On the Regio- and Stereoselective Synthesis of Aminocyclitols from Cyclitol Epoxides: The Effect of Li as a Chelating Agent

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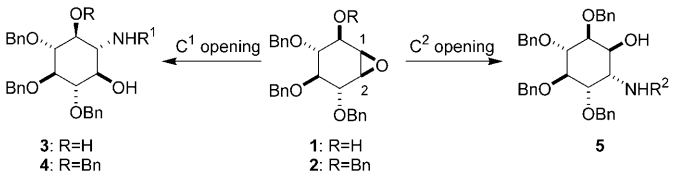
Abstract: Experimental and theoretical studies on the influence of Li ions on the regio- and the stereoselectivity of the reaction of cyclitol epoxides with nitrogen nucleophiles have been carried out. Model studies with NaN_3 as a nucleophile in the absence of Li ions predict a mixture of C1 and C2 regioadducts. The inclusion of two Li ions as a chelating agent favours the operation of a low populated "all-axial" conformation leading ultimately to the C1 adducts. In all cases, the results can be rationalised by geometric and energetic considerations of the corresponding transition states. Predictions of the theoretical calculations are in good agreement with the experimental results using primary and secondary amines as nucleophiles, and thus confirm the validity of this study.

Keywords: ab initio calculations · amino alcohols · conformation analysis · epoxides · regioselectivity

Introduction

Over the last years, aminocyclitols have gained interest as pharmacological tools for the study of cellular processes linked to the inositol phosphate cycle, as well as potential glycosidase inhibitors.[1–3] As part of our ongoing research directed towards the design and synthesis of new amino and diaminocyclitols as modulators of sphingolipid metabolism,[4] we became interested in the regio- and stereoselective synthesis of aminocyclitol derivatives of types **3–5** from regioselective epoxide opening of suitably protected cyclitol epoxides **1**[5] and **2**[6] (Scheme 1).



Scheme 1. Regio- and stereocontrolled opening of cyclitol epoxides.

Examples of regiocontrolled epoxide opening of cyclitol derivatives with nitrogen nucleophiles to give the corresponding C1 or C2 adducts are scarce in the literature.[7] In a previous work,[6] we described an unexpected regioselective chelation-controlled C1 azidolysis and aminolysis of epoxide **1** in the presence of $Yb(OTf)_3$. This method required

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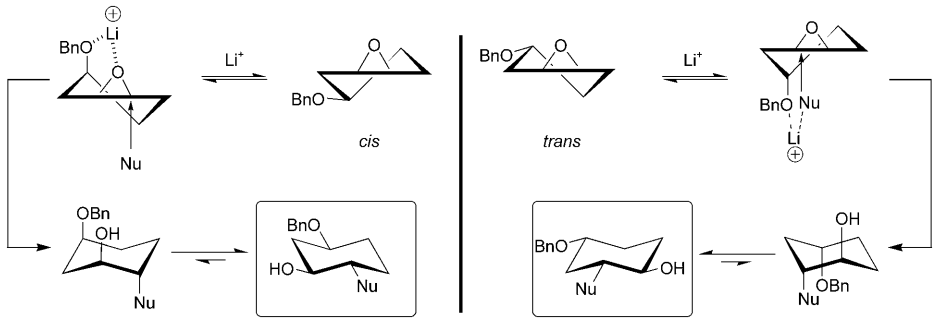
the presence of a vicinal free hydroxyl group for an efficient metal coordination, which prevented their practical use on fully protected cyclitol derivative **2**. Along this line, we were interested in the search of an alternative, more general protocol for this regioselective transformation.

Epoxide opening of substituted 1,2-epoxycyclohexanes is well documented in the literature.[8] In general, a *trans*-diaxial stereoselectivity is found, as dictated by stereoelectronic effects.[9–13] However, the observed regioselectivity depends largely on conformational bias and can be modulated by a judicious choice of reaction conditions. In this context, model studies on the reactivity of *cis*- and *trans*-4-benzyloxy-1,2-epoxycyclohexane with nitrogen nucleophiles have shown the dramatic effect of some metals, particularly Li salts, to promote a complete regiochemical epoxide opening.[14] Thus, in the presence of $LiClO_4$, the conformational equilibrium in the *cis* isomer is shifted towards a reactive conformation in which the benzyloxy group adopts an axial disposition to enable intramolecular metal chelation with the epoxide. On the other side, the conformational equilibrium in the *trans* isomer is also shifted to allow a lithium-assisted regiocontrolled intramolecular nucleophile delivery (Scheme 2).

