Theoretical Studies on the Gas-Phase Nucleophilic Ring Opening of 3,4-Epimino-, 3,4-Epoxy-, and 3,4-Epithio-1-butene

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Received: October 21, 1996⊗

The ring opening reaction of 3,4-epimino-1-butene (EIP), 3,4-epoxy-1-butene (EOB) and 3,4-epithio-1-butene (ETB) initiated by the attack of hydroxide ion at three carbons (C^{α}, C^{γ}, and C^{δ}) have been investigated using MP2/6-31+G*//MP2/6-31+G* *ab initio* molecular orbital theory. The $C^{\alpha}{=}C^{\beta}\overline{C^{\gamma}C^{\delta}X}$ process by the α-attack is favored by the strong frontier orbital interactions due to the low π^* orbital, but is disfavored by a lower degree of progress in the developing π orbital as well as in the ring opening. In contrast, the processes by the γ-and δ-attacks are disfavored by the high σ^* orbitals, but are favored by a greater strain energy release in a greater degree of ring opening in the transition state. The barriers to the ring opening processes are found to depend on the strain energy of the three-membered heterocycles, bond strength of the C−X bonds, frontier orbital (π^*, $\sigma^*_{(1)}$, and $\sigma^*_{(2)}$) levels, exothermicity of the reaction, and steric and entropy effects.

Introduction

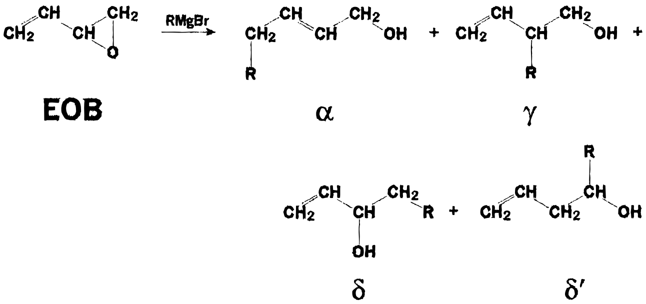
Three-membered heterocycles show higher reactivity than their acyclic analogs because of bond weakening due to the inherent ring strain; for example, nucleophilic additions to oxiranes and their sulfur analogs, thiiranes, are well-known,[1] although nucleophilic reactions of ethers and thioethers are rare. The reaction of 3,4-epoxy-1-butene (EOB) with alkyl and aryl Grignard reagents has been shown to result in diverse mixtures of alcohols, α, γ, δ, and δ' type adducts in Scheme 1.[2] On the other hand, diphenylcopper lithium (R_2CuLi with $R = C_6H_5$) in ether−benzene, 5:1, and EOB are reported to give a mixture of α and γ derivatives only.[3] The high strain energy (conventional strain energy of 26.9 kcal mol^{-1})[4] in the oxirane ring overcomes the disadvantage of cleaving a strong C−O bond (bond energy of 85 kcal mol^{-1}).[5]

The thiiranes also react with nucleophiles to result in a wide variety of products.[1,6] The most common reaction is nucleophilic attack at a ring carbon to give an addition product.

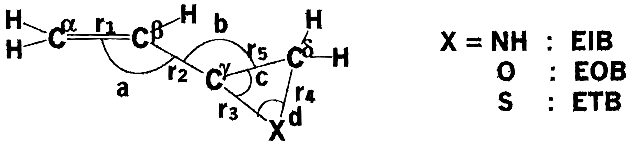
In addition to these nucleophilic addition products, alkyl substituted oxiranes undergo elimination reactions to yield allylic alcohols when strong, nonnucleophilic bases are used.[7] Little work has been reported, however, on the reactivity of alkylthiiranes with strong, nonnucleophilic bases, although elimination is known to occur in systems activated at a β-carbon.[8] It is also known that alkyllithiums attack at sulfur in the thiiranes thereby producing an alkene and the lithium salt of an alkyl thiolate.[9]

In recent years, various gas phase kinetic studies have been conducted to elucidate the mechanisms of substitutions, eliminations, and other nucleophilic processes. These gas phase studies have provided valuable and important insights into reaction mechanisms through measurements of rates that are dependent only on the reaction partners without any interferences from solvent or ion-pairing effects. Majority of the gas phase studies was, however, on S_N2[10] and acyl transfer reactions,[11] and relatively little work has been reported on the reactivity of three-membered ring heterocycles. The gas phase reaction of OH^- with oxirane was reported to give an addition product which subsequently loses molecular hydrogen subsequently.[12] The reactions of OH^- with alkyloxiranes, methyl or 1,2-dimethyloxirane, in the gas phase have no addition products, however, but resulted in elimination products, such as allylic alkoxides, only.[13] The only observed product of the reaction of SH^- with thiirane was the addition compound $HSCH_2CH_2S^-$.

