

A First Theoretical Study on the Origin of the Metal-Mediated Regioselective Opening of 2,3-Epoxy Alcohols

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Hybrid density functional theory (B3LYP) method allows the study of the role of metal ions (Li^+) in the regioselective opening of 2,3-epoxy alcohols with lithium halides (Cl, Br, I) to the corresponding halohydrins. The theoretical results largely confirm the experimental results, especially with regards to the regioselectivity observed in the opening of the oxirane ring. The C3 halogen attack is always preferred to the C2 attack, with a significant difference in the TS structures with the reaction pathway under kinetic control. The central role of the lithium cation, linked to the oxygen atoms of the epoxy alcohol, is well documented in the reaction mechanisms presented. The energy differences between the two structures of the proposed TS appear to be ascribed to the different contribution of the X–H–O hydrogen bond between the hydroxyl groups of the reactant and the incoming halogen nucleophile.

1. Introduction

The Sharpless–Katsuki asymmetric epoxidation of allylic alcohols¹ to the corresponding chiral 2,3-epoxy alcohols has been reviewed several times recently,^{2a–d} with deep discussion on the mechanism of the reaction as well as on its synthetic utility and utilization in asymmetric synthesis. In the numerous applications of the chiral epoxy alcohols as precursors to diversely functionalized compounds the key point to distinguish among the three possible reactive sites of the epoxy alcohols (see Figure 1, sites a, b, and c) has been exhaustively explored, with excellent results in the regio- and stereocontrol of its transformation.

The epoxy ring opening at C2 or C3 (paths b and c) can depend on steric and electronic factor of the substrates but often also on the reaction conditions. From many synthetic examples,^{2b,d} it has been pointed out that the presence of a metal ion always enhances not only the reactivity of the substrate but also the C3 selectivity in the nucleophilic opening of the oxirane ring. In the early approach³ the use of different nucleophiles in the presence of $\text{Ti}(\text{OiPr})_4$ raised the C3 selectivity from moderate

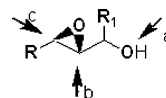


FIGURE 1. Three possible active site (a, b, c) of the epoxy alcohols.

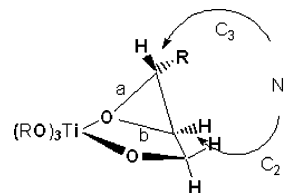


FIGURE 2. In the presence of $\text{Ti}(\text{OiPr})_4$ complexes, the ring opening of the 2,3-epoxy alcohols can be obtained on the C2 or C3 carbon atom sides (the C3 is the preferred one).

(5–15:1) to high (>100:1) depending on the nucleophile. The C3 regioselectivity has been rationalized by Sharpless on the hypothesis of a coordination between the two oxygen atoms and the centered Ti, which has been transesterified by the free hydroxyl (see Figure 2). It was suggested that the bond between the C3 atom and the oxygen of the epoxide was better oriented to overlap with an empty d orbital of the Ti than the bond between the C2 and oxygen atoms. On the basis of this model, to the same aim, different Ti derivatives have been employed^{2b,d} also on epoxy acids and esters. Furthermore, several different metal ions have been successfully used to enhance the C3 regioselective opening,^{2b,d} thus demonstrating that not only the Ti species are able to coordinate between the oxygen atoms as first described by Sharpless.

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TABLE 1. Different Reaction Conditions for the Experimental C3 and C2 Regioselective Opening of Epoxy Alcohols with Metal Halides

	metal halide			
	MgX ₂ (X = I, Br) ^{4d,5}	LiI ⁴	LiBr ⁴	LiCl ⁴
catalyst	none	Amberlyst 15	Amberlyst 15	Amberlyst 15
solvent	Et ₂ O	CH ₃ CN	CH ₃ CN	CH ₃ CN
temp (°C)	-60	rt	rt	rt
time	1–2 h	5 min	1 h	2 h
yield (%)	90–95	100	100	100
regioselectivity (C3:C2)	97:3–99:1	99:1	92:8–99:1	76:24–87:13

Among these different metals we have used Li⁴ and Mg^{4d,5} ions for the introduction of halogen nucleophiles at the C3 position. By this approach excellent ratios of the corresponding halohydrins⁶ have been obtained especially in the use of MgI₂ and LiI and this methodology also has been extended to 2,3-epoxy esters⁷ and to aziridino derivatives⁸ as well. The experimental results showed (see Table 1 for general conditions and results) that Li and Mg ions are indeed able to greatly enhance the C3 regioselectivity depending on the halogen nucleophile (Cl, Br, or I).

So far, a possible model for explaining the behavior in such reactions has been only speculated in the above-described terms for the Ti metal centered ring opening reaction: this prompted us to utilize a computational approach for a better understanding of the reaction pathways in this metal mediated ring opening of simple epoxy alcohols. Lithium halides have been chosen as a system to perform a theoretical study, using the hybrid density functional theory to gain a deeper insight into intricacies of the above-mentioned mechanism.⁴

