Reactive Cleavage of Epoxides. Molecular Mechanics Model for Regiochemical Control of the Ring-opening Reactions

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A molecular mechanics model has been developed to predict the relative activation energies of nucleophilic ($LiAlH_4$) ring-opening reactions of epoxides leading to regioisomeric products. The model developed is entirely empirical, representing linear combination of calculated steric-hindrance and product-stability effects. The conformational, steric and electronic effects in the transition state, calculated by MM2, enable prediction of product distribution in 19 ring-opening reactions.

Epoxides are an important class of organic compound and valuable intermediates in the synthesis of complex organic molecules. Among epoxide reactions, the addition of nucleophiles is one of the most thoroughly studied and most widely used.[1] Ring opening may occur under neutral, basic or acidic conditions. It is generally accepted that in neutral and basic media the reaction follows an S_N2 mechanism,[1-3] with *anti*-stereochemistry of (at least) the kinetic product. The regiochemical control of ring-opening reactions has also been studied,[1-3] and it was found that two types of regioisomer could be obtained depending on the site of attack of the nucleophile. Therefore, identification and calculative prediction of factors determining regiochemistry in these reactions may play an important role in the synthesis of complex molecules.

Extensive experimental studies of nucleophilic oxirane-opening reactions established their major features.[2,3] It has been suggested[2-6] that electronic, steric and conformational effects are important in the control of the regiochemistry of these reactions. Therefore, we applied the MM2 molecular mechanics[7] program in an effort to treat quantitatively all the effects influencing the transition state of these reactions, and to calculate the product distribution.

Methodology

The reduction of epoxides to alcohols with metal hydrides, most commonly $LiAlH_4$, has been extensively studied.[1] Since this reaction is still interesting and widely used, and because the experimental data for ring opening of oxiranes with $LiAlH_4$ are widely available, we focused our calculations primarily on this reaction.

$LiAlH_4$ acts as a source of nucleophilic H^-. Our original intention was to follow the method of transition-state modelling,[8] applying MNDO calculations[9] to derive the transition-state geometry for the reaction of both oxirane and *cis*-2,3-dimethyloxirane. However, despite considerable effort, we could locate only the symmetrical transition state. This turned out to be the transition state of hydrogen transposition (see Fig. 5). In order to represent better the species likely to exist in solution, Li^+ was included in the calculation, but the result was not improved.

Therefore, we turned to molecular mechanics, assuming that it is possible to calculate the energy of a transition state even if its exact geometry is not known. Actually we calculated the difference in energy of transition states leading to regioisomeric products. This was done by taking into account all major contributions to the energy of a transition state: electronic, conformational and the steric hindrance effect to approach of the nucleophile. Based on the accumulated experimental evidence, the assumption was made that transition states differ in type depending on the degree of steric hindrance to approach of the nucleophile. If it is severe, the transition state would be reactant-like, and its energy will be determined by steric hindrance (E_{SH}). On the other hand, if steric hindrance to approach is small, the transition state would be product-like. Its energy will be determined by heat of formation (H_f) of the product. The heat of formation (H_f), calculated by MM2, includes the conformational (steric) energy (E_c). It has been further assumed that the energy of the transition state, which generally lies between those of the reactant-like and product-like species, might be represented by the sum of steric hindrance energy, calculated using the steric-hindrance model of an early transition state (see below), and the heat of formation of the product. The calculations refer only to the difference in energy of the possible transition states of one reaction, and were used in this work for quantitative predictions of product distribution of nucleophilic ($LiAlH_4$) ring-opening reactions of the epoxides.

