2508 *J. Am. Chem. Soc.* **1994,** *116,* 2508–2514

Nucleophilic Ring Opening of Epoxides by Organolithium Compounds: Ab Initio Mechanisms

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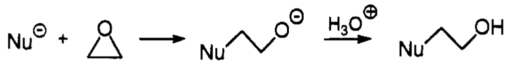
Received May 25, 1993. Revised Manuscript Received December 7, 1993•

Abstract: Ab initio calculations (MP4/6-31+G*//6-31+G*+ΔZPE) have been performed on the ring-opening reaction of ethylene oxide by monomeric and dimeric lithium hydride and by dimeric methyllithium, both with retention and with inversion of configuration at the carbon being attacked. Several highly ionic transition structures were located. The large preference for reaction with inversion is due to the higher degree of rupture of the C–O bond in the retention transition structure. Cationic assistance, i.e. Li$^+$ coordination to the epoxide oxygen, significantly lowers the activation energies. An intermolecular push–pull mechanism, or an intramolecular mechanism in which the lithium aggregate is opened to form a chain, is proposed for reaction in moderately polar solvents.

Introduction

The β-hydroxyalkylation of nucleophiles (eq 1) is one of the most valuable and generally applied methods for the synthesis of β-substituted alkyl alcohols.[1]



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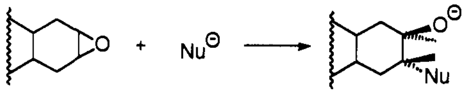
Its high regioselectivity[1] (generally nucleophilic attack at the least substituted carbon) and stereoselectivity[1–4] (inversion of configuration at the attacked carbon) account for its frequent use in the synthesis of natural compounds.[2] For example, the high selectivity in trans-diaxial ring opening of cyclohexene oxides[3] is generally applied in designing steroid syntheses (eq 2).



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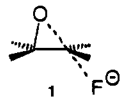
A theoretical study corroborates this experimentally observed preference for inversion of configuration at the attacked carbon, i.e. the transition state for rear-side attack (1) is lower in energy than the one for front-side attack (2).[5] The higher energy of the retention transition structure has been attributed to a strong repulsive electrostatic interaction between the nucleophile and the epoxide oxygen on which a negative charge is developing.[5]



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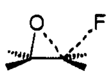

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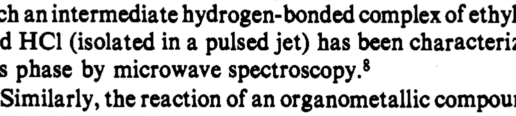
However, these transition structures are simplified and at least the cation should be involved in such an ionic mechanism. Distinction should be made between (i) reactions of a strong acid with an epoxide (eq 3) which are usually performed in strongly polar protic solvents (cation = H$^+$) and (ii) reactions of polar organometallic compounds with epoxides (eq 4) which are usually carried out in polar or nonpolar organic solvents (cation = M$^+$).



(3)

(4)

The addition of an acid to an epoxide was found to proceed via the protonated species as shown in eq 3.[6] *Ab initio* calculations have shown this oxonium cation to be activated for nucleophilic ring opening.[7] Protonation of the epoxide weakens the C–O bond and increases the positive charge on the carbon atoms. Recently, such an intermediate hydrogen-bonded complex of ethylene oxide and HCl (isolated in a pulsed jet) has been characterized in the gas phase by microwave spectroscopy.[8]

Similarly, the reaction of an organometallic compound and an epoxide is generally assumed to involve an intermediate complex, as shown in eq 4, and to proceed via a relatively late S_N2-like transition state.[9] The proposed intermediate metal–epoxide complex could be isolated for 2-methoxyphenyllithium and has been characterized in the solid state (X-ray) as well as in solution (NMR).[10] Experimental observations suggest such a complex to be the reactive species:

(a) Addition of strongly cation-solvating agents (glymes, crown ethers, or cryptands) to a fluoradenyllithium/ethylene oxide mixture significantly *decreases* the reaction rate by complete solvation of the cation which thus destroys cationic assistance.[11]

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• Abstract published in *Advance ACS Abstracts,* February 1, 1994.

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Table 1. Total Energies (6-31+G*//6-31+G*, au), Zero-Point Energies (6-31+G*, kcal/mol), and Energies Relative to Separated Reactants (kcal/mol)

compound[a]	point group	HF	MP4	ZPE	$\Delta E_{(HF)}$	$\Delta E_{(MP4)}$	$\Delta H°$
S1	$C_{\infty v}$	−7.981 01	−8.001 90	2.0(0)			
S2	C_{2v}	−152.871 83	−153.350 54	39.0(0)			
			−153.335 93[b]				
C1	C_{2v}	−160.886 40	−161.385 90	42.8(0)	−21.3	−21.0	−19.4
TS1 (ret)	C_s	−160.822 11	−161.339 20	42.1(1)	+19.1	+8.3	+9.3
TS2 (inv)	C_s	−160.802 72	−161.330 48	41.8(1)	+31.2	+13.8	+14.5
P1	C_s	−160.979 83	−161.483 67	46.9(0)	−79.9	−82.3	−77.0
S3	D_{2h}	−16.035 81	−16.078 25	7.4(0)			
C2	C_s	−168.935 03	−169.459 19	47.8(0)	−17.2	−19.1	−17.8
C3	C_{2v}	−168.914 09	−169.441 31	47.7(1)	−4.0	−7.9	−6.7
C4	C_{2v}	−168.915 72	−169.435 41	46.7(0)	−5.1	−4.2	−3.9
TS4 (inv)	C_s	−168.843 52	−169.378 87	45.7(2)	+40.2	+31.3	+30.7
					+15.0[c]	+5.6[c]	+6.4[c]
TS5 (ret)	C_s	−168.861 24	−169.397 47	46.1(1)	+29.1	+19.7	+19.4
TS6 (inv)	C_1	−168.876 53	−169.418 51	47.3(1)	+19.5	+6.5	+7.3
TS7 (inv)	C_s	−168.868 51	−169.412 23	47.5(1)	+24.6	+10.4	+11.4
TS8 (ret)	C_s	−168.864 22	−169.399 87	46.6(1)	+27.2	+18.1	+18.3
TS9 (ret)	C_s	−168.849 77	−169.393 74	46.7(1)	+36.3	+22.0	+22.3
P2	C_s	−169.049 61	−169.574 12	51.8(0)	−89.1	−91.2	−86.3
C5	C_{2v}	−160.174 93	−160.650 74	40.5(0)			
C5a	C_s	−168.179 31	168.676 92	43.6(0)	−14.7	−15.2	−14.2
TS10 (inv)	C_s	−168.167 81	−168.673 70	43.5(1)	−7.4	−13.2	−12.3
S4	C_{2h}	−94.101 67	−94.437 29[b]	45.4(0)			
C6	C_1	−246.998 38	−247.800 84[b]	85.6(0)	−15.6	−17.3	−16.2
TS11 (ret)	C_1	−246.908 26	−247.721 54[b]	84.5(1)	+40.9	+32.4	+32.5
TS12 (inv)	C_1	−246.931 22	−247.750 81[b]	85.4(1)	+26.5	+14.1	+15.0
P3	C_1	−247.116 37	−247.917 16[b]	89.7(0)	−89.7	−90.3	−85.5

