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A Computational Study To Elucidate the Extraordinary Reactivity of Three-Membered Heterocycles in Nucleophilic Substitution Reactions

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The accelerated rates of small-membered heterocycles relative to acyclic analogues are typically rationalized solely in terms of relief of ring strain. The relative rates of attack of ammonia on oxirane, oxetane, thiirane, and thietane were determined computationally in the gas phase at the MP2(Full)/6-31+G(d) level with respect to the model acyclic compounds methoxyethane and thiomethylethane. Because the cyclic ether and thioether pairs have very similar strain energies, they should react at similar rates by the S_N2 mechanism if the degree of strain energy release in the transition state is approximately equal. The reactivity of the four-membered rings could be explained almost entirely by relief of strain. The three-membered rings reacted at rates at least 10^6 times faster than calculated from ring strain considerations alone. The electronic distribution of the transition states was determined using AIM methodology and found to indicate that bond cleavage was virtually complete, while bond formation was incomplete. Calculation of atomic charges by the Mulliken, AIM, CHELPG, and NBO methods indicated that positive charge at the reaction center was significantly lower for the three-membered rings than other members of the series. A simple electrostatic model identified differences in energy sufficient to account for the observed rate acceleration. The unique topological features of a three-membered ring make it possible for the partially negatively charged oxygen or sulfur to reduce the positive charge on the reaction center.

Introduction

Nucleophilic substitution has long been recognized as one of the most important reactions in synthetic organic chemistry. Because of their predictable regio- and stereochemistry, reactions proceeding through the S_N2 mechanism have received considerable attention. The ease of displacement of the leaving group plays a significant role in determining the reactivity of a given substrate; however, even compounds that contain extremely poor leaving groups such as ethers, amines, or thioethers are reactive and synthetically useful if these functional groups are structured in such a manner that the heteroatom is incorporated into a three-membered ring.[1] Relief of ring strain in the transition state is typically cited as the sole source of the increased reactivity of heterocycles with nucleophiles relative to acyclic analogues.[2]

Over a decade ago, however, it was noted that ring strain alone is insufficient to account entirely for rate increases in S_N2 reactions relative to suitably chosen acyclic model compounds. Lillocci found the rate of the cleavage reaction of an aziridinium triflate with acetonitrile in the presence of *N*-ethyldiisopropylamine to be at least 10^3 times faster than that of the corresponding azetidinium salt despite similar ring strain energies.[3,4] This phenomenon has also been observed in nucleophilic cleavage of these ions by sodium methoxide.[5] Recently, Hoz recognized that an "additional factor," as yet uncharacterized, must be included to explain the high computed reactivity of anionic nucleophiles with three-membered relative to four-membered heterocycles.[6] Although Houk and co-workers[7] have recently proposed that orbital interactions through-bonds are responsible for the large rate enhancement in cleavage of three- with

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respect to four-membered rings, the present investigation was designed to attempt to discover an alternative explanation of this rate increase in terms of effects, herein named *disjoined* effects, present for three- but not four-membered rings after strain relief in the transition state has been taken into account.

We have been interested[8,9] in the study of the relative rates of the reactions of small ring heterocycles with amines. These Menschutkin-type reactions are examples of the general type of S_N2 reactions in which an uncharged nucleophile reacts with an uncharged substrate. Charge separation occurs along the reaction coordinate as the nucleophile assumes a partial positive charge and the heteroatom a partial negative charge. Due to extreme endothermicity occasioned by separation of developing opposite charges in the transition state in the absence of stabilizing intereactions with solvent, for example, attempts to gain a fundamental understanding of this reaction in the gas phase have been limited to one experimental study.[10] This reaction type can be contrasted with the extensively studied[11] gas-phase "anionic" S_N2 reaction, exemplified by the attack of bromide ion on methyl chloride. Because Menschutkin-type reactions[12] are of considerable synthetic importance in solution, a fundamental understanding of this chemistry in the absence of a potentially complex solvent effect is desirable.[13] Computational studies combining an appropriate method and basis set of reasonable size are a cost-effective approach to elucidating the mechanistic parameters.[14]