2. Computational Methods

The potential energy surface of the reaction of the model *trans*-2,3-epoxypentan-1-ol + LiX (X = Cl, Br, I) has been investigated by using the density functional theory approach. All calculations were carried on by the Gaussian98 (DFT) program.⁹ DFT¹⁰ energies were determined by using the

nonlocal hybrid functional B3LYP,¹¹ which is a mixture of gradient corrections to the local density approximation and Hartree–Fock exchange. Basis sets on lithium, carbon, oxygen, and hydrogen atoms are of 6-31g* quality; while for halogen atoms (chlorine, bromine, and iodine), we have chosen the 6-311g* one. All minima (zero imaginary frequencies) and transition states (one imaginary frequency) have been characterized evaluating the second-order derivative matrix. All molecular interaction energies along the reaction path have been corrected for basis-set superposition error (BSSE), using the counterpoise method of Boys and Bernardi.¹² Transition states and reactant complexes were analyzed in terms of the natural bond orbital (NBO) scheme.¹³ This scheme allows the transformation of the delocalized MO's into the orthogonal localized natural bond orbitals. The density matrix is searched for lone and bond pair orbitals possessing an occupancy over a fixed threshold (generally, $\rho_{\text{thresh}} = 1.90$). Moreover, the σ_{AB} bond pair can be expressed as a linear combination of the normalized contributions h_a and h_b : $\sigma_{\text{AB}} = c_a h_a + c_b h_b$, giving in this way the hybrid localized point of view.

3. Results and Discussion

In the following sections, we will discuss the different possible reaction pathways and mechanisms between the lithium halide LiX (X = Cl, Br, I) and the *trans*-2,3-epoxypentan-1-ol. In Figures 3 and 4 the relative energies of stationary points along the reaction path and their geometries are summarized. Moreover, we performed the analysis of the potential energy surface of the reaction at the B3LYP level using the largest basis set 6-31g*/6-311g*. A NBO study was used to determine bonding energy between various fragments of the transition state structures to interpret the regioselectivity in the opening of the 2,3-epoxy alcohol.

3.1. Reaction Pathway and Mechanism: LiCl + 2,3-Epoxy Alcohol. In the first step the two reactants (2,3-epoxy alcohol and LiCl) combine to yield the reactant complex [epoxyLiCl], with a complexation energy (ΔE) of -29.2 kcal/mol (6-31g* on C, O, Li, and H and 6-311g* on Cl) corrected for basis set superposition error (BSSE). In this complex, the lithium atom chelates two oxygen atoms: one from the oxirane ring (Li–O bond distance of 1.904 Å) and the other one from the alcoholic unit (Li–O bond distance of 1.911 Å). Moreover, the chlorine atom is involved in a hydrogen bond with the hydrogen atom of the alcoholic unit (Cl–H bond of 2.208 Å). The complexation determines a stretching of the LiCl bond from 2.078 Å in LiCl to 2.260 Å in [epoxyLiCl]. By the same token, the C2–O bond (close to alcoholic function)

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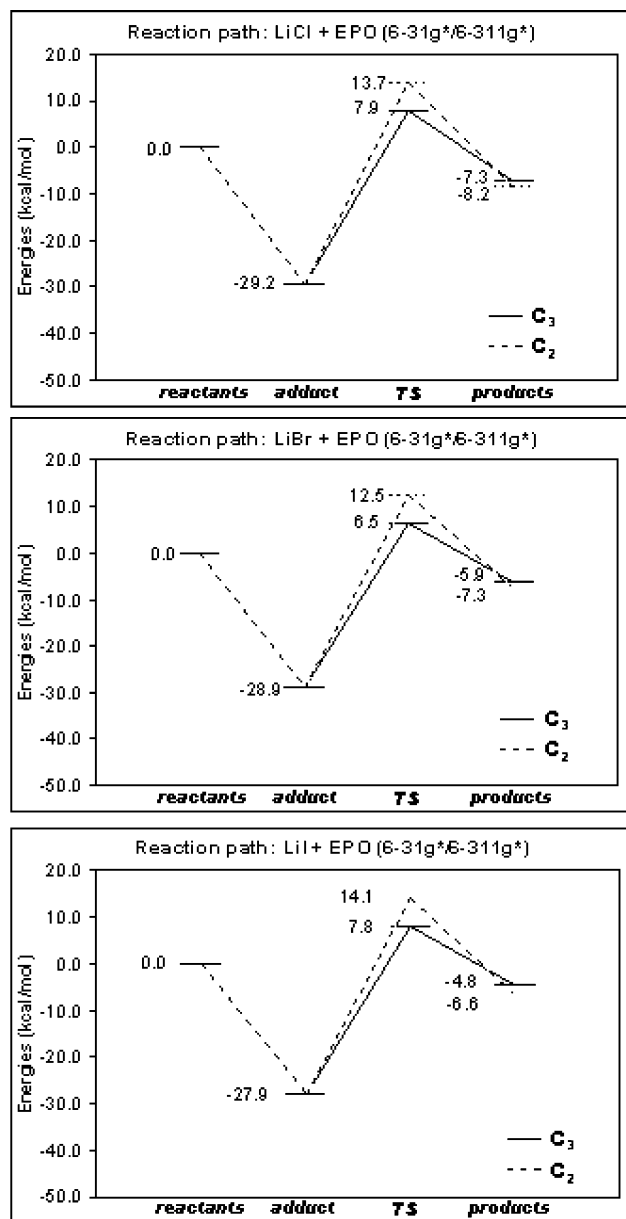


FIGURE 3. Energy reaction profiles (kcal/mol) relative to the interaction between the LiX (X = Cl, Br, I) and the *trans*-2,3-epoxypentan-1-ol. All molecular energies are obtained in a vacuum at the B3LYP/6-31g*(6-311g*) level.