[a] ret: retention of configuration. inv: inversion of configuration. [b] MP4SDQ/6-31+G* energy. [c] Energy relative to **C1** + **S1**.

(b) Fluoradenyllithium, -sodium, and -potassium, which are separated ion pairs in ethylene oxide, react with ethylene oxide in the order Li > Na > K, which is the order of Lewis acidity. In addition, fluoradenyllithium reacts smoothly with oxetane whereas the sodium and potassium compounds do not react at all. These observations have been rationalized by assuming a complex between the cyclic ether and the cation as the reactive species.[11]

(c) The rate of anionic epoxide polymerization is strongly reduced by metal capture in a Lewis base cage, i.e. by adding a cryptand.[12]

(d) Reduction of 2,3-epoxy-2,4,4-trimethylpentane by $LiAlH_4$ results in low yields (even under forcing conditions), whereas addition of $AlCl_3$ leads to fast product formation under mild reaction conditions.[13] More efficient complexation of the epoxide to the stronger Lewis acid, the mixed hydride $LiCl/AlCl_nH_{3-n}$, is held responsible for this acceleration. However, to account for the formation of rearranged products in the presence of $AlCl_3$, a reaction mechanism via carbocation intermediates is proposed.

(e) Cationic assistance has been observed in reactions of the highly nucleophilic anion, $Cp(CO)_2Fe^-$, with several epoxides. The more Lewis acidic lithium compound $Li^+Cp(CO)_2Fe^-$ showed a markedly higher reactivity than the sodium analogue, $Na^+Cp(CO)_2Fe^-$; $(Bu_4N)^+Cp(CO)_2Fe^-$ even failed to react.[14]

(f) Methyllithium preferentially adds transannularly, under epoxide ring opening, to 9,10-didehydrodianthracene 9′,10′-epoxide. In the presence of crown ethers or cryptands, addition to the double bond *without* opening of the epoxide ring becomes the main reaction pathway.[15]

In spite of the many observations which corroborate the assisting role of the metal cation in the reaction of epoxides with polar organometallic compounds, a theoretical study on a reaction mechanism which includes the metal cation is still lacking. This paper describes an *ab initio* study of the nucleophilic ring opening of ethylene oxide by organolithium compounds.

Calculational Methods

All geometries were fully optimized within the designated symmetry constraints at the restricted Hartree-Fock level by using the gradient optimization techniques and standard basis sets (3-21G, 6-31G*, 6-31+G*) incorporated in the GAMESS[16] and GAUSSIAN[17] programs. Stationary points were characterized by frequency calculations (i.e. minima with 0 and transition structures with 1 imaginary frequency). Zero-point vibrational energies (ZPE) were calculated at HF/6-31+G* and scaled by the empirical factor of 0.91.[18] Influence of electron correlation was estimated using Møller-Plesset theory[19] carried out to fourth order (MP4SDTQ for the LiH and $(LiH)_2$ systems, but only MP4SDQ for the $(CH_3Li)_2$ systems) keeping the core electrons frozen. Atomic charges and bond orders were calculated using the Natural Population Analysis method.[20] The calculations were performed on a Convex C120 (Utrecht), a Cyber 205 (SARA, Amsterdam), a Convex C220 (Erlangen), and a Cray YMP/4-432 (LRZ, München).

Results and Discussion

Absolute and relative energies of the optimized minima and transition structures are given in Table 1. Unless noted otherwise, all energies and bond lengths given in the text and figures correspond to MP4SDTQ/6-31+G*//6-31+G* computations, corrected for zero-point vibrational energy.