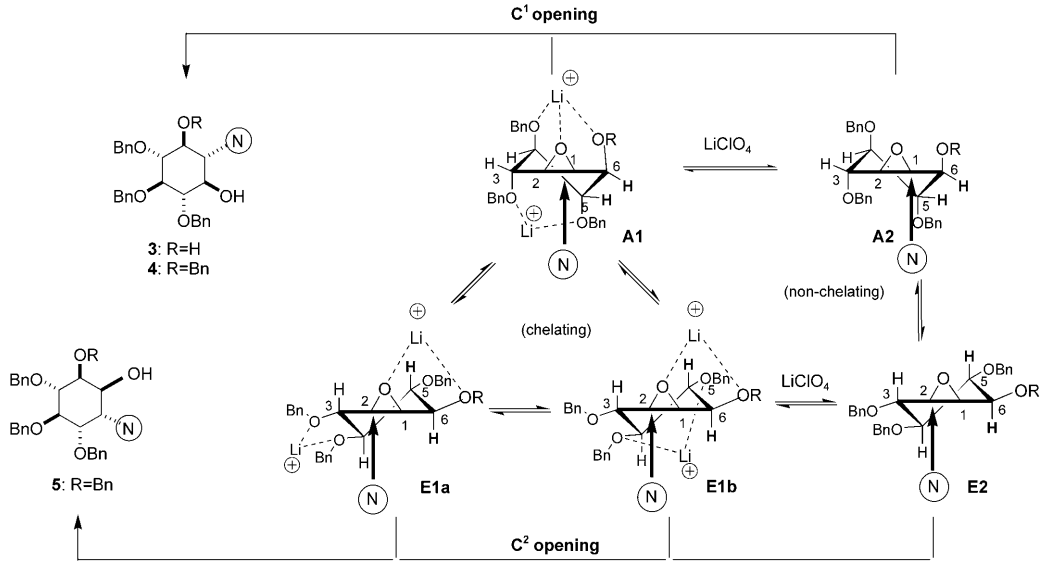
Reactivity of cyclitol epoxides with nitrogen nucleophiles: Based on these premises, epoxides **1** and **2** represent challenging models to confront the above mechanistic hypotheses. Thus, intramolecular chelation would require the participation of an apparently highly energetic "all-axial" conformation **A1**, in equilibrium with the equatorial conformations **E1a** and **E1b** (Scheme 3). Both axial and equatorial conformations would lead to different regioadducts on the basis of the above-mentioned stereoelectronic effects. However, treatment of epoxides **1** and **2** with NaN_3 in the presence of 2 N $LiClO_4$ in CH_3CN at 80 °C[15] cleanly afforded the corresponding azidoalcohols **3a**, and **4a** in high yields from the regio- and diastereoselective C1 opening of the starting epoxides (see Table 1, entries 1 and 5).[16] The use of primary or secondary amines as nucleophiles also afforded the corresponding C1 regioadducts (Table 1, entries 2, 3, 4, 6, 7, and 8). The role of the $CH_3CN/LiClO_4$ system seems crucial for the reaction outcome, as evidenced in entries 9 to 12, where $LiClO_4$ was suppressed and/or CH_3CN was replaced with THF.

The regioselective formation of C1 adducts **3** and **4** with azide and amines can be interpreted as a result of an exclusive *trans*-diaxial opening of epoxides **1** and **2** through the "all-axial" Li-chelated conformation **A1** shown in Scheme 3.

Conformation **A1** is expected to be strongly stabilized by a double intramolecular chelation between Li and epoxide and/or benzyloxy groups. This conformation is consistent with the observed regiochemical outcome arising from the expected stereocontrolled *trans*-diaxial opening.

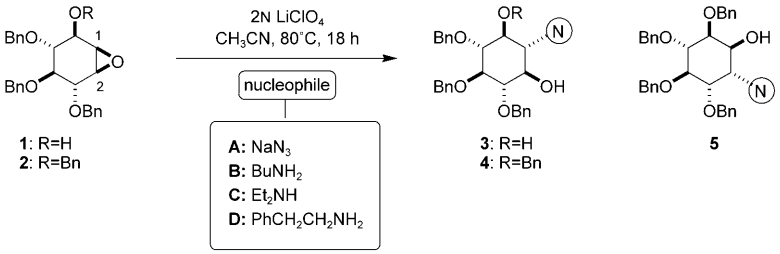


Scheme 2. Effect of Li ions on epoxide ring opening in 4-benzyloxy-1,2-epoxycyclohexane.[14]



Scheme 3. Lithium promoted opening of cyclitol epoxides **1** (R = H) and **2** (R = Bn).

Table 1. Opening of epoxides **1** and **2** in the presence of 2 N $LiClO_4$.



	Substrate	Nucleophile	Products	*dr*[a]	Yield[b] (%)
1	**1**	A	**3a**	single	92
2		B	**3b**	single	90
3		C	**3c**	single	85
4		D	**3d**	single	91
5	**2**	A	**4a**	single	91
6		B	**4b**	single	94
7		C	**4c**	single	92
8		D	**4d**	single	95
9		A[c]	**(d)**	–	–
10		A[e]	**(d)**	–	–
11		B[c]	**4b/5b**	2:3	87
12		B[e]	**4b/5b**	2:3	83

[a] Determined by ^{1}H NMR or HPLC. [b] Isolated yields. [c] No $LiClO_4$ was added. [d] No reaction. [e] THF as solvent.