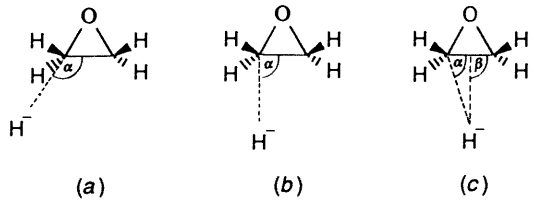
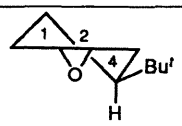
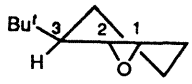
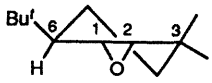
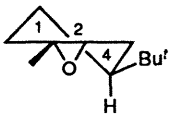
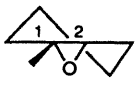
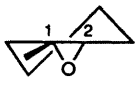
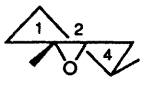
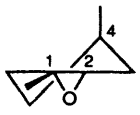
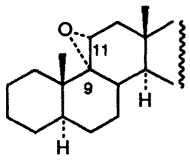
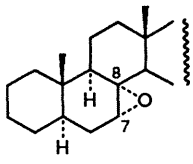
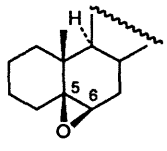
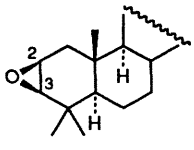
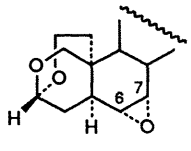


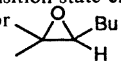
Fig. 1 Models for nucleophilic approach of H^- to epoxides

The molecular-mechanics calculations were performed using the MM2(88) program[10-12] with epoxide parameters[13] added. E_c and H_f were calculated in the standard manner. For the calculation of E_{SH} we adopted the model where H^- was treated as a non-bonded atom located at a fixed distance (see below) from the attacked carbon of an epoxide ring. The nucleophile (H^-) was placed in the plane of the epoxide ring (see Fig. 1). H^- and the attacked carbon were restricted in motion in all degrees of freedom, while the oxygen of the epoxide ring was allowed to move only in one plane, because of orbital requirements for S_N2 reaction. The remaining atoms were free of any restriction and their positions were located during the course of the energy minimization for this steric hindrance model. The van der Waals parameters for the H^- ion, $r = 1.78$ Å, and $\varepsilon = 0.166$ kcal mol^{-1},† were determined as follows. The van der Waals radius (r) was calculated[14] as 1.0 Å plus the radius of maximum electron density, equal to 0.78 Å in the case of H^- ion. The value of the ε parameter was estimated by comparison of atomic and ionic refractions,[15] and the MM2 values of the ε parameter.

† 1 cal = 4.184 J.

Table 1 Calculated energies (kcal mol $^{-1}$) and product distribution (%)

	Compound	Attack at atom	H_f[a]	E_{SH}[b]	E_{TS}[c]	E_{CSH}	p_{calc}[d]	p_{exp}[d]	Ref
1		C^1	0.0	0.0	0.0	10.6	99.7	100	18
		C^2	2.62	0.74	3.36	11.4	0.3	0	
2		C^2	0.0	2.08	0.0	13.6	79	65	17
		C^1 boat	2.87	0.0	0.79	11.5	21	35	
		tw-boat	3.33						
3		C^1	0.0	0.36	0.0	14.0	97	99	17
		C^2 tw-boat	2.33	0.0	1.97	13.6	3	1	
		boat	2.78						
4		C^3	0.0	0.0	0.0	11.2	99	95	19[e]
		C^2	1.12	1.84	2.96	13.0	1	5	
5		C^1	0.0	1.53	0.0	13.0	60	69	16
		C^2	1.77	0.0	0.24	11.4	40	31	
6a		C^1	1.16	2.67	3.83	12.8			
		C^2	3.46	1.20	4.66	11.5			
							C^1 0.2	0.6	
							C^2 99.8	99.4	16
6b		C^1	4.45	3.56	8.01	13.7			
		C^2	0.0	0.0	0.0	10.3			
7a		C^1	0.0	1.45	0.14	12.8			
		C^2	2.39	0.0	1.08	10.5			
							C^1 40	33.5	
							C^2 60	66.8	16
7b		C^1	8.20	5.40	12.29	16.8			
		C^2	0.57	0.74	0.0	11.3			
8		C^9	2.73	10.27	13.0	25.5	0(1)[f]	0(0)	22, 23
		C^{11}	0.0	0.0	0.0	15.2	0(99)	0(100)	(20)
9		C^8	0.0	6.24	0.0	21.8	0(100)	0(100)	20
		C^7	9.82	0.0	3.58	16.5	0(0)	0(0)	(24)
10		C^5	0.0	3.79	0.58	15.7	27(100)	0(93)	20
		C^6	3.21	0.0	0.0	11.9	73(0)	100(7)	
11		C^2	1.01	0.0	0.0	13.8	82	100	21
		C^3	0.0	1.9	0.89	15.7	18	0	
12		C^6	0.0	0.0	0.0	15.5	0	0	5
		C^7	4.18	0.49	4.67	16.0	0	0	

[a] Relative heats of formation of the product-like transition states. [b] Relative steric hindrance. [c] Relative transition-state energy, $E_{TS} = H_f + E_{SH}$. [d] Percentage of all products resulting from $LiAlH_4$ attack at the corresponding carbon. [e] Experimental data for  . [f] Parenthesized values refer to the reaction with Li–$EtNH_2$.