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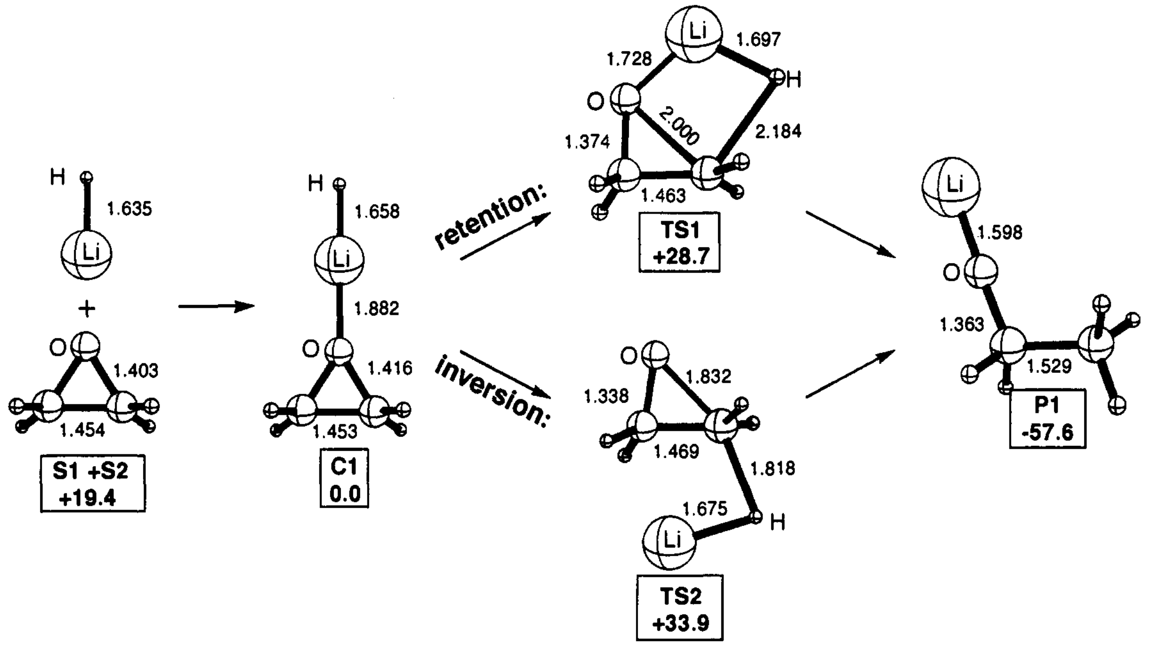

Figure 1. Reaction of ethylene oxide with lithium hydride monomer with relative energies (kcal/mol) and bond distances (Å) at the MP4SDTQ/6-31+G*//6-31+G*+ΔZPE level.

LiH Monomer and Ethylene Oxide. The simplest model system for ring opening of epoxides by organolithiums consists of lithium hydride and ethylene oxide. The usual first step in organolithium reactions is complexation between the lithium compound and the substrate.[21] The formation of the C_{2v} LiH–ethylene oxide coordination complex (**C1**, Figure 1) is exothermic by 19.4 kcal/mol.

Starting from complex **C1**, an intramolecular reaction leads to a C_s transition structure **TS1** with retention of configuration at the CH_2 group being attacked. This is an example of a four-center transition structure in which two bonds are being broken while two bonds are being formed. However, cleavage of the C–O bond is the major step since the LiH bond distance is only elongated to a small extent. The activation energy for this reaction is 28.7 kcal/mol, relative to **C1**.

A transition structure with inversion (i.e. rear-side attack) can only be realized by breaking a bond within the complex. Heterolytic dissociation of LiH into Li^+ and H^- is very endothermic (MP4/6-311++G** 166 kcal/mol; expt[22] 160.2 kcal/mol). Although solvation is expected to decrease this energy, breaking the Li–O coordinative bond is a much better alternative. The resulting C_s transition structure **TS2** is relatively high in energy (33.9 kcal/mol relative to the complex **C1**), due to loss of the stabilizing Li–O interaction and the concomitant cationic assistance. Compared to the separated reactants, the activation energy is only 14.5 kcal/mol.

The high exothermicity of the ring-opening reaction leading to the product **P1**, −57.6 kcal/mol relative to **C1**, results from the transformation of a strong base (LiH) into a much weaker base ($LiOC_2H_5$) and the release of epoxide ring strain (27.2 kcal/mol[23]).

Tests with the more extended 6-31++G** basis set (i.e. with diffuse and p-type polarization functions on hydrogen) did not result in significant changes in structure and in relative energies. No indication for biradical character was found in CASSCF energy calculations on **C1**, **TS1**, **TS2**, and **P1**. Thus, the reaction proceeds via a polar mechanism with ionic transition states.

Atomic charges and bond orders calculated with the natural population analysis and natural bond orbital analysis methods[20] provide insight into the nature of the bonding in the transition structures (Table 2). Complexation of LiH to ethylene oxide polarizes the epoxide moiety: the negative charge on oxygen increases, while the CH_2 group becomes more positive, making it more susceptible to nucleophilic attack. Both the positive charge on lithium and the negative charge on oxygen increase during the reaction.

Table 2. NPA Charges and NLMO[20c] Bond Orders

compd[a]	CH_2[b]	H[c]	O	Li(O)[d]	Li(H)[e]	C–O	C–H[c]
S1		−0.725			+0.725		
S2	+0.314		−0.628			0.676	
C1	+0.371	−0.717	−0.726	+0.701		0.621	
TS1 (ret)	+0.517	−0.643	−0.977	+0.840		0.195	0.227
TS2 (inv)	+0.323	−0.562	−0.796	+0.859		0.284	0.323
P1	−0.246	+0.200	−1.219	+0.937		−0.023	
S3		−0.791			+0.791		
C2	+0.359	−0.796	−0.698	+0.775	+0.774	0.629	
C3	+0.354	−0.794	−0.695	+0.788		0.627	
C4	+0.380	−0.699	−0.736	+0.840	+0.612	0.612	
TS4 (inv)	+0.412	−0.644	−0.944	+0.709	+0.889	0.302	0.206
TS6 (inv)	+0.422	−0.647	−0.905	+0.886	+0.750	0.356	0.167
TS7 (inv)	+0.326	−0.597	−0.928	+0.888	+0.761	0.345	0.223
TS5 (ret)	+0.571	−0.675	−0.989	+0.830	+0.783	0.171	0.195
TS8 (ret)	+0.585	−0.657	−1.007	+0.861	+0.707	0.231	0.155
TS9 (ret)	+0.497	−0.657	−0.965	+0.819		0.260	0.189
P2	−0.254	+0.215	−1.218	+0.879		−0.023	
C5	+0.416		−0.823	+0.990		0.577	
C5a	+0.450	−0.801	−0.861	+0.989	+0.817	0.536	
TS10 (inv)	+0.499	−0.728	−1.000	+0.988	+0.889	0.323	0.131
compd[a]	CH_2[b]	CH_3[f]	O	Li(O)[d]	$Li(CH_3)$[g]	C–O	C–CH_3[f]
S4		−0.887			+0.887		
C6	+0.358	−0.884	−0.689	+0.865	+0.872	0.633	
TS11 (ret)	+0.591	−0.762	−0.988	+0.900	+0.870	0.154	0.165
TS12 (inv)	+0.422	−0.741	−0.890	+0.916	+0.887	0.359	0.156
P3	−0.044	+0.001	−1.203	+0.923		−0.021	

[a] ret: retention of configuration. inv: inversion of configuration. [b] Attacked CH_2 group. [c] Attacking H^-. [d] Li bound to O. [e] Li bound to H^-. [f] Attacking CH_3^-. [g] Li bound to CH_3^-.