Attempts to detect the putative reactive conformation **A1** by ^{1}H or ^{13}C NMR experiments were unsuccessful (see Supporting Information). Thus, only minor changes on the NMR pattern for the cycloaliphatic protons were observed when a 0.02 M solution of epoxide **2** in CD_3CN was treated with $LiClO_4$ at concentrations ranging from 0 to 1.5 M[17] and temperatures from 25 to 60 °C. These results indicate that, contrary to our own observations in model *cis*-4-benzyloxy-1,2-epoxycyclohexane[14] (see also Supporting Information), the conformational equilibrium of cyclitol epoxide **2** is not altered in the presence of Li salts.[18] It seems thus reasonable to assume that the major conformers in solution are the equatorial ones (**E1** and **E2**, Scheme 3) and that most of the Li ion is coordinated with the solvent.[19] The major or exclusive formation of C1 regioadducts can thus be explained either by operation of the postulated "*trans*-diaxial" opening from a low populated reactive conformation **A1** or by an alternative, formal "*trans*-diequatorial opening" from any of the equatorial conformers, in clear conflict with the accepted stereoelectronic control for these processes.[9–13]

Theoretical calculations: With the aim of gaining insight into this intriguing mechanism, we have performed a computational work on different reaction paths concerning the possible formation of C1 and C2 adducts by a nucleophilic attack on cyclitol epoxides **1** or **2**, as shown in Scheme 3. In order to have a computationally feasible system, a model structure analogous to **1**, in which the OBn groups have been replaced with OCH_3 groups has been considered. Moreover, the nucleophilic attack on each of the epoxides has been modelled by using the azide ion as a nucleophile. The density functional theory with the B3LYP functional[20] has been used to compute the different stationary points along the reaction paths. The polarized continuum model (PCM) of Tomasi and co-workers[21,22] has been employed to analyse the solvent effects (acetonitrile, $\varepsilon = 36.64$). All the energetic values discussed below are also based on results taking into account both the entropic corrections and the solvent effects. Additionally, the bonding features for the Li chelated structures have been analyzed with the atoms-in-molecules theory by Bader.[23] Herein we describe only an schematic representation of the optimized structures corresponding to reactants and transition states, while the structures of the remaining investigated stationary points and final products are available as Supporting Information.

For the sake of clarity, we have first modelled the process without including the chelating agent. Thus, in the absence of Li ions, only two stable conformations are found, namely **A2** and **E2** with "all-axial" and "all-equatorial" substituents, respectively (see Scheme 3 and Figure 1). Both conformers adopt a pseudo-chair ring disposition and, according to our calculations, they are energetically "quasi-degenerate" (**E2** is computed to be more stable than **A2** by only 0.8 kcal mol^{-1}; ΔG value). In our study, we have considered the nucleophilic attack by the azide ion at both C1 and C2 for each of the conformers and a free energy profile of the corresponding reactions paths have been plotted in Figure 2. In each case, the reaction starts with the formation of a van der Waals pre-reactive complex between the epoxide and the azide ion, prior to the transition state and the formation of the corresponding products. Figure 2 also shows that the most favourable reaction path for the nucleophilic attack from **A2** (all axial substituents) involves a *trans*-diaxial epoxide opening process, with a computed free energy barrier of 32.4 kcal mol^{-1} (**A2-TSC1**) and, consequently, it would give rise to the C1 adduct, while the attack at C2 requires a higher free energy barrier of 36 kcal mol^{-1} (**A2-TSC2**). It is also apparent from Figure 2 that, in the absence of Li ions, the reaction is endoergic by 7.3 kcal mol^{-1} and that the pre-reactive complex is unstable with respect to the reactants. This can be interpreted as a result of a differential entropic effect and it points out that the equilibrium is shifted to the reactants side. Noteworthy our calculations predict the product **A2-P2**, having a boat-like ring structure, to be about 4 kcal mol^{-1} more stable than **A2-P1**, with a chair-like ring

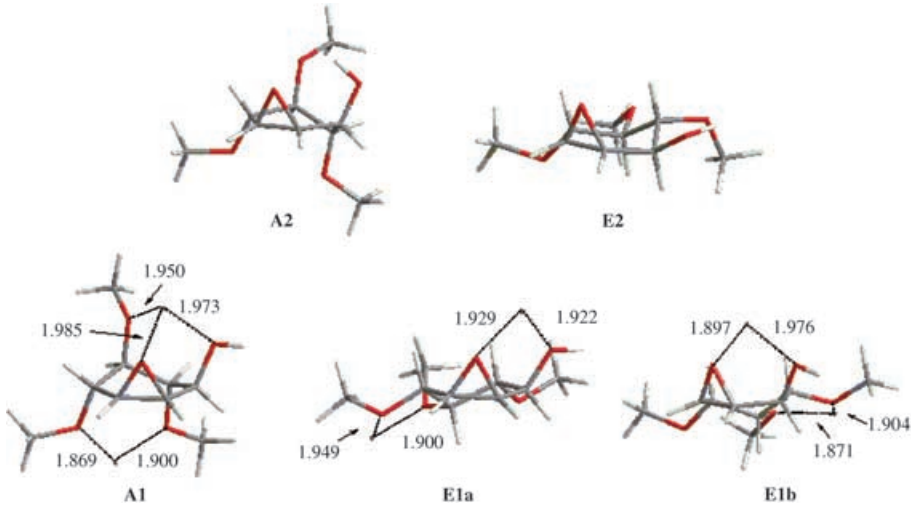


Figure 1. Structure of the reactants. Bond lengths are in angstroms.