Oxirane (**1**) and oxetane (**2**) have nearly the same ring strain energies, 27.3 and 25.5 kcal/mol, respectively, while for thiirane (**3**) and thietane (**4**) these values are 19.8 and 19.6 kcal/mol, respectively.[15] These pairs of
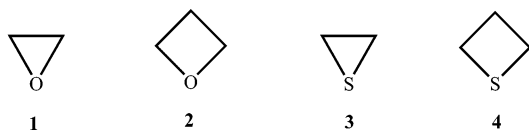
compounds offer an opportunity to address the question of whether ring strain relief is largely responsible for their rates of reaction with nucleophiles. In this investigation, we undertook a computational investigation of the rates of reaction of each of these compounds with ammonia in the gas phase. In the absence of solvent effects, the results may be interpreted in terms of the intrinsic properties of the reaction. To assess the effect of ring strain, the rate of reactions with acyclic model compounds were also investigated.

TABLE 1. Strain Energies and Verification of Computational Method (kcal/mol)

	expt[15]	MP2(Full)/6-31+G(d)// MP2(Full)/6-31+G(d)	B3LYP/6-31+G(d)// B3LYP/6-31+G(d)
1	27.3	26.1	31.2
2	19.8	19.3	20.8
3	25.5	26.3	28.8
4	19.6	23.1	22.1

Computational Methods

The computations were performed in the gas phase using Gaussian 94.[16] Clearly a method that incorporates electron correlation is required for these studies of nucleophilic displacement reactions. The 6-31+G(d) basis set which includes diffuse functions to accommodate the lone pairs and anionic species found in these reactions was chosen. The small differences in results for selected calculations at the 6-311+G-(2d,p) level did not justify the additional computational cost. Two methods, B3LYP and MP2(Full), were evaluated in terms of their ability to reproduce the reported strain energies of the heterocycles studied using the method of Dudev and Lim.[17] Zero-point correction factors of 0.9804 and 0.9646 were used, respectively.[18] As can be gleaned from Table 1, the MP2(Full) method agreed more closely with the experimental values and was selected for the subsequent rate calculations.

Transition states and ground states were identified by the presence of one and zero imaginary frequencies, respectively. Transition states were further corroborated by animation of the imaginary frequency using GaussView 2.03[19] and by means of intrinsic reaction coordinate (IRC) calculations to illustrate that the calculated structure was found on the potential energy surface connecting the reactants and the products.

The strain energy of a cyclic molecule was measured relative to a suitable acyclic analogue, methoxyethane or thiomethylethane. The most stable conformation, initially obtained by means of an AM1 semiempirical conformational search, was used for computations for the acyclic compounds. One of the difficulties inherent in calculating relative rates of cyclic with respect to acyclic compounds is that there are no perfect acyclic models for cyclic compounds. Dimethyl ether and dimethyl thioether were rejected as models even though they possess the correct number of carbon atoms as oxirane and thiirane because they lack secondary carbons. The reactions of ammonia at the secondary carbons of methoxyethane and thio-

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TABLE 2. Calculation of Relative Rates of the Reactions of Heterocycles and Acyclic Analogues with NH₃.

	$E_{gs}{}^a$	$E_{ts}{}^b$	$\Delta E^\ddagger$	$S_{gs}{}^c$	$S_{ts}{}^c$	$-T\Delta S^{\ddagger\,d}$	$\Delta G^{\ddagger\,d}$	k_{rel}
oxirane	−209.6025972	−209.5336137	43.2878626	82.151	71.408	3.2030	46.4909	1.8042E+23
oxetane	−248.7422803	−248.6638302	49.2281665	97.301	75.003	6.6481	55.8763	2.3999E+16
MeOEt	−249.9219699	−249.8110204	69.6219194	117.958	87.084	9.2051	78.2342	1.0000
thiirane	−532.2316819	−532.1670415	40.5624629	85.553	73.605	3.5623	44.1248	1.8042E+23
thietane	−571.3713285	−571.2932221	49.0125781	91.542	77.997	4.0384	53.0510	4.6595E+15
MeSEt	−572.5409791	−572.4348702	66.5843876	121.844	93.517	8.4457	74.4373	1.0000