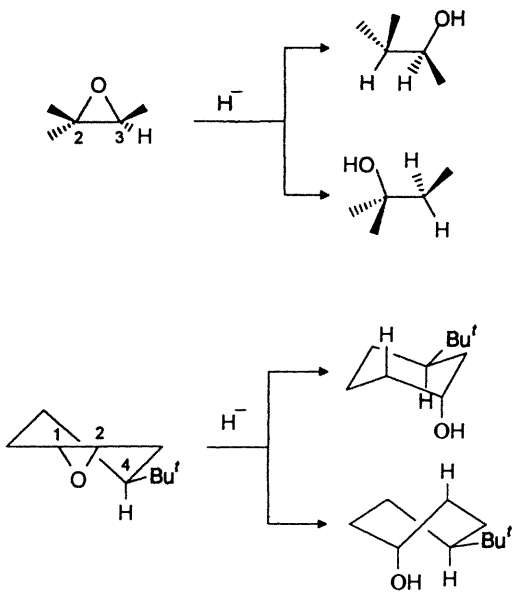


Fig. 2 Examples of epoxide-opening reactions with alcoholic products adopting transition-state conformation

For the calculations on steroids (Table 1) we used the cholestane molecule as a model skeleton with the side chain replaced by a methyl group.

For the calculations on *cis*-1,2-epoxy-3-methoxycyclohexane **13** and similar compounds, the following parameters, not existing in the MM2 program, have been assigned: the torsional constants $V1 = V2 = V3 = 0.0$ for the following angles C°–C–O–lp (lone pair), C°–C–O–H, C°–C°–C–O, H–C°–C–O, O°–C°–C–O and C°–C–O–Si; superscript 'o' denotes epoxide ring atoms. The bending parameters for the C°–C–O angle have been taken equal to the C–C–O (type 1–1–6) angle parameters. This was justified by the fact that torsional constants of the corresponding open-chain angles are generally small and the contribution of one angle to the torsional energy difference is small compared with steric-hindrance energy and the heat of formation.

Results and Discussion

At the beginning we investigated the steric requirements for the nucleophilic approach of H^- to oxirane (Fig. 1), and *cis*-2,3-dimethyloxirane, following three possible angles (α) of attack. The intention was to find the lowest-energy path for the approach of the nucleophile. The H^- ion was in the plane of the epoxide ring, starting at a distance of 4.0 Å from the attacked ring carbon. The line joining the H^- ion and the attacked ring carbon made an angle α with the C–C bond of the epoxide ring. The H^- then approached the oxirane ring, point by point, along with $H^- \cdots C$ line, (*a*) or (*b*), or along the line perpendicular to the C–C bond (*c*) (Fig. 1). At each point the system was subjected to energy minimization. In the first case (*a*), the attack of nucleophile was collinear with the C^1–O bond. The angle α was ~ 120° at a $H^- \cdots C$ distance of 4.0 Å and 3.5 Å. However, at a distance of 3.0 Å or less, H^- was forced by steric interactions to a nearly perpendicular approach ($\alpha \sim 90°$), the dihedral angle H^-–C–C–O remaining at 180°. This picture was confirmed by calculational model (*b*) where the perpendicular approach was followed from the starting $H^- \cdots C$ distance of 4.0 Å. The approach (*b*) provides a quantitatively identical picture as that in (*a*) at a $H^- \cdots C$ distance of 3.0 Å or less. The approach (*c*), where α varies and β is equal to 90°, is a minimum-energy-path approach as well, but it is of consistently higher energy than routes (*a*) and (*b*). Besides, at a $H^- \cdots C$ distance of 2.2 Å or less H^- is forced to the plane perpendicular to the oxirane ring.

