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Strain-Free Transition States in the Formation of Strained Rings: An ab Initio Study of Thiirane, Thietan, and Tetrahydrothiophene

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Ab initio calculations (MP2/6-31+G**//MP2/6-31+G*) have been used to probe the potential energy surfaces of the ring closures of HSCH$_2$CH$_2$S$^-$, HSCH$_2$CH$_2$CH$_2$S$^-$, and HSCH$_2$CH$_2$CH$_2$CH$_2$S$^-$ to give thiirane, thietan, and tetrahydrothiophene. The calculated activation barriers (19.2, 29.4, and 23.1 kcal/mol, respectively) indicate that formation of the 3-membered ring has the smallest barrier. Moreover, the barrier to thiirane formation is smaller than that of the corresponding S$_N$2 reaction of an acyclic analog (25.0 kcal/mol for CH$_3$S$^-$ + CH$_3$CH$_2$SH). The surprisingly small barrier to forming thiirane is the result of two factors. First, the nature of the bonding in the transition state limits the angular strain. Second, geometric constraints force the nucleophilic sulfur to be near the electrophilic carbon in HSCH$_2$CH$_2$S$^-$. This proximity effect destabilizes the ring-opened form (part of the typical S$_N$2 barrier is built into the ground state) and consequently lowers the barrier to ring formation.

Introduction

Chemical intuition suggests that reactions that lead to highly strained products should be difficult and have relatively large activation barriers. Numerous experimental investigations of the relationship between ring strain and formation rate have led to conflicting conclusions as a result of the convoluting effects of solvation, ion-pairing, and substituents.[1−13] In this paper, computational studies are used to show that strain does not necessarily lead to large barriers to forming small rings. In fact, the activation energies for forming 3-membered rings can be significantly smaller than those found in analogous, acyclic systems. This is independent of and in addition to the known entropic advantages of forming small rings.[1,5,7,9,12,13] Although not predicted in his landmark paper, this result is consistent with Ruzicka's analysis of the relationship between ring strain and ease of formation.[14]

In a recent computational study of the reactions of nucleophiles with methyloxirane and methylthiirane, we discovered an unusually stable transition state for the HS$^-$-induced ring opening of methylthiirane to give HSCH$_2$CH(CH$_3$)S$^-$.[15,16] Comparisons to acyclic analogs suggested that the transition state is stabilized by more than the total strain energy of thiirane even though the transition state appears to occur fairly early on the reaction coordinate. This result clearly indicates that factors other than conventional ring strain release play an important role in these systems.

In the present study, we provide a detailed analysis of the role of strain energy in the formation and opening of small ring systems. Specifically, the ring closures of HSCH$_2$CH$_2$S$^-$, HSCH$_2$CH$_2$CH$_2$S$^-$, and HSCH$_2$CH$_2$CH$_2$CH$_2$S$^-$ to give thiirane, thietan, and tetrahydrothiophene are explored at the MP2/6-31+G**//MP2/6-31+G* level. Transition states have been located for each reaction, and an intrinsic reaction coordinate (IRC) pathway (HF/6-31+G*) is presented for the thiirane system. To evaluate the effects of ring strain, the reaction of CH$_3$S$^-$ with CH$_3$CH$_2$SH is included as an acyclic analog (Scheme 1).

Computational Methods

All calculations were carried out on HP-720 or HP-735 computers using the GAUSSIAN92 quantum mechanical package developed by Pople and co-workers.[17] All structures were fully optimized using a 6-31+G* basis set.[18−22] The curvature of the potential energy surface at all minima and transition states was confirmed with analytical second derivatives at the Hartree−Fock level. When appropriate, the possibility of multiple rotamers was investigated. To account for correlation effects, the geometries were reoptimized at the MP2/6-31+G* level and final energies are reported at the MP2/6-31+G** level. Using the Hartree−Fock frequencies, corrections were made for zero-point energy differences (scaled by 0.91).[23] Intrinsic reaction coordinate calculations were com-

