Cyclizations of 3-Chlorocarbanions to Cyclopropanes: "Strain-Free" Transition States for Forming Highly Strained Rings

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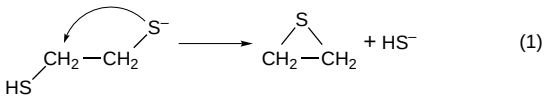
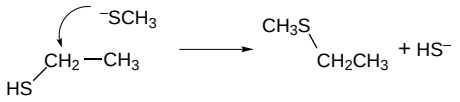
Abstract: Ab initio calculations at the MP2/6-31+G(d,p)//MP2/6-31+G(d) level have been used to investigate the cyclizations of a series of stabilized 3-chlorocarbanions ($ClCH_2CH_2CHZ^-$ where Z = C(O)H, CCH, or CN) to cyclopropane derivatives. In each case, the cyclization barrier is smaller than the S_N2 barrier of an analogous acyclic system, despite the fact that the cyclization is over 25 kcal/mol less exothermic. The surprisingly small enthalpic barrier to the cyclizations is the result of the nucleophile being held in close proximity to the electrophilic site in the cyclization substrate. This destabilizes the ground state of the cyclization process and leads to 6−9 kcal/mol of barrier lowering, enough to overcome the angular strain of the transition state. Although cyclizations to three-membered rings have well-known entropic advantages, it appears that the proximity effect may be the dominant barrier-lowering factor in many cases. Other examples are given, and the results are compared to the available condensed-phase data.

Introduction

In 1995, we used ab initio calculations to demonstrate that although three-membered rings have high ring strain, the enthalpic barrier to forming them can be surprisingly small.[1] In fact, cyclization to thiirane (eq 1) has a smaller barrier than an analogous S_N2 reaction (eq 2) despite the fact that the



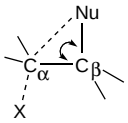
(1)



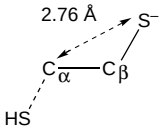
(2)

cyclization is 20 kcal/mol more endothermic. This result is in obvious opposition to the Hammond postulate[2] and suggests that the cyclization process has some intrinsic advantage over a typical S_N2 reaction. It is important to note that the advantage we calculate is purely enthalpic and is augmented by the known entropic advantage of forming small rings.[3−7] Moreover, our work indicates that this enthalpic effect is probably the key to the facile formation of three-membered-ring systems.[1]

In analyzing this unusual result, we found that two important factors were responsible for the low barrier to cyclization. First, little ring strain is realized in the transition state of the cyclization because the forming bond between the nucleophile and the α-carbon is relatively long and has only a weak covalent component in S_N2-like transition states. As a result, deformation of the $C_\alpha-C_\beta-Nu$ angle is the only major strain element in the transition state (the valencies of C_α and Nu suffer little distortion at this point on the reaction coordinate).



Molecular mechanics parameters indicate that for a $C_\alpha-C_\beta-Nu$ angle of about 90°, the transition state contains only a few kilocalories/mole of angular strain.[8,9] It is after the transition state where completion of the $C_\alpha-Nu$ bond leads to a dramatic increase in ring strain, as valencies are distorted and eclipsing interactions are developed throughout the ring. This explains why little strain is seen in the transition state but does not explain how the cyclization could be favored over a "strain-free" analogue.



The second factor involves the stability of the cyclization substrate. In the gas phase, a significant part of the S_N2 barrier is associated with bringing the nucleophile close to the α-carbon because a long-range repulsion develops long before the transition state is reached. For example, in the S_N2 reaction of CH_3S^- with CH_3CH_2SH (eq 2), the potential energy begins to rise at a CH_3S^----C_α distance of nearly 3.5 Å, yet the transition state does not occur until a distance of ∼2.5 Å.[1] The situation is much different in the substrate for cyclization because the nucleophile is geometrically constrained to be close to the

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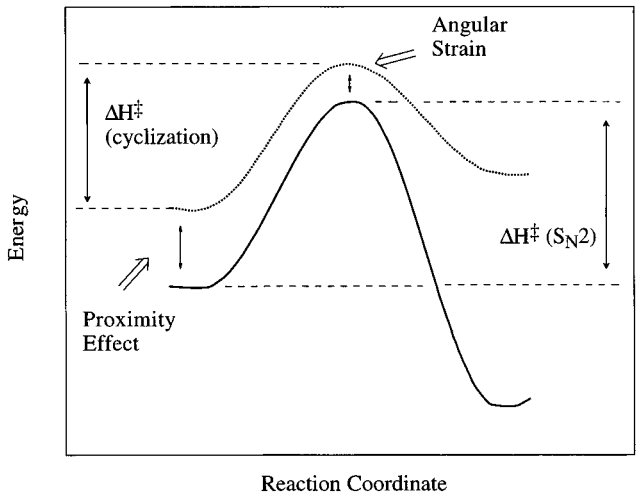


Figure 1. Idealized potential energy surfaces for cyclizations and S_N2 reactions (acyclic analogues).

