

# Structural and Solvent Effects on the Mechanism of Base-Induced Rearrangement of Epoxides to Allylic Alcohols

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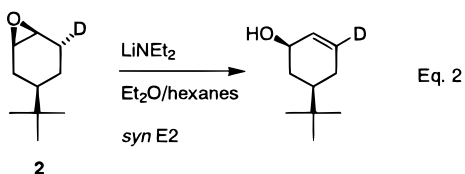
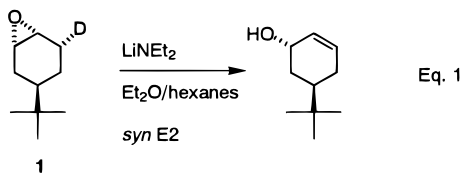
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A combined experimental and computational study is presented which explores the influence of structure and solvent on the base-catalyzed isomerization of cyclopentene- and cyclohexene oxides. Cyclohexene oxide is known to rearrange via a *syn*  $\beta$ -elimination in nonpolar solvents. Cyclopentene oxide instead undergoes  $\alpha$ -elimination to a carbenoid intermediate in nonpolar solvents due to the unusual acidity of the  $\alpha$ -proton, not because of an unfavorable conformation. In HMPA, cyclopentene oxide undergoes  $\beta$ -elimination. To explore the origins of this mechanistic change, deuterium-labeled *cis*-4-*tert*-butylcyclohexene oxide was rearranged in HMPA and was found to react via *anti*  $\beta$ -elimination, as presumably do cyclopentene oxide and other epoxides.

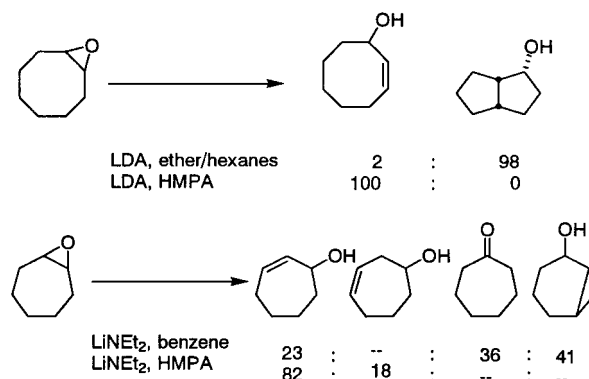
## Introduction

Base-promoted rearrangement of epoxides often provides a convenient method to prepare allylic alcohols in high yield.<sup>1</sup> Asymmetric variants of this reaction have been the subject of recent investigation.<sup>2</sup> As such, it is desirable to understand the mechanistic details as well as limitations of this reaction. An elegant experiment by Rickborn and Thummel revealed that the rearrangements of substituted cyclohexene oxides **1** and **2** are *syn*  $\beta$ -eliminations when conducted in ether/hexanes (eqs 1, 2).<sup>3</sup> The nonpolar solvent promotes ion pairing which drives the elimination to occur via the normally less favorable *syn* pathway.



However, in some medium-ringed cyclic and bicyclic epoxides, ketones and cross-ring insertion products are

## Scheme 1



obtained in nonpolar media.<sup>1</sup>  $\alpha$ -Elimination to a carbenoid intermediate is consistent with the products formed (for example, see Scheme 1). A higher or exclusive yield of allylic alcohol is found when the rearrangement is conducted in a polar solvent such as hexamethylphosphoramide (HMPA).<sup>1,4</sup> The aggregation, and hence reactivity, of lithium amides is a complex issue depending on solvent, amide substituents, and substrate; in general, donor solvents such as HMPA tend to increase the reactivity of lithium amides.<sup>5</sup> Ramirez and Collum found that  $\alpha$ -eliminations occur with epoxide complexed to dimeric lithium diisopropylamide (LDA) having ethereal or hemilabile ligands, while  $\beta$ -eliminations undergo a monomer-based reaction.<sup>6</sup> Clearly, epoxide structure and solvent are influential in the course of base-promoted epoxide rearrangement.

Deuterium-labeling studies showed that cyclopentene oxide rearrangement using LDA changes from  $\alpha$ -elimination in ether or benzene to  $\beta$ -elimination in HMPA (Scheme 2).<sup>7</sup> Note that cyclopentanone is a minor product

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(1) Crandall, J. K.; Apparau, M. *Org. React.* **1983**, *29*, 345–443. Satoh, T. *Chem. Rev.* **1996**, *96*, 3303–3325. Mordini, A.; Ben Rayana, E.; Margot, C.; Schlosser, M. *Tetrahedron* **1990**, *46*, 2401–2410.