and C3–O bond (close to ethyl group) are stretched: from 1.442 to 1.525 Å (C2–O) and from 1.449 to 1.548 Å (C3–O), respectively. The reactant complex can follow two different fates: the former in which the chlorine atom attacks the C2 carbon atom of the epoxide and the latter in which the chlorine attacks the C3 one. In the first case (via chlorine insertion on the C2 carbon atom) the energy barrier from the reactant complex is $\Delta E = +42.9$ kcal/mol (6-31g*/6-311g*), higher than that obtained in the latter, via chlorine insertion on the C3 carbon atom: $\Delta E = +37.1$ kcal/mol (6-31g*/6-311g*) (see also Figure 3). The conformations of the two transition states, TS(C2–Cl) and TS(C3–Cl), are characterized by the formation of six and five term cycles, respectively. Both structures exhibit only one imaginary frequency: $394i$ cm⁻¹ for TS(C2–Cl) and $320i$ cm⁻¹ for TS(C3–Cl). The two bond lengths

C2–O and C3–O of the two TS structures are elongated from 1.525 to 1.860 Å and from 1.548 to 1.906 Å, respectively. This suggests the breaking of the C–O bond is due to the insertion of the halogen atom, which in turn promotes the opening of the oxirane ring. After the transition state the two TS complexes relax to two different products, P(C2–Cl) and P(C3–Cl), the former being more stable than the latter by ~ 1 kcal/mol.

In conclusion, the overall activation energies are rather low for both substitutions: $\Delta E^\ddagger = +7.9$ kcal/mol (6-31g*/6-311g*) for the C3–Cl insertion and $\Delta E^\ddagger = +13.7$ kcal/mol (6-31g*/6-311g*) for the C2–Cl insertion. Therefore, kinetically the nucleophilic substitution on the C3 carbon atom is easier than that on the C2 atom. Vice versa from a thermodynamic point of view, the attack on the C2 atom is slightly more exothermic ($\Delta E = -8.2$ kcal/mol) than the attack on the C3 atom ($\Delta E = -7.3$ kcal/mol).

3.2. Reaction Pathway and Mechanism: LiBr + 2,3-Epoxy Alcohol. The reaction energy profiles are depicted in Figures 3 and 4. The two reactants can combine to determine the reactant complex [epoxyLiBr]. The complexation energy ($\Delta E = -28.9$ kcal/mol) is of the same order with respect to the formation of [epoxyLiCl] ($\Delta E = -29.2$ kcal/mol). Furthermore the lithium cation coordinates two oxygen atoms, forming two Li–O bonds which have analogous distances (Li–O (1.904 Å) and Li–O (1.918 Å)) to those obtained for [epoxyLiCl] complex. Also in this case, the halogen determines a hydrogen bond (Br...H–O) with the H–O alcoholic group with a bond distance of 2.227 Å, 0.033 Å shorter than the Cl...H–O H-bond. The presence of the bromine, as for the chlorine atom, has the same effect in elongating the C2–O and C3–O bonds: 1.525 and 1.548 Å, respectively. Furthermore, the bromine attack on the C3 atom [TS-(C3–Br)] induces the formation of a five-term cycle whereas a six-term cycle is produced in the case of an attack on the C2 atom [TS(C2–Br)]. They are characterized by one imaginary frequency: $383i$ cm⁻¹ for TS(C2–Br) and $310i$ cm⁻¹ for TS(C3–Br). The overall activation energies are low and slightly smaller than the [epoxyLiCl] complex: $\Delta E^\ddagger = +6.5$ kcal/mol with respect to $\Delta E^\ddagger = +7.9$ kcal/mol for C3–Cl insertion and $\Delta E^\ddagger = +12.5$ kcal/mol respect to $\Delta E^\ddagger = +13.7$ kcal/mol for C2–Cl insertion. Despite a less exothermic process to the final products [$\Delta E = -5.9$ kcal/mol for P(C3–Br) compared to $\Delta E = -7.3$ kcal/mol for P(C3–Cl) and $\Delta E = -8.2$ kcal/mol for P(C2–Br) compared to $\Delta E = -8.2$ kcal/mol for P(C2–Cl)], the formation of the P(C2–Br) complex is still slightly thermodynamically more favorable than the formation of the P(C3–Br) complex.

3.3. Reaction Pathway and Mechanism: LiI + 2,3-Epoxy Alcohol. The reaction energy profiles are depicted in Figures 3 and 4. Neither relativistic Hamiltonian nor relativistic pseudopotentials have been taken into account to correct the potential energy surface of processes involving iodine atoms. Therefore we performed nonrelativistic calculations, as in the case of bromine and chlorine, at the 6-311g* basis set level on halogen atom and at the 6-31g* one on all other atoms. The complexation energy ($\Delta E = -27.9$ kcal/mol) is smaller than that for [epoxyLiCl] (-29.2 kcal/mol) and [epoxyLiBr] (-28.9 kcal/mol). The iodine atom influences more drastically the structure of the reactant complex [epoxyLiI]. Indeed, the calculated Li–O bond distance (1.971 Å) is ~ 0.07 Å