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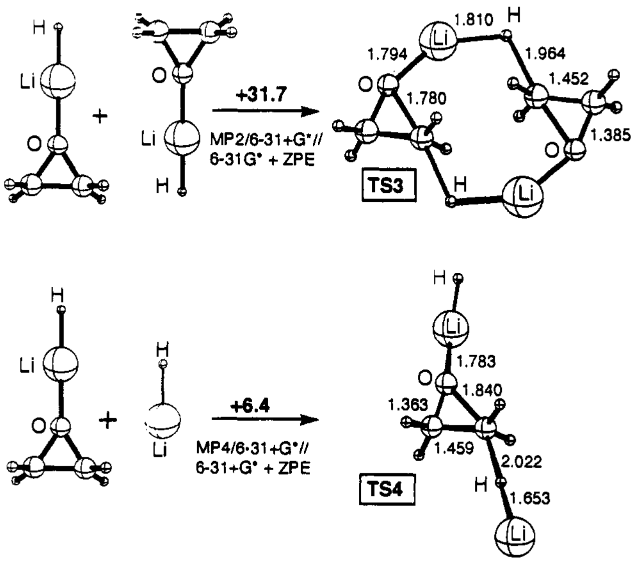

Figure 2. The "Escher" (TS3) and "push–pull" (TS4) transition structures.

The differences between the electron distributions in transition structures **TS1** and **TS2** are instructive. The degree of polarity is significantly higher in the transition state with retention at CH_2, **TS1**, than in the inversion transition structure **TS2**. Charges on the CH_2 group being attacked, on the hydride ion, and on the oxygen are higher in **TS1** than in **TS2**, while the C–O bond being broken and the C–H bond being formed are longer, with lower covalent bond orders. Thus, **TS1** is characterized by more advanced cleavage of the carbon–oxygen bond and a less developed carbon–hydrogen bond than **TS2**.

The rationalization[5] of Fujimoto et al. of the higher activation barrier of ring opening with retention, i.e. destabilization due to electrostatic repulsion between oxygen and the attacking nucleophile, does not hold when a counterion is present. The charge alternation in **TS1**, O^-, Li^+, H^-, is *stabilizing*.

Cationic assistance, absent in **TS2**, is preserved in an *intermolecular* reaction in which two C_2H_4O–LiH complexes are involved. We have studied a C_{2h} transition structure in which a LiH-complexed ethylene oxide molecule is attacked on the rear side by a neighboring C_2H_4O-complexed LiH molecule and *vice versa* (**TS3**, Figure 2). In this "Escher"-type transition structure (reminiscent of a drawing by the famous Dutch artist M. C. Escher showing two hands drawing each other), a synchronous ring opening of both epoxides is presumed. However, this possibility appears to be refuted by frequency analysis. *Three* imaginary vibrational frequencies are present, two of which have large values. One (943i cm^{-1}) describes the synchronous ring opening of both epoxide rings while the other (775i cm^{-1}) describes opening of one ring and closure of the other epoxide ring. Apparently, a two-step process in which both rings open separately is favored. Thus we can simplify the model by omitting one of the ethylene oxide molecules, i.e. an intermolecular reaction of LiH and a C_2H_4O–LiH complex. This "push–pull" transition structure (**TS4**, Figure 2) is characterized by a "pulling" LiH, which provides cationic assistance, and a "pushing" LiH, which attacks the epoxide at the rear side resulting in inversion of the epoxide methylene group. Although the activation energy for this process is quite low (6.4 kcal/mol relative to LiH + C_2H_4O–LiH), this structure also is characterized by *two* imaginary frequencies, 764i and 13i cm^{-1}. The latter corresponds to bending the "pushing" and "pulling" LiH molecules toward each other, creating an extra Li^+–H^- contact. The resulting transition structure for reaction involving a C_2H_4O–$(LiH)_2$ complex is described below.

LiH Dimer and Ethylene Oxide. In line with the lower Lewis acidity expected for Li^+ in larger aggregates,[24] the complexation energy of ethlyene oxide with dimeric lithium hydride in the C_1 complex **C2** (Figure 3), −17.8 kcal/mol, is somewhat smaller than the −19.4 kcal/mol complexation energy in **C1**. An alternative structure, *i.e.* with side-on coordination (C_{2v} complex **C3**), also is possible with $(LiH)_2$. However, this type of coordination is less favorable: the complexation energy is only 6.7 kcal/mol.

A C_s transition structure for intramolecular reaction with retention of configuration at the attacked CH_2, **TS5**, requires an activation energy of 37.2 kcal/mol relative to the coordination complex **C2**. The Li^+–H^- bonds in the LiH dimer are preserved in this transition structure.

An intramolecular reaction with *inversion* at CH_2 requires opening of the four-membered $(LiH)_2$ ring (**C2** → **C4**, +13.9 kcal/mol) and bending of the LiHLiH chain to enable rear-side attack. The resulting C_1 transition structure **TS6** corresponds to an activation barrier, relative to **C2**, of only 25.1 kcal/mol and represents the modified "push–pull" transition structure (**TS4**, see above) in which an extra Li^+/H^- contact has been created. Frequency analysis indicates only one imaginary frequency. Alternative transition structures (also with one imaginary frequency) for ring opening with both inversion and retention of the CH_2 group are shown in Figure 4. Creation of an extra Li^+–H^- contact in the "push–pull" transition structure **TS4** to give **TS6** results in an energy lowering of 23.4 kcal/mol. A transition structure with C_s symmetry, **TS7**, in which the LiHLiH chain is situated in the epoxide COC plane, is 4.1 kcal/mol higher in energy than **TS6**.