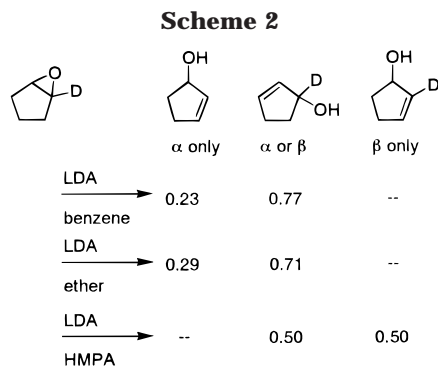
(2) For example, (a) Nilsson Lill, S. O.; Arvidsson, P. I.; Ahlberg, P. *Tetrahedron: Asymmetry* **1999**, *10*, 265–279. (b) Asami, M.; Ogawa, M.; Inoue, S. *Tetrahedron Lett.* **1999**, *40*, 1563–1564. (c) Södergren, M. J.; Andersson, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 10760–10761. (d) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439–1457. (e) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361–14384. (f) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1–26.

(3) Thummel, R. P.; Rickborn, B. *J. Am. Chem. Soc.* **1970**, *92*, 2064–2067.

(4) Apparau, M.; Barrelle, M. *Tetrahedron* **1978**, *34*, 1541–1546.

(5) Collum, D. B. *Acc. Chem. Res.* **1993**, *26*, 227–234. Rutherford, J. L.; Collum, D. B. *J. Am. Chem. Soc.* **1999**, *121*, 10198–10202. Hilmersson, G.; Arvidsson, P. I.; Davidsson, Ö.; Hakansson, M. *Organometallics* **1997**, *16*, 3352–3362.

(6) Ramirez, A.; Collum, D. B. *J. Am. Chem. Soc.* **1999**, *121*, 11114–11121.



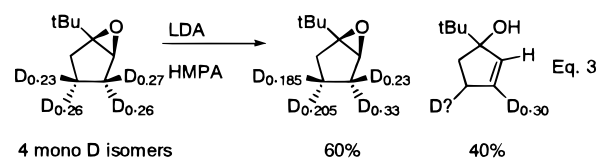
in ether and benzene but is not formed in HMPA. Analogous deuterium labeling studies on cyclohexene oxide show  $\beta$ -elimination occurs in both ether and benzene. Interestingly, the rearrangement of cyclopentene oxide in ether or benzene, via a carbenoid intermediate, was found to occur *faster* than the E2 elimination of cyclohexene oxide during in situ competition experiments. It is not unusual for cyclopentyl and cyclohexyl systems to exhibit different reactivity; for example, experiments<sup>8</sup> and calculations<sup>9</sup> show that conformational differences affect the relative ease of *syn* versus *anti* eliminations.

The literature on E2 reactions is immense. It is generally true that antiperiplanar eliminations occur more easily than synperiplanar eliminations. However solvent, base, and reactant structure are known to have a substantial effect on the occurrence of *syn* versus *anti* elimination,<sup>10</sup> and solution-phase studies often cloud the inherent reactivity of a molecule. Elimination reactions in the gas phase have been studied in detail using high-level theory.<sup>9,11,12</sup> Recent computational studies show that there is a large amount of flexibility in the dihedral angle for a *syn* elimination, since energetic benefits of orbital alignment are offset by eclipsing interactions.<sup>11b,c</sup> In addition, the calculations suggest that *syn* E2 transition states tend to be more E1cb-like, and as such the preference for periplanarity is lessened because at the transition state the double bond is not highly developed.

Given the known importance of ring size on eliminations, we were interested in finding out whether conformational differences explained the divergent behavior of cyclopentene- and cyclohexene oxides in nonpolar solvents. Simple molecular mechanics calculations on the lowest-energy conformations of ground-state epoxides supported this argument: cyclopentene oxide has *syn* H-C-C-O dihedral angle of 72.1° and undergoes  $\alpha$ -elimination, while in cyclohexene oxide the dihedral angles are 45.7° and -77.1°.<sup>7</sup> A detailed ab initio study

of the *syn* versus *anti* elimination pathways is described herein, with some surprising results.

In addition, experiments are presented to account for the observed switch between  $\alpha$ - and  $\beta$ -elimination for cyclopentene oxide, believed to arise from the solvent dependence on the faciality of the elimination process. The idea of epoxides undergoing *anti* elimination in HMPA is not new,<sup>1,4</sup> yet only one experiment in the literature gives evidence that this is the case (eq 3).<sup>7</sup> In the deuterium-labeling study shown in eq 3, 1-*tert*-butylcyclopentene oxide, known from other labeling studies to undergo  $\beta$ -elimination in HMPA, was recovered after 40% conversion, and the analysis suggests *anti* elimination occurs. However, due to experimental uncertainty, this result is not conclusive, and more evidence was sought for *anti*  $\beta$ -elimination in HMPA.