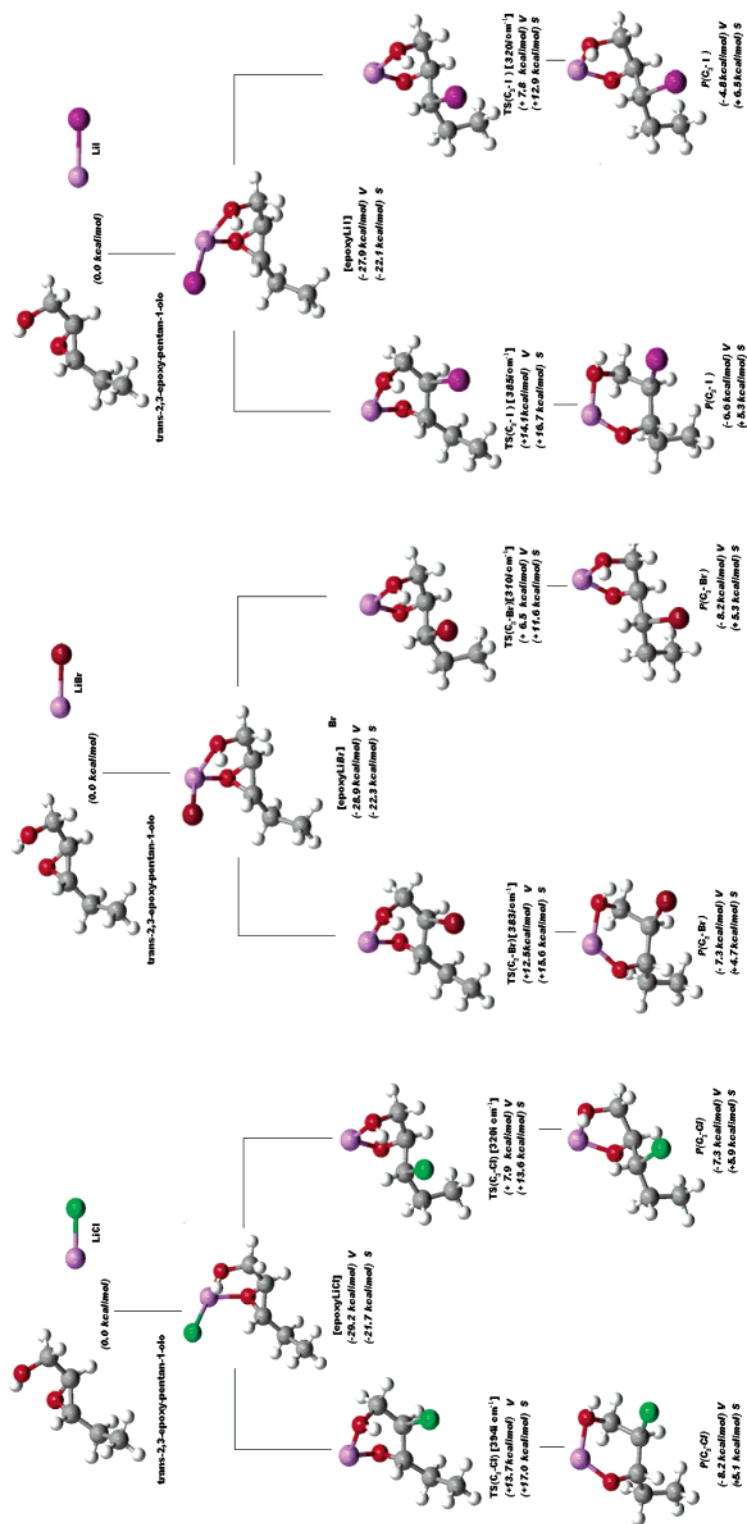


FIGURE 4. Schematic view of the geometries involved in the reaction pathways (V = vacuum, S = solvent). In all the three cases, the separated reactants have been chosen as reference.

longer than in the [epoxyLiCl] and in the [epoxyLiBr] complexes. The same effect is found for the other Li–O bond distance, which is 1.971 Å, with respect to 1.901 Å [epoxyLiCl] and 1.918 Å [epoxyLiBr]. Also the hydrogen bond I–H–O distance is stretched and it is found to be 3.051 Å, significantly longer than 2.260 Å (Br–H–O) and 2.208 Å (Cl–H–O). The two transition state structures, TS(C2–I) and TS(C3–I), have conformation

similar to those described above and present one imaginary frequency: 385i cm^{-1} for TS(C2–I) and 320i cm^{-1} for TS(C3–I). The overall activation energy for the iodine insertion on the C3 carbon atom is $\Delta E^\ddagger = +7.8$ kcal/mol, similar to that of the [epoxyLiBr] complex (+7.9 kcal/mol) and slightly larger than that of the [epoxyLiCl] complex (+6.5 kcal/mol). Moreover, the C2–O ring opening exhibits the largest activation energy ($\Delta E^\ddagger = +14.1$

kcal/mol) found in comparison to the +13.7 and 12.5 kcal/mol values in the case of [epoxyLiCl] and [epoxyLiBr], respectively. Finally again in this case, the opening of the oxirane ring on the C2–O side appears thermodynamically more favorable than the opening on the other side.

3.4. Electronic Structure and Bonding. We have also analyzed the electronic structure of the LiX (X = Cl, Br, I) and the epoxy alcohol for the reactant complexes [epoxyLiX], the two transition states TS(C3-X) and TS(C2-X), and the two products P(C3-X) and P(C2-X). To understand the origin of the regioselectivity we performed bonding energy analysis on the transition structures.