^{a} Corrected energy in hartrees of the dipolar complex for the reactions with the heterocycles of of the separated reactants for the acyclic reactions. ^{b} Corrected energy in hartrees of the transition state. ^{c} In cal mol⁻¹ K⁻¹. ^{d} In kcal mol⁻¹.
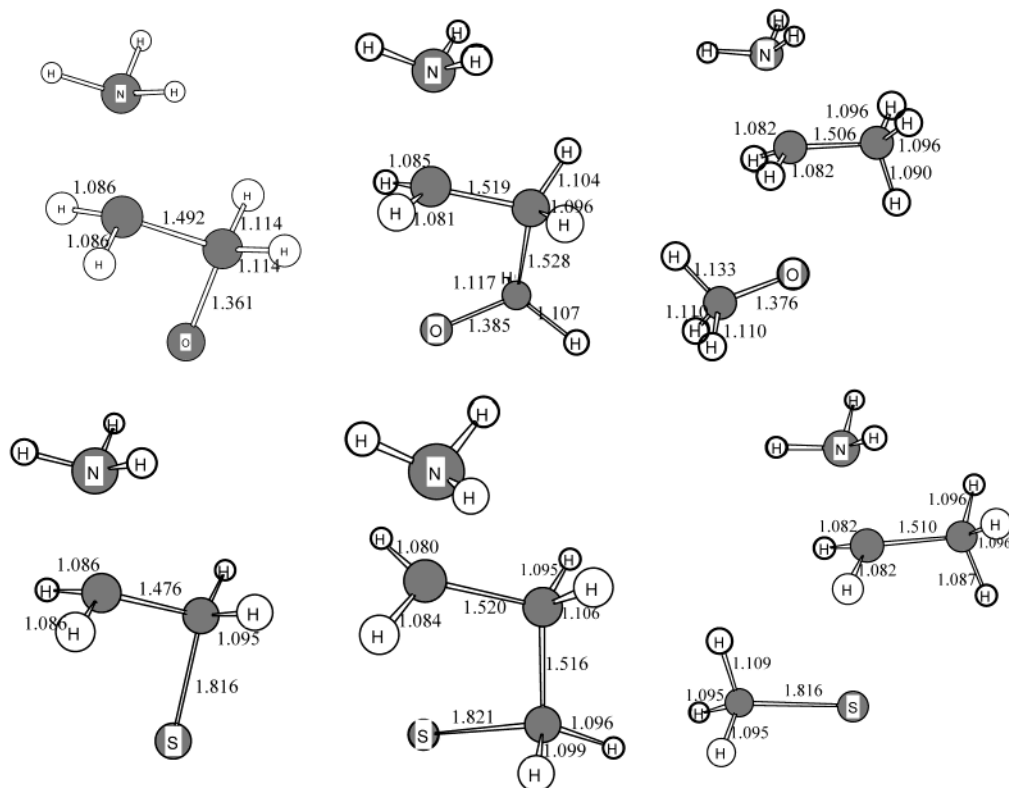
FIGURE 1. Atomic distances (in angstroms) in the transition states.

methylethane were deemed the best choices to model reactivity for the oxygen and sulfur heterocycles, respectively.

Calculations using atoms in molecules theory (AIM) were performed by means of the AIM 2000 program.[20]

Results and Discussion

Relative rates of reaction with ammonia for each series of compounds are provided in Table 2. At this level of theory, IRC calculations identified dipolar complexes for oxirane, thiirane, oxetane, and thietane that were 3.2, 2.6, 0.3, and 2.2 kcal/mol, respectively, more stable than the separated reactants; no species other than the separated reactants could be identified for the remaining (acyclic) substrates (Table S1, Supporting Information). These small differences in stability may be due to the fact that the heterocycles have their alkyl groups pinned back so as to avoid steric interaction with ammonia when it approaches close enough to produce an effective dipole−dipole interaction. Not unexpectedly, both three- and four-membered heterocycles were very much more reac-

tive than their corresponding model compounds. Moreover, the three-membered rings were more than 10⁶ times more reactive than the four-membered heterocycles.