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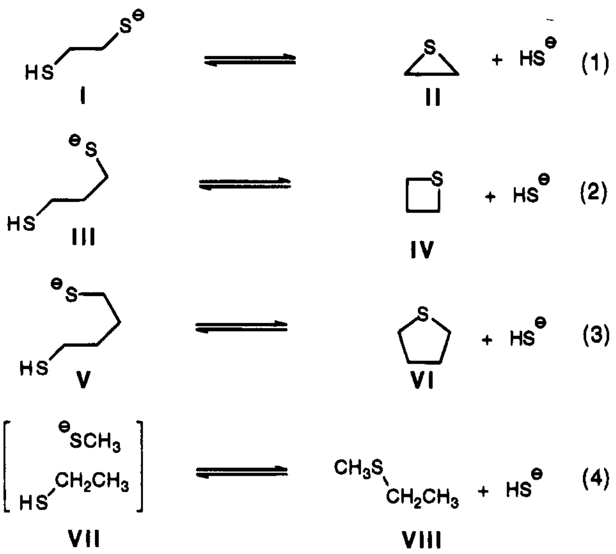
Scheme 1



pleted at the HF/6-31+G* level using the method of Gonzalez and Schlegel and involved steps of 0.25 au.[24]

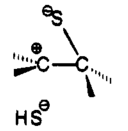
Electron density analysis was completed at the MP2/6-31+G**//MP2/6-31+G* level using Bader's method with a modified version of the PROAIM program.[25] The application of Bader's approach has been discussed in detail elsewhere,[26,27] so only a brief description is provided here. Bader has shown that the Laplacian of the electron density ($\nabla^2\varrho$) is a useful tool for characterizing bonding interactions. Regions where the Laplacian is negative correlate with electronic charge concentration and in the interatomic region are characteristic of covalent bonding interactions. Regions where the Laplacian is positive correlate with charge depletion and indicate areas where the electron density has contracted toward the nuclei. Little shared density and only a weak covalent interaction are anticipated in these regions. In the present study, contour representations of the Laplacian were generated using the MACGRIDZO program.[28]

Results and Discussion

For the sake of clarity, the discussion will focus on the reactions in the ring-forming (forward) direction as illustrated in Scheme 1. In Figure 1, the structures of the ring-opened species and the corresponding transition states for ring closure are shown. Energies are reported in Table 1. For the acyclic analog, $CH_3S^- + CH_3CH_2SH \rightarrow HS^- + CH_3CH_2SCH_3$, the reactant state is taken as the ion–dipole complex of CH_3S^- and CH_3CH_2SH (reaction 4).[29] This is the only choice that allows for fair comparisons of the energetics because in each of the ring-opened species (**I**, **III**, and **V**) the thiolate is stabilized by an intramolecular ion–dipole interaction similar to that found in **VII**. Strong support for this choice can be found in the calculated ring strain energies. Using the complex (**VII**) for these comparisons, strain energies of 19.1, 22.2, and 3.1 kcal/mol are found for thiirane, thietan, and tetrahydrothiophene, respectively.[30] These values are reasonably close to the accepted strain energies (19.8, 19.8, and 5.8 kcal/mol).[9] If the strain energy comparisons are based on the uncomplexed species ($CH_3CH_2SH + CH_3S^-$), unreasonably large values (29.3, 32.4, and 13.3 kcal/mol) are calculated because the ring-opened forms are electrostatically stabilized by an interaction not available to the acyclic analog.[31]

Having chosen reaction 4 for comparisons, the effect of strain on the ring closure barriers can be assessed. In the conversion of $HSCH_2CH_2S^-$ (**I**) to thiirane and HS^- (reaction 1), a barrier of 19.2 kcal/mol is calculated whereas the S_N2 process in reaction 4 has a barrier of 25.0 kcal/mol. *That is, the more endothermic process leading to the more highly strained product has the smaller activation barrier.* This surprising result is not an artifact of choosing reaction 4 for comparisons. If one considers the back reactions (HS^- + **II** → **TS1** → **I** vs HS^- + **VIII** → **TS4** → $CH_3CH_2SH + CH_3S^-$), the values in Table 1 indicate that ring strain relief provides 24.9 kcal/mol of stabilization to the thiirane-opening transition state (barriers of 0.6 and 25.5 kcal/mol, respectively). This calculation does not involve the energy of complex **VII** but indicates that *the transition state stabilization is greater than the overall ring strain energy of thiirane*, a result that is possible only if the barrier to ring closure is smaller than the S_N2 barrier of the acyclic analog. These results are striking given that the transition state (**TS1**) has an acute C–C–S angle (82°) and must contain some of the strain energy of thiirane. How can ring strain development activate the reaction system?