## Results and Discussion

**Structural Effects on Reactivity.** The barriers to the *syn* and *anti* elimination pathways in the gas phase for cyclopentene oxide versus cyclohexene oxide with hydroxide ion were evaluated computationally. These results will be compared to a previous study of propene oxide with hydroxide<sup>12</sup> which was found to agree well with gas-phase flowing afterglow experiments.<sup>13</sup> These experiments also showed that in the gas phase, the reaction of propene oxide with OH<sup>-</sup> is qualitatively the same as with NH<sub>2</sub><sup>-</sup>. In addition, we report  $\alpha$ -acidities of the epoxides and discuss their relevance to elimination mechanisms.

The structures of the epoxides are shown in Figure 1. Cyclopentene oxide adopts a boatlike structure, and cyclohexene oxide is a half-chair. The calculated structural parameters agree well with those determined by electron diffraction and NMR.<sup>14</sup> Only the lowest-energy conformations were used to find elimination transition states. Note that a recent NMR and computational study on cyclohexene oxide shows that several conformations rapidly interconvert at room temperature, though all are more than 3 kcal/mol higher in energy than the ground state.<sup>15</sup>

**$\beta$ -Eliminations.** The structures of the *anti* and *syn* transition states are shown in Figure 2. Relative energies of the transition states compared to isolated reactants are shown in Table 1. Note that ion-molecule complexes form potential energy minima which precede the transition states, and in gas-phase ion reactions it is not unusual for the transition states to be lower energy than isolated reactants.

The *anti* transition states from cyclopentene oxide and cyclohexene oxide both show elongation of the C-H bond to 1.48 Å, shortening of the C-C bond to 1.46 Å, and

(7) Morgan, K. M.; Gajewski, J. J. *J. Org. Chem.* **1996**, *61*, 820–821.

(8) DePuy, C. H.; Thurn, R. D.; Morris, G. F. *J. Am. Chem. Soc.* **1962**, *84*, 1314–1315. DePuy, C. H.; Morris, G. F.; Smith, J. S.; Smat, R. J. *J. Am. Chem. Soc.* **1965**, *87*, 2421–2428.

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(11) (a) Gronert, S. *J. Am. Chem. Soc.* **1991**, *113*, 6041–6048. (b) Gronert, S. *J. Am. Chem. Soc.* **1992**, *114*, 2349–2354. (c) Gronert, S. *J. Am. Chem. Soc.* **1993**, *115*, 652–659. (d) Gronert, S.; Merrill, G. N.; Kass, S. R. *J. Org. Chem.* **1995**, *60*, 488–489. (e) Merrill, G. N.; Gronert, S.; Kass, S. R. *J. Phys. Chem. A* **1997**, *101*, 208–218. (f) Gronert, S.; Kass, S. R. *J. Org. Chem.* **1997**, *62*, 7991–8000, and references therein.

(12) Gronert, S.; Lee, J. M. *J. Org. Chem.* **1995**, *60*, 4488–4497.

(13) Bierbaum, V. M.; DePuy, C. H.; Shapiro, R. H.; Stewart, J. H. *J. Am. Chem. Soc.* **1976**, *98*, 4229–4235. DePuy, C. H.; Beedle, E. C.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1982**, *104*, 6483–6488.

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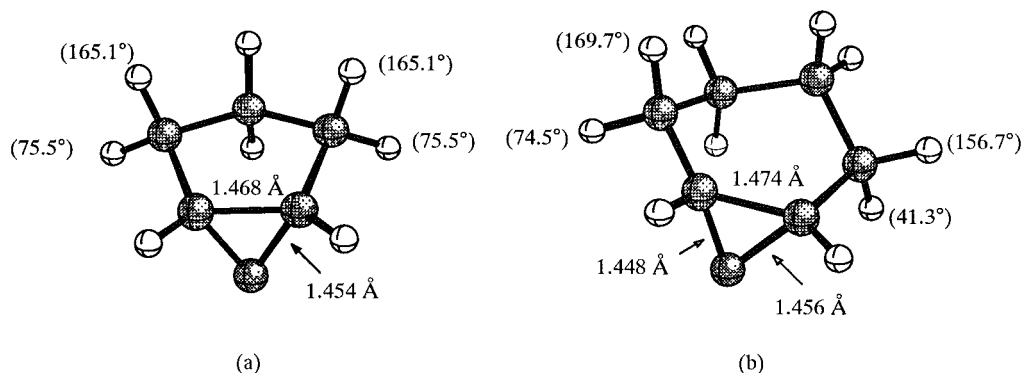


Figure 1. Structures of epoxides (MP2/6-31+G\*).