3.4.1. Separated Reactants. Energy diagrams relative to the interaction between the separated reactants (LiX and 2,3-epoxy alcohol) to form the adduct [epoxyLiX] are displayed in Figure 5. The plane that contains the three atoms of the oxirane ring has been chosen as the $x-y$ plane of the molecule. The 2,3-epoxy alcohol belongs to the C_1 point group and it is characterized by a hydrogen bond between the oxygen atom of the oxirane cycle and the hydroxy group. The HOMO is formed mainly by a p_z AO centered on the oxirane oxygen atom and by a p AO on the hydroxyl oxygen atom and shows a nodal plane that contains the O–H axis. The LUMO is 6.20 eV higher in energy with respect to the HOMO. It is characterized by an sp^2 hybrid orbital on the O_1 oxygen atom and it is antibonding with a sp^3 hybrid orbital centered on the C3 carbon atoms; moreover there is a sp^2 contribution from the oxirane oxygen atom, which is turned toward the hydrogen atom. The LiX molecule belongs to the $C_{\infty v}$ point group. The HOMO is characterized by a doubly degenerate π MO centered on the $3p_{\pi}$ AO of the halogen atom, while HOMO-1 and LUMO are respectively the σ_g bonding and antibonding combination between the lithium $2s$ AO and the halogen $3p_{\sigma}$ AO. The HOMO-1 has a strong halogen character, while the LUMO is mainly a lithium $2s$ orbital. Moreover, the LUMO is 5.21 eV higher in energy than the HOMO.

3.4.2. Reactant Complexes. The stabilization energy of the [epoxyLiX] adducts is not related to the interaction between the frontier orbitals of the two separated reactants. Indeed, the HOMO/LUMO gaps are too large to allow the formation of a bond between the two fragments. Therefore, to better analyze the complexation energy, we have studied the charge transfer from a localized point of view using the NBO framework. First, the molecule has been decomposed into two fragments: LiX and the epoxy alcohol. We have then evaluated the binding energy, given by the difference between the total energy of the adduct and the molecular energies of the two separated fragments, using the geometries they have in the adduct: $\Delta E = E_{\text{tot}} - \sum E_{\text{frag}}$. This energy can be further decomposed in a charge-transfer component (CT) and a non-charge-transfer component (NCT): $\Delta E = E_{\text{CT}} + E_{\text{NCT}}$. The CT term is due to the contribution given by the electron transfer from the filled orbitals of one fragment to an unoccupied orbital of the other fragment and it is evaluated by computing the change in total energy on deleting the Fock matrix element connecting these two manifolds. The NCT is provided by the difference between the total binding energy ΔE and the E_{CT} and it is given by the Pauli repulsion term added to the

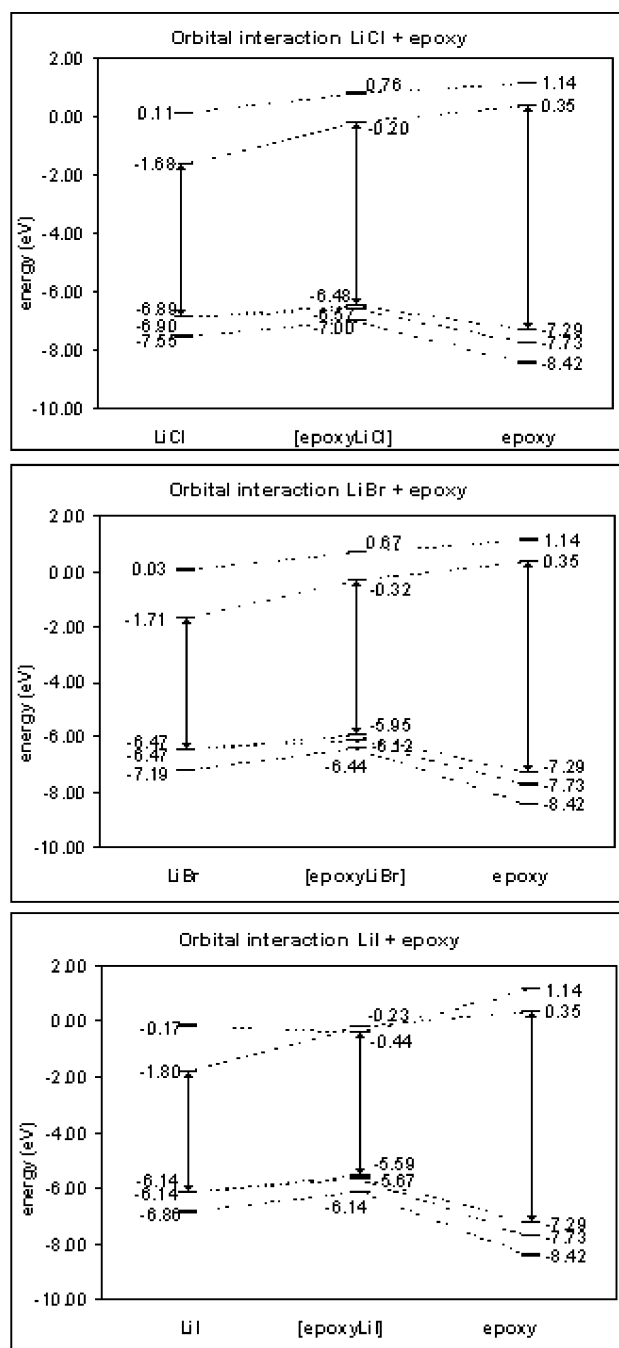


FIGURE 5. Energy diagrams relative to the interaction between the separated reactants (LiX and 2,3-epoxy alcohol) to form the adduct [epoxyLiX]. The highest and lowest MO energies calculated at B3LYP/6-31g*(6-311g*) level are depicted. All the MO's belong to the a irreducible representation (C_1 symmetry).

electrostatic term and can be either positive or negative. The electronic structure of the adduct is depicted in Figures 5 and 6 and the bonding energy contributions are given in Table 2.

The largest binding energy is found in the case of the [epoxyLiCl] adduct, $\Delta E = -41.8$ kcal/mol, which is close in energy to the formation of the [epoxyLiBr] adduct, $\Delta E = -41.6$ kcal/mol. The smallest, in absolute value, contribution is shown by the [epoxyLiI] molecule with $\Delta E = -40.3$ kcal/mol.