The answer rests not only on the timing of strain development but also on the nature of strain in small rings. Data from ring-opening reactions suggest that much of the strain in 3-membered rings is released early in heterolytic cleavages.[9] For example, Stirling has used substituent effects in cyclopropane systems to show that ring openings with early transition states can convert a majority of the strain into transition state stabilization.[32,33] This result can be rationalized by examining the bonding in the transition state. Bader and others have argued that S_N2 transition states are strongly influenced by an ionic resonance form.[34-36]



Evidence for this resonance form can be seen in the integrated Bader charges (Table 2). The analysis is somewhat complicated because the nucleophilic sulfur of **I** is linked to the S_N2 reaction center; however, this problem can be minimized by breaking the system into three parts: S^- (ring sulfur), HS^-, and the CH_2CH_2 linkage. In going to the transition state from **I**, the S^- fragment loses 0.24 electron, but the HS^- fragment gains 0.56 electron. Therefore the CH_2CH_2 group loses 0.32 electron in the process (−0.16 e → +0.16 e).[37] This

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[28] MacGRIDZO Rockware, Inc., Wheat Ridge, CO.

[29] Many complexes are possible, but for consistency with the ring-opened species, a conformation where the thiolate interacts with the backside of the C–SH bond was chosen. A geometric constraint was maintained to prevent a hydrogen bonding interaction with the thiol.

[30] These values are derived from the following equation: [**I**, **III**, or **V**] + **VIII** → [**II**, **IV**, or **VI**] + **VII**.

[31] The difference is simply the complexation energy of CH_3S^- + CH_3CH_2SH to give **VII**.

[32] Hughes, S.; Stirling, C. J. M. *J. Chem. Soc., Chem. Commun.* **1982**, 237.

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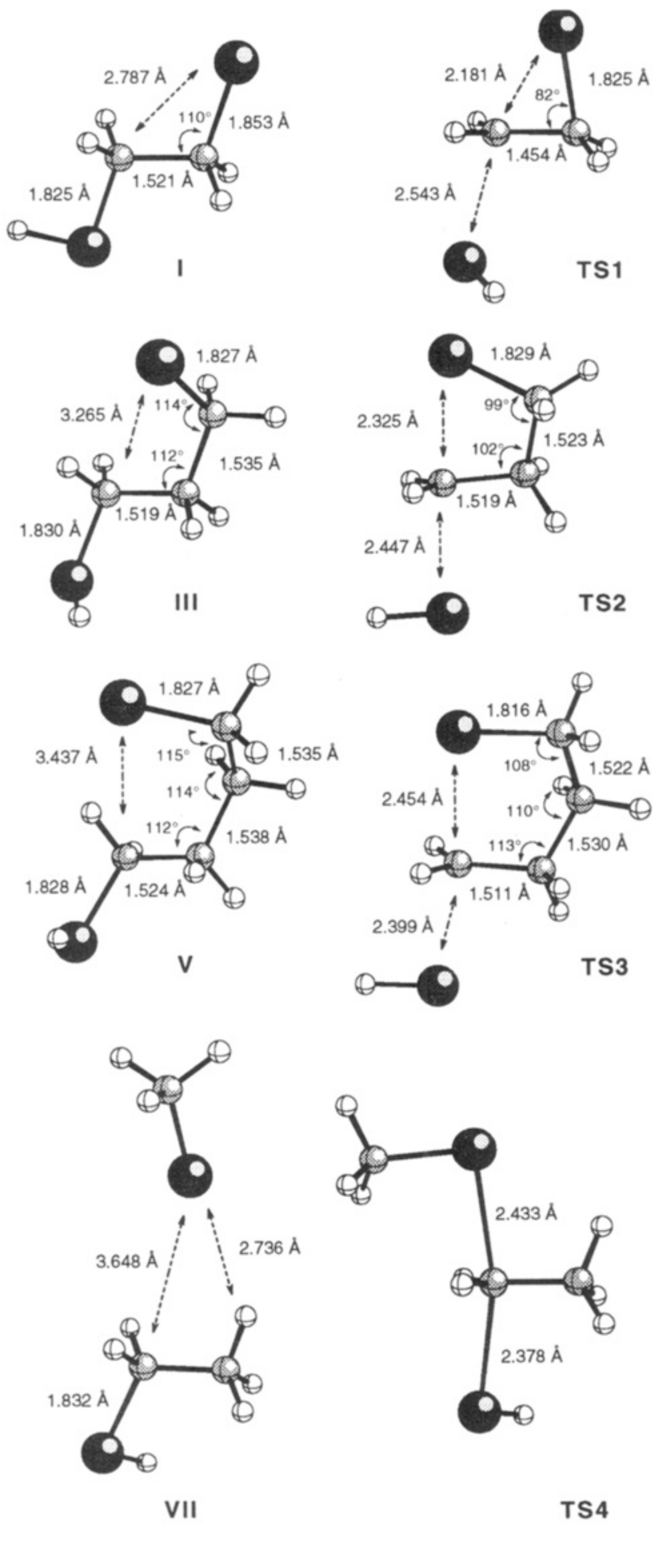