To assess the importance of disjoined effects, the amount of strain energy remaining at the transition state must be determined. The total strain of a molecule in the gas phase, V, is given by[21]

$$V = \Sigma V_{stretch} + \Sigma V_{bend} + \Sigma V_{torsion} + \Sigma V_{VDW}$$

where the sums of bond stretching and bending energies and the sums of torsional and nonbonded interactions are included. Stretching energies and nonbonded interactions are unimportant for these transition state structures (Figure 1.) For purposes of this discussion, it will be assumed that the bending energies and torsional interactions involving the atoms of the reaction center are small and approximately equal for the members of each series. Inspection of the transition-state geometries provided in Figure 1 establishes that this is a reasonable

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supposition. Using the usual harmonic potential based on Hooke's Law functions with 0.025 kcal mol^{-1} deg^{-2} as the constant for angle bending,[22] and using 3.5 kcal mol^{-1} and 3.3 kcal mol^{-1}, the torsional barriers for ethanol[23] and ethanethiol,[24] respectively, for the torsional barriers in the corresponding transition states, one can estimate the sum of the angle deformation and torsional energies of the transition states for oxirane, oxetane, thiirane, and thietane to be 3.3, 4.6, 2.7, and 1.5 kcal mol^{-1}, respectively. If these estimates are subtracted from the calculated strain energies of the heterocycles, the strain energy released in the transition state for each substrate is obtained. Addition of these values to the enthalpies of activation (Table 2) for each reaction permits one to calculate $\Delta G^{\ddagger} = 69.3$, 77.6, 60.7, and 74.7 kcal mol^{-1}, respectively for oxirane, oxetane, thiirane, and thietane if each contribution from strain relief were removed. The calculated values for the four-membered rings agree quite well with the expected values based solely on relief of ring strain relative to the strain-free acyclic model compounds ($\Delta G^{\ddagger} = 78.2$ and 74.4 kcal mol^{-1} for MeOEt and MeSEt, respectively.) The three-membered rings are quite exceptional. Including the correction for strain energy, oxirane is found to react with ammonia at a rate 3.27×10^{6} times faster than methyl ethyl ether. Thiirane reacts at a rate of 1.08×10^{10} faster than its acyclic model compound after this adjustment is made.

The structure of the transition state is critical to understanding the relative rates of these reactions. While the geometry of the transition states is useful, it fails to address directly the distribution of electrons in these species. Bader's[25] theory of atoms in molecules (AIM) is ideally suited to studying the electronic distributions of the transition states. This approach has demonstrated that the negative of the Laplacian of the electron density coincides with electronic charge concentration (bonding) in treatments of localized electron density by the Lewis and VSEPR models. The results of an AIM calculation of $-\bar{V}^{2}\rho$ for a reaction representative of those obtained for every reaction investigated, attack of ammonia on thiirane, are provided in Figure 2. This relief graph clearly demonstrates the localization of electron density between the bonded atoms, i.e., the carbons and between sulfur and the carbon that is not under attack by ammonia.

It is noteworthy that electron density is absent in the region between the reaction center and sulfur, while capture of electron density from nitrogen is only modest. Some years ago, doubt was cast on the classical representation of the transition state in S_N2 reactions that involves essentially equivalent degrees of bond making and bond breaking. Bader, Duke, and Messer[26] calculated that the S_N2 reactions of fluoride or cyanide ion with fluoromethane proceed through a partially positively charged carbon fragment. The present results indicate
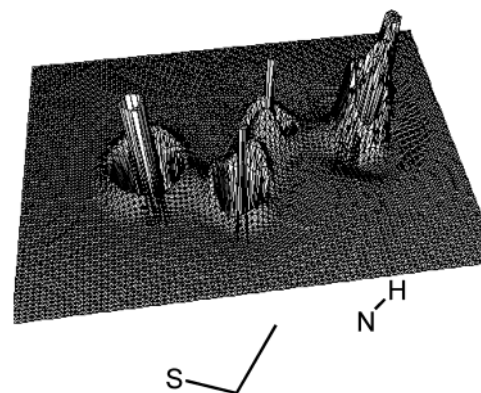

