Communications

Mechanisms of the Base-Induced Isomerizations of Cyclopentene and Cyclohexene Oxides: Influence of Structure and Solvent on α and *β* Proton Removal

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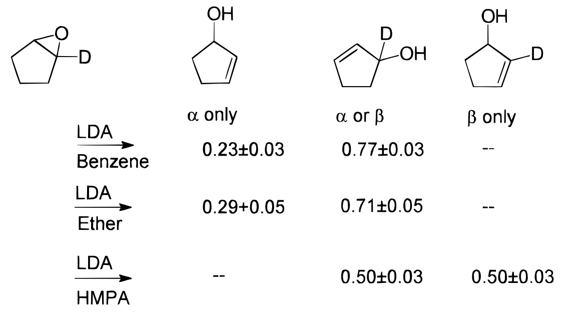
Because of the synthetic value of base-induced rearrangements of alkyl-substituted epoxides to allyl alcohols, the reaction has been investigated in some detail.[1] Frequently, allyl alcohols can be formed with high regioselectivity, and preparation of optically active products using chiral lithium amide bases has shown some success.[2] In acyclic systems, the reaction proceeds via a *β*-elimination (i.e., 1,2- or E2-type).[1] Cyclohexene oxide has been shown through deuterium-labeling studies to undergo exclusive *syn β*-elimination in ether.[3] Complexation of Li^+ to the epoxide oxygen apparently directs the facial selectivity via a six-atom cyclic transition state. Some epoxides, generally those of medium-sized cyclic and bicyclic olefins, appear to react via a carbenoid formed by an α-elimination followed by epoxide opening. This pathway is supported by the observation of ketones and transannular C−H bond insertion products.[1] Allyl alcohols are sometimes formed competitively, but whether they result from α- or *β*-elimination is unclear. We report here that cyclopentene oxide gives 2-cyclopentenol via an α-elimination in benzene or in ether solvents but via *β*-elimination in HMPA.

Cyclopentene oxide gives a mixture of three products—2-cyclopentenol, cyclopentanone, and the product of nucleophilic addition—whose proportions depend strongly on the base used.[4] The steric bulk and poor nucleophilicity of lithium diisopropyl amide (LDA) prevent its addition to cyclopentene oxide; thus, LDA was employed to study the mechanism(s) of allyl alcohol formation. First, it was ascertained that cyclopentanone is a primary reaction product and not due to rearrangement of allyl alcoholate to enolate under the highly basic reaction conditions.

When 1-deuteriocyclopentene oxide was treated with 2.5 equiv of LDA in benzene or in ether,[1] 2-cyclopentenol and cyclopentanone were formed after quenching. NMR analysis of the GC-purified alcohol showed some deuterium loss, and the remaining deuterium (0.77D in benzene and 0.71D in ether) was exclusively on the carbinol carbon (i.e., no vinyl deuterium), consistent with the carbenoid mechanism and not *β*-elimination (Scheme 1). From the amount of deuterium present, primary kinetic deuterium isotope effects of 3.3 ± 0.5 (benzene) and 2.4 ± 0.4 (ether) were calculated for rate-determining removal of the α-proton. Under these reaction conditions, cyclopentanone is also formed (15 ± 2% in benzene, 25 ± 4% in ether), but its deuterium content could not be determined since H/D exchange occurs with workup.[5] Hexamethylphosphoric triamide (HMPA) is known to promote allyl alcohol formation for compounds which exhibit carbenoid behavior in nonpolar solvents,[1] and, in fact, when treated with LDA in HMPA, cyclopentene oxide gives only allyl alcohol with a deuterium distribution consistent with *β*-elimination (Scheme 1).[6] In all three solvents, the half-life of the reaction is 15−30 min at 0 °C.

Scheme 1



For comparison purposes, 1-deuteriocyclohexene oxide was subjected to an identical series of reaction conditions, and the allyl alcohol produced had a deuterium distribution consistent with exclusive *β*-elimination in all three solvents. Cyclopentene oxide reacts 2−10 times faster than cyclohexene oxide during *in situ* competition, yet other epoxides thought to rearrange via the α-elimination mechanism react much more slowly.[1] This might be due to greater acidity of the bridgehead proton of cyclopentene oxide or to relief of ring strain at the transition state. It is also possible that cyclohexene oxide undergoes a rapid, unproductive reversible α-deprotonation, followed by productive *β*-elimination. However, the GC/MS spectra of ether and benzene reaction mixtures quenched after partial isomerization showed no evidence of a preequilibrium. For the reaction of 1-deuteriocyclopentene oxide in HMPA, GC/MS data showed that at long reaction times (>50% reaction) the recovered epoxide was a mixture of non-, mono-, and dideuterated material, though not in a statistical mixture. The 1-deuteriocyclohexene oxide recovered from the reaction conducted in HMPA shows minimal equilibration.

The importance of Li^+ complexation in the nonpolar solvents was investigated by treating epoxides with LDA in ether containing 12-crown-4 (1 equiv with respect to LDA). Neither cyclopentene nor cyclohexene oxide underwent reaction yet, in HMPA, a strong cation-complexing solvent, cyclopentene oxide reacts as rapidly as in the less polar solvents without crown. HMPA, no doubt, favors the dipolar transition state, and complexation of Li^+ to the epoxide oxygen is apparently not necessary for *β*-elimination in this solvent.