SCHEME 1



SCHEME 2



Theoretical works on the ring-opening reaction of small ring heterocycles are also scarce. Cremer and Kraka[15] have reported *ab initio* studies of ring strains in various three-membered heterocycles. Ford and Smith[16] have studied the gas phase unimolecular ring opening of protonated oxirane using *ab initio* MO methods. Gronert and Lee[14] carried out *ab initio* studies of addition and elimination reactions of methyloxirane with OH^- and methylthiirane with OH^- and SH^-. Glad and Jensen[17] have reported high-level calculations on the reactions of oxirane with a series of nucleophiles.

Theoretical,[18] as well as gas phase experimental results,[19] have shown that elimination can be competitive with substitution for localized, first-row nucleophiles such as OH^-. In this work, however, we have focused on the nucleophilic ring opening reactions of three-membered heterocycles in 3,4-epimino- (EIB), 3,4-epoxy- (EOB), and 3,4-epithio-1-butene (ETB), $C^{\alpha}H_2{=}C^{\beta}H\text{-}\overline{C^{\gamma}HC^{\delta}H_2X}$ (where X = NH, O, and S, respectively) with hydroxide ion.

The main purpose of the present work is to explore systematically, through *ab initio* calculations, the effects of the

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⊗ Abstract published in *Advance ACS Abstracts,* March 1, 1997.