From the above findings we concluded that the approach of H^- along the C–O bond direction, case (*a*), is not possible, and that path (*c*) requires a higher energy than does path (*b*). Therefore, the approach has to be perpendicular, $\alpha \sim 90°$, case (*b*). The reaction model (*b*) was used in all further E_{SH} calculations.

cis-2,3-Dimethyloxirane provided qualitatively the same picture. Only the H^-–C^2–C^3–O dihedral angle was not exactly 180°. Its deviation, however, did not exceed 10°.

The calculations* described above, performed with *trans*-4-*tert*-butyl-1,2-epoxycyclohexane **1**, helped in establishing the $H^- \cdots C^1$ distance of 2.3 Å as a limiting value in E_{SH} calculations. Below this value the steric energy increased considerably, and the geometry of the epoxide ring underwent changes unlikely to happen in the reaction, *e.g.*, elongation of the C^1–C^2 bond instead of the C^1–O bond. Therefore, the distance between the nucleophile H^- and the attacked carbon of the epoxide ring was fixed at a value of 2.3 Å for the remaining E_{SH} calculations.

It is known that under basic conditions unsymmetrical alkyl-substituted epoxides open with cleavage of the C–O bond of the less substituted carbon due to its greater steric accessibility.[2] At the same time, the regioselectivity of the opening of epoxycyclohexanes is usually explained[2,16] by assuming more product-like (chair or twist-boat) than epoxide-like transition states. Heats of formation calculated by MM2 for products adopting the transition-state conformation (Fig. 2) comprise electronic and conformational effects operating in the ring-opening reactions. The bond and structural increments of H_f comprise the electronic effects associated with bond formation and bond breaking. The conformational effects are included in the calculation of H_f. Thus, calculated heats of formation indeed predicted almost exclusive formation of the secondary (or tertiary) alcohols from the 2-methyl- and 2,2-dimethyloxirane, respectively. They predicted, as well, the exclusive formation of *trans*-3-*tert*-butylcyclohexanol from *trans*-4-*tert*-butyl-1,2-epoxycyclohexane **1**, and predominant formation of the secondary alcohol from *trans*-4-*tert*-butyl-1,2-epoxy-1-methylcyclohexane **5**, Table 1.

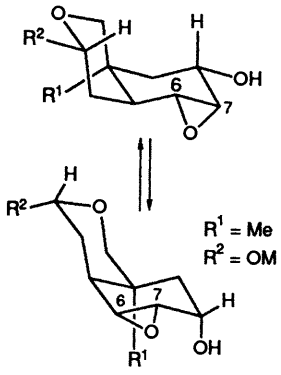
However, H_f failed to reproduce the experimental distribution of products[17] arising from *trans*-1-*tert*-butyl-2,3-epoxycyclohexane **2**.† Here, the twist-boat transition state was calculated to be disfavoured even more than in its regioisomer **1**, predicting exclusive attack at C^2. The boat-like transition state was somewhat lower in energy, but insufficiently to explain the fact that only about 65% of the product, resulting from attack at C^2, was found experimentally. This was attributed to steric hindrance at C^2 by the neighbouring *tert*-butyl group. E_{SH} was added to the calculated H_f values to yield transition-state energy ($E_{TS} = H_f + E_{SH}$). Comparing calculated to experimental energies[16] of **5** and **6**, we found that the MM2-calculated preference for formation of tertiary alcohol was overestimated by 1.2 kcal mol^{-1} compared with the secondary alcohol. The conformational preference of the chair-like transition state was overestimated by 2.1 kcal mol^{-1}. With these corrections made, the calculated energies and product distributions are compared with the experimentally found ones in Tables 1 and 2.

Tables 1 and 2 contain one more column with E_{CSH} (complete steric hindrance) values. The E_{CSH} values were calculated as the

* The calculations with H^- parameters equal to MM2 hydrogen (type 5) parameters produced a qualitatively identical picture, except that the nucleophile was forced into a perpendicular trajectory at a smaller $H^- \cdots C^1$ distance.

† Only the more stable conformation, with an equatorial *tert*-butyl group, was considered.

