis sets. When the calculations were repeated using the 6-31+G(d) basis set, followed by a single point energy B3LYP calculation, the disparity between the relative rates of reaction of thiirane derivative could be rationalized. To determine if the results for the relative rates have converged at the B3LYP/6-31+G(d)//HF/6-31+G(d,p) level, the higher level 6-311++G(d,p) basis set was used for selected reactions. The results are provided in Table 4. The relative rates for the reactions of the regiotopic positions of 2-fluorothiirane agree quite well with those at the lower level of theory, but the value obtained for dimethylamine is almost three times higher. While it is clear that additional refinements can be made in the values for the relative rate employing this larger basis set, they are not sufficiently dramatic to warrant the considerably greater investment of computational time. Calculations for this series of reactions at the B3LYP/6-31+G(d)//HF/6-31+G(d) level appears to be the best compromise of computational cost and accuracy.

To assess the appropriateness of the computation with respect to incorporation of electron correlation, selected reactions that had been subjected to the B3LYP/6-31+G-(d)//HF/6-31+G(d) method were initally chosen subjected to MP2/6-31+G(d)//MP2/6-31G(d) calculations. Acceptable qualitative agreement, with the exception of the reaction of thiirane with dimethylamine, was achieved for the relative rates obtained when MP2/6-31+G(d) was used for geometry optimization and transition state energies. The results are presented in Table 4. Attack at

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either position of 2-methylthiirane is slower than that calculated for thiirane, with high regioselectivity for attack at the C_3 position in agreeement with the previous result. The large acceleration calculated for the unsubstituted position of 2-fluorothiirane is an order of magnitude higher, a difference that would be experimentally insignificant in most cases. In addition, *cis*- and *trans*-2,3-dimethylthiirane are considerably less reactive than thiirane, with the former being the most reactive as was the case for the DFT single point energy calculation. There is considerable disparity between the relative rate for dimethylamine and that found by the prior calculation. The MP2 result appears to be quite inflated, possibly due to an overestimate of the stabilization of the incipient ammonium ion by the attached electron-donating groups.

The geometries of the transition states for each method of calculation were determined (see Supporting Information.) To assess the validity of the data, the bond length of the retained carbon−sulfur bond was measured in each case. The values obtained regardless of the method were all close to the expected value of 1.80 Å.[31] More than one entry for a particular nucleophile indicates that more than one approach of the nucleophile to the amine produced a unique transition state and, in the case of diethylamine and diisopropylamine, that more than one conformation of the amine reacted at a significant fraction of the total rate. The dihedral angles refer to that formed by one of the atoms attached to nitrogen, nitrogen, the reaction center, and the vicinal carbon. Departure of one of the three angles from an absolute value of 180° is a measure of how far the orientation about the forming carbon−nitrogen bond differs from a staggered orientation. Because of the geometry of the strained heterocyclic substrate, the angle formed by the incoming nitrogen, the reaction center, and the leaving sulfur atom departed from the trigonal bipyramidal angle of 180°. The average angle for the compounds examined by the MP2 calculation was 156° and only slightly smaller for the B3LYP//HF (155°.) For this same group of compounds, considerable bond breaking was found to have occurred. The distance between the departing sulfur and the reacting carbon had increased considerably to 2.443 and 2.448 for the MP2 and B3LYP//HF methods, respectively. The MP2 transition state required the nucleophile to approach closer to the reaction center; i.e., 1.81 as opposed to 1.92 Å.

General agreement of the B3LYP/HF and MP2 results in most cases was found. Descrepancies may be due to the observation that MP2 calculations can overestimate the effect of electron correlation.[32] Since the latter calculations are several times slower, B3LYP/HF was determined to be the approach of choice.

Conclusions

The reaction of thirane and some of its derivatives with ammonia and amines was investigated in the gas phase by means of ab initio calculations. It was determined that the B3LYP/6−31 + G(d)//HF/6−31 + G(d) level provided acceptable results at a reasonable computational cost. The reaction was found to be quite sensitive to polarization and steric effects due to the development of a dipolar transition state in the absence of the stabilizing forces found in the condensed phase. Rate retardation upon methyl substitution on the thiirane, and the remarkable reactivity of 2-fluorothiirane at C_3 are evidence for this analysis of the results. It has been possible to determine the relative rates of an S_N2 reaction between neutral partners that would be difficult to study experimentally.

It is well-established that the Menschutkin reaction is quite responsive to steric effects.[33] In the original study of the reaction of triethylamine with iodoethane, change from a less polar to more polar solvent resulted in rate acceleration. This observation is consistent with a transition state in which there is considerable charge separation in the transition state. Since the intrinsic relative rates of reaction of amines with thiiranes have been derived in the present study, it would be useful to assess solvent effects by comparison to experimental data. Unfortunately, while these studies should prove straightforward, the literature only contains kinetic results for the reactions of aliphatic amines and a few simple haloalkanes.[34] A discussion of the reasons for the huge rate acceleration of thiiranes relative to model acyclic compounds will be addressed in a future report.

Supporting Information Available: Z-matrixes and tables of transition state geometries are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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