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(4) Crandall, J. K.; Chang, L.-H. *J. Org. Chem.* **1967**, *32*, 435−439. Kissel, C. L.; Rickborn, B. *J. Org. Chem.* **1972**, *37*, 2060−2063.

(5) It is interesting to note that here the carbenoid gives more of the thermodynamically less stable allyl alcoholate. The origins of this effect are under investigation.

(6) Note that at longer reaction times the deuterium content of the allyl alcohol is diminished, indicative of α-deprotonation that does not lead to product. The data have been corrected to take this into account.

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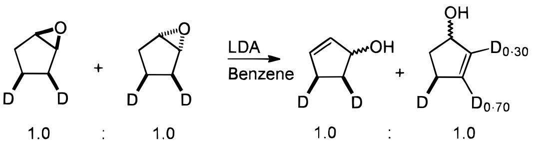
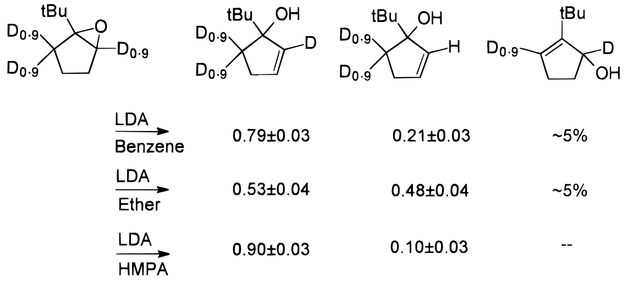
Scheme 2



Scheme 3



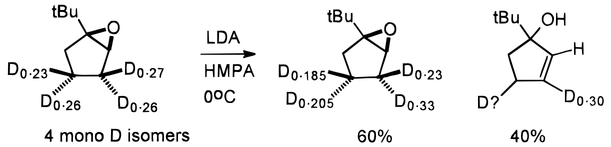
To determine the isotope effect on the carbene insertion into the β-CH bond, a mixture of *syn*- and *anti*-3,4-dideuteriocyclopentene oxide was treated with LDA in benzene (Scheme 2).

The NMR spectrum of the allyl alcohol showed deuterium at all positions except the carbinol carbon. No deuterium was lost, and the distribution is interpreted in terms of the products shown in Scheme 2. Thus, the carbenoid mechanism derives further support. The observed distribution of deuterium indicates a primary kinetic isotope effect of approximately 2.3 for insertion of the carbenoid into the adjacent carbon−hydrogen (deuterium) bond.

A bulky α-*tert*-butyl group on cyclopentene oxide was found to sterically inhibit α-elimination by a rate factor of 1/200 relative to the parent so that β-elimination is more favorable in both ether and benzene. As expected, HMPA solvent promotes exclusive β-elimination (Scheme 3: note that the 9:1 ratio of the first two products represents the ratio of D and H at C-2 of the starting material), and here the reaction is 10 times slower than the parent.

HMPA has been known to reverse the facial selectivity of E2 eliminations from that which occurs in nonpolar solvents.[7] This was also found to be the case in the cyclopentene oxide system (Scheme 4). A mixture of four monodeuterated compounds was treated with LDA in HMPA, and the epoxide was recovered after 40% reaction. Significant enhancement of deuterium at the *anti* β position is observed along with diminution at all other positions; thus, *anti* β-elimination occurs here. The distribution of deuterium in the tertiary allyl alcohol is consistent with these observations, and the product ratio suggests a primary deuterium isotope effect of approximately 3 for rate-determining deprotonation at the *anti* β position.

Scheme 4



AM1,[8] ab initio,[9] and density functional theory[10] calculations agree that, in simple E2 reactions of primary derivatives with strong base, the transition state is quite reactant-like, with minimal dihedral angle distortion. The gas-phase structures of cyclopentene and cyclohexene oxides have been determined by electron diffraction,[11] but the appropriate H−C−C−O torsional angles were not determined. However, the heavy-atom geometries were reproduced using PCMODEL,[12] which then provided the desired torsional angle. These calculations suggest that cyclohexene oxide can adopt a favorable *syn-gauche* conformation, but the structure of cyclopentene oxide will not easily lead to *syn* β-elimination. The geometry of both epoxides is reasonably favorable for *anti*-eliminations, which occur for cyclopentene oxide in HMPA.

Acknowledgment. We thank Professors Jack Crandall and Scott Gronert for helpful discussions. This work was supported by the National Science Foundation.

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[7] There is precedent for this type of mechanistic switch: Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: New York, 1988; Chapter 5, p 255.

[8] Dewar, M. J. S; Yuan, Y.-C. *J. Am. Chem. Soc.* **1990**, *112*, 2088−2094. Dewar, M. J. S; Yuan, Y.-C. *J. Am. Chem. Soc.* **1990**, *112*, 2095−2105.

[9] Gronert, S. *J. Am. Chem. Soc.* **1993**, *115*, 652−659. Gronert, S. *J. Am. Chem. Soc.* **1992**, *114*, 2349−2354. Gronert, S.; Lee, J. M. *J. Org. Chem.* **1995**, *60*, 4488−4497.

[10] Bickelhaupt, F. M.; Baerends, E. J.; Nibbering, N. M. M.; Ziegler, T. *J. Am. Chem. Soc.* **1993**, *115*, 9160−9173.

[11] Landolt-Börnstein; Springer-Verlag: Berlin, Vol. II/7, 1976; Vol. II/15, 1987.

[12] PCMODEL, Version 5.1 for Windows, Serena Software, Box 3076, Bloomington, IN 47402.