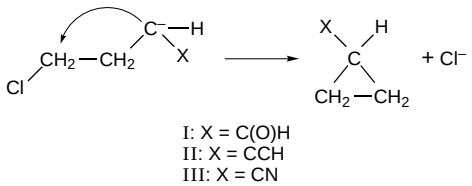
α-carbon. In $HSCH_2CH_2S^-$, the thiolate is only 2.76 Å away from the α-carbon, and therefore, much of the energetic cost associated with bringing the nucleophile close to the α-carbon is already built into the substrate for cyclization.[10] This effectively destabilizes the reactant[11−13] and therefore reduces the barrier to cyclization. We have referred to this as a "proximity effect".[1] Various approaches to estimating the magnitude of this effect suggest that it could account for the observed cyclization preference. In other words, it is large enough to overcome the angular strain in the transition state and lead to a situation where the cyclization barrier is smaller than that of an acyclic analogue. This is illustrated in Figure 1. From the idealized potential energy surface, it can be seen that it is the relatively high energy of the reactant rather than the unusual stability of the transition state that leads to the low barrier.

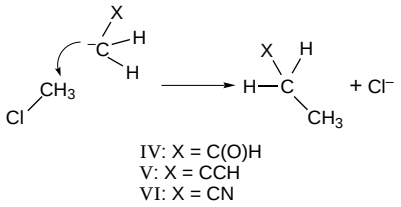
Our original study focused exclusively on reactions related to eq 1, a somewhat unusual system that is significantly endothermic. To test the generality of the proximity effect and its overall importance, a wider range of systems needs to be evaluated. In the present study, we have investigated the formation of cyclopropane derivatives using a series of systems where a stabilized carbanion is the nucleophile and chloride is the leaving group. These reactions are exothermic and, as a result, provide more realistic examples of the proximity effect in action.

The systems included in the present study are outlined in Scheme 1. The carbanions in this series were chosen, in part, because they have fairly similar gas-phase proton affinities (within 15 kcal/mol based on values for $^-CH_2X$) but varying degrees of delocalization. To assess the effect of strain, we have also investigated a series of acyclic strain-free analogues (Scheme 1). To limit any biases toward cyclization, we have chosen the best possible S_N2 substrate (methyl) for the comparisons.

For each system, the reactants, products, and transition states were optimized at the MP2/6-31+G(d) level and the energies

Scheme 1





were determined at the MP2/6-31+G(d,p) level. For each acyclic analogue, an ion−dipole complex precursor to the substitution was also characterized.

Methods

All calculations were carried out on HP-720, HP-735, or IBM 39H computers using the Gaussian 92[14] or Gaussian 94[15] quantum mechanical packages developed by Pople and co-workers. All structures were fully optimized using a 6-31+G(d) basis set. 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(d) level, and the final energies are reported at the MP2/6-31+G(d,p) level. Using the Hartree−Fock frequencies, corrections were made for zero-point energy (ZPE) differences (scaled by 0.9135).[16] All energies in the text are reported at 0 K and include ZPE corrections. Previous work indicates that this approach leads to energies that are in good accord with more demanding computational methods (i.e., (G2+)).[17,18] In addition, the computed values from this study are reasonably consistent with the available thermochemistry, and comparisons with experimental values (298 K) for the acyclic S_N2 reactions are given in the footnotes of Table 1.[19,20] Moreover, the ability of the computational approach to deal with cyclopropanes was confirmed by comparing the calculated and experimental isomerization energies of propene to cyclopropane (5.8 and 8.0 kcal/mol,[19] respectively).

Results

Cyclization to Formylcyclopropane (Ip). The reactant (Ir) and transition state (Its) in the cyclization of the formyl-

(10) The importance of steric effects in S_N2 reactions has been well documented; however, their early appearance on the reaction coordinate may not have been appreciated.

(11) The destabilization results from a 1,3 repulsive interaction (nucelophile/α-carbon) in the cyclization substrate. Wiberg and Bauld have discussed this type of interaction and the resulting destabilization previously. We will present a detailed analysis soon.