FIGURE 2. Laplacian of the electron density of the transition state for thiirane + NH$_3$. The atoms in the plane are included beneath the relief map.

that Menschutkin-type reactions also depart from classical S_N2 mechanistic formalism with bond breaking significantly advanced relative to bond making. The virtually complete cleavage of the carbon−heteroatom bond in the transition state prior to formation of the carbon−nitrogen bond requires that charge be distributed over the carbon chain. Molecules that are more efficient in lowering the energy of this species will react faster.

What effect or effects are producing such dramatic rate increases? Since separation of opposite charges occurs along the reaction coordinate, it appeared reasonable to calculate atomic charges in the transition states. Small changes in charge can produce profound changes in energy.[27] If, for example, a charge of $+0.237$, separated at a distance of 2.08 Å from a charge of -1.13, is increased to $+0.250$, the energy of the system along the reaction coordinate required to maintain separation increases by 11.3 kcal mol^{-1}.

Interpretation of the results of atomic charge calculations, however, must be approached with caution. Atomic charges are not physical observables; they are dependent upon the method by which they are derived. The calculated charges are not necessarily centered on atomic nuclei.[28] An excellent discussion that compares various methods for calculating atomic charges is available.[29]

The approach chosen here was to calculate the attractive energy using the atomic charges obtained from four methods: Mulliken, AIM, CHELPG, and NBO. The results are provided in Table 3 with the charges of the hydrogens summed into the heavy atoms to which they are attached. The distances between the key atoms in the transition state are given in Table 4. Using a classical electrostatic model,[22] a dielectric constant of 1.0,[30] and neglecting the charges on all atoms other than the reaction center and leaving group,[31] the attractive energy

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TABLE 3. MP2(Full)/6-31+G(d) Atomic Charges[a] for the Transition States of the Reactions of the Substrates with Ammonia

		Mulliken	AIM	CHELPG	NBO
oxirane	**C1**	0.271351	0.23756	0.172182	0.22344
	N2	0.312573	0.29859	0.349875	0.42019
	C3	0.220432	0.59959	0.354069	0.18717
	O6	−0.804356	−1.13571	−0.876125	−0.83080
oxetane	**C1**	0.38218	0.353176	0.543769	0.30547
	N2	0.27997	0.289832	0.279226	0.42764
	C3	−0.01379	−0.040330	−0.265070	−0.09869
	C6	0.16623	0.560537	0.383929	0.24137
	O14	−0.81460	−1.164017	−0.941857	−0.87580
methoxy-ethane	**C2**	0.44562	0.39336	0.63594	0.29713
	N3	0.33087	0.30231	0.27400	0.46802
	C4	0.02113	0.11125	−0.06304	0.04488
	C12	0.02907	0.46179	0.19113	0.12077
	O14	−0.82668	−1.22189	−1.03803	−0.93081
thiirane	C1	0.00067	0.07920	0.06000	−0.17722
	C2	0.17450	0.10300	0.24732	0.23115
	S3	−0.50250	−0.48030	−0.69850	−0.47511
	N6	0.32733	0.29740	0.39117	0.42115
thietane	**C1**	0.34583	0.27187	0.39235	0.25603
	C2	−0.04393	0.05058	−0.10163	−0.06128
	N5	0.25747	0.28364	0.31396	0.39920
	C6	0.01918	−0.06086	0.14124	−0.13110
	S12	−0.57855	−0.51997	−0.74619	−0.46284
thiomethyl-ethane	C1	0.09570	0.01479	-0.16812	0.03741
	C2	0.22134	0.31194	0.65026	0.26009
	N8	0.30609	0.28597	0.28998	0.41070
	S9	-0.49528	-0.85201	- 0.89622	-0.51503
	C13	-0.12785	-0.17608	0.12410	-0.19316

[a] Hydrogens are summed into heavy atoms to which they are attached. Bold atoms are the reaction centers.