Figure 1. Structures of ring-opened species and transition states. Optimizations at the MP2/6-31+G* level. All structures are C_1.

Table 1. Energies of Reactants, Transition States, and Products[a]

structure	HF/6-31+G*// HF/6-31+G*	MP2/6-31+G**// MP2/6-31+G*	ZPE	relative energies HF	relative energies MP2
I	−873.683 79	−874.241 18	40.0	0.0	0.0
TS1	−873.648 44	−874.207 50	38.1	20.3	19.2
II	−475.548 32	−475.966 14	33.9	15.4	18.6
III	−912.717 23	−913.426 16	57.5	0.0	0.0
TS2	−912.663 27	−913.376 67	55.8	32.2	29.4
IV	−514.583 12	−515.146 97	51.8	15.0	21.7
V	−951.748 23	−952.607 96	74.9	0.0	0.0
TS3	−951.706 97	−952.569 14	73.6	24.6	23.1
VI	−553.646 10	−554.360 14	69.8	−4.5	2.6
VII	−913.874 36	−914.600 01	68.3	0.0	0.0
TS4	913.825 49	−914.558 48	67.2	29.6	25.0
VIII	−515.772 15	−516.358 22	64.0	−3.7	−0.5
HS^-	−398.106 89	−398.241 35	3.6		

[a] Absolute energies in hartrees. Relative energies and zero-point energy (ZPE) in kcal/mol. ZPE scaled by 0.91. Relative energies for **II**, **IV**, **VI**, and **VIII** include contribution from HS^-.

Table 2. Bader Integrated Charges for Thiirane Systems[a]

structure	group	charge
I	S	−0.69
	SH	−0.15
TS1	S	−0.45
	SH	−0.71

[a] MP2/6-31+G**//MP2/6-31+G*. Under group, S refers to ring sulfur.

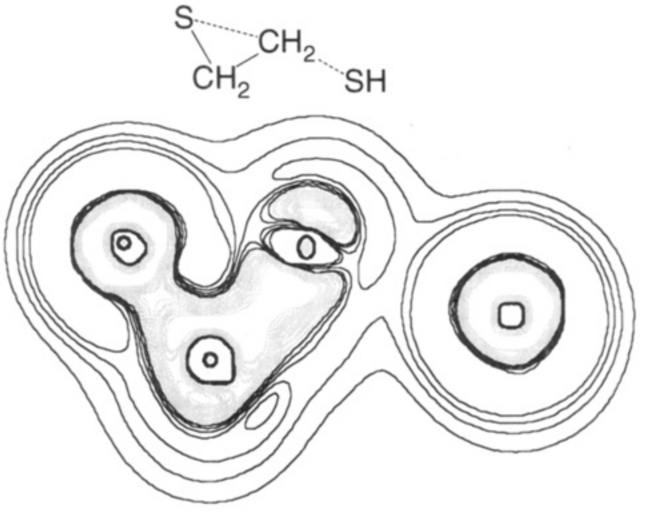

Figure 2. Contour plot of the Laplacian of the electron density for **TS1**. The wave function was generated at the MP2/6-31+G** level. Contours from −0.45 to 0.40 with a step size of 0.05 au (black, positive; grey, negative).

development of positive charge on the alkyl linkage suggests a significant contribution from the above ionic resonance form. More insight into the bonding is found in a contour plot of the Laplacian of the electron density in **TS1** (Figure 2).[25,27] The gray areas (negative contours) in the figure correspond to regions of charge concentration and are related to strong covalent bonding interactions. There are large bands of negative contours between the two complete bonds in the ring, C−C and C−S; however, the regions between the breaking and forming C−S bonds are exclusively positive. The absence of charge accumulation in these regions is consistent with a significant ionic component and suggests that the bonding electrons are not strongly oriented along a bond path. If the forming and breaking bonds are dominated by nondirectional interactions (*i.e.* electrostatic), it is not surprising that much of the strain is released in the transition state—with only two strong covalent interactions in the 3-membered ring and a partially inverted reaction center (no eclipsing hydrogens), the only re-

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(37) If one only considers the charges on the reactive CH_2 group, a similar conclusion results.