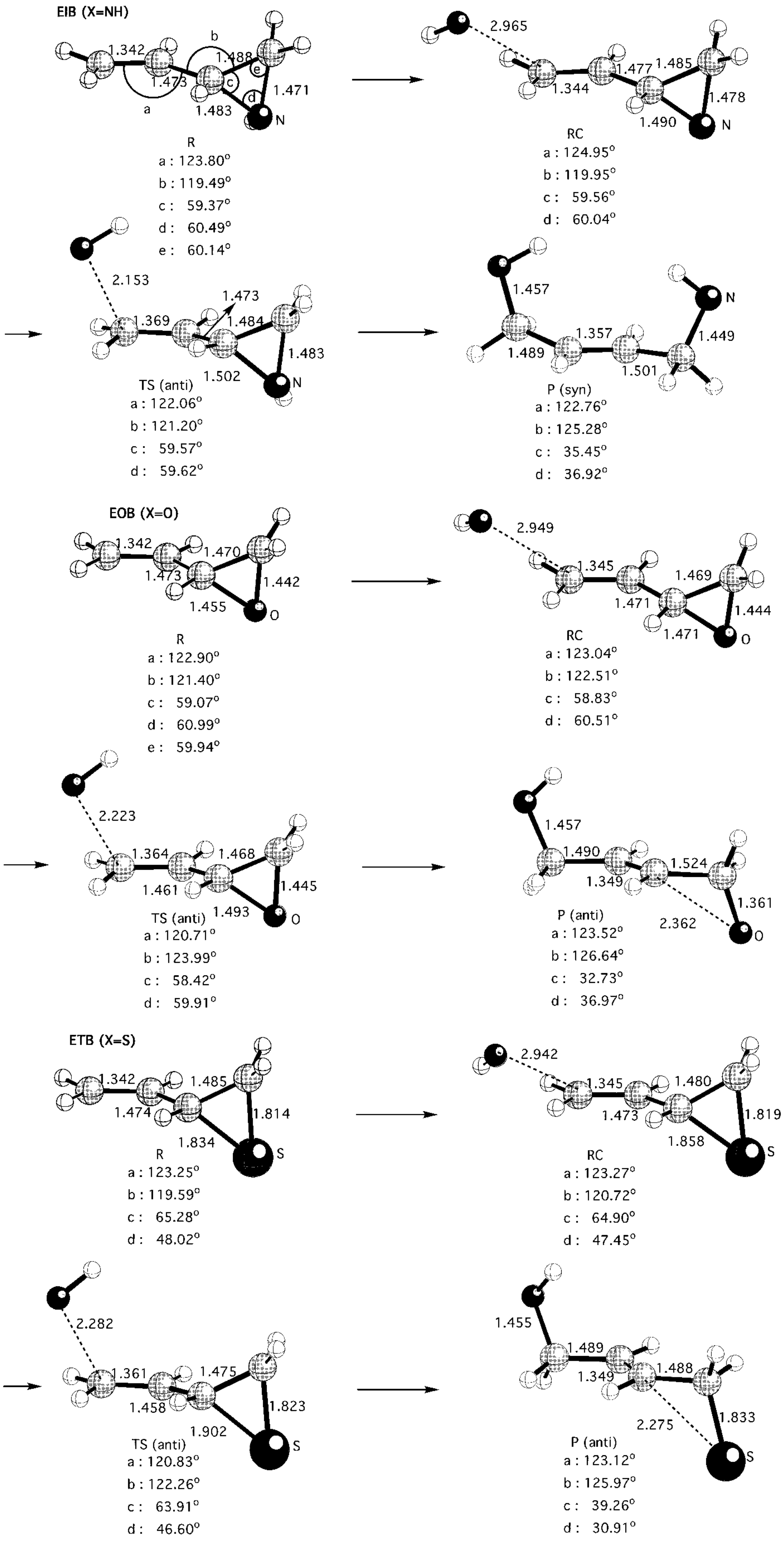

Figure 1. Structures of reactants (R), reactant complexes (RC), transition states (TS), and products (P) involved in the ring opening initiated by nucleophilic attack of OH^- at C^α.

heteroatom X on the mode of nucleophilic ring opening; OH^- may attack and add at α, γ, or δ positions resulting in the α–δ-type adducts in Scheme 1, the preference of which will be dependent upon the heteroatom X. We have examined factors that affect the relative activation barriers to nucleophilic additions at three positions α, γ, and δ. Numbering is shown in Scheme 2, where α–δ are carbons, r_1–r_5 are bonds or bond lengths, a–d are angles, and X is a heteroatom.