TS8 represents a product-like transition structure, with C_s symmetry, in which the epoxide oxygen bridges both Li atoms (as in the product **P2**). This structure even is 1.1 kcal/mol lower in energy than **TS5**. However, opening of the $(LiH)_2$ ring is necessary to create the additional Li–O contact. A C_s transition structure, similar to **TS8**, but with "out-of-plane" Li atoms, **TS9**, is 2.9 kcal/mol higher in energy. **TS9** can be imagined to arise from the alternative complex **C3** (Figure 3).

Even for the lowest transition structure for ring opening with retention, **TS8**, the activation barrier is 11.0 kcal/mol higher than the barrier toward ring opening with inversion, via **TS6**. Ring opening with inversion at carbon is clearly favored over ring opening with retention of configuration. The NPA charges and NLMO bond orders (Table 2)[20] of the C_2H_4O–$(LiH)_2$ systems show trends comparable to those of the C_2H_4O–LiH systems discussed above. Complexation of $(LiH)_2$ to ethylene oxide leads to an increase of the negative charge on oxygen and of the positive charge on the CH_2 groups, but the effect is less pronounced than for C_2H_4O–LiH. The C–O bond being broken is longer and more polarized in the retention transition structures **TS5**, **TS8**, and **TS9** than in the inversion transition structures **TS6** and **TS7**. Interestingly, a somewhat higher bond order is computed for the C–H bond being formed in **TS5** than in **TS6**, although the C–H distance is smaller in the latter. The lowest retention transition structure **TS8** has the longest and weakest C–H bond. The inversion transition structures **TS6** and **TS7** can be viewed as earlier on the reaction coordinate than the retention transition structures **TS5**, **TS8**, and **TS9**.

The Importance of Cationic Assistance. Many experimental observations[11–15] suggest that metal cations assist in the reaction of epoxides with polar organometallics. A Lewis acid/epoxide interaction is believed to activate nucleophilic C–O bond cleavage. Previous theoretical work on Lewis acid/epoxide complexes[10] suggested that the C–O bond of the epoxide is activated only to a very limited extent when complexed to an organolithium compound. However, these conclusions were based only on an evaluation of the C–O bond lengths and their force constants in the complexes. In the present work, we have computed the actual transition structures. We compare three different model reactions

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[24] van Eikema Hommes, N. J. R.; Schleyer, P. v. R. To be submitted for publication.

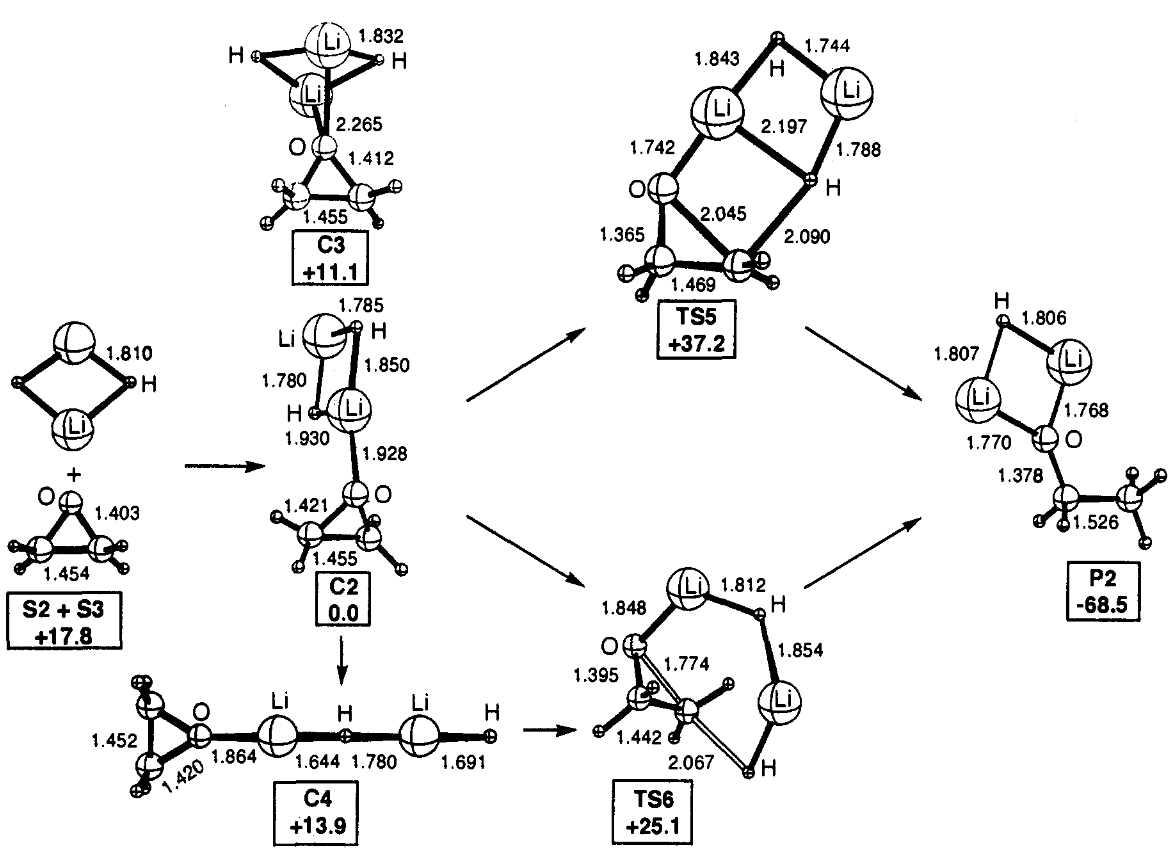


Figure 3. Reaction of ethylene oxide with lithium hydride dimer with relative energies (kcal/mol) and bond distances (Å) at the MP4SDTQ/6-31+G*//6-31+G*+ΔZPE level.