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Table 1. Energies of Reactants, Ion−Dipole Complexes, Transition States, and Products[a]

				relative energies	
structure	HF	MP2	ZPE	HF	MP2
Ir	−689.304 07	−690.201 12	61.5	0.0	0.0
Its	−689.291 83	−690.185 85	60.7	7.0	8.9
Ip	−229.793 94	−230.537 86	61.5	−18.5	−4.9
IIr	−652.221 00	−653.057 33	60.2	0.0	0.0
IIts	−652.209 49	−653.049 21	59.1	6.2	4.1
IIp	−192.738 11	−193.425 02	61.3	−34.6	−23.4
IIIr	−668.299 10	−669.159 80	53.4	0.0	0.0
IIIts	−668.290 89	−669.151 20	53.0	4.8	5.1
IIIp	−208.799 69	−209.512 01	54.4	−24.4	−13.8
IVr	−152.311 65	−152.789 87	28.4	10.0	11.7
IVid	−651.422 56	−652.190 21	54.4	0.0	0.0
IVts	−651.399 71	−652.168 99	54.6	14.6	13.5
IVp	−191.955 95	−192.571 44	56.9	−43.5	−30.6
Vr	−115.232 41	−115.649 25	27.1	8.9	10.7
Vid	−614.341 89	−615.048 30	53.4	0.0	0.0
Vts	−614.322 88	−615.034 51	53.0	11.5	8.3
Vp	−154.904 48	−155.463 44	57.0	−60.9	−50.8
VIr	−131.311 85	−131.754 02	20.3	8.1	10.0
VIid	−630.420 05	−631.152 04	46.6	0.0	0.0
VIts	−630.406 87	−631.139 64	46.9	8.5	8.0
VIp	−170.966 65	−171.551 54	50.1	−51.0	−41.2
VIIr	−308.2477 94	−309.1521 58	54.4	0.0	0.0
VIIts	−308.2058 36	−309.1285 43	53.7	25.6	14.1
VIIp	−208.7996 86	−209.5120 05	54.4	18.5	10.2
VIIIr	−131.311 85	−131.754 02	20.3	6.8	9.1
VIIIid	−270.368 02	−271.146 73	47.7	0.0	0.0
VIIIts	−270.329 34	−271.125 07	48.1	24.7	14.0
VIIIp	−170.966 65	−171.551 54	50.1	−8.6	−15.8
IXr	−612.381 34	−613.007 36	38.7	0.0	0.0
IXts	−612.372 37	−612.997 93	38.2	5.2	5.5
IXp	−152.871 83	−153.346 24	35.1	−22.2	−9.6
Xr	−114.411 12	−114.769 89	24.2	13.1	13.7
Xid	−613.526 93	−614.173 42	50.2	0.0	0.0
Xts	−613.521 20	−614.168 60	50.7	4.0	3.4
Xp	−154.069 43	−154.562 14	53.9	−48.2	−34.2
Cl^-	−459.539 66	−459.671 15	0.0		
F^-	−99.4185 86	−99.6238 47	0.0		
CH_3Cl	−499.094 16	−499.380 92	25.5		
CH_3F	−139.0442 26	−139.3771 05	26.6		

[a] Absoulte energies in hartrees. Relative energies and zero-point energies (ZPE) in kcal/mol. Relative energies include ZPE correction scaled by 0.9135. For the acyclic systems, the reactant refers to the bare nucleophile. Comparisons to experiment (experimental values in parentheses): IVr ⇒ IVp = −42.3 (−40.0); Vr ⇒ Vp = −61.5 (−56.2); VIr ⇒ VIp = −51.2 (−47.3); and Xr ⇒ Xp = −47.9 (−45.1).[19,20]

substituted system are shown in Figure 2, and the relevant energies are listed in Table 1. In the transition state, the C−C−C angle is ∼87° and the forming C−C distance is 2.034 Å. Of course, the small C−C−C angle suggests that some angular strain has developed at the transition state. Although cyclization to a five-membered ring is also possible (dihydrofuran), it was not pursued in the present study. For comparison, the ion−dipole complex (IVid) and the transition state (IVts) for the reaction of acetaldehyde enolate with methyl chloride (C alkylation) are also shown in Figure 2. In the ion−dipole complex, the strongest interaction is between the oxygen and the backside of the C−Cl bond, but the potential energy surface is relatively flat.[21] As noted in our earlier work,[1] the cyclization appears to have a later transition state as evidenced by a shorter C−C (forming) distance and a longer C−Cl distance. In addition, the importance of the proximity effect is foreshadowed in the length of the C−Cl bond in Ir. The interaction with the internal nucleophile stretches the C−Cl bond by 0.023 Å in

(21) In fact, we started with a geometry where the carbanion interacted most strongly with the methyl chloride but it relaxed to IVid.

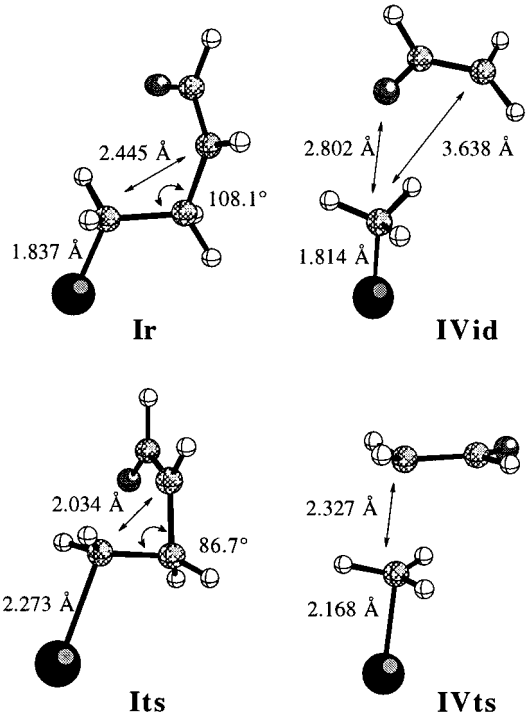


Figure 2. Structures involved in the reactions of the formyl-substituted systems. Geometries at the MP2/6-31+G(d) level (carbon, patterned; hydrogen, white; chlorine, black; and oxygen, gray).

comparison to the ion−dipole complex of the acyclic analogue (IVid).