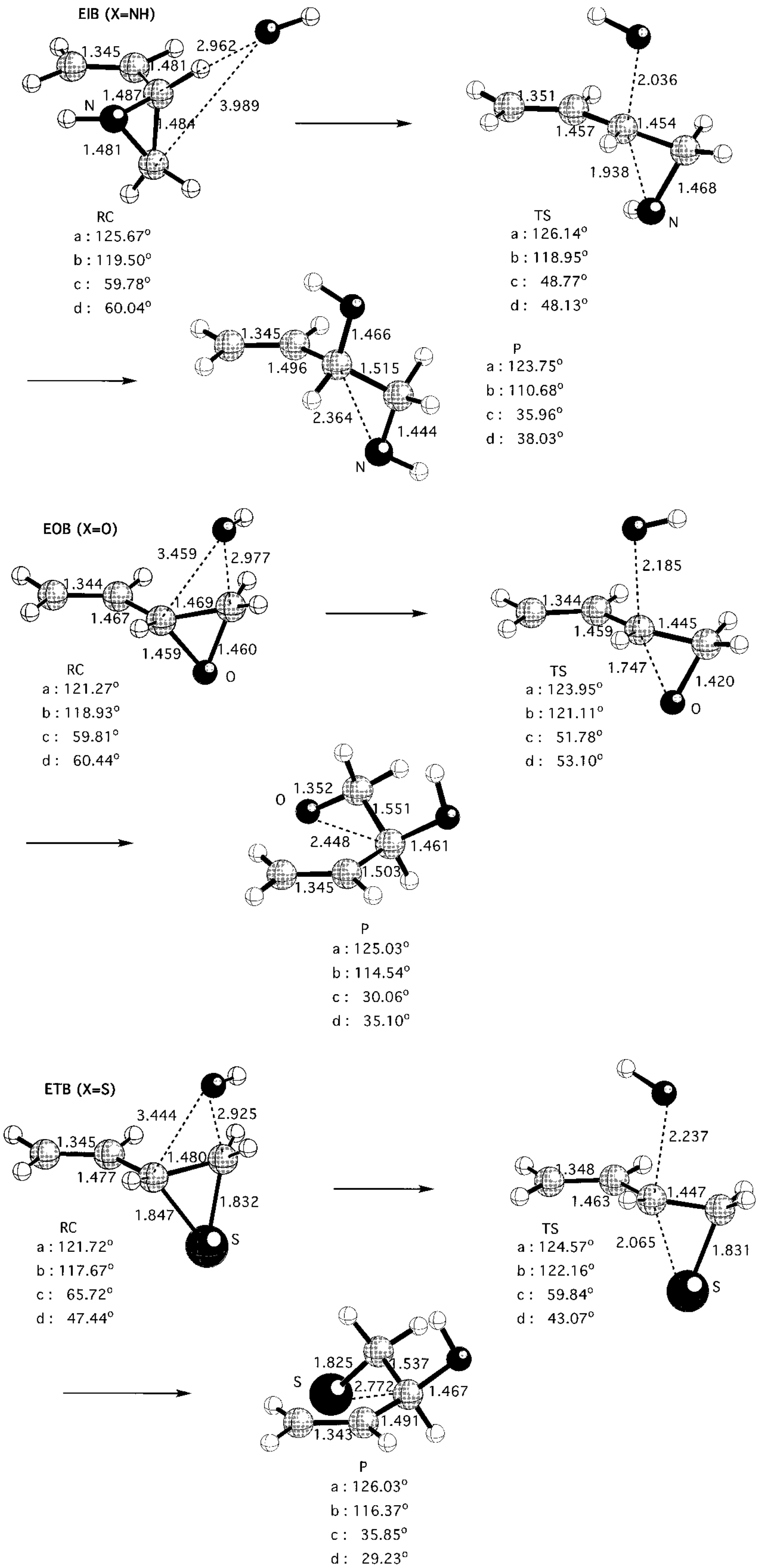

Figure 2. Structures of reactant complexes (RC), transition states (TS), and products (P) involved in the ring opening initiated by nucleophilic attack of OH^- at C^γ.

Calculations

All calculations have been carried out using the Gaussian 92 program packages.[20] Geometries of the stationary point species on the reaction coordinates were fully optimized using the 6-31+G* basis sets. Electron correlation effects were accounted for by Møller−Plesset perturbation theory through second order (MP2:FULL).[21] All the stationary point species including the transition state (TS) were confirmed by calculating the harmonic frequencies at both RHF and MP2 levels of theory. No frequency scaling has been employed. Corrections were made for zero-point energy differences, thermal energies, and entropy changes to derive Gibbs free energies of reaction, ΔG^0, and

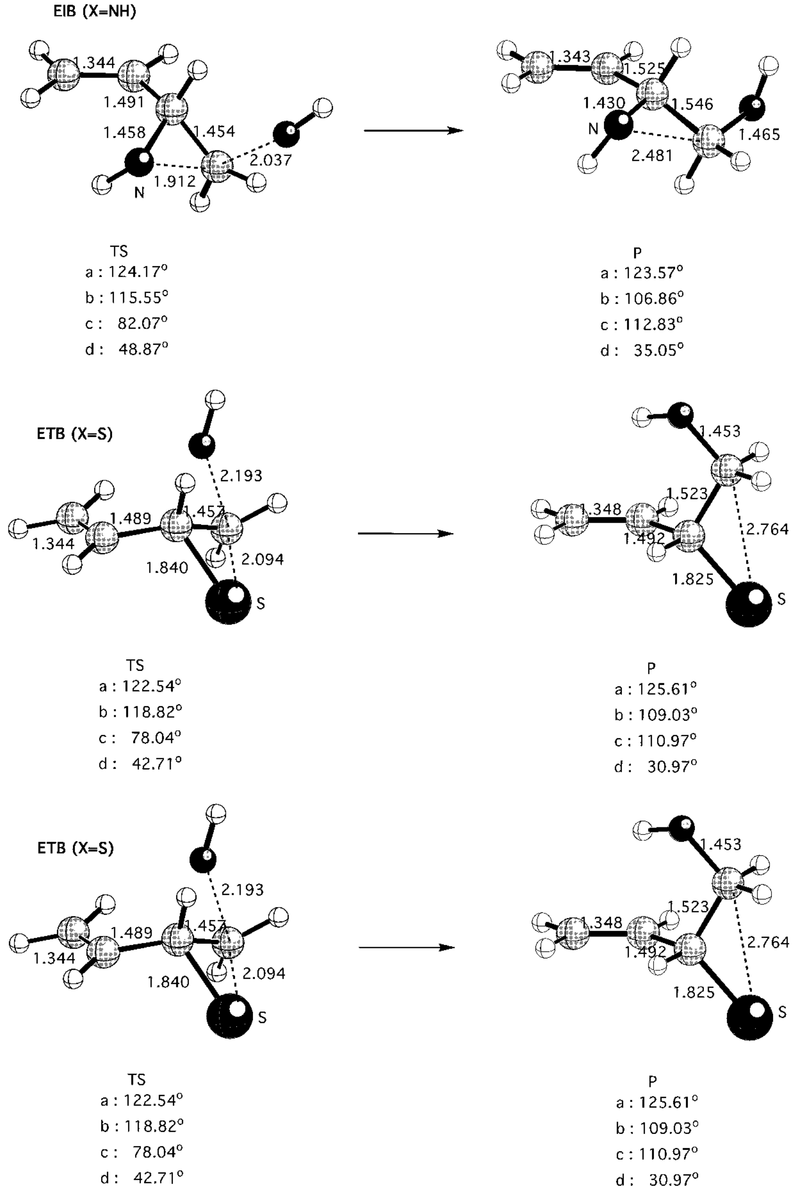

Figure 3. Transition states (TS) and products (P) involved in the ring opening initiated by nucleophilic attack of OH^- at C^δ.

activation, $\Delta G^\ddagger$. Natural bond orbitals (NBO) were used in the analysis of frontier orbital interactions.