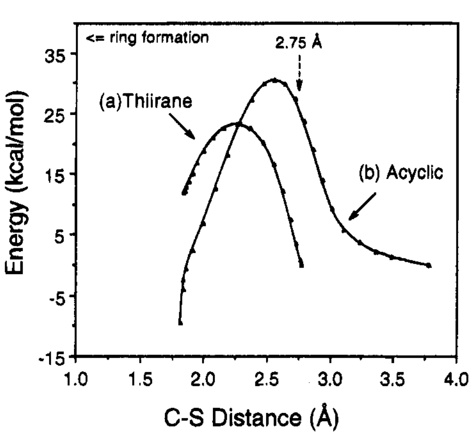

Figure 3. Plot of intrinsic reaction coordinate pathways for (a) reaction 1 and (b) reaction 4. The forming C−S distance is used as the reaction coordinate. Calculations at the HF/6-31+G* level. At this level of theory, the thiirane system starts with a C−S distance of 2.75 Å.

maining major strain component is the deformation of the C−C−S^- angle. A simple molecular mechanics approach leads to an estimate of about 3−5 kcal/mol for the deformation. This analysis explains why the transition state would exhibit little ring strain but not why it would be favored over the acyclic analog.

Plots of the intrinsic reaction coordinates (vs ring-forming C−S distance) for reactions 1 and 4 reveal an important difference (Figure 3).[38] In the acyclic system, the energy begins to rise from the ion−dipole complex (C−SCH_3 distance = 3.7 Å) as a result of van der Waals repulsions with groups on the α-carbon. In contrast, the reaction coordinate of the thiirane system begins at ~2.8 Å, the C−S distance in the anti conformer of **I**. The bonding scheme in $HSCH_2CH_2S^-$ requires that the nucleophile be closer to the α-carbon, and therefore a part of the typical S_N2 barrier is already built into the ground state of **I** as an unfavorable 1,3 interaction. In other words, part of the reaction path is already complete at **I** and the system starts closer to the transition state (Figure 3). We will refer to this as a proximity effect. A direct comparison of the two graphs would suggest a large energetic effect (it costs over 20 kcal/mol to reach a C−S distance of 2.79 Å in the acyclic system), but this is an overestimation because interactions with other groups on the electrophilic carbon lead to partial inversion and significant C−SH cleavage at this point in the acyclic analog. If the ring-opened product **I** is strained, then the estimated deformation energy of thiirane is effectively too low. In a previous study, Wiberg[39] has pointed out that the measured strain energy of 3-membered rings is somewhat lower than expected because 1,3 interactions are absent in the ring. Bauld and co-workers[40] have also identified 1,3 interactions as an important contributor to strain energies and have used a computational approach to estimate a value of ~7 kcal/mol for the carbon−carbon interaction in propane. Although the absolute accuracy of this value is questionable, Bauld's work suggests that it is large enough to have important chemical consequences. On the basis of the inversion barrier in cyclobutane, Cremer *et al.* have argued that Bauld's values are too large.[41,42] Nonetheless, Cremer's value (~3 kcal/mol) for the 1,3 interaction (or Dunitz−Schomaker strain)[43] in propane also indicates a meaningful effect, particularly when one of the partners is a diffuse sulfur anion. As others have pointed out,[40,42] it is difficult to quantify this effect because there is no appropriate reference for an unstrained methylene with no 1,3 interactions.[44] Fortunately, it is possible to estimate the extent of the proximity effect in the thiirane system by calculating the energy required to bring the nucleophile close enough to the reaction center to initiate rehybridization. That is, one finds the point on the reaction coordinate where the CH_2SH carbon first exhibits signs of a Walden inversion process. To reach such a point, the acyclic model system requires ~6 kcal/mol more energy than the thiirane system. Because this point is reached early on the thiirane-forming reaction coordinate, the value is contaminated by little angular strain development.[45] In the ring closure to thiirane, this effect is amplified because a second unfavorable 1,3 interaction also is lost—when the SH group departs, a 1,3 interaction is lost and not replaced as the new C−S bond is formed. From this analysis, we can see that although thiirane has 20 kcal/mol of total strain relative to an acyclic analog, this strain is composed of a high level of angular strain (>20 kcal/mol) balanced by a stabilization related to the absence of 1,3 interactions.[46]