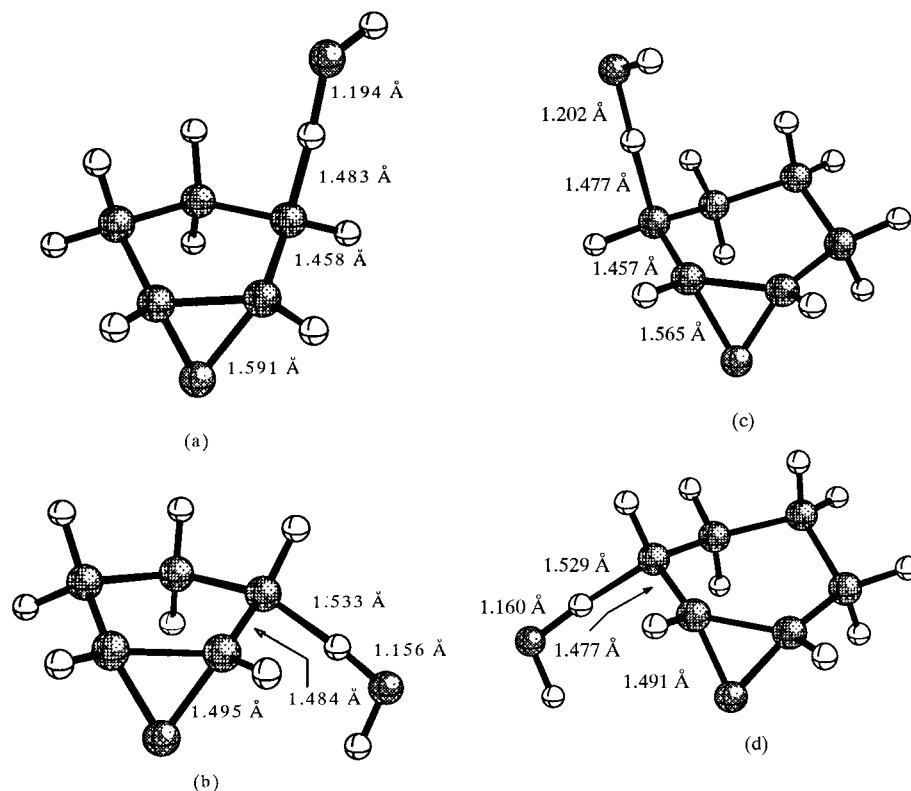


Figure 2. Structures of *anti* and *syn*  $\beta$ -elimination transition states (MP2/6-31+G\*).

lengthening of the C–O bond (1.59 and 1.57 Å, respectively). The H–C–C–O dihedral angles are 156° and 165° for cyclopentene- and cyclohexene oxides. These parameters are almost the same as those for the transition state from propene oxide.<sup>12</sup> The transition state from cyclohexene oxide was particularly difficult to find; the potential energy surface has a very flat shelf for elongation of the *anti* C–H bond.

The *syn* transition states are also very similar to each other, and are more E1cb-like. The C–H bonds are lengthened to 1.53 Å, the C–C bonds are moderately shortened to 1.48 Å, and the C–O bonds have lengthened to ~1.50 Å. The H–C–C–O dihedral angle is 63.3° for the transition state from cyclohexene oxide versus 58.8° from cyclopentene oxide. These transition structure parameters are again almost identical to the *syn* transition state from propene oxide.<sup>12</sup>

In all three cases, *anti* elimination is more favorable than *syn* by about 4 kcal/mol. The difference in energy from isolated reactants to transition states ranges from

–9.2 to –10.0 kcal/mol for *anti* eliminations and from –4.8 to –5.9 kcal/mol for *syn* eliminations. Overall, these calculations show that there is nothing structurally or energetically unusual about the *syn* elimination from cyclopentene oxide compared to other epoxides.

**$\alpha$ -Anions.** To explore the  $\alpha$ -elimination mechanism, the relative  $\alpha$ -acidities of cyclopentene-, cyclohexene-, and 2-butene oxides were compared (Table 1). From the carbanions, the potential energy surface becomes exceptionally complex in the conversion to carbene-derived products. For the purposes of this study we have assumed that the stability of the carbanion will provide a useful measure of the barrier to reaching carbene or carbene-like intermediates. The energies listed are for forming the bare carbanion and therefore are not comparable with the elimination barriers because the carbanion is not stabilized by hydrogen bonding to the departing water molecule or to a lithium counterion. One must not conclude from the data in Table 1 that  $\alpha$ -elimination is inherently less favorable.