Care must be taken in comparing the energetics of the reactions because the stability of the anionic site in Ir is enhanced by an ion−dipole interaction with the C−Cl bond. In other words, this intramolecular interaction makes the enolate in Ir less reactive than a typical enolate (e.g., acetaldehyde enolate). To take this into account, we have argued that in the acyclic analogue system, the ion−dipole complex (IVid) is a reasonable ground state for making comparisons with the cyclization process. By doing so, the reactivity of the nucleophiles in the two systems is balanced because the complex incorporates the ion−dipole interaction that is found in the substrate for cyclization. This can be seen in a comparison of the reaction enthalpies. At the MP2 level, the cyclization (Ir ⇒ Ip) is exothermic by 4.9 kcal/mol, whereas the conversion of IVid to products (propanal and chloride) is exothermic by 30.6 kcal/mol. The difference in reaction enthalpies (25.7 kcal/mol) is close to the expected strain (∼27 kcal/mol)[6,22] of the cyclization product (Ip). That is, the only energetic difference between the two systems is the strain energy in the cyclization product. Of course, this is absolutely necessary for the acyclic analogue to be a useful strain-free model. In contrast, if we were to use the separated reactants (acetaldehyde enolate and methyl chloride) as the ground state in the acyclic analogue system, the reaction would be 37.4 kcal/mol more exothermic than the cyclization and the strain energy in Ip would be grossly exaggerated. Consequently, we will adopt this convention throughout the discussion, and in each case, the ion−dipole complex will be used as the ground state in the acyclic analogue system.[23] A more detailed discussion of this choice has been presented elsewhere.[1]

Using IVid as the ground state for the acyclic analogue, the S_N2 activation barrier is 13.5 kcal/mol; however, the barrier to

(22) In each case, it is assumed that the strain in the substituted system is similar to the parent (cyclopropane). Available thermochemistry indicates that this will introduce only a small error; see ref 19.

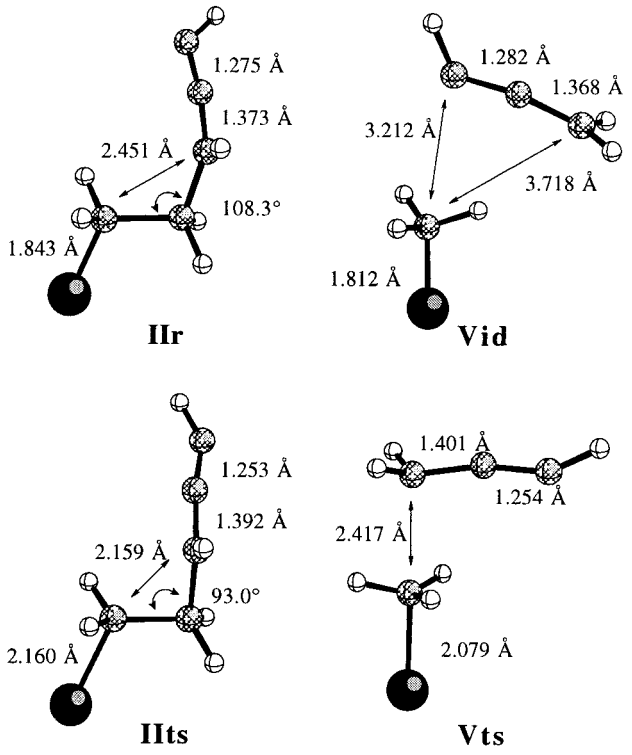


Figure 3. Structures involved in the reactions of the propargyl-substituted systems. Geometries at the MP2/6-31+G(d) level (carbon, patterned; hydrogen, white; and chlorine, black).

cyclization in Ir is only 8.9 kcal/mol. In other words, despite being over 25 kcal/mol less exothermic, the cyclization has a barrier that is about 5 kcal/mol smaller. This is striking anti-Hammond behavior and indicates that the proximity effect is operative and significant in this system. Because the transition state obviously suffers from angular strain (C−C−C angle = 87°), the proximity effect must be providing *more* than 5 kcal/mol of barrier lowering. This is an enthalpic advantage and would add to the known entropic advantage of the cyclization process.