Table 2 Calculated energies (kcal mol^{-1}) and product distribution (%) in the reaction of epoxides bearing a polar α-substituent

Compound[a,h]	Attack at atom	H_f[b]	E_{SH}[c]	E_{TS}[d]	I_{corr}[e]	$E_{TS.corr}$[f]	p_{calc}[g]	p_{exp}[g]	Ref.
13 *trans*, R = OMe	C^3	1.37	0.05	1.42	0.0	0.0	90	90	2
	C^2	0.0	0.0	0.0	2.7	1.28	10	10	
14 *cis*, R = OMe	C^3	0.0	0.0	0.0	0.0	0.0	100	100	2
	C^2	1.40	0.46	1.86	2.7	4.56	0	0	
15 *cis*, R = $OSiMe_3$	C^3	0.54	0.0	0.50	0.0	0.0	98	76	26
	C^2	0.0	0.04	0.0	2.7	2.20	2	24	
16 *trans*, R = $OSiMe_3$	C^3	2.47	0.12	2.59	0.0	0.0	55	82	26
	C^2	0.0	0.0	0.0	2.7	0.11	45	18	
17 *cis*, R = OH	C^3	1.24	1.38	2.62	0.0	0.42	33	25	26
	C^2	0.0	0.0	0.0	2.2	0.0	67	75	
18 *trans*, R = OH	C^3	2.48	0.25	2.73	0.0	0.53	40	24	26
	C^2	0.0	0.0	0.0	2.2	0.0	60	76	
19 	C^6	1.76	2.92	4.68	0.0	2.48	2	0	25
	C^7	0.0	0.0	0.0	2.2	0.0	97	100	

[a] E_{CSH} is less than 15 kcal mol^{-1} for all the compounds in Table 2. [b,c,d,g] See Table 1. [e] Inductive effect correction. [f] Transition-state energy corrected for the inductive effect. [h] In the case of **13** and **14** the nucleophile is CH_3O^- and the products contain two methoxy groups (Fig. 4). In the case of compounds **15**–**19**, in this work, the nucleophile $LiCH_2CO_2Li$ is replaced by CH_3^- ion in order to simplify the calculations.

difference in energy between the parent epoxide and the steric-hindrance model described above. It is known[2,5] that $LiAlH_4$ reduction of some sterically congested epoxides affords no alcohol product. This was attributed to complete steric hindrance to approach of the nucleophile. While the product distribution is determined by the difference in E_{TS}, E_{CSH} is related to the reaction rate. It reflects the difference in steric energy between the reactants and transition state. If E_{CSH} is great, the activation energy will be too high, *i.e.*, the approach of the nucleophile will be completely hindered. Consequently, the yield of the corresponding product will be zero regardless of the value of E_{TS}. Inspection of E_{CSH} values enables us to estimate the borderline E_{CSH} value as 15 kcal mol^{-1}. Above this value the reaction does not take place.

The results summarized in Table 1 reflect a good correlation of the calculated product distributions with the experimentally found ones, so enabling a comparison of the relative importance of various effects to be made. For instance, the conformationally favoured attack at C^2 in compound **2** is hindered by the *tert*-butyl group, and a fraction of the corresponding product decreased compared with the case of compound **1**. On the other hand, the product distribution arising from **3** is similar to that arising from **1** since the steric hindrance at C^1 caused by the 6-*tert*-butyl group is counterbalanced by the steric hindrance at C^2 caused by the two neighbouring methyls.

The conformational effects compete with electronic effects and steric hindrance in **5** to give approximately equal amounts of two possible products, while they add in **6** to favour attack at C^2 in conformation B.