structure, in agreement with the large electronic repulsion of the all-axial substituents in **A2-P1**. On the other side, the free energy profile also displayed in Figure 2, shows that the most favourable reaction path for the nucleophilic attack on **E2** (all equatorial substituents) would occur through **E2-TSC2**, (with a computed free energy barrier of 28.2 kcal mol^{-1}) to afford the C2 adduct (**EP2**), while for the corresponding attack on C1 (**E2-TSC1**) a higher free energy barrier of 33.2 kcal mol^{-1} has been found. The reaction path is again endoergic by about 14 kcal mol^{-1} and the pre-reactive complexes are unstable with respect to the reactants, this pointing out that the equilibrium between the reactants and the pre-reactive complexes is also shifted to the reactants side.

The observed preference for the nucleophilic attack on C1 or C2 depending on the axial (**A2**) or equatorial (**E2**) disposition of the substituents can be rationalized by considering the geometries of the corresponding transition states (Figure 2). In both cases, the transition states of lower activation barriers (**A2-TSC1** and **E2-TSC2**, respectively) present a chair-like structure, while those of higher activation barrier present a more strained boat-like structure (**A2-TSC2** and **E2-TSC1**). In addition, the results displayed in Figure 2 show that the chair-like transition states are between 4–5 kcal mol^{-1} more stable than the corresponding boat-like ones, and this energy compares well with the relative stability of a cyclohexane chair conforma-

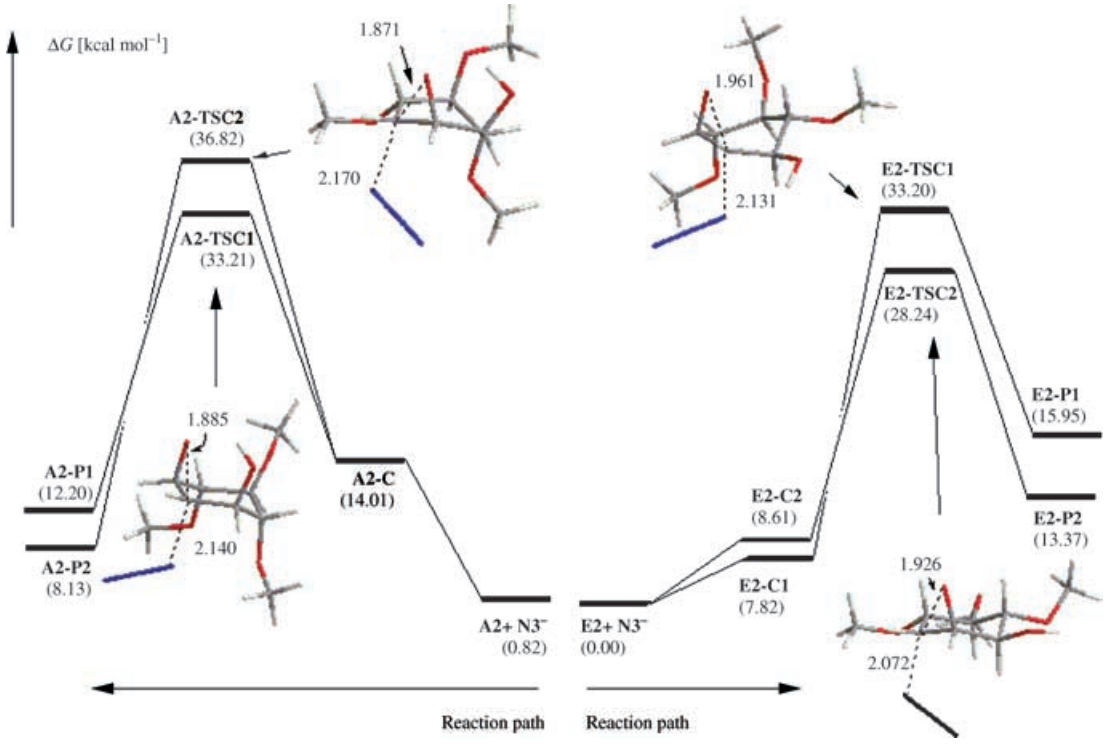


Figure 2. Schematic free energy diagram for the nucleophilic attack of azide to **A2** and **E2**. Each stationary point along the reaction path is labelled by the letter of the reactant followed by a letter designing the van der Waals complex (C), the transition state (TS) or the product (P). In addition, a suffix 1 or 2 denotes that the nucleophilic attack takes place at C1 or C2, respectively. The structures of the transition states are also included and the bond lengths are in angstroms.

tion with respect to the boat one (around 5.5 kcal mol^{-1}).[24] Thus, our theoretical calculations predict that the nucleophilic attack on the "all-axial" epoxide **A2** takes place at C1 while attack on the "all-equatorial" epoxide **E2** occurs at C2, as a result of the *more* favourable ring conformation for each transition state. Moreover, the small energetic difference between **A2** and **E2** predict the low regioselectivity found for this process in the absence of Li ions. Our experimental results are in agreement with these predictions (Table 1, entry 11).