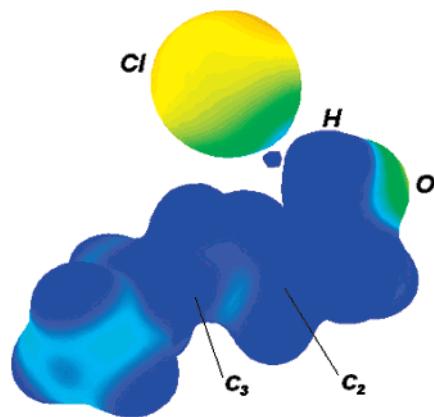


FIGURE 6. Charge distribution of the [epoxyLiCl] adduct obtained depicting the electrostatic potential on the electronic density. The most negative charge regions are depicted in yellow, whereas the most positive are depicted in blue.

TABLE 2. The Natural Bonding Decomposition Scheme Analysis (NBO) Has Been Used To Extract the Total Bonding Energy Relative to the Formation of the [epoxyLiX] Adduct^a

interaction	ΔE	E_{CT}	E_{NCT}
LiCl \leftrightarrow epoxide	-41.8	-40.2	-1.6
LiBr \leftrightarrow epoxide	-41.6	-42.9	+1.3
LiI \leftrightarrow epoxide	-40.3	-40.1	-0.2

^a The bonding interaction energy (kcal/mol) is also further decomposed, expressed as the sum of the charge transfer (E_{CT}) and non-charge-transfer terms contributions (E_{NCT}).

Besides, although a E_{NCT} is small in the case of all the [epoxyLiX] adducts, the non-Lewis contribution determines the most negative bonding energy in the case of the [epoxyLiCl]. Indeed, the electrostatic and the Pauli repulsion terms tend to negate each other, giving a rather low total E_{NCT} term. But it seems that the high electronegativity of the chlorine atom, with respect to the bromine and iodine atoms, provides a higher asymmetric distribution of charge and therefore a more negative electrostatic term ($E_{NCT} = -1.6$ kcal/mol). In conclusion, the ΔE bonds for all [epoxyLiX] adducts are of the same order of magnitude when different halogen atoms are used.

3.4.3. Regioselectivity. The insertion of the halogen atom into the C3 or C2 carbon atoms is classified as a nucleophilic substitution, therefore we can suppose that the regioselectivity of the 2,3 cycle opening can be ascribed to the different electrophilicity of the two C3 and C2 centers in the [epoxyLiX] adduct. For the reactant complex the electrostatic potential reported on an electron isodensity surface as depicted in Figure 6, does not reveal large differences in the case of the two sites. Besides, in Table S1 (in the Supporting Information) we have reported the electronic charges on each atom calculated using the natural population analysis (NPA). This approach does not suffer from the intrinsic drawbacks of the Mulliken population analysis, which is strongly basis-set dependent.¹³ The two C2 and C3 carbon atoms are slightly positively charged (+0.03 and +0.06 for all [epoxyLiX] adducts) and the electrophilic difference between them is not very large, although it can give an indication for the halogen atom preference during the attack to one carbon atom with respect to the other. Therefore we performed a NBO analysis on transition

TABLE 3. The NBO Scheme Analysis Has Been Used To Decompose the E_{CT} Term (kcal/mol) into Four Main Components^a

interaction	TS(C2-X)	TS(C3-X)
	E_{CT}	E_{CT}
Cl \rightarrow C2 ₍₃₎ O _E	42.9	42.1
O _E \rightarrow Li	12.1	12.4
O _A \rightarrow Li	14.5	16.3
Cl \rightarrow H-O _A	8.9	14.7
total	78.4	85.5
Br \rightarrow C2 ₍₃₎ O _E	39.3	36.9
O _E \rightarrow Li	12.1	12.4
O _A \rightarrow Li	14.5	16.1
Br \rightarrow H-O _A	12.1	17.7
total	78.0	83.1
I \rightarrow C2 ₍₃₎	35.0	35.3
O _E \rightarrow Li	11.9	12.2
O _A \rightarrow Li	14.17	15.8
I \rightarrow H-O _A	11.7	15.3
total	72.7	78.6

^a The O_A and O_E labels are related to the oxygen atoms belonging to the alcoholic and epoxy units, respectively. The \rightarrow symbol indicates the direction of the electron transfers. C2₍₃₎ means atom 2 or 3 according to the column.