Results and Discussion

The three-membered rings in 3,4-epimino-1-butene (EIB) and 3,4-epoxy-1-butene (EOB) are almost regular, but the three-membered heterocycle with X = S in ETB has longer r_3 (S$-$C$^\gamma$) and r_4 (S$-$C$^\delta$) bonds than r_5 (C$^\gamma-$C$^\delta$) so that the angle at S is far more acute ($\angle d = 48°$) than the other two ($\sim 65°$). In the α-addition of OH^-, a loosely bound, ion$-$dipole complex (reactant complex, RC) is formed between OH^- and a hydrogen on C$^\alpha$, whereas for the γ and δ-additions, a common, ion$-$dipole complex is obtained between the OH^- ion and a hydrogen on C$^\gamma$ as well as one on C$^\delta$. In both of these two types of ion$-$dipole complex formations, geometries of the reactants change very little.

In the ring opening reaction initiated by OH^- attack at α-carbon of EIB, the product has a syn structure in which the two heteroatoms, NH and OH, are facing each other on the same side of the molecular frame. The syn form corresponds to the global minimum, since optimization starting from an anti form invariably leads to the syn form. This is a result of overcoming unfavorable steric repulsion by forming two weak hydrogen bonds between a hydrogen on one heteroatom toward the other heteroatom. The structures of the reactants, reactant complexes, transition states and products are shown in Figures 1$-$3. Energetics for the ring opening initiated by attack at the α-, γ- and δ-carbon of the three compounds with X = NH (EIB), O (EOB), and S (ETB) are summarized in Table 1.

Nucleophilic Attack at C$^\alpha$. The ring opening initiated by the nucleophilic attack of OH^- at C$^\alpha$ corresponds to an allylic S$_N$2′ process leading to a rearranged product: a π-bond between C$^\alpha$ and C$^\beta$ shifts to that between C$^\beta$ and C$^\gamma$ in the reaction. In this process, one π and one σ (r_3) bonds are broken while a new π-bond is formed. The π^* orbital is the lowest unoccupied MO (LUMO), and hence provides the most favored frontier orbital (FMO) interaction with the nonbonding (n) orbital, which is the highest occupied (HOMO) of the OH^- nucleophile, Figure 4. Thus the ring opening initiated by the attack at C$^\alpha$ leading to an α-addition should be the lowest pathway provided other conditions are equal. However, as noted above in the α-attack, two bonds (a π and a σ) are required to be broken, whereas in the γ-and δ-attack only one σ bond (r_3 or r_4) breaks. The α-attack will not cause any disadvantage if the developing π (on r_2) bond is formed synchronously with the breaking π-bond (on r_1) and the two π-bonds have the same bond strength.

TABLE 1: Calculated Electronic Energies of the Stationary Point Species on the Potential Surface at the MP2/6-31+G*//MP2/6-31+G* Level

			activation and reaction energy[g]									
	initiated attack at	electronic energy,[d] R	$\Delta E^{\ddagger}$	ΔE^{0}	$\Delta E_{o}^{\ddagger}$	$\Delta(\mathrm{ZPE})^{\ddagger}$ [e]	$\Delta(\mathrm{PV})^{\ddagger}$ [f]	$-\Delta TS^{\ddagger}$	$-\Delta TS^{0}$	$\Delta G^{\ddagger}$	ΔG_{o}	$\Delta G_{o}^{\ddagger}$
X = NH	C^{α}	−286.22324	−5.46	−18.14	8.58	0.84	0.67	8.66	9.06	4.71	−4.40	10.02
(27.7)[a]	C^{γ}	−286.22324	5.07	−13.42	20.46	−0.05	−0.09	9.30	9.01	14.23	−1.78	20.23
(73)[b]	C^{δ}	−286.22324	4.77	−18.47	20.15	0.05	0.00	8.89	9.41	13.71	−5.62	19.70
X = O	C^{α}	−306.06894	−7.83	−38.43	6.66	0.71	0.61	8.59	9.11	2.08	−23.47	8.06
(26.9)[a]	C^{γ}	−306.06894	−6.73 (−4.0)[c]	−39.97	13.22	0.35	0.37	8.71	9.78	2.70	−25.45	11.85
(85)[b]	C^{δ}	−306.06894	−8.31 (−6.6)[c]	−45.46	11.63	0.57	0.55	8.67	10.43	1.48	−29.23	10.62
X = S	C^{α}	−628.69763	−8.60	−48.41	6.12	0.66	0.68	8.27	9.14	1.01	−31.00	7.22
(19.7)[a]	C^{γ}	−628.69763	−12.81 (−9.0)[c]	−46.64	9.25	0.73	0.75	8.84	9.82	−2.49	−29.45	8.59
(65)[b]	C^{δ}	−628.69763	−13.74 (−11.8)[c]	−54.34	8.33	1.16	0.98	9.33	9.92	−2.27	−36.44	8.83