**Table 1. Reactions of Oxirane Derivatives with Hydroxide<sup>a</sup>**

mechanism	HF/6-31+G**//	MP2/6-31+G**//	ZPE	relative energies	
	HF/6-31+G*	MP2/6-31+G*		HF	MP2
Cyclohexene Oxide					
E2 ( <i>anti</i> )	-383.23230	-384.52720	95.9	2.6	-10.1
E2 ( <i>syn</i> )	-383.22793	-384.51816	95.7	5.3	-5.9
$\alpha$ -anion	-307.19056	-308.24944	83.5	18.5	17.5
Cyclopentene Oxide					
E2 ( <i>anti</i> )	-344.19300	-345.33698	77.8	2.4	-10.0
E2 ( <i>syn</i> )	-344.18833	-345.33010	77.8	5.4	-5.7
$\alpha$ -anion	-268.15740	-269.06806	65.7	14.6	13.5
1,2-Dimethyloxirane					
$\alpha$ -anion	-230.27917	-231.06315	60.1	19.5	18.7
Methyloxirane <sup>b</sup>					
E2 ( <i>anti</i> )				1.5	-9.2
E2 ( <i>syn</i> )				4.8	-4.8
hydroxide	-75.37642	-75.60206	5.1		

<sup>a</sup> Absolute energies are reported in Hartrees, and relative energies and zero-point energies are in kcal/mol. ZPE is scaled by 0.9135. <sup>b</sup> Reference 11.

**Table 2. Heats of Formation and Strain Energies of Simple Epoxides<sup>a</sup>**

epoxide	$\Delta H_f$ (gas), kcal mol <sup>-1</sup>	strain energy, kcal mol <sup>-1</sup>		
		by additivity	PCMODEL total strain	PCMODEL angle strain
propene oxide	-22.6 ± 0.1		23.3	1.2
cyclopentene oxide	-23.2 ± 1.7	28.6	28.7	5.0
cyclohexene oxide	-30.0 ± 0.3	26.8	26.6	2.2
cycloheptene oxide	-36.4 ± 0.7	25.4	29.6	3.4
cyclooctene oxide	-39.5 ± 0.6	27.2	30.4	4.7
<i>exo</i> -norbornene oxide	-12.9 ± 0.6	42.8	46.0	15.7

<sup>a</sup> Heats of formation and strain energies determined by additivity are from ref 15b.

$\alpha$ -Proton removal from cyclopentene oxide by hydroxide is easier by about 4 kcal/mol compared to the other epoxides. The greater strain in cyclopentene oxide<sup>16</sup> (Table 2) stabilizes the anion in an orbital having more s-character. This argument is borne out by the greater pyramidalization calculated at the carbanion in cyclopentene oxide. The sum of the angles is 262°, compared to 274° for the cyclohexyl anion and 277° for the 2-butyl anion. Structures of the three  $\alpha$ -anions are shown in Figure 3.

This enhanced acidity of cyclopentene oxide is in accord with experimental observations.<sup>7</sup>  $\alpha$ -Deuterated cyclopentene oxide was recovered after partial reaction with LDA in ether, and GC/MS analysis revealed a nonstatistical mixture of di-, mono-, and undeuterated epoxide, indicative of a reversible deprotonation. However, no dideuterated cyclohexene oxide was recovered, confirming that here the  $\alpha$ -proton is not nearly as labile.

**Counterion Effects.** The calculations do not include a counterion, and while this omission simplifies the calculations, it complicates the analysis of solvent-induced reactivity differences. For example, in ethereal solution, neither cyclopentene- or cyclohexene oxide reacts with LDA when 12-crown-4 is present.<sup>7</sup> Clearly the lithium counterion is an essential part of the reaction

coordinate for both  $\alpha$ - and *syn*-eliminations. Here, the counterion could interact with both the base and leaving group, unlike the case in *anti* elimination.

Nilsson Lill, Arvidsson, and Ahlberg recently reported a computational study of the *syn*- $\beta$ -elimination of cyclohexene oxide with a chiral lithium amide.<sup>2a</sup> The *syn* transition states, optimized at RHF/3-21G, have less C-H cleavage (1.43–1.47 Å) and more C-O breaking (1.58–1.64 Å) than found in the present study. With the lithium counterion, these *syn* transition states are less E1cb-like, with the oxyanion being stabilized by the lithium as it forms.

**$\alpha$ - versus  $\beta$ -Eliminations.** It would be useful to be able to predict which mechanism would predominate in nonpolar media. In this section, we discuss the importance of epoxide conformation as well as acidity of the  $\alpha$ -proton. In addition, two borderline examples are presented, which highlight the complexity of these reactions.

The H-C-C-O dihedral angle of the ground state appears to coincide with the reactivity of simple epoxides in nonpolar media. Epoxides such as cyclopentene oxide with H-C-C-O greater than 60° undergo  $\alpha$ -elimination, and those epoxides such as cyclohexene oxide or propene oxide with at least one H-C-C-O between 0° and 60° undergo  $\beta$ -elimination. This analysis appears to be a coincidence rather than have any physical meaning.