The effect of lithium as a chelating agent has been investigated by including two Li ions.[25] The number of Li ions included in the calculation has been done by taking into account the geometric disposition of the "all-axial" reactant conformer, which allows one of the Li ions to simultaneously chelate to three different oxygen atoms from one side of the molecule (the epoxide, the OH group and one of the OMe groups, respectively), the second Li atom being able to chelate to two different oxygen atoms (two OMe groups) from the opposite side, this giving rise to the **A1** chelated conformer shown in Figure 1. The possibility of Li atoms to simultaneously chelate to two or three oxygen atoms is supported by recent literature reports.[26–31] Regarding the "all-equatorial" conformation, there are two possibilities for Li chelation leading to **E1a** and **E1b** conformers, respectively (see Scheme 3 and Figure 1). In each case, each Li atom binds to two oxygen atoms, namely the epoxide and the OH group from one face and the two OMe groups from the opposite face of the molecule. From an energetic standpoint, the ability of one Li ion to simultaneously chelate to three oxygen atoms in the "all-axial" conformation results in a significant extra stabilization of **A1** with respect to the two "all-equatorial" chelated conformers **E1a** and **E1b** ($\Delta G =$ 13.64 and 10.09 kcal mol^{-1}, respectively), which shifts the equilibrium to the "all axial" **A1** conformer (Figure 3).

For each elementary process, the reaction path begins with the formation of a van der Waals complex between the corresponding Li-chelated conformer and the azide anion, prior to the evolution to the corresponding transition states. The effect of the Li ions is also remarkable, compared with the reactions described above in the absence of Li, and produces a strong energetic stabilization of all stationary points along the reaction path (compare the energetic profiles in Figure 2 with those displayed in Figure 3). For the nucleophilic attack on **A1** ("all-axial" substituents), our calculations show that the pre-reactive complexes (**A1-C1** and **A1-C2**) are 22.1 and 22.7 kcal mol^{-1} more stable than the reactants and, as expected, the lower activation barrier (10.77 kcal mol^{-1} relative to the pre-reactive complex **A1-C1**) corresponds to the C1 attack, in agreement with the chair-like structure of the corresponding transition state (**A1-TSC1**) (see Figure 3). On the other side, C2 attack has a higher free energy barrier (18.34 kcal mol^{-1} relative to the pre-reactive complex **A1-C2**), as expected from the boat-like structure of the corresponding transition state **A1-TSC2** (see Figure 3). The reaction path displayed in Figure 3