Cyclization to Ethynylcyclopropane (IIp). The reactants and transition states for the reactions of the ethynyl-substituted systems are shown in Figure 3. The carbanions in these systems can be described as either propargyl or allenyl anions.

The geometries of the carbanion components of IIr and Vid indicate that both electronic structures contribute to the geometry. For example, the H−C≡C angle is much less than 180° (indicating allenyl character), but there is a significant difference in the lengths of the two C−C bonds (indicating propargyl character).[24] As in the previous system, the cyclization transition state has a C−C−C angle of ∼90° and occurs later on the reaction coordinate than the acyclic analogue.

(23) It can easily be shown that the low cyclization barriers are not an artifact of this choice. In the reverse reactions, the barrier to ring opening (Ip + Cl^- ⟹ Ir) is 30.3 kcal/mol smaller than the S_N2 barrier of IVp + Cl^- ⟹ IVr. For these calculations, the separated reactants are used as the ground state in each case, but the ring-opening transition state is favored by more than the entire ring strain of Ip. As a result, a factor other than ring strain must be at work.

(24) Cyclization with the allenyl anion resonance form acting as the nucleophile leads to a very unstable product (1,2-cyclopentadiene), and this process was not studied. Methylation at each of the carbons in $C_3H_3^-$ was investigated, and similar barriers were found for the formation of 1,2-butadiene and 1-butyne.

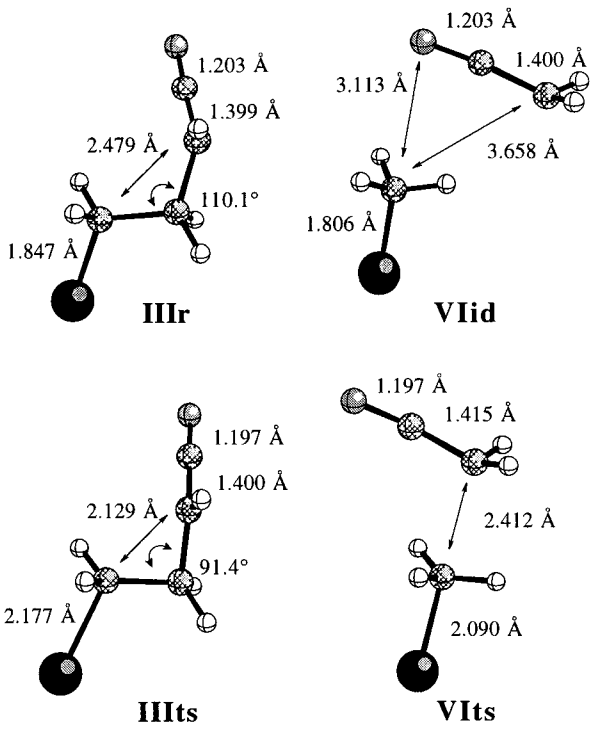


Figure 4. Structures involved in the reactions of the cyano-substituted systems. Geometries at the MP2/6-31+G(d) level (carbon, patterned; hydrogen, white; chlorine, black; and nitrogen, gray).

The propargyl anion is a more reactive nucleophile than the enolate, and these reactions are much more exothermic. However, when the enthalpies of the cyclization and the acyclic analogue are compared (IIr ⟹ IIp + Cl^- vs Vid ⟹ Vp + Cl^-), the difference (27.4 kcal/mol) is close to the expected strain energy in IIp. Therefore, V is a useful strain-free model for the cyclization of II. Once again, the cyclization barrier (4.1 kcal/mol) is smaller than the S_N2 barrier (8.3 kcal/mol) of the acyclic analogue. In this case, the proximity effect gives the cyclization a 4.2 kcal/mol advantage in terms of activation enthalpies.

Cyclization to Cyanocyclopropane (IIIp). The relevant structures in the reactions of the cyano-substituted anions are given in Figure 4. Relative to the two prior examples, the carbanions are more localized in these systems. The geometries are similar to those already described, and the transition state of the cyclization again has a C−C−C angle near 90°. Like the enolate, the strongest interaction in VIid is between the heteroatom (nitrogen) and the backside of the C−Cl bond.

The cyclization of IIIr is exothermic by 13.8 kcal/mol, whereas the S_N2 reaction of VIid is exothermic by 41.2 kcal/mol. The difference in reaction enthalpies (27.4 kcal/mol) again is close to the expected strain energy in the cyclization product (IIIp). As in the previous systems, the proximity effect overwhelms the angular strain of the transition state and the cyclization barrier is 2.9 kcal/mol smaller than the S_N2 barrier of VIid.