The calculations show that H-C-C-O dihedral angles for *syn* elimination change substantially from reactant to transition state. Ground-state cyclopentene oxide has *syn* H-C-C-O of 75.5°, whereas the transition state has 58.8°. Cyclohexene oxide in the half-chair conformation has H-C-C-O dihedral angles of 74.4° and 41.1°, while the transition state has 63.3°. Recall that the energy for *syn*  $\beta$ -elimination is nearly the same for these two epoxides. The geometry of the reactant thus should *not* be used to predict reactivity in nonpolar media. In addition, basing the reactivity preference on the most stable conformer puts one at risk of violating the Curtin-Hammett Principle. However, there are examples of especially rigid epoxides in which structural effects prevent *syn*  $\beta$ -elimination. Norbornene oxide cannot undergo  $\beta$ -elimination because the product would have an unstable bridgehead double bond and instead gives nortricyclanol, the carbenoid cross-ring insertion product.

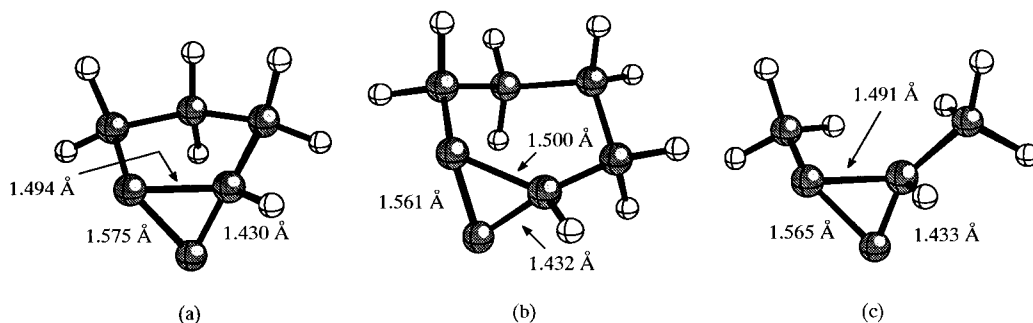
The enhanced acidity of cyclopentene oxide is thought to arise from an especially strained epoxide ring. Experimentally determined heats of formation are available for few epoxides; fortunately, many relevant to this study are known (Table 2).<sup>16</sup> Strain energies of the epoxides are also included in Table 2 and were calculated by additivity<sup>16b</sup> or by molecular mechanics.<sup>17</sup> All entries except cyclohexene- and propene oxide are believed to give  $\alpha$ -elimination in nonpolar solvents, as evidenced by the formation of ketones or cross-ring insertion products. These epoxides also have a greater strain than does cyclohexene oxide.

However, it is often true that larger molecules have more strain; thus, it would be useful to identify which type(s) of molecular distortions promote  $\alpha$ -elimination. For the six epoxides listed in Table 2, those which undergo  $\alpha$ -elimination are found to have a larger *angle strain* component compared to cyclohexene oxide and propene oxide. Norbornene oxide, calculated to have the greatest angle strain and by this reasoning the most

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(17) PCMODEL version 5.13, Serena Software, Bloomington IN.





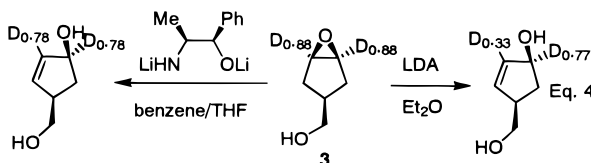
**Figure 3.** Structures of  $\alpha$ -anions (MP2/6-31+G\*).

acidic  $\alpha$ -hydrogens, was found to react even faster than cyclopentene oxide; norbornene oxide is completely consumed in 15 min at 0 °C, using 2.5 equiv of LDA in ether.

The trend in epoxide angle strain is also observed in the corresponding alkenes. There was no correlation between epoxide reactivity and eclipsing strain. Strain analysis can also be problematic; differences in angle strain on the order of a few kilocalories per mole can be difficult to interpret. In addition, some angle strain may be due to distortions remote from the epoxide ring which are less likely to contribute to  $\alpha$ -acidity. Strain in the epoxide ring is explicitly manifest by a structural deformation resulting in an increased pyramidalization of the carbanion carbon.