state structures, TS(C2-X) and TS(C3-X), decomposing the E_{CT} term into four components. We have also considered, in Table 3, the charge transfer from the lone pair orbitals of the halogen atom to the virtual C2-O and C3-O oxirane orbitals. Indeed, these terms are important in the interaction process, though the small energy difference between the two processes gives only a minor contribution to the regioselectivity. In fact it can be observed that the X-C2O oxirane interaction, for the X-C2 insertion, and the X-C3O oxirane interaction, for the X-C3 insertion, are very similar. In particular, we can find that the chlorine atom shows the following energy: 42.9 kcal/mol for TS(C2-Cl) and 42.1 kcal/mol for TS(C3-Cl). Also the iodine atom provides a similar contribution: 35.0 kcal/mol for TS(C2-I) and 35.3 kcal/mol for TS(C3-I). Moreover, the bromine attack at the C2 atom is larger by 2.4 kcal/mol than the C3 one: 39.3 kcal/mol for TS(C2-Br) and 36.9 kcal/mol for TS(C3-Br). These data, considering only the contribution of the halogen attack on carbon atoms, do not explain any significant regioselectivity and, in the case of the bromine atoms, the insertion on the C2 carbon atom appears even preferred. The second energy term is characterized by the formation of a hydrogen bond between the electron donor, which is represented by the lone pair orbitals on the halogen atom, and the electron acceptor, which is represented by the virtual H-O bond orbital. A significant contribution to the insertion on the C3 carbon atom is provided by the charge transfer from the lone pairs of the oxygen atom of the alcoholic group to the 2s AO of the lithium atom. For the chlorine atom, the effect is more important on the TS(C3-Cl) structure, with an energy stabilization 1.8 kcal/mol larger than the that obtained on the TS(C2-Cl) structure. Analogous behavior can be found in the case of the bromine atom (1.6 kcal/mol) and for the iodine atom (1.7 kcal/mol) (see also Table 3). Indeed, the most important term is due to the formation of a hydrogen bond between the electron donor, i.e., the lone pair orbitals on the halogen atom, and the electron acceptor, i.e., the virtual H-O bond orbital. From the data shown in Table 3, we can observe that the

regioselectivity of the 2,3-epoxy ring opening appears to be driven mainly by the different hydrogen bond interaction, which is different in both transition structures, TS(C2–X) and TS(C3–X). For example, the attack of the chlorine atom on the C3 carbon atom is determined by a stronger interaction (5.8 kcal/mol) than that on the C2 atom. The same behavior can be observed in the case of bromine (5.6 kcal/mol) and iodine (3.6 kcal/mol).

3.5. Comparison between the Different Reaction Pathways and Mechanisms: LiX (X = Cl, Br, I) + 2,3-Epoxy Alcohol. From the above discussion, the ring opening of the epoxy alcohol is kinetically more favorable on the C3–O side in all reaction mechanisms. The best regioselectivity is provided by the insertion of iodine atom, with an energy gap $\Delta E(\text{C2-O-C3-O}) = 6.3$ kcal/mol. The differences with respect to the other halogen atom attacks are not significantly lower: $\Delta E(\text{C2-O-C3-O}) = 6.0$ kcal/mol (bromine) and $\Delta E(\text{C2-O-C3-O}) = 5.8$ kcal/mol (chlorine). These results, although in vacuo, are in agreement with the experimental trend¹⁴ as reported in Table 1.

On the other hand, the used solvent in the experiments, although aprotic, is characterized by a small if not negligible value of the dielectric constant that can have some influence on the energy of the computed stationary structures and that might modify the in vacuo findings. We have, then, taken into account also this effect within a continuum model of the solvent, i.e., without any specific interaction between the reactant and solvent molecules.

3.6. Solvent Effects. We have therefore used the polarized continuum model (PCM) of Tomasi and co-workers¹⁵ to analyze the effects of a polar solvent (acetonitrile, $\epsilon = 36.64$) on the reaction path relative to the cycle opening of the studied epoxy alcohol. These kinds of calculations can provide a better understanding of the experimental reactions between the epoxide and the LiX (X = Cl, Br, I) which are performed in a acetonitrile solution. The complexation, activation, and reaction energies are somewhat different from those obtained in vacuo (Figures 7 and 8). These effects can be ascribed to the rather large dipole moments (Table S2, Supporting Information) of the complexes involved in the entire reaction and to the nonnegligible dielectric constant of the solvent.

The lower stability of the reactant complexes in solution than in vacuo (about 7 kcal/mol) is similar along the whole halogen series. This is due to the more stabilizing effect of the solvent on the separated reactant LiX (X = Cl, Br, I) and 2,3-epoxy alcohol. Also the energy difference between the transition states is affected by the solvent. Although the dominating process remains the insertion of the halogen on the C3 carbon atom, the energy gap