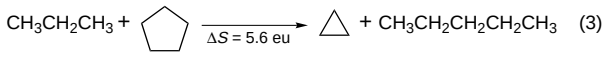
Discussion

Proximity Effect. The proximity effect is clearly operative in these systems, and the cyclization barriers are all smaller than the barriers of the corresponding acyclic, strain-free analogues—the cyclization advantage is about the same for each of the systems (varying from 2.9 to 4.6 kcal/mol). This is very similar to what we observed in the cyclization to thiirane (eq 1). Given these results, one must conclude that the proximity effect is general and should play a role in all nucleophilic cyclizations to three-

membered rings. This does not mean that all these cyclizations will have lower barriers than the strain-free analogues, but it does mean that the barriers will be surprisingly small given the apparent angular strain of the transition state.

As noted above, the proximity effect (an enthalpic effect) augments the known entropic advantage of cyclizations to small rings. The relative importance of the two effects can be evaluated in the following way. First, the observed proximity effect (barrier lowering) must be corrected for the strain in the transition state. Using typical molecular mechanics parameters for a C−C−C bend, the transition states (∠C−C−C = ∼90°) have about 3−4 kcal/mol of angular strain.[8,9] Combined with the cyclization advantages seen in these systems (∼3−5 kcal/mol), it can be concluded that the proximity effect provides 6−9 kcal/mol of stabilization to the cyclization.

Second, the entropic advantage of the cyclization must be estimated. Since most experiments have evaluated the ease of forming three-membered rings relative to analogous cyclizations to larger rings (five-membered rings in particular), we will use the same tactic in estimating the entropy effect. With a simple hydrocarbon model (eq 3), it can be seen that the overall entropic



(3)

advantage of forming a three-membered ring relative to a five-membered ring is only about 6 eu.[7] Assuming that the entropy advantage is fully realized in the transition state (i.e., $\Delta\Delta S \approx \Delta\Delta S^{\ddagger}$), the entropy provides only about 2 kcal/mol of barrier lowering ($\Delta\Delta G^{\ddagger}$) at 298 K. This is much smaller than our estimate of the proximity effect in these systems, and consequently, the major factor in the facile formation of three-membered rings (relative to five-membered rings) appears to be the proximity effect rather than an entropic effect.[6,25,26]

Variation of the Proximity Effect with Structure. The systems listed above give exothermic cyclizations with relatively early transition states (∠C−C−C = ∼90°). As the transition state moves to later on the reaction coordinate, the amount of angular strain in the transition state naturally will increase. At some point, this will overcome the proximity effect and the cyclization will be disfavored relative to an acyclic analogue. To investigate this point, the cyclization of the carbanion derived from 1-cyano-3-fluoropropane has been studied. This system is related to III, but the transition state occurs later because fluoride is a poor leaving group compared to chloride. In fact, the cyclization is calculated to be endothermic by 10 kcal/mol. Relevant structures for the cyclization and the acyclic analogue (eq 5) are given in Figure 5. In the transition state (VIIts), the C−C−C angle is reduced to 82.4°, which leads approximately to an 80% increase in the angular strain (∼7 kcal/mol using the MM2 bending term).[8,9] The energies listed in Table 1 indicate the cyclization barrier of VII is similar to the S_N2 barrier of the corresponding acyclic analogue (VIIIid). In this case, the angular strain of the transition state almost perfectly matches the advantage gained from the proximity effect and the cyclization has no enthalpic advantage.

Another way to reduce the proximity effect is to shift to a smaller nucleophile. In this case, steric repulsion is less important and the nucleophile pays a smaller energetic price in

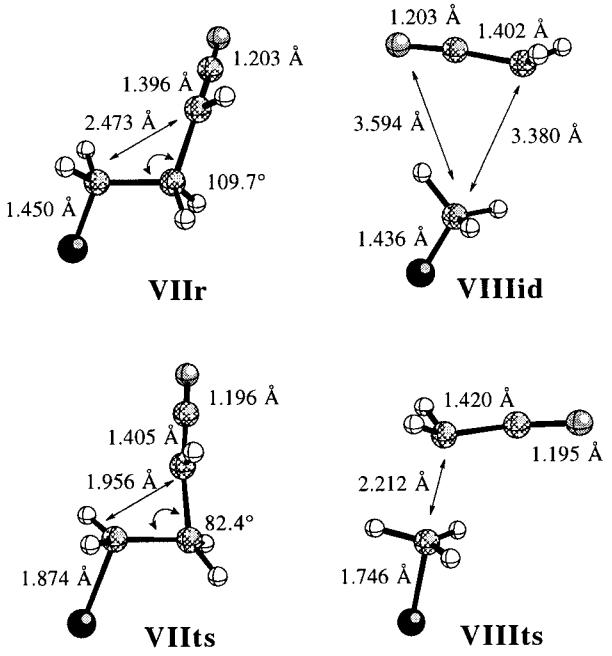
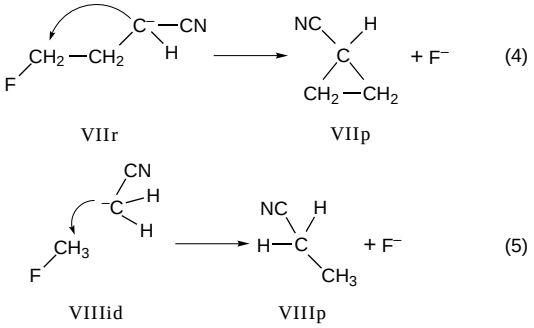
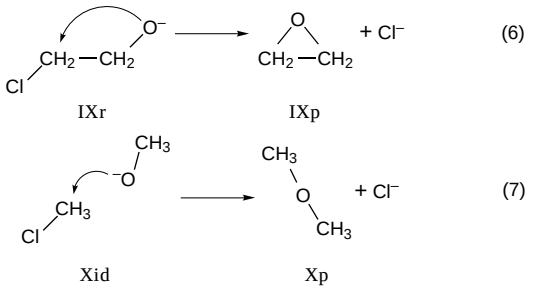