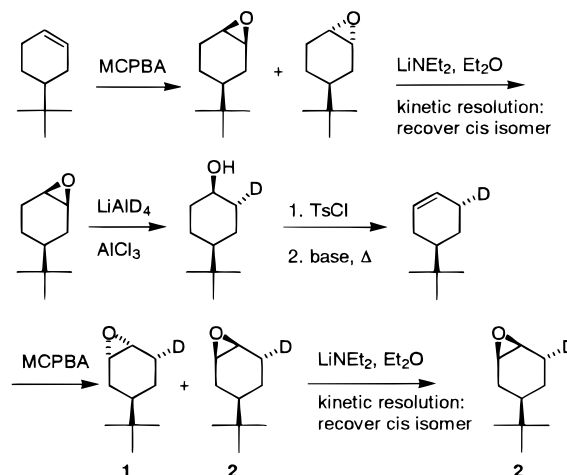
The balance between  $\alpha$ - and *syn*  $\beta$ -eliminations in cyclopentene oxide systems is delicate. For example, additional studies on an isotopomer of 1-*tert*-butylcyclopentene oxide show that in ether or benzene, a mixture of  $\alpha$ - and  $\beta$ -eliminations takes place, unlike in the parent cyclopentene oxide.<sup>7</sup> Note also that this substituted cyclopentene oxide is much less reactive than the parent, presumably since steric hindrance slows down the  $\alpha$ -elimination, making *syn*  $\beta$ -elimination competitive.

In addition, Hodgson has shown through deuterium labeling studies that epoxide **3** gives  $\beta$ -elimination in benzene/THF with a chiral base, but in ether or THF with LDA a mixture of  $\alpha$ - and  $\beta$ -eliminations is observed (eq 4).<sup>18</sup> In molecules such as **3** with a remote heteroatom, it is reasonable to expect that the lithium complexes to both oxygens, making the *syn*  $\beta$ -proton much more accessible than the  $\alpha$ -proton. Note that again these reactions were slower than the parent cyclopentene oxide under similar conditions. Hodgson also reports examples of similar 4-substituted cyclopentene oxides undergoing solely  $\beta$ -elimination in nonpolar solvents, using chiral lithium amides.



It is clear that the acidity of the  $\alpha$ -proton is not the only factor which influences the type of elimination which occurs. The mechanism which is observed is determined by a complex blend of factors, and no simple rule can be used to predict reactivity. Energy differences between

### Scheme 3



competing  $\alpha$ - and *syn*  $\beta$ -eliminations appear to be small, so subtle changes can influence the preferred pathway.

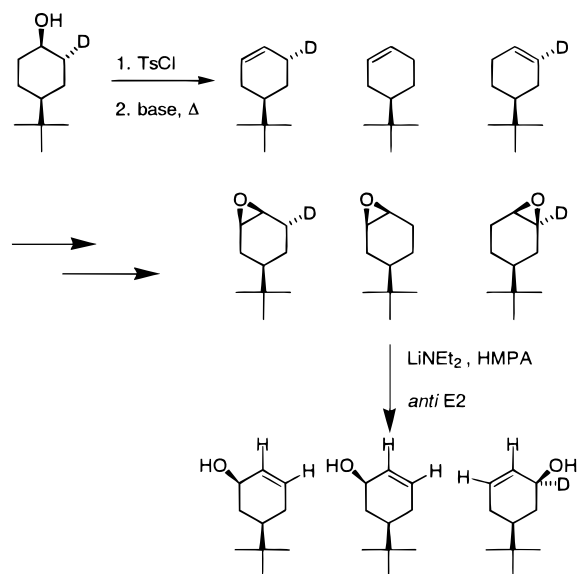
**Solvent Effects on Stereochemistry.** The stereochemistry of epoxide  $\beta$ -elimination in HMPA was explored using the isotopically labeled epoxide first studied by Rickborn and Thummel,<sup>3</sup> synthesized as shown in Scheme 3. Oxidation of 4-*tert*-butylcyclohexene gives a mixture of *cis* and *trans* epoxides. Lithium diethylamide in ether consumes the *trans* isomer preferentially, thus through this kinetic resolution the *cis* diastereomer is obtained. In practice, approximately 5% of the *trans* isomer remained as determined from the integrals of <sup>1</sup>H NMR resonances at 3.15 ppm (*cis* isomer) and 3.25 ppm (*trans* isomer). Elimination from the tosylate gives the alkene having deuterium in the allylic position, as well as nondeuterated and vinyl-deuterated alkenes (Scheme 4). Rickborn and Thummel found that the alkene mixture contained 0.78 D, with approximately 0.2 D in the vinyl position. In the present study, a similar isotope distribution is suggested by the <sup>1</sup>H NMR spectrum of allylic alcohol produced from the *cis* epoxide in ether.

When the deuterated *cis* epoxide **2** was treated with lithium diethylamide in HMPA, the epoxide was completely consumed after 2 h at room temperature. <sup>1</sup>H NMR analysis of the allylic alcohol showed two vinyl resonances at 5.9 and 5.75 ppm in a ratio of 1.00 to 0.97,  $\pm$  5%. This finding is consistent with *anti*  $\beta$ -elimination. In this study, the isotopic impurities do not complicate the analysis since all three epoxides give two vinylic hydrogens on *anti* elimination (Scheme 4).