The steroid field is rich in examples of epoxide ring-opening reactions. We investigated some reactions in which various factors affecting regiochemistry compete. The exceptions are 9α,11α-epoxides **8**[22,23] where conformational and electronic effects, and steric hindrance, favour the formation of 9α-ols. However, the E_{CSH} value for the attack at both C^9 and C^{11} is higher than 15 kcal mol^{-1}. This explains the inertness of these compounds to $LiAlH_4$ (see Table 1). In 7α,8α-epoxides **9**[20] the epoxide ring is also protected from axial attack to the β-face of the molecule (see Table 1), and these compounds do not react with $LiAlH_4$. An interesting example is 5β,6β-epoxycholestane **10**, where H_f values favouring the formation of the 6β-ol are counterbalanced by E_{SH} values. The net result is formation of the 5β-ol while the approach to C^5 is completely hindered, so preventing the formation of the 6β-ol. Reduction of 2β,3β-epoxy-4,4-dimethyl-5α-cholestane **11** with $LiAlH_4$ is controlled by E_{SH} values favouring formation of the 3β-ol, although conformational effects favour formation of the 2β-ol. Nucleophilic opening of the epoxide ring in 6α,7α-epoxy-3α,19-epoxymethano-2-oxa-5α,10α-cholestane **12** was the subject of our own investigation.[5] Although it is known[27] that the nucleophilic opening of steroidal 6α,7α-epoxides yields the products of 6β-attack, in **12** we expected 7β-attack to occur due to steric hindrance at C^6. The calculations showed (Table 1, Fig. 3), that steric hindrance at C^6 and at C^7 is about equal, C^7 being slightly more hindered. The value of E_{CSH} > 15 kcal mol^{-1} for the attack on both C^6 and C^7 explains the resistance of this compound to epoxide ring-opening with $LiAlH_4$ and other reagents.[5]

The reaction of epoxides with alkali metals, especially lithium, has been described in terms of nucleophilic ring-opening by solvated electron[20] or in analogy to radical-anion reductions of organic halides.[28] It has been suggested[28] that direction of the opening may be determined solely by the stability of the corresponding product. It means that, in contrast

with $LiAlH_4$ reduction, the reduction of epoxides with alkali metals occurs under thermodynamic control and the product distribution (parenthesized values in Table 1) may be calculated from the values of heat of formation (H_f) of the products. Indeed, the calculated H_f values (Table 1) predicted the formation of the 9α-ol (attack at C^{11}) from compound **8** and the formation of the 6β-ol (attack at C^5) from **10**.[20] Predicted formation of the 7α-ol from **9** is in disagreement with ref. 20 but in accord with more recent work.[24]

Consideration of factors affecting the $LiAlH_4$ opening of the epoxide ring may serve well as the basis for at least qualitative prediction and rationalization of the product ratio of the ring-opening reactions of epoxides bearing polar α-substituents (see Table 2).

It is known[2] that both *cis*-1,2-epoxy-3-methoxycyclohexane **14** (Fig. 4) and *trans*-1,2-epoxy-3-methoxycyclohexane **13**, open preferentially at C^3 under nucleophilic attack by CH_3O^-. This observation was ascribed[2] to an inductive effect of the alkoxy substituent. Taking into account the suggested different nature of the α-oxygen,[26] we introduced the inductive effect correction (Table 2). Its magnitude was estimated on the basis of product distribution from compound **13**. Only the chair-like transition states were considered since the boat-like structures are more than 3.0 kcal mol^{-1} higher in energy. The most stable of the OR rotamers were considered and the OH rotamer is the one that resembles most closely the actual transition-state ion (see Fig. 4). From Table 2 it could be concluded that the inductive effect of the α-substituent is the dominant one in *trans*-compound **13**, leading to the formation of 2-methoxycyclohexanol. In the *cis*-isomer **14** the other effects contribute as well.

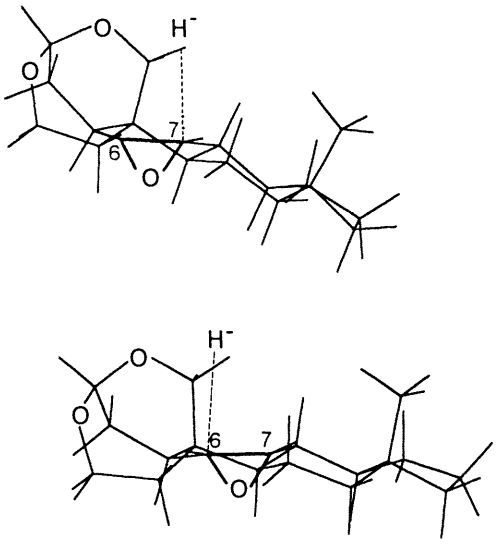


Fig. 3 Energy-minimized (MM2) steric-hindrance models of **12** for the hydride attack at C^6 and C^7