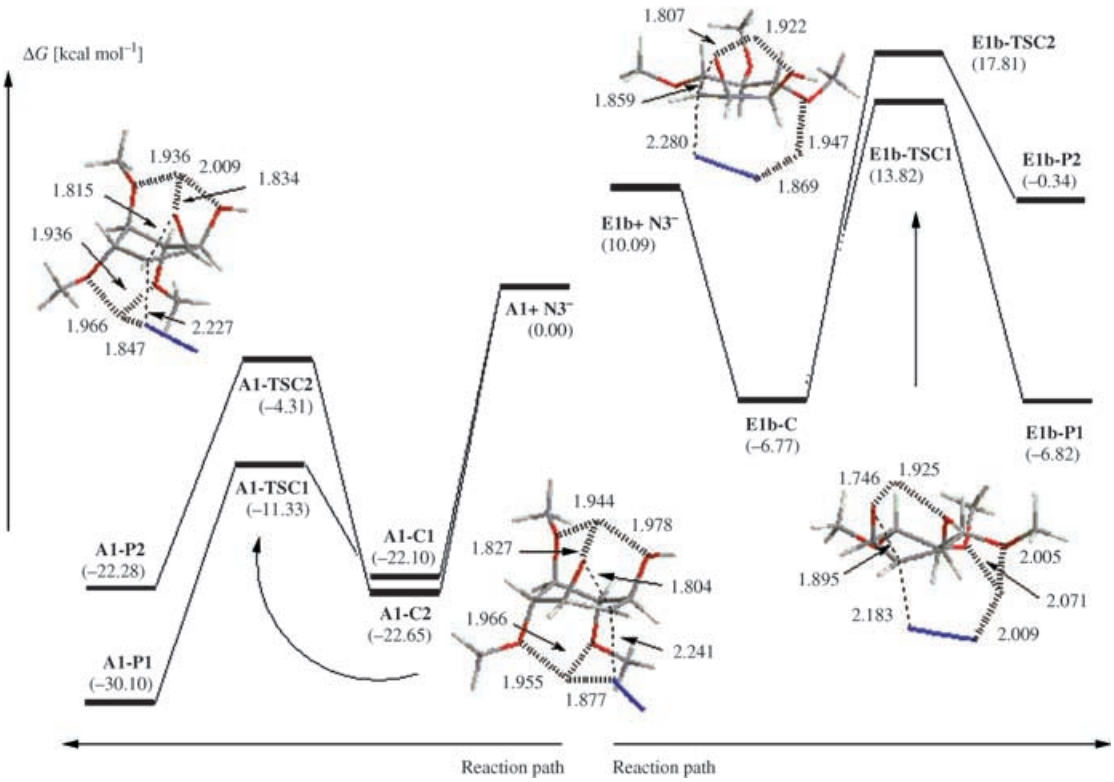


Figure 3. Schematic free energy diagram for nucleophilic attack of azide ion to **A1** and **E1b**. The stationary points are named as in Figure 2 and the structures of the transition states are also included. Bond lengths are in angstroms.

shows that both transition states lay energetically below the reactants and the reaction is exoergic, being the C1 adduct (**A1-P1**) the most stable product.[32]

Despite the large stability computed for **A1**, and for the sake of completeness, we have also investigated the nucleophilic attach of the azide ion upon C1 and C2 for the most stable "all-equatorial" chelated conformer **E1b**. Free energy profiles of the corresponding reaction path is also plotted in Figure 3. The nucleophilic attack also starts with the formation of the corresponding van der Waals pre-reactive complexes (**E1b-C1** and **E1b-C2**) between the Li-chelated epoxide and the azide ion. Our calculations predict those pre-reactive complexes to be more stable than the corresponding reactants (ΔG = 16.73 and 16.86 kcal mol^{-1}, respectively). Unexpectedly, the lower activation barrier (ΔG = 20.46 kcal mol^{-1} relative to the pre-reactive complex) corresponds to the C1 attack, with a boat-like transition state structure (**E1b-TSC1**). On the other hand, C2 attack shows a higher free energy barrier (ΔG = 24.58 kcal mol^{-1}, relative to the corresponding pre-reactive complex) despite the fact that the corresponding transition state (**E1b-TSC2**) has a chair-like structure. In addition, the reaction is computed to be exoergic by about 17 kcal mol^{-1}. The unexpected preference for the C1 attack upon **E1b**, in comparison with the preference for C2 attack observed for the also "all-equatorial", although not Li-chelated, **E2** (see Figure 2) can be explained by the effect of Li ions. Thus, as shown in Figure 3, the nucleophilic attack at C2 takes place through a transition state (**E1-TSC2**) where both Li atoms chelate to two different atoms: the OH group and the epoxide from one face and one of the OMe groups and the azide terminal nitrogen atom from the opposite face. On the contrary, in transition state **E1-TSC1** (leading to the nucleophilic attack at C1), one of the Li atoms is three-fold chelated with two of the OMe substituents and with the azide terminal nitrogen atom. This gives rise to an extra stabilization that compensates for the most favourable chair-like **E1-TSC2** conformation and accounts for the unexpected preference for C1 attack. These results let us conclude that, from a mechanistic standpoint, the nucleophilic attack at C1 is the preferred pathway for both "all-axial" and "all-equatorial" conformers in the presence of Li ions, as experimentally observed.

Conclusion

We have carried out an experimental and a theoretical study of the influence of Li ions on the reactivity of cyclitol epoxides with nitrogen nucleophiles aiming at rationalizing the regio- and stereoselective formation of the corresponding aminocyclitol derivatives.

The computational work on model studies with azide ion as nucleophile in the absence of Li atoms predicts that the nucleophilic attack upon the "all-axial" conformer **A2** will give rise to the C1 adduct while attack upon the "all-equatorial" conformer **E2** leads to the C2 adduct. These results may be rationalized by considering the geometric features of the corresponding transition states. In each case, a chair-like transition state is energetically favoured in comparison with the more strained boat-like ones. These predictions are in agreement with our experimental results.

The inclusion of two Li ions as a chelating agent has a dramatic effect. From an energetic standpoint, a remarkable stabilization of all stationary structures along the reaction paths has been observed when compared with the process in the absence of Li ions. Moreover, the "all-axial" conformer **A1** has a greater ability to chelate Li ions than the "all-equatorial" conformers **E1a** and **E1b**, which results in a larger energetic stability of the former and a shift of the conformational equilibrium towards the **A1** side. In addition, nucleophilic attack upon **A1** leads to the C1 adduct, as expected from the chair-like structure of the corresponding transition state. However, this reactive conformation is low populated at RT and not observable by ^{1}H NMR spectroscopy due to the higher tendency of Li ions to coordinate with acetonitrile, the solvent system. Our calculations also predict that, unexpectedly, nucleophilic attack on **E1b** would also lead to the C1 adduct, despite the apparently more strained boat-like structure of the corresponding transition state. This can be interpreted as a result of its higher ability for Li chelation in comparison with the alternative chair-like transition state, which counterbalances the above effect. In both scenarios, the theoretical calculations are in good agreement with the experimental results, thus confirming the validity of this study.