Figure 5. Structures involved in the reactions of the cyano-substituted systems with fluoride as the leaving group. Geometries at the MP2/6-31+G(d) level (carbon, patterned; hydrogen, white; fluorine, black; and nitrogen, gray).



approaching the backside of the C−Cl bond. As a result, much less is gained by forcing the nucleophile to start close to the electrophilic center (i.e., as in the cyclization substrates). This effect can be seen in the cyclization of 2-chloroethoxide to oxirane. Of course, the oxyanion presents a smaller nucleophile than the delocalized carbanions discussed above. The data for reactions 6 and 7 are given in Table 1, and relevant structures are shown in Figure 6.



Evidence for the small size of the nucleophile can be seen in the ion−dipole complex of methoxide with methyl chloride (Xid). The nonbonded C−O distance (2.685 Å) is the shortest of any of the complexes in this study. This is driven in part by the stronger complexation energy but is also due to the small size of the nucleophile. Further evidence is seen in the transition

(25) Examples have been reported where cyclizations to three-membered rings have large entropic advantages (>20 eu); however, these are undoubtedly the result of solvation effects.

(26) The entropic advantage of forming a three-membered ring is much greater when compared to an intermolecular S_N2 reaction; however, the proximity effect is still significant (it can provide nearly 50% of the free-energy advantage).

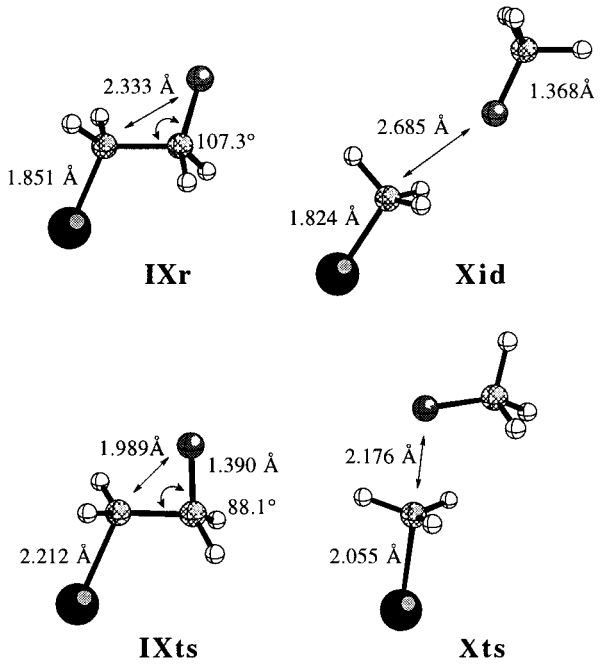


Figure 6. Structures involved in the reactions of the alkoxides. Geometries at the MP2/6-31+G(d) level (carbon, patterned; hydrogen, white; chlorine, black; and oxygen, gray).

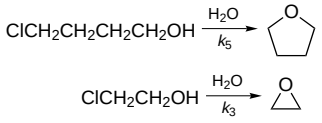
state (Xts) where the forming carbon−nucleophile bond (C−O) is the shortest of all the methyl chloride reactions. This is not an artifact of a late transition state because Xts also has the shortest C−Cl distance in the series.

In the reactions of the oxyanions, the cyclization to oxirane has a larger barrier (5.5 kcal/mol) than the corresponding S_N2 reaction (3.4 kcal/mol) of Xid, indicating that the proximity effect cannot overcome the angular strain of IXts.[27] As noted above, the proximity effect is attenuated in this system because the small size of the oxyanion reduces the steric repulsion associated with bringing the nucleophile close to the electrophilic site. Therefore, the advantage of the proximity effect (short distance between the nucleophile and electrophile) is less dramatic than in the previous systems where bulky nucleophiles were involved. Nonetheless, the difference in barriers (2.1 kcal/mol) is smaller than the angular strain in IXts, so the cyclization does derive some benefit from the proximity effect.