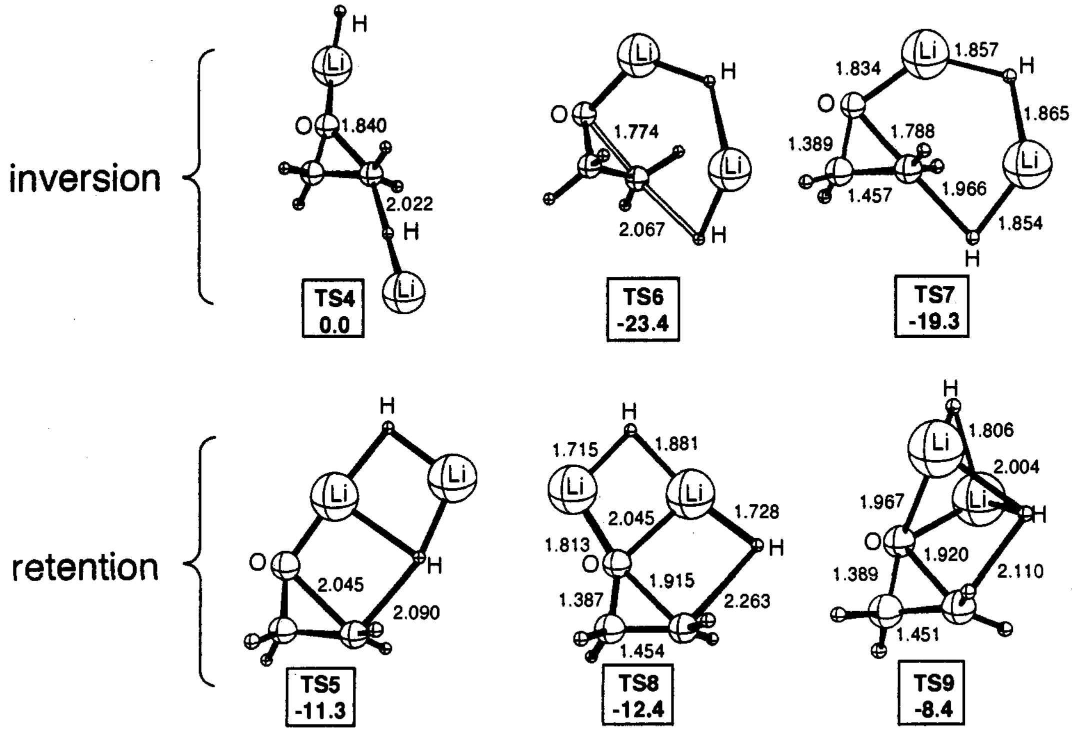


Figure 4. Alternative transition structures arranged according to retention and inversion of the attacked carbon center. Energies (kcal/mol) are given relative to the "push-pull" transition structure (TS4) at the MP4SDTQ/6-31+G*//6-31+G*+ΔZPE level.

for epoxide ring opening by lithium hydride with inversion at the methylene group being attacked (Figure 5): (1) reaction of ethylene oxide and LiH, via transition structure **TS2** [no cationic assistance is involved here; the activation energy, relative to the separated reactants, is 14.5 kcal/mol]; (2) reaction of LiH-complexed ethylene oxide, **C1**, with LiH [reaction proceeds via the "push-pull" transition structure **TS4**; cationic assistance is provided by the "pulling" LiH and leads to a reduction of the activation barrier by more than half to only 6.4 kcal/mol]; and (3) reaction of Li^+-complexed ethylene oxide, **C5**, with LiH [the cationic assistance by a lithium cation, a much stronger Lewis acid than LiH, reduces the activation barrier sharply to -12.3 kcal/mol, relative to separated **C5** and LiH, or to 1.9 kcal/mol, relative to the coordination complex **C5a** (in which lithium hydride

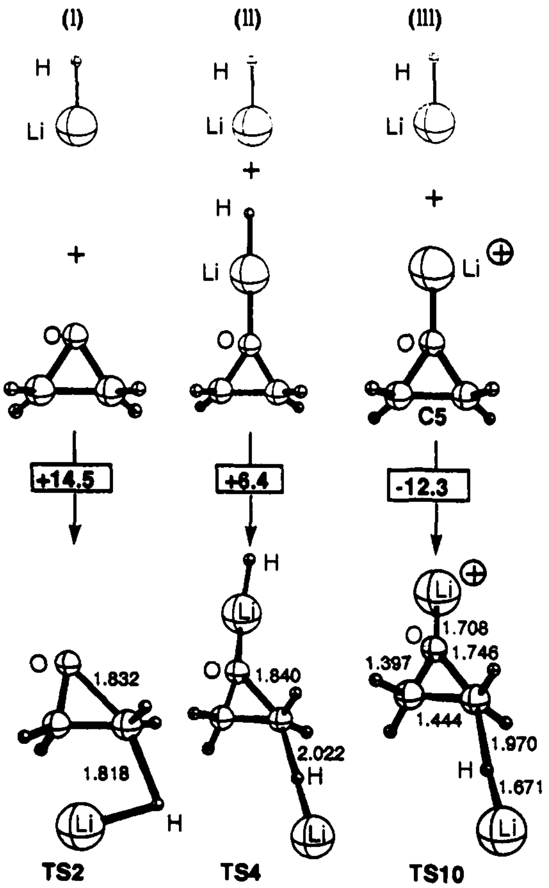


Figure 5. Three reactions which show the importance of cationic assistance: (i) LiH + C_2H_4O, (ii) LiH + C_2H_4O–LiH, and (iii) LiH + C_2H_4O–Li^+. Relative energies (kcal/mol) given are at the MP4SDTQ/6-31+G*//6-31+G*+ΔZPE level.

is bound to one of the epoxide methylene groups); this large Li^+ influence on the activation barrier is electrostatic in origin,[25] and will be reduced strongly by solvation of the cation].