Experimental Section

For general experimental procedures, see Supporting Information. Epoxides **1**[5] and **2**[6] were prepared according to described procedures. ^{1}H and ^{13}C NMR spectra have been recorded in $CDCl_3$ at 300 and 75.5 MHz, respectively, unless otherwise stated.

Technical details of the calculations: All stationary points in the potential energy surfaces described in this work have been fully optimized with the hybrid density functional B3LYP method[20] by using the 6-31G(d,p) basis set.[33] At this level of theory we have also calculated the harmonic vibrational frequencies to verify the nature of the corresponding stationary point (minima or transition state), to provide the zero point vibrational energy (ZPE) and the thermodynamic contributions to the enthalpy and free energy. Moreover, to ensure that the transition states connect the desired reactant complexes and products, we have performed intrinsic reaction coordinate calculations (IRC), plus geometry optimization at this level of theory. The effect of the solvent has been taken into account by performing single point calculations at the optimized geometries by using the PCM model by Tomasi et al.[21,22] In this case, a dielectric constant of 36.64 corresponding to acetonitrile has been used. These calculations have been performed using the Gaussian 98 program package.[34]

In several stationary points of interest, we have also analysed the bonding features of the chelate by using the atoms in molecules (AIM) theory by Bader.[23] To do this, we have employed the AIMPAC program package[35] to obtain the topological properties of the B3LYP/6-31G(d,p) wave function. The Molden program[36] was also used to visualize the geometrical and electronic features of the different stationary points. The Cartesian coordinates and the absolute energies of all stationary points are also available as Supporting information.

General synthetic methods and compound characterization—Reaction of epoxides with nucleophiles in the presence of $LiClO_4$: A solution of the

starting epoxide **1** and **2** (0.5 mmol) in CH_3CN (9 mL) was added dropwise under argon over $LiClO_4$ (80 mg, 0.75 mmol) at RT. A solution of NaN_3 (0.5 mmol) or the corresponding amine (see Table 1) in CH_3CN (1 mL) was next added and the reaction mixture was stirred at 80 °C under argon. After 18 h, the reaction mixture was cooled to RT, quenched with H_2O (10 mL), extracted with CH_2Cl_2 (3×20 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation afforded crude aminoalcohols (See Table 1), which were purified as indicated below.

Compound **3a**: Purified by flash chromatography (silica gel pretreated with Et_3N) on elution with hexanes/EtOAc 1:1. ^{1}H NMR (200 MHz): δ = 2.78 (br, 1H), 3.46 (m, 5H), 3.67–3.99 (m, 6H), 7.20–7.35 (m, 15H); ^{13}C NMR (50 MHz, C_6D_6): δ = 53.5, 65.9, 73.0, 75.7, 82.4, 82.9, 127.8–128.7, 138.1; IR (film): $\tilde{\nu}$ = 3350 (br), 2109 cm^{-1}.

Compound **3b**: Purified by flash chromatography (silica gel pretreated with Et_3N) on elution with hexanes/EtOAc 1:1. ^{1}H NMR: δ = 0.90 (t, J = J' = 7.5 Hz, 3H), 1.26–1.47 (m, 4H), 2.41 (t, 2H, J=9.4 Hz), 2.69 (t, 2H, J=6.9 Hz), 3.40–3.59 (m, 4H), 4.81–4.94 (m, 6H), 7.25–7.38 (m, 15H); ^{13}C NMR: δ = 13.9, 20.3, 32.7, 44.5, 61.4, 71.3, 75.4, 75.7, 82.8, 84.3, 127.7, 127.8, 128.0, 128.4, 128.5, 138.5; IR (film): $\tilde{\nu}$ = 2920, 1499, 1451 cm^{-1}; MS: m/z: 506 $[M+H]^+$.

Compound **3c**: Purified by flash chromatography (silica gel pretreated with Et_3N) on elution with hexanes/EtOAc 1:1. ^{1}H NMR: δ = 1.09 (t, J = J' = 7.5 Hz, 6H), 2.57 (t, 1H, J = J' = 9.2 Hz), 2.76 (m, 4H), 3.48 (m, 5H), 4.83–4.98 (m, 10H), 7.24–7.40 (m, 25H); ^{13}C NMR: δ = 15.1, 63.8, 70.3, 75.3, 75.5, 82.8, 84.5, 127.6, 127.7, 127.9, 128.3, 138.4, 138.5; IR (film): $\tilde{\nu}$ = 3418, 1605, 1492 cm^{-1}; MS: m/z: 506 $[M+H]^+$.

Compound **3d**: Purified by flash chromatography (silica gel pretreated with Et_3N) on elution with hexanes/EtOAc 1:1. ^{1}H NMR: δ = 2.40 (m, 1H), 2.77 (t, J=7.2 Hz, 3H), 2.99 (t, J=7.8 Hz, 2H), 3.43 (m, 4H), 4.7–5.0 (m, 6H), 7.2–7.4 (m, 20H); ^{13}C NMR: δ = 36.9, 46.1, 61.4, 71.5, 75.3, 75.7, 82.8, 84.2, 126.1, 127.7, 127.8, 127.9, 128.2, 128.4, 128.6, 138.3, 138.5, 139.7; IR (film): $\tilde{\nu}$ = 3575, 3421, 3087, 2923, 2856, 1953, 1879, 1741, 14396, 1454 cm^{-1}.