Having dissected the strain into these two components, the seemingly small barrier to forming the 3-membered ring can be rationalized by recognizing that the strain components manifest themselves at different points on the reaction coordinate.[47] In the cyclic system, the nucleophilic sulfur can come closer to the electrophilic carbon because there is effectively less steric crowding. A plot of the IRC's using the breaking C−SH distance as the reaction coordinate clearly illustrates that the proximity effect aids in the ionization of the breaking C−S bond in the cyclic system (Figure 4). That is, a large portion of the strain (1,3 interactions) in $HSCH_2CH_2S^-$ is applied toward the transition state barrier and can overwhelm the angular strain present at this point on the reaction coordinate. On the basis of the ring-forming C−S distances in Figure 3, it appears that ring closure to thiirane has a much later transition state than the acyclic analog. Since the thiirane reaction has a smaller barrier, this implies anti-Hammond behavior;[48,49] however, the short C−S (forming) distance in **TS1** is mainly

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[38] For the IRC calculations, the HF/6-31+G* level is used for economy. Although the absolute values differ slightly, the results in Table 1 indicate that this level is appropriate for the qualitative arguments in this analysis.

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[43] Dunitz, J. D.; Schomaker, V. *J. Chem. Phys.* **1952**, *20*, 1703.

[44] Attempts to compare systems with and without 1,3 interactions inevitably lead to differences in bonding schemes. For example, $CH_3CH_3 + CH_3CH_3 \rightarrow CH_3CH_2CH_3 + CH_4$ has all CH_3 groups on the left side of the equation, but a CH_2 and CH_4 group on the right. As a result, a direct evaluation of this effect is not possible.

[45] In our study, the criteria was based on a 5° increase in the dihedral angle between the two hydrogens on the CH_2SH group.

[46] Many attempts have been made to identify all of the strain components in 3-membered rings. For example, Cremer has argued that they are stabilized by σ-aromaticity (ref 42). Inagaki suggests that destablizing geminal delocalization effectively causes angular strain to deviate from a Hooke's law approximation when angles are acute (Inagaki, S.; Goto, N.; Yoshikawa, K. *J. Am. Chem. Soc.* **1994**, *116*, 5954). If these factors are important, it is likely that they manifest themselves later on the reaction coordinate and for our purposes can be lumped together and treated generically as an overall ring strain effect.

[47] Stirling has used a partitioning approach to compare 3- and 4-membered rings; however, the strain was partitioned in a fundamentally different way. See ref 9.

[48] Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.

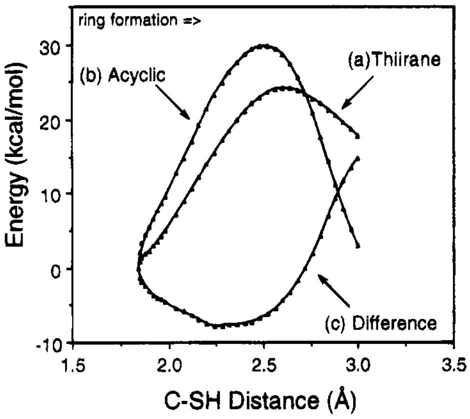

Figure 4. Plot of intrinsic reaction coordinate pathway for (a) reaction 1, (b) reaction 4, and (c) the difference (reaction 1 − reaction 4). The breaking C−SH distance is used as the reaction coordinate. Calculations at the HF/6-31+G* level. See ref 50.

the result of reduced steric crowding. The C−SH (breaking) distance (Figure 4) is a better gauge of the relative progression of the two reactions and suggests less severe anti-Hammond behavior.