CH_3Li Dimer and Ethylene Oxide. Previous theoretical investigations of organolithium reactions[21] suggested that lithium hydride can be used effectively as a convenient calculational model for organolithiums. Nevertheless, the longer C–Li bond distance of 2.145 Å in dimeric methyllithium, compared to the Li–H distance of 1.810 Å in $(LiH)_2$, may well influence the relative energies of retention and inversion transition structures, especially since carbanion⋯Li chains are involved in the latter. We have therefore included calculations on $(CH_3Li)_2$ systems in the present study.

Complexation of ethylene oxide by methyllithium dimer is exothermic by 16.2 kcal/mol. The resulting complex **C6** (Figure 6) has C_1 symmetry. Two transition structures for ring opening of ethylene oxide by methyllithium dimer, via a retention pathway (**TS11**) and with inversion (**TS12**), were located without symmetry constraints. These structures are very similar to the C_2H_4O + $(LiH)_2$ transition structures **TS5** and **TS6**. Attempts to locate a transition structure similar to **TS8**, with both lithium cations coordinated to oxygen, were unsuccessful. Inversion transition structure **TS12** displays ring opening early on the reaction coordinate. The C–O bond is still relatively short and the C–C distance comprising the bond being formed is still long. The activation barrier is 31.2 kcal/mol (relative to the complex **C6**). The barrier toward ring opening with retention via **TS11** is 48.7 kcal/mol. This transition structure corresponds to a later ring opening process with a longer, more weakened C⋯O bond. The new C–C bond is almost 0.2 Å longer in **TS11** than in **TS12**, but it has a slightly higher bond order. The preference for inversion over retention, 17.5 kcal/mol, even larger than the 11.2 kcal/mol for the corresponding difference in transition-state energy in the $(LiH)_2$ systems, can be ascribed to the more advanced rupture of the C–O bonds in **TS11** than in **TS12**. This is not compensated by differences in C–C bond formation. The $(CH_3Li)_2$ calculations thus clearly confirm the preference for inversion calculated for the $(LiH)_2$ models.

The Influence of Solvation. The β-hydroxyalkylation reaction is usually carried out in polar solvents, like diethyl ether or THF. The calculated model systems discussed so far refer to isolated entities and do not take solvent effects into account. We suggest that the following overall mechanisms (see Scheme 1) are followed in such media (the influence of polar solvents on the mechanisms of organolithium reactions will be discussed in a forthcoming publication):

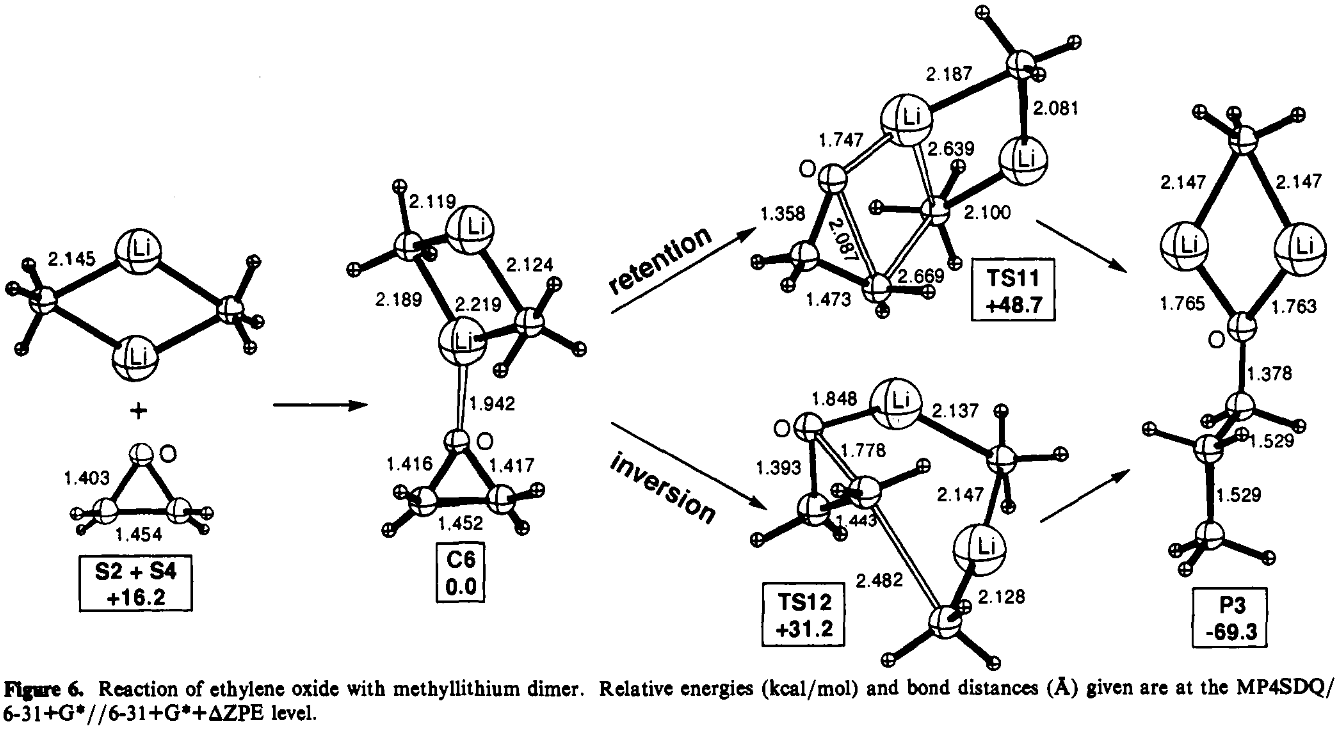
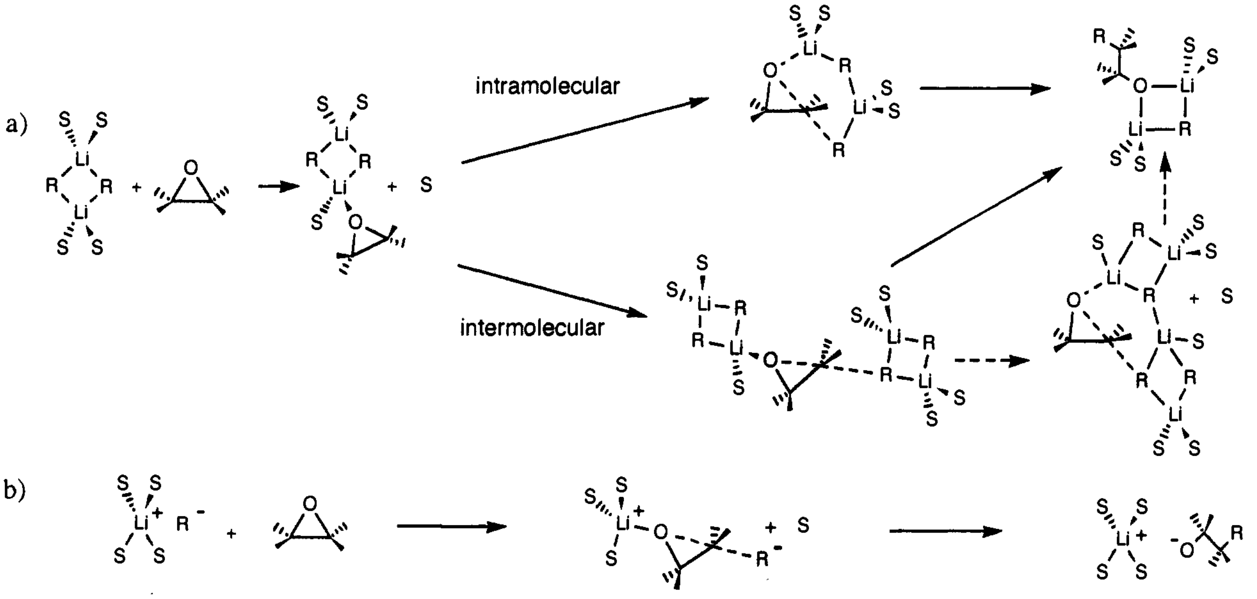