TABLE 4. Distances[a] between Key Atoms in the Transition States in Nucleophilic Attack by NH₃

	oxirane	oxetane	MeOEt	thiirane	thietane	MeSEt
C−N	1.763	1.757	1.685	1.768	1.808	1.777
C−X	2.075	2.127	2.217	2.437	2.540	2.630
N−X	3.753	3.881	3.879	4.135	4.345	4.352

[a] In angstroms.

for oxetane is 20 kcal mol^{-1} higher than that for oxirane, and that for thietane is 12 kcal mol^{-1} higher than that of thiirane, using AIM atomic charges.[32] The higher the attractive energy, the greater the energy required to reach the transition state. These estimated energies are more than sufficient to account for rate accelerations of oxirane and thiirane above and beyond that due to relief of ring strain. The same conclusion is reached using the values obtained using the remaining atomic charge methods with the sole exception the NBO method for the sulfur heterocycles.

A reasonable explanation for the charge distributions observed in these transition states for the ethers was suggested by Wiberg[33] in his discussion of calculated results for alkoxide ions at the MP3/6-311++G** level. The negatively charged oxygen was postulated to repel electron density of the back lobe of the adjacent atom, resulting in the adjacent atom becoming relatively positive and the atoms attached to it relatively negative with respect to the corresponding alcohol. These results were found to be similar to those obtained at our lower MP2-(Full)/6-31+G(d) level of theory. Atomic charge values for ethanethiol and its anion are presented in Tables S2 and S3 (Supporting Information). A rationalization similar to that used above for the transition states for the ethers cannot be applied to the transition states for the reactions of the thioethers with ammonia. It is found that negative charges reside on both the geminal and vicinal carbons, differing from the results for ethoxide ion where large positive charge is found on the geminal carbon. Using perturbation molecular orbital theory, the destabilizing ethyl π−sulfur 3p interaction was found to be more important that the stabilizing ethyl π^*−sulfur 3p interaction. This interaction results in the repulsion of electrons by the negatively charged sulfur and an accumulation of negative charge on the neighboring carbons.[33] Partial negative charge is found at the positions next to sulfur in the transition states using every method (with the exception of CHELPG), mirroring the results for ethanethiolate ion. It is most interesting that the charge at the position vicinal to sulfur for the thiirane transition state, which is also the reaction center, is the least positive of all reaction centers. When this position is compared to that of the transition state of thietane whose alkyl chain is one carbon longer, it is found that there is slight negative charge at this position. This result parallels that of the thiolate ion and suggests that negative charge is also released to this position for the thiirane transition state. The net result is that the reaction center for the thiirane transition state is rendered less positive than the other members of this series. In the case of thietane, the reaction center is one carbon further removed along the chain and unable to significantly benefit from this electron release. For thiomethylethane, the chain necessary for this electron repulsion mechanism to reduce the partial positive charge of the reaction center has been ruptured, rendering stabilization of its reaction center by this process impossible. A similar explanation can be readily applied to the ethers.

Within the assumptions of transition-state theory,[35] one can calculate that thiirane, thietane, and thiomethylethane react 57.4, 608, and 112 times faster than oxirane, oxetane, and methoxyethane, respectively. The higher reactivity of the thioethers is consistent with the significantly lower atomic charges of the thioether transition states leading to a decrease in the energy required to reach the transition state (Table 3). The simplest explanation of the larger charges for the ethers is that

(31) Since the atomic charge on nitrogen in the transition state was similar within each method, and nitrogen was about twice as distant from the heteroatom as the reaction center, it was assumed to have a minor overall influence.