[a] Conventional strain energy of the three-membered heterocycles in kcal/mol.[4] [b] Bond energy of the CX bond in kcal/mol.[5] [c] Barrier height from the isolated reactants for methyloxirane[14] calculated at the MP2/6-31+GG** level. [d] Electronic energy of reactants in hartrees. [e] Zero-point energy correction term, in kcal mol^{-1}. [f] Thermal energy correction term, in kcal mol^{-1}. [g] ln kcal mol^{-1}.

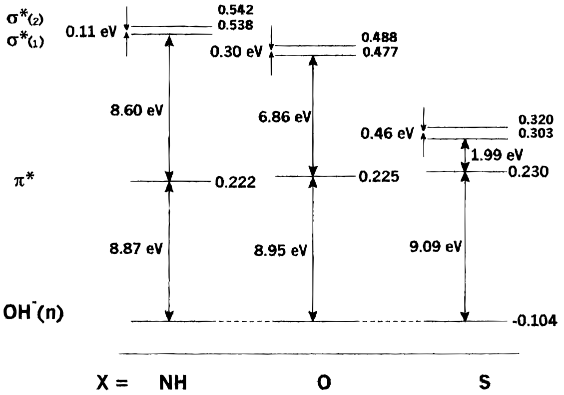

Figure 4. Frontier molecular orbitals (levels in hartree and level gaps in eV, based on natural bond orbitals). The $\sigma^{*}_{(1)}$ and $\sigma^{*}_{(2)}$ obitals are σ antibonding orbitals for the X−C$^{\gamma}$ and X−C$^{\delta}$ bonds, respectively.

However, we find that this is not the case; the developing π-bond invariably lags behind the progress in the π-bond cleavage in the TS, *i.e.*, the two π-bond changes in the activation are not perfectly synchronized (nonperfect sychronization)[23] as evidenced by the percentage changes of the orders of the π-bonds, $\%\Delta n^{\ddagger}$, which is defined by eq 1 where $n^{\ddagger}$, n_{R}, and n_{P}

$$\%\Delta n^{\ddagger} = \{(n^{\ddagger} - n_{\mathrm{R}})/(n_{\mathrm{P}} - n_{\mathrm{R}})\}100 \qquad (1)$$

are the orders of the corresponding bond in the TS, reactant, and product, respectively. Introducing the Pauling type relationship,[25] eq 2, leads to a convenient form, eq 3, in which r_{o}, the

$$n = \exp[(r_{\mathrm{o}} - r)/a] \qquad (2)$$

$$\%\Delta n^{\ddagger} = \frac{[\exp(-r^{\ddagger}/a) - \exp(-r_{\mathrm{R}}/a)]}{[\exp(-r_{\mathrm{p}}/a) - \exp(-r_{\mathrm{R}}/a)]}100 \qquad (3)$$