The use of a different chelating cosolvent such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in asymmetric reactions of meso-epoxides using chiral lithium amide bases

(18) Hodgson, D. M.; Gibbs, A. R. *Tetrahedron Lett.* **1997**, *38*, 8907–8910.

## Scheme 4



has been productive.<sup>19</sup> In one study,<sup>19b</sup> the influence of DBU concentration on the enantiomeric purity of the allylic alcohol was studied. With 6 equiv of DBU, the enantiomeric purity of the product matched that of the catalyst, while with fewer equivalents the enantiomeric purity was compromised. These data suggest that a change in mechanism may occur, possibly to *syn*, when insufficient DBU is used.

## Conclusions

The computational and experimental results presented suggest that base-induced rearrangement of epoxides to allylic alcohols will occur via *anti* elimination in solvents which do not induce ion pairing of the base. The *anti* elimination was found computationally to be a more favorable pathway for cyclopentene- and cyclohexene oxide with hydroxide ion in the gas phase, as it is for propene oxide. Deuterium-labeling experiments show that in HMPA, *cis*-4-*tert*-butylcyclohexene oxide undergoes *anti* elimination, as presumably do other epoxides. As such, the change in mechanism for cyclopentene oxide in HMPA is believed to occur because ion pairing plays a smaller role, and the reactivity is more similar to the gas-phase, with *anti*  $\beta$ -elimination being the dominant pathway.

In less polar solvents, the complexation of the base with the epoxide drives the  $\beta$ -elimination to occur from the *syn* face. However, in strained cyclopentene oxide,  $\alpha$ -deprotonation occurs due to the unusually large acidity of the  $\alpha$ -hydrogen. The elimination dihedral angle of the ground-state epoxide had a very small effect on the ease of *syn* versus *anti* elimination for the three epoxides compared. It appears that several factors must be considered to rationalize  $\alpha$ - versus *syn*  $\beta$ -eliminations in nonpolar solvents.

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## Experimental Section

**General Methods.** Reagents were purchased from Aldrich, except diethylamine, methylene chloride, and hexanes (Fischer) and ether (Mallinckrodt). <sup>1</sup>H NMR spectra were obtained on a GE QE-300 at 300 MHz in CDCl<sub>3</sub> solution. When integrals were needed from the <sup>1</sup>H NMR spectrum, the receiver delay was set to 10 s. Preparative gas chromatography was performed on a Gow-Mac 580 using a 6 ft long, 1/4 in. column containing 15% OV-3 on 80/100 Supelcoport-7. Reactions were run under nitrogen using standard techniques.

**Epoxide Rearrangements.** Epoxide **2** was prepared according to literature procedures<sup>3</sup> and was purified by column chromatography on alumina using 1:1 ether/hexanes. Rearrangements were carried out as described in the literature with the following modifications. After quenching the reaction mixture with deionized water, the organic fraction was separated. The aqueous phase was extracted with ether, and the combined organic solutions were dried over sodium sulfate. Magnesium sulfate was avoided because previous study shows it causes slow degradation of epoxides. After removal of solvent by rotary evaporation, the products were analyzed by <sup>1</sup>H NMR. In some cases, allylic alcohol and epoxide were isolated by preparative GC with 105 °C column and 145 °C injector and detector. Integrations of diagnostic NMR resonances were the same for crude and purified allylic alcohol and epoxide.

**Computational Methods.** All ab initio calculations were carried out on HP-720 or HP-735 computers using the GAUSSIAN92<sup>20</sup> suite of programs developed by Pople and co-workers. All structures were fully optimized using the 6-31+G\* basis set.<sup>21</sup> The curvature of the potential energy surface at all minima and transition states was confirmed with analytical second-derivatives at the Hartree–Fock level. Earlier work has shown that Hartree–Fock calculations overestimate the degree of E1 character in concerted eliminations;<sup>11c</sup> as such, all structures were reoptimized at the MP2/6-31+G\* level of theory. Single-point energies were obtained at the MP2/6-31+G\*\* level of theory. Using the Hartree–Fock frequencies, corrections were made for zero-point energy differences (scaled by 0.9135).<sup>22</sup> Previous work indicates that this approach leads to elimination energies that are in good accord with more demanding computational methods (i.e., G2+).<sup>11d,e</sup>

Molecular mechanics calculations were performed using PCMODEL.<sup>17</sup> Attempts were made to find other low-energy conformations. The higher-energy conformers contributed less than 1% to the energy and were ignored.

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**Supporting Information Available:** Cartesian coordinates from computational studies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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