(32) The absolute values of the atomic charges in the transition state were used as opposed to changes in atomic charge at each position from ground state to transition state. This is appropriate because even though the carbon reaction center and the heteroatom have nonzero atomic charges in the ground state, these charges contribute nothing to the electrostatic work that develops along the reaction coordinate since they are held separate by means of a bond.

(33) Wiberg, K. B. *J. Am. Chem. Soc.* **1990**, *112*, 3379−3385.

(34) Janousek, B. K.; Reed, K. J.; Brauman, J. I. *J. Am. Chem. Soc.* **1980**, *102*, 3125−3129. (b) DeFrees, D. J.; Bartmess, J. E.; Kim, J. H.; McIver, Jr., R. T.; Hehre, W. J. *J. Am. Chem. Soc.* **1977**, *99*, 6451−6452. Perturbation molecular orbital theory can also be used to explain the electron distribution in the oxygen transition states. In this instance, the importance of the interacting orbitals is the reverse of that for sulfur, with the stabilizing interaction closely related to the polarizability of the alkyl group.

(35) See Hirsch, J. A. *Concepts in Theoretical Organic Chemistry*; Allyn and Bacon: Boston, MA, 1974; pp 120−124 and references therein.

there is a large difference in electronegativity for carbon and oxygen, while that of carbon and sulfur is close to zero.[36]

Supporting this explanation of the accelerated rate of reaction of the three- with respect to four-membered heterocycles in nucleophilic reactions with ammonia is the observation that the calculated carbon−carbon bonds connecting the reaction center to the chain in the transition states for thiirane and oxirane, 1.476 and 1.492 Å, respectively, are significantly shorter than the corresponding distances for the other transition states (Figure 1.) These stronger bonds are occasioned by the higher electron density found in these bonds due to electron repulsion by sulfur and oxygen in the manner described above decreasing charge at the reaction center.

It should be borne in mind that it is not possible, given the assumptions in assigning atomic charges (vide infra), to quantitate the magnitude of this electrostatic effect. Other factors may contribute to the disjoined effect;[37] however, it is likely that the major, if not sole contributor, is one having an electrostatic origin.

The results suggest that a significant increase in reaction rate could be observed for any compound that is able to attain a transition state similar to those for the three-membered heterocycles in this investigation. In general, any substrate that contains a negatively charged substituent at the vicinal position in the transition state should react at an increased rate. In a trivial extension, one would expect nucleophilic cleavage of aziridines to proceed considerably faster than azetidines. Moreover, it should be possible to observe enhanced rates for nucleophilic substitution reactions of *acyclic* compounds. Preliminary calculations confirm this expectation. These results will be reported in due course.

Conclusions

The results presented above demonstrate that the accelerated rates of four-membered heterocycles with ammonia relative to acyclic model compounds were due almost entirely to release of ring strain in the transition state. Three-membered rings were calculated to react more than 10^6 times faster than four-membered rings. These accelerations are due to a combination of relief of ring strain and the disjoined effect. The best explanation of this effect appears to be the favorable topography for minimizing the attractive interaction between the partially negatively charged heteroatom and the reaction center that is significant only in the transition states for three-membered rings. Using different mechanisms, electron-rich oxygen and sulfur can release electron density to the reaction center, minimizing its absolute positive charge, and therefore, make separation of the heteroatom easier due to decreased electrostatic attractive interactions.

Supporting Information Available: Relative energies of the separated reactants with respect to the dipolar complexes, the atomic charges of ethanethiol and its anion, as well as the Cartesian coordinates and energies of the reactive species, transition states, and dipolar complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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(36) Ferguson, L. N. *Organic Molecular Structure*; Willard Grant Press: Boston, MA, 1975; p 47.

(37) The disjoined effect is unleashed only when the bond connecting the leaving group to the reaction center in a cyclic molecule is cleaved. It is distinguished from the classical inductive effect whether through-bond or through-space (field) that is present in the reactant and throughout the reaction, typically having the most profound effect on the transition state.