length of a “normal” bond of the same kind (arbitrarily given as $n_{\mathrm{o}} = 1.00$), disappears. For interpolation between bond orders in the range 1−3, the constant a is usually set to 0.26 (or 0.3).[25,26] This value is, however, too small for extrapolating to bond orders less than 1, and the a values in the range 0.6−1.0 are reported to be more appropriate.[24,27] Adopting $a = 0.6$ and 0.9, we calculated the $\%\Delta n^{\ddagger}$ values for the relevant bonds as summarized in Table 2. We note that for the α-attack, the two values calculated with $a = 0.6$ and 0.9 are practically the same. Clearly, the developing π-bond (r_2) lags behind the cleaving π-bond (r_1). The progress of ring opening (cleavage of r_3) is also less than that for the π-bond (r_1) cleavage in the TS except for the X = S case, for which the ring opening (*ca.* 20%) occurs before the π-bond cleavage (14%). This is most probably due to the weak bond strength of the C−S bond (bond energy[5] of 65 kcal mol^{-1}) in contrast to the stronger bond strength of C−N (bond energy of 73 kcal mol^{-1}) and C−O (bond energy of 85 kcal mol^{-1}) bond. It is also to be noted that the ring opening has an advantage of strain energy release (*vide infra*). The TS for the α-attack is reached relatively early on the reaction coordinate, from *ca.* 20% (EIB) to 14% (ETB) of π-bond cleavage, even though the progress of bond formation between OH^{-} and C$^{\alpha}$ is somewhat greater, from *ca.* 25% (EIB) to 21% (ETB). We note that the progress of π-bond formation (r_2) is much smaller than either of these. It is quite interesting, however, the progress of ring opening initiated by the α-attack is ahead of that for π-bond formation for ETB; the progress of ring opening is the same as that of bond formation (21%). The progress of ring opening in the TS is no doubt closely related to the strain energy of the ring,[4,15] which is released, and the bond energy of the C−X bond, which should be supplied. On the other hand, the progress in the developing π (r_2) bond should be dependent on the progress of the π-bond (r_1) cleavage as well as on the progress of ring opening. This is why the $\%\Delta n^{\ddagger}$ values for π-bond development (r_2) increase from EIB to ETB.

TABLE 2: The $\%\Delta n^{\ddagger}$ Values Calculated with $a = 0.6$ (Upper Value) and 0.9 (Lower Value)

	X = NH				X= O				X = S			
	r_1	r_2	r_3	r_4	r_1	r_2	r_3	r_4	r_1	r_2	r_3	r_4
	20	0	4		16	9	8		14	12	21	
C^{α}-attack	(25)[a]				(22)				(21)			
	20	0	3		16	9	7		14	12	19	
			69				48				40	
C^{γ}-attack			(33)				(27)				(25)	
			64				41				35	
				64				47				47
C^{δ}-attack				(38)				(26)				(23)
			57				41				41	

[a] Values in the parentheses are the $\%\Delta n^{\ddagger}$ values for bond formation between OH^{-} and C$^{\alpha}$, C$^{\gamma}$, and C$^{\delta}$, respectively, calculated with $a = 0.6$.

The ring-opening process is overall exothermic, and the exothermicity increases in the order EIB < EOB < ETB. We find that the TS for the α-attack process occurs successively earlier on the reaction coordinate and also the barrier heights becomes successively lower in that order, in accordance with the Bell−Evans−Polani (BEP) principle.[28]

Nucleophilic Attack at C$^{\gamma}$ and C$^{\delta}$. The ring opening initiated by a nucleophilic attack of OH^{-} at C$^{\gamma}$ and C$^{\delta}$ is a simple S$_{\mathrm{N}}$2 type process. The ion−dipole complex is common to both the attack at C^{γ} and C^{δ} (Figure 2). Examination of Figure 4 reveals that the σ LUMOs for the ring opening by the $\gamma-\sigma^*_{(1)}$ (σ-antibonding orbital between C^{γ} and X) and $\delta-\sigma^*_{(2)}$ (σ-anitibonding orbital between C^{δ} and X) attacks are much higher than the π^* level. This means that the γ- and δ-attack-processes are expected to be much more unfavorable, especially for EIB and EOB, than the α-attack process when the aspect of frontier orbital interaction only is considered for the reactivity. The barrier heights ($\Delta G_o^{\ddagger}$ as well as $\Delta G^{\ddagger}$) to the γ-attacks for EIB and EOB are indeed higher than the barriers to the α-attacks. However, there is a large difference in the barrier height between α- and γ-attack for EIB, $\delta\Delta G^{\ddagger} = \Delta G_{\gamma}^{\ddagger} - \Delta G_{\alpha}^{\ddagger} \cong 10$ kcal mol^{-1}, in contrast to a very small $\delta\Delta G^{\ddagger}$ (<1.0 kcal mol^{-1}) for EOB. This large difference in $\delta\Delta G^{\ddagger}$ between EIB and EOB mostly results from very large exothermicities of the reactions for EOB ($\Delta G^0 = -23$ to -25 kcal mol^{-1}) compared to a much lower ΔG^0 (-2 to -4 kcal mol^{-1}) for EIB, besides a reversal in the order of product stability: $\Delta G_{\alpha}^0 < \Delta G\gamma^0$ for EIB whereas $\Delta G_{\alpha}^0 > \Delta G\gamma^0$ for EOB. For ETB, the σ^* levels are only higher by *ca.* 2 eV than the π^* level, which is in contrast to 7−8 eV differences for EIB and EOB. Since steric effects (secondary(δ) *vs* tertiary(γ) carbon) and exothermicity favors the δ-attack (Table 1), the δ-attack is preferred to the γ-attack for EOB, albeit the $\sigma^*_{(2)}$ level for the δ-attack is higher by *ca.* 0.3 eV than the $\sigma^*_{(1)}$ level for the γ-attack. In contrast, however, the larger energy gap between the two σ^* levels (*ca.* 0.5 eV) makes the γ-attack more favorable than the δ-attack for ETB. Besides the lower $\sigma^*_{(1)}$ level, entropy effects (Table 1) also seem to favor the γ-attack.