Comparison to Condensed-Phase Experiments. Although cyclizations to three-membered rings have been studied for many years, there is surprisingly little data concerning the activation energies of these processes.[3,6,28−31] Therefore, no direct comparisons can be made between our gas-phase systems and experimental data. However, some useful, qualitative comparisons can be made. In most cases, the data involve comparisons between forming three-membered rings and larger rings.

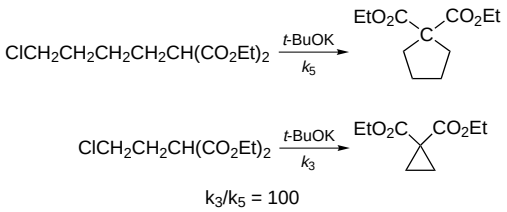
In terms of activation enthalpies and entropies, data are available for the ring closures of a series of ω-chloroalkylamines. In these systems, the $\Delta H^{\ddagger}$ values for forming three-membered rings are about 3 kcal/mol larger than for forming five-membered rings.[29] In contrast, the cyclizations of ω-chlorosulfides (to sulfonium ions) give $\Delta H^{\ddagger}$ values that are *smaller* for forming three-membered rings than for forming five-membered rings (by about 1.5 kcal/mol).[28] These and other condensed-phase results indicate that cyclizations to three-membered rings do not suffer from excessive strain in the transition state and therefore are not at a large disadvantage in terms of $\Delta H^{\ddagger}$. In fact, they may have lower activation enthalpies than cyclizations to five-membered rings—a clear manifestation of the proximity effect.[32]

Much more data are available for the relative rates of cyclizations. Analysis of the available data presents an interesting trend.[4,33−45] Cyclizations where the nucleophile is either an alcohol or an amine have higher rate constants for forming five-membered rings than for forming three-membered rings. For example, 4-chlorobutanol cyclizes to tetrahydrofuran 930 times faster than 2-chloroethanol cyclizes to oxirane.[43] Other examples include amines[41] and carboxylates[42] substituted with good leaving groups.



$k_3/k_5 = 1.08 \times 10^{-3}$

When the nucleophile is a stabilized carbanion, the opposite is true and k_3/k_5 ratios of up to 1000 have been observed. For example, the cyclization of the corresponding chloromalonates gives a k_3/k_5 ratio of 100.[44] Other examples include phenols (C alkylation),[35−37] enolates (C alkylation),[39] and sulfone-stabilized carbanions.[38,45] Sulfides also give k_3/k_5 ratios greater than unity.[40]



$k_3/k_5 = 100$

The trend is remarkably consistent, and numerous experimental examples fit this generalization.[46] This relationship between nucleophile type and ring size preference is easily rationalized by our computational data and the proximity effect.[47] We have

(27) The difference is not the result of additional angle strain in the cyclization transition state. The O−C−C angle is about the same as the C−C−C angles in the carbanion systems. In fact it is wider than the C−C−C angle in the enolate system.

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(46) In fact, it is difficult to find exceptions. One exception involves systems where an aniline nitrogen is the nucleophile—a higher rate constant for forming a three-membered ring is observed. However, delocalization is possible, and therefore, it is not surprising that they do not behave like simple amines. See ref 29.

shown that the proximity effect is sensitive to the size of the nucleophile and is less important with small, localized nucleophiles (i.e., oxygen and nitrogen). In this case, the proximity effect is too small to overcome the angular strain of the transition state for forming a three-membered ring. When bulky, delocalized nucleophiles are involved (i.e., carbanions), the proximity effect is enhanced and cyclization to a three-membered ring becomes more favorable kinetically.

Conclusions

In comparison to acyclic analogues, cyclizations to three-membered rings have unusually small enthalpic barriers because in the cyclization substrate, the nucleophile is held in close proximity to the electrophilic site ("proximity effect"). Consequently, the system does not have to pay the energetic price of forcing the nucleophile to approach the electrophile (steric repulsion), and therefore, a portion of the S_N2 barrier is built into the cyclization substrate. For the cyclizations of 3-chlorocarbanions to cyclopropanes, the proximity effect amounts to 6−9 kcal/mol of barrier reduction and can outweigh the angular strain of the transition state. As a result, the cyclization barrier can be smaller than the S_N2 barrier of an analogous, acyclic ("strain-free") system. The proximity effect is purely enthalpic and augments the known entropic advantage of forming three-membered rings. However, it appears that in many cases, the proximity effect may be the most important factor in facile cyclizations to three-membered rings. Finally, these results are reminiscent of the classic work of Ruzicka, who stated over 70 years ago that the barrier to cyclizations is related to the distance between the reaction partners.[48]

Acknowledgment. We thankfully acknowledge the financial support provided by the donors of the Petroleum Research Fund, administered by the American Chemical Society (PRF-30674-B4).

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(47) All the cyclizations to three-membered rings have an entropy advantage. It is the shift in preference from five-membered rings to three-membered rings that involves the proximity effect.

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