Figure 6. Reaction of ethylene oxide with methyllithium dimer. Relative energies (kcal/mol) and bond distances (Å) given are at the MP4SDQ/6-31+G*//6-31+G*+ΔZPE level.

Scheme 1. Proposed Reaction Paths in Which Li Solvation Has Been Included[a]



[a] Reaction a shows possible routes in moderately polar solvents, such as diethyl ether and THF. Reaction b shows a possible mechanism in the presence of strongly polar cosolvents, such as HMPTA.

(a) In *moderately polar solvents*, such as diethyl ether or THF, solvated aggregates of lithium compounds are common.[26] The first step is a solvent–epoxide exchange which might be favorable since ethylene oxide is an even better Lewis base than THF.[11] This complex can react intramolecularly. Cleavage of an Li–R bond, to form an Li–R–Li–R chain necessary for backside attack, will be promoted by additional solvation. The ethylene oxide–organolithium complex also may react via an intermolecular route in which another organolithium species attacks the epoxide at the backside. The actual transition structure might involve bonding between the two lithium aggregates (see Scheme 1, reaction a). This gives rise to a RLiRLi-chain moiety similar to that proposed for the intramolecular route.

Solvation is more effective in transition structures, since the bonds to lithium are weakened relative to the ground states, i.e. complexes and products.[27] The stabilization will be even more pronounced when the number of coordinating solvent molecules increases on going to the transition state. The lithium atoms in complex **C2** and in the retention transition structures **TS5** and **TS8** are three- and two-coordinated, while both lithiums in the inversion transition structures **TS6** and **TS7** are two-coordinated. Hence, more effective solvation is expected in **TS6** and **TS7**, increasing the preference for ring opening with inversion over ring opening with retention of configuration. The effect of cationic assistance on the activation energies will be attenuated by solvation, since solvated Li^+ is a weaker Lewis acid than unsolvated Li^+.

(b) Addition of *strongly polar cosolvents*, such as HMPTA, increases the rate of the β-hydroxyalkylation.[28] Under these conditions, solvent separated ion pairs can be formed. Exchange of a cosolvent molecule (strongly bound to the lithium cation) by the more weakly coordinating epoxide is endothermic. However, cationic assistance by a solvated lithium cation will be stronger than that by organolithiums. In addition, a "free" carbanion will be more reactive than an organolithium. We expect the exchange of cosolvent by the epoxide to be rate determining, after which the reaction will take place without an appreciable activation barrier.

(c) *Cryptands*, which function as extremely efficient cation solvent cages, decrease the rate of β-hydroxyalkylation.[11] Here, too, solvent-separated ion pairs are formed. However, Li^+ is unavailable due to complexation by the cryptand. The absence of cationic assistance in this case leads to the lower reactivity.

Conclusions

Nucleophilic ring opening of epoxides by organolithium compounds with inversion of configuration at carbon is strongly preferred energetically. The higher barrier toward ring opening with retention of configuration is not, as previously proposed,[5] due to electrostatic repulsion between the (negatively charged) epoxide oxygen and the attacking carbanion in the transition structure. Instead, the more advanced breaking of the carbon–oxygen bond in the retention transition structure, which is not accompanied by more developed bonding to the incoming carbon, is responsible. Cationic assistance, i.e. coordination of the metal cation to the epoxide oxygen, facilitates the reaction considerably.

Acknowledgment. The Deutsche Forschungsgemeinschaft, the Fonds der Deutsche Chemische Industrie, and Convex Computer Corp. provided support. We also thank the Dutch Supercomputing Working Group (WGS, Amsterdam) and Leibniz Rechenzentrum (München) for computer time and the Alexander von Humboldt Foundation for fellowships (S.H. and N.v.E.H).

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