Finally, we considered reactions of some other α-oxygenated epoxides (**15**–**19**) with dilithioacetate. In the product-like transition state the $-CH_2CO_2^-Li^+$ fragment was replaced by Me. The E_{SH} values calculated for H^- were used and were considered to be the lowest limit of E_{SH} values for the actual nucleophile. In the case of silyl ethers **15** and **16** the two conformations of the starting epoxide are of about equal energy. It seems that formation of the major product resulting from the attack at C^3 is not governed by stereochemical effects, but primarily by an inductive effect of the α-substituent. On the other hand, it seems that steric factors dominate the reactions of all compounds with an α-hydroxy substituent. The major product (attack at C^2) obtained from *trans*-hydroxy epoxide **18** is primarily due to the H_f term (lower conformational energy and favourable structure-fragment formation in the product-like transition state) which is partially counterbalanced by the α-substituent's inductive effect favouring attack at C^3. In contrast with **18**, the OH group is preferentially axial in *cis*-hydroxy epoxide **17** owing to its electrostatic interactions with the epoxide oxygen. This stabilization persists during nucleophilic approach and is reflected in the steric hindrance effect. Therefore, despite a much smaller H_f term in **17** compared with that in its *trans*-stereoisomer **18**, similar product distribution is expected in both cases, reflecting preferential attack at C^2.

Compound **19** is the intermediate in the total synthesis of (±)-vernolepin.[25] In order to simplify the calculations, the methyl group was used instead of the CH_2OBz substituent at C^{10}. Unexpected attack at C^7 may well be understood on the basis of calculated energies (see Table 2). The conformation bearing an equatorial OH substituent is not the low-energy conformation. Actually, the two conformations are of about equal energy. Opening at C^7 is favoured by the H_f term, primarily due to formation of the more favourable structure

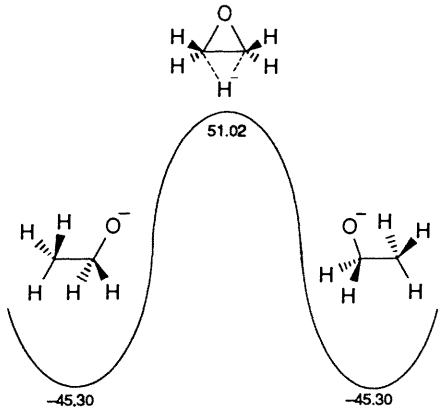


Fig. 5 Calculated (MNDO) enthalpy profile (kcal mol^{-1}) for hydrogen-transposition reaction

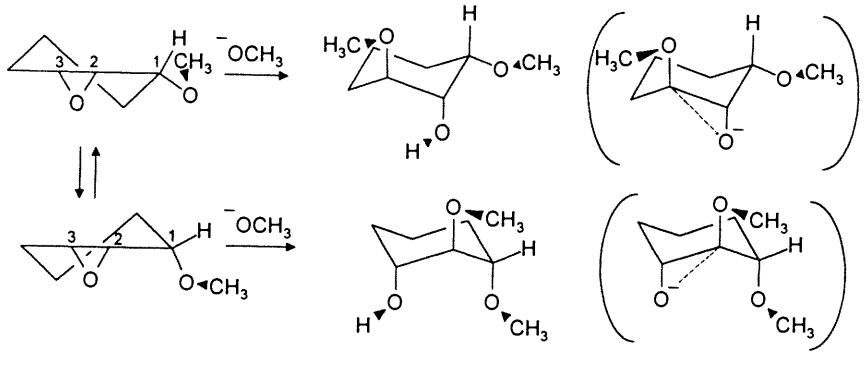


Fig. 4 Product-like transition states **14** under nucleophilic attack by CH_3O^- ion

fragment. Steric hindrance to approach to C^6 is still highly important although C^3 bears only an axial hydrogen. These effects are partially counterbalanced by the α-substituent's inductive effect, which favours attack at C^6, but insufficiently to prevent almost exclusive formation of the 6α-ol.

Conclusions.—Although further corroborating evidence on transition-state geometry and energy is needed from other more recent semiempirical methods such as AM1 or PM3, or from *ab initio* calculations, we believe that the model described herein may be used for accurate prediction of regioselectivity in ring-opening reactions of epoxides with $LiAlH_4$. With some limitations, it may also be used for qualitative rationalization and prediction of product distribution in this reaction using other reagents.

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