Overall, the barriers ($\Delta G^{\ddagger}$) to ring opening initiated by the γ- and δ-attacks are much lower (by more than 10 kcal mol^{-1}) for EOB and ETB than those of the corresponding processes for EIB (Table 1). The factors controlling these large barrier height differences are (i) much higher σ^* levels than the π^* level and (ii) lower exothermicity (by *ca.* 20−30 kcal mol^{-1}) for EIB than for EOB and ETB. Reference to Table 2 reveals that for the γ- and δ-attack processes, the progress of ring opening in the TS (%$\Delta n^{\ddagger} \cong$ 40%−70%) is *ca.* twice of that for bond formation by OH^- (%$\Delta n^{\ddagger} \cong$ 20−40%). This is in contrast to the rather low degree of ring opening in the TS for the α-attack processes (except for ETB (~20%), ring opening is less than 10%). According to the Leffer−Hammond postulate,[28,29] the slope A in eq 4 can be taken as a measure of the

$$\delta\Delta G^{\ddagger} = \mathrm{A}\delta\Delta G^0 \qquad (4)$$

TS position along the reaction coordinate. The plot of $\Delta G^{\ddagger}$ against ΔG^0 gave $A \cong 0.1$ and $A \cong 0.5$ for the α-attack and for the γ-and δ-attack processes, respectively. The extents of reaction progressed at the TS (*ca.* 10% and 50%, respectively) are in fair agreement with our estimates made using the %$\Delta n^{\ddagger}$ values for the ring opening (cleavage of r_3 and r_4 in Table 2).

The fact that over 50% of the ring opening occurs in the γ- and δ-attack TS suggests that the majority of the ring strain is released in the TS in spite of the fact that the TS is reached early on the reaction coordinate. The greater extent of ring-strain release in advance of the progress of bond making by OH^- in the γ-and δ-attacks than in the α-attack should provide a major part of driving force (lowering of the barrier height) for the ring opening initiated by the γ- and δ-attack which overcomes the disadvantage of unfavorable FMO interaction due to much higher σ^* levels.

Gronert and Lee[14] reported that the addition of a methyl group to the carbon adjacent to the reaction center in the ring opening of oxirane by OH^- reduces the barrier by *ca.* 1.5 kcal mol^{-1} (at the MP2/6-31+G* level of theory) due to the polarizability of the methyl group stabilizing the charged TS. Examination of Table 1 reveals that the addition of a vinyl group instead of a methyl group lowers the barrier further by 2−4 kcal mol^{-1} (total of *ca.* 4−6 kcal mol^{-1} relative to oxirane and thiirane). Similarly, in the identity chloride exchange (S_N2) reactions, $Cl^- + RCH_2Cl \rightleftharpoons RCH_2Cl + Cl^-$, substitution of a vinyl (R = CH_2-CH_2) for a methyl (R = CH_3) group was found to lower the activation barrier by ~4 kcal mol^{-1} at the MP2/6-31+G* level of theory.[30] The ability to stabilize the charged TS by a vinyl group is therefore considerably stronger than that achieved of a methyl group.

In summary, the ring opening process initiated by the attack at C^{α} is favored by the strong FMO interaction due to the low π^* orbital of the butenes, but is disfavored by a lower degree of progress in the developing π as well as in the ring opening. In contrast, however, the ring opening processes by the attack at C^{γ} and C^{δ} are disfavored by the high σ^* orbitals, but are favored by a greater strain energy release in a more advanced degree of ring opening in the TS. For EOB the two σ^* orbitals are also high and are very close together, but for ETB the two are relatively low and are relatively more apart: these together with the greater exotherimicity for ETB than for EOB lead to comparable barriers to the ring opening by the γ- and δ-attacks for EOB and ETB

Acknowledgment. We thank Inha University and the Korean Ministry of Education through Research Fund (BSRI-96-3428) for support of this work.

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