In Figure 4, curve c,[50] a plot of the energy differences (cyclic − acyclic) indicates that early on the reaction coordinate (short C−SH distances) the cyclic system benefits from the proximity effect. There is a sharp gain initially from having the nucleophile at a closer starting point and then a more gradual gain because a new 1,3 interaction is not developed as the nucleophile adds. After the transition state, the formation of the new C−S bond leads to a rapid development of angular strain (two more acute bond angles + eclipsing interactions) and the cyclic system is disfavored; however, the potential energy surface of an S_N2 process drops off rapidly after the transition state (Figure 4, curve b) and therefore the development of ring strain has relatively little effect on the transition state energy or the position of the transition state with respect to C−SH cleavage. The net result of this order of events is that the ground-state destabilization term (proximity effect) outweighs the ring strain term in the transition state and the ring-forming reaction is activated. It is interesting to point out that nearly 70 years ago Ruzicka suggested that a short distance between the reaction centers favored ring formation (*i.e.* the proximity effect).[14]

The situation is markedly different for the formation of thietan. Although thietan has approximately the same overall strain energy as thiirane, **TS2** contains considerably more strain than **TS1**. The barrier to the ring closure of **III** is 10.2 kcal/mol larger than that of **I**. Moreover, this barrier is 4.4 kcal/mol larger than the acyclic analog (reaction 4). These results can be explained by two important factors. First, the transition state contains more of thietan's ring strain (probably in the form of close-range 1,3 interactions that are enhanced as the system begins to cyclize).[9,43] The magnitude of this effect must be limited, however, because the barrier is only somewhat larger than the acyclic analog. Nonetheless, unlike thiirane, the nucleophilic sulfur in thietan does not lose its 1,3 interaction during the course of the reaction.[51] Second, the ring-opened form of thietan (**III**) does not require that the nucleophilic sulfur be exceptionally close to the electrophilic center and therefore the proximity effect is diminished. The non-bonded C−S distance in a gauche conformer of $HSCH_2CH_2CH_2S^-$ (**III**) is 3.26 Å, or 0.48 Å longer than that in $HSCH_2CH_2S^-$.

Tetrahydrothiophene (THT) has much less strain energy (~6 kcal/mol) than the smaller rings, and consequently the energetics are more similar to those of the acyclic analog. The barrier to ring formation in reaction 3 is 23.1 kcal/mol or 1.9 kcal/mol less than that of the acyclic analog. This suggests that THT formation is slightly activated. The activation can be rationalized in the following way. First, the long C−S distance in **TS3** allows for normal bond angles with little torsional strain. Second, a comparison of the reaction energies of THT and the acyclic analog suggests that the overall strain in THT is only ~3 kcal/mol (2.7 kcal/mol less than the accepted value[10]). This is because we are using the direct product of THT ring opening (**V**, a conformation with three gauche interactions) for this calculation. Presumably, a larger strain energy would be calculated if a more extended conformation were considered for the ring-opened form. For example, a molecular mechanics survey of a neutral analog,[52] $HSCH_2CH_2CH_2CH_2Cl$, indicates that conformations such as **V** are ~2 kcal/mol less stable than extended structures. Moreover, the large C−C−C and C−C−S angles in **V** (112−115°) also suggest that this conformation is strained. Of course, any instability built into **V** directly leads to a lower barrier for ring closure.

The theoretical results suggest the following order of reactivity in terms of ring closures: **II** > **VI** > **VIII** (acyclic analog) > **IV**. Although experimental studies have led to a variety of reactivity orders depending on nature of the substrate and solvent, a few important correlations can be made. First, experimental studies of ring closures suggest that although 3- and 4-membered rings have large strain energies, the transition states for ring closure are not at a large enthalpic disadvantage in comparison to 5-membered rings (usually <5 kcal/mol).[9] Second, in most cases, 4-membered rings involve the smallest rate constants and the largest activation enthalpies. For example in the cyclization of bromoalkylamines, the following results have been obtained (relative rate, $\Delta H^{\ddagger}$): 3-membered ring (1, 19.4 kcal/mol); 4-membered ring (0.019, 21.7 kcal/mol); 5-membered ring (9.55, 16.2 kcal/mol).[3] Third, in at least one instance it has been observed that formation of a 3-membered ring has a smaller activation enthalpy than the formation of a 5-membered ring. In the cyclization of chlorinated sulfides to give sulfonium ions, Stirling found activation enthalpies of 17.8 and 19.4 kcal/mol for the formation of 3- and 5-membered rings, respectively.[2] In addition, Stirling has found in the cyclization of chlorinated carbanions that 3-membered rings are formed faster than 5-membered rings.[1] In this system, the reactivity difference is attributed to entropy effects; however, this must be an artifact of solvation or ion pairing changes. The ring closure entropies of cyclopropane and cyclopentane are −7.7 and −13.3 eu (a difference of 5.6 eu),[10] yet

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(49) Ford has noticed anti-Hammond behavior in the openings of protonated oxiranes: Ford, G. P.; Smith, C. T. *J. Chem. Soc., Chem. Commun.* **1987**, 44.