Compound **4a**: Purified by flash chromatography (silica gel pretreated with Et_3N) on elution with hexanes/EtOAc 2:1. $[\alpha]_D$ = −6.2 (c = 0.95, $CHCl_3$); ^{1}H NMR: δ = 3.40–3.44 (m, 4H), 3.50–3.65 (m, 2H), 4.75–4.96 (m, 8H), 7.26–7.35 (m, 20H); ^{13}C NMR: δ = 45.5, 66.4, 72.7, 75.6, 75.8, 75.9, 81.1, 82.4, 82.6, 83.5, 127.6, 127.7, 127.8, 127.9, 128.1, 128.4, 128.6, 137.9, 138.0, 138.1; IR (film): $\tilde{\nu}$ = 3448, 3107, 1456, 1359, 1200 cm^{-1}.

Compound **4b**: Purified by flash chromatography (silica gel pretreated with Et_3N) on elution with hexanes/EtOAc 2:1. $[\alpha]_D$ = +7.4 (c = 1.5, $CHCl_3$); ^{1}H NMR: δ = 0.89 (t, J = J'=8.5 Hz, 3H), 1.21–1.42 (m, 4H), 2.4–2.8 (m, 3H), 3.20–3.45 (m, 5H), 4.80–5.02 (m, 8H), 7.26–7.34 (m, 20H); ^{13}C NMR: δ = 13.9, 20.3, 32.8, 45.9, 61.6, 71.7, 75.1, 75.7, 75.8, 80.3, 83.0, 84.0, 85.0, 85.5, 125.6–128.5, 138.1–138.3; IR (film): $\tilde{\nu}$ = 3418, 3062, 3028, 1669, 1492 cm^{-1}; MS: m/z: 596 $[M+H]^+$.

Compound **4c**: Purified by flash chromatography (silica gel pretreated with Et_3N) on elution with hexanes/EtOAc 2:1. $[\alpha]_D$ = +21.5 (c = 1.75, $CHCl_3$); ^{1}H NMR: δ = 1.11 (t, J=6 Hz, 6H), 2.55 (m, 1H), 2.75 (q, J= 6 Hz, 4H), 3.18 (m, 1H), 3.51 (m, 2H), 3.63 (m, 2H), 4.6–5.0 (m, 8H), 7.2–7.4 (m, 20H); ^{13}C NMR: δ = 15.7, 63.9, 69.7, 74.2, 74.9, 75.8, 75.89, 79.0, 82.8, 84.3, 85.7; IR (film): $\tilde{\nu}$ = 3421, 3058, 3028, 2906, 2897, 1659, 1493, 1456 cm^{-1}; EI-HRMS: m/z: calcd for $C_{38}H_{45}NO_5$: 595.3297; found: 595.3321.

Compound **4d**. Purified by flash chromatography (silica gel pretreated with Et_3N) on elution with hexanes/EtOAc 2:1. ^{1}H NMR: δ = 3.4–4.0 (m, 8H), 4.7–5.0 (m, 8H), 7.2–7.4 (m, 25H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 46.9, 51.6, 75.1, 75.2, 75.8, 75.9, 81.2, 83.1, 83.9, 84.9, 127.1, 127.4, 127.5, 127.7, 128.1, 128.2, 129.3, 129.4, 129.5, 138.2, 138.3, 138.4, 138.6, 140.2; IR (film): $\tilde{\nu}$ = 3416, 3923, 2912, 1426, 1455, 1357, 1245 cm^{-1}; $[\alpha]_D$ = −4.2 (c = 2.85, $CHCl_3$).

Compound **5b**: Purified by flash chromatography (silica gel pretreated with Et_3N) on elution with hexanes/EtOAc 2:1. ^{1}H NMR: δ = 0.83 (t, J=7.5 Hz, 3H), 1.25–1.40 (m, 4H), 2.49 (t, J=10.2 Hz, 1H), 2.56 (m, 1H), 268 (m, 1H), 3.34–3.63 (m, 5H), 4.6–5.0 (m, 8H), 7.2–7.4 (m, 20H); ^{13}C NMR: δ = 13.9, 20.3, 32.9, 45.9, 61.5, 71.7, 75.2, 75.7, 75.8, 80.3, 83.0, 84.0, 85.0, 127.6, 127.7, 127.8, 127.9, 128.2, 128.3, 128.4, 128.5, 138.3, 138.4, 138.6; IR (film): $\tilde{\nu}$=3412, 3017, 2984, 2972, 1465, 1436 cm^{-1}.

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[17] Higher concentrations of $LiClO_4$ led to precipitation.
[18] A conformational shift should alter the ^{1}H NMR pattern of the cyclohexane moiety, since dihedral angles should be significantly different for both limit conformations (A1 and E1). Thus, high J values would be indicative of any of the "all-equatorial" conformations, whereas small J values would be expected for the "all-axial" one.
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