(50) To have identical C−S distances for the two IRC's, an interpolation was made. This led to a greater number of points for the graph than were actually located.

(51) In the ring closure to thietan, a single 1,3 interaction is lost instead of two.

(52) MM2: Molecular Mechanics. Burkert, U.; Allinger, N. L.; American Chemical Society, Washington, DC, 1982.

in the cyclization of the chlorinated carbanions the 3-membered ring is favored by 22 eu in terms of activation entropy—far too much for a ring-size effect. Finally, there are several other examples were 3-membered rings are formed faster than analogous 5-membered rings.[13,53-55] Unfortunately, the ΔH and ΔS terms have not been analyzed in these systems. Although solvation and ion pairing prevent direct comparisons with our gas-phase study, it is clear that previous experimental results can be accommodated by our analysis and that the unusual reactivity of 3-membered rings can be rationalized by the proximity effect.

It is anticipated that this analysis is general and applicable to most ionic reactions leading to small rings. However, the sulfur system may represent an extreme example because the 1,3 carbon–sulfur interaction is strong and the transition state requires relatively little distortion of the C–C–S angle. For example, the transition state of the reaction of oxirane with HO^- does not exhibit the exceptional stability found in the thiirane system and contains ~25% of the strain found in oxirane.[15,16] This can be explained by two factors. First, because C–O bonds are shorter than C–S bonds, the transition state in the oxirane reaction requires a greater distortion of the $C-C-X^-$ angle to place the nucleophilic center near the electrophilic center. Moreover, the S_N2 reactions of oxyanions have relatively "tight" (short C–O distances) transition states.[56] Second, the ring-opened form suffers less destabilization from the 1,3 carbon–oxygen interaction because oxygen has a smaller van der Waals radius than sulfur. Nonetheless, the transition state for forming oxirane contains surprisingly little strain given that it occurs late on the reaction coordinate ($\angle C-C-O^- = 77°$) and the factors described above must play a role in this result. Moreover, we have identified other systems (including carbon nucleophiles) that have unusually small barriers to forming 3-membered rings.[57] These results will be presented in a future contribution.

Conclusion

In nucleophilic ring closures, two factors lead to surprisingly small barriers for forming small rings. First, the nature of the bonding in S_N2 transition states limits angular strain. Second, in the formation of 3-membered rings, destabilization of the ring-opened form by an unfavorable 1,3 interaction between the nucleophile and the electrophilic carbon reduces the barrier and can activate the system with respect to acyclic analogs. Although entropic effects are often used to explain facile formation of 3-membered rings, the proximity effect cannot be ignored. For example, if the full entropic advantage of forming a 3-membered ring over a 5-membered ring were realized at the transition state, it would result in about a 2 kcal/mol preference[58] in terms of free energy at 298 K whereas in the present work the proximity effect leads to almost a 4 kcal/mol advantage for the formation of thiirane over tetrahydrothiophene.

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Supporting Information Available: Tables of Cartesian coordinates for all species (4 pages). This material is available in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(53) Bohme, E.; Sell, R. *Chem. Ber.* **1948**, *81*, 123.

(54) Baird, R.; Winstein, S. *J. Am. Chem. Soc.* **1963**, *85*, 567.

(55) Heck, R.; Winstein, S. *J. Am. Chem. Soc.* **1957**, *79*, 3105.

(56) It should be noted that the experimental examples of 3-membered ring formation being favored over 5-membered ring formation have all involved soft nucleophiles (delocalized carbanions, sulfur) that are expected to yield relatively "loose" transition states. This effect is presently under study.

(57) Gronert, S. Unpublished results.

(58) Of course it is possible that special constraints in the transition states could lead to a situation where the difference in activation entropies could be larger than the difference in overall reaction entropies. As a result, a larger effect could be observed.