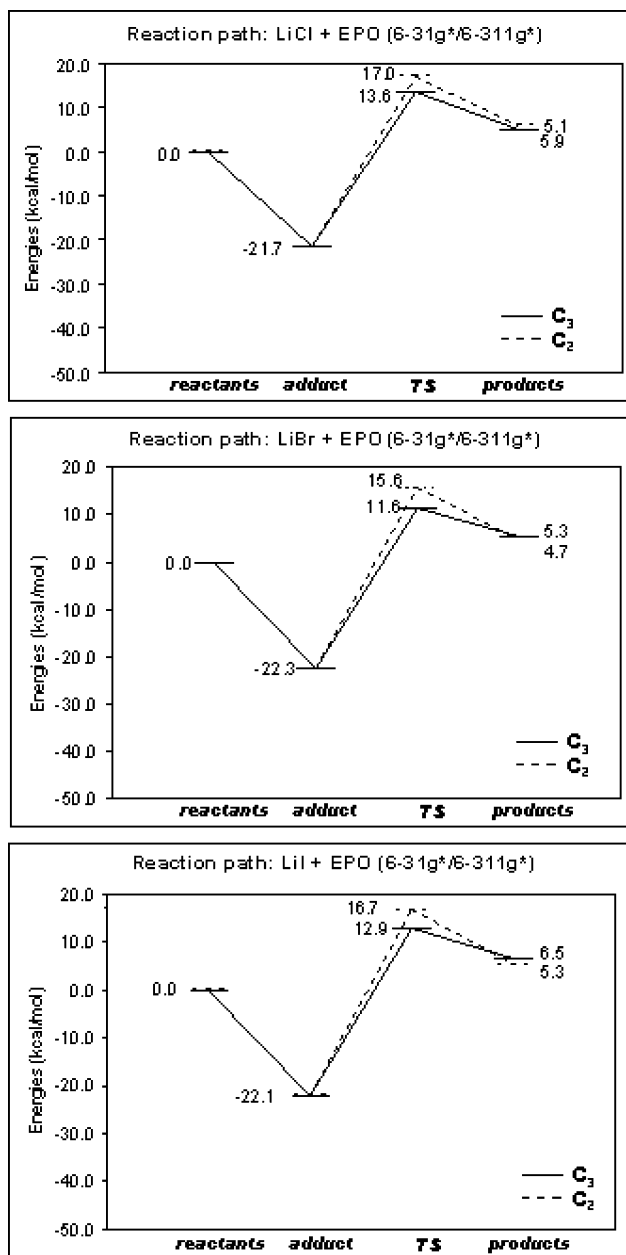


FIGURE 7. Energy reaction profiles relative to the interaction between the LiX (X = Cl, Br, I) and the *trans*-2,3-epoxypentane-1-ol. All molecular energies are obtained at the B3LYP/6-31g^{*}-(6-311g^{*}) level and the polarized continuum model (PCM) has been used to simulate the acetonitrile (solvent) effects.

between the two transition states TS(C3–X) and TS(C2–X) is reduced: for example, in the case of the chlorine, the TS energy gap drops from 5.6 kcal/mol in vacuo to 3.4 kcal/mol in solution. The same reduction is found also in the case of the bromine atom (from 6.0 to 4.0 kcal/mol) and the iodine atom (from 6.3 to 3.8 kcal/mol). This contraction can be attributed to the different stabilization of the two transition states due to the different dipole moments of the activated structures. In particular, the TS(C3–X) structures show a larger dipole (X = Cl, 8.0578 D; X = Br, 7.9015 D; X = I, 9.0153 D) than the TS(C2–X) structures (X = Cl, 7.4210 D; X = Br, 7.3604 D; X = I, 8.5318 D). As concerns the products, we can observe that they show a similar behavior of their

(14) The slightly different trend in the case of LiCl, which does not change also considering the solvent effect (see following section 3.6) may be due to the difference in the rate of the opening reaction, which appears much slower with LiCl conditions (2 h, see Table 1). In fact the solubility in CH₃CN of the Li salts is quite different, with LiCl as the most insoluble and therefore with a significant difference in the concentration of the reactant. In fact the activation energy is related to the rate constant whereas the rate of reaction is also due to the concentration of reactants. The low solubility of LiCl and the related slow reaction rate could favor the equilibrium process between the starting epoxide and the opened intermediates, thus justifying the lower observed regioselectivity

(15) Tomasi J.; Persico M. *Chem. Rev.* **1994**, *94*, 2027.

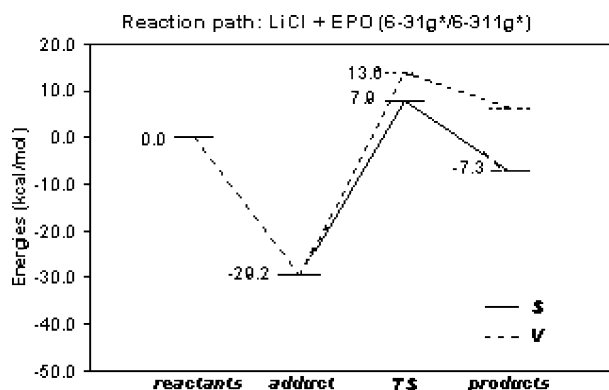


FIGURE 8. Energy reaction profiles relative to the chlorine attack in the C3 site. Comparison between the solvent in solution (S) and the in vacuo (V) energies calculated at the B3LYP/6-31g*(6-311g*) level. The same picture can be straightforwardly extended to attacks by bromine and iodine to the C2 site and to the bromine and iodine attacks showing the same general trends. Reactant energies in vacuo and in solvent have been used as reference for the corresponding energy profile.

energies with respect to the vacuum. In fact, the P(C2-X) complex is more stable than the P(C3-X) one or in other words the opening of the oxirane ring at the C2-O side is thermodynamically but not kinetically more favorable than the opening at the C3-O side. The exception is represented by the reaction with the chlorine atom, where the P(C3-Cl) complex is more stable than the P(C2-Cl) complex by about 0.8 kcal/mol. The remarkable difference between the vacuum and the solution processes in the latter case depends on the high-lying energies of the products with respect to the separated reactants or in other words if the reaction is endothermic. To verify the fate of the reaction products we have evaluated the stability of the final halodiols, provided by the elimination of the lithium atom from the epoxide complex. The most stable conformations in the case of both kinds of products (C2 or C3 attacks) show that, irrespective of the halogen atom, the two adducts have

almost comparable stability even though the product due to the C3 attack is slightly more stable by about 0.2–0.3 kcal/mol. This suggests that the selectivity is not due to the thermodynamics but to the kinetics of the process. Furthermore, this effect takes into account the relevant role of the acid resin Amberlyst (see Table 1) whose presence strongly enhances the global yield of the reaction. In fact, without the driving force of the Li⁺ cation elimination the process remains strongly endothermic and only the treatment of the P(C2-X) and P(C3-X) products with H-X to form the final halodiols and LiX provides a stabilization of 10–11 kcal/mol.

4. Conclusions

B3LYP/6-31g* DFT calculations have allowed, for the first time, the investigation of the role of a metal (Li) in the regioselective opening of 2,3-epoxy alcohols. Computational results confirm the trend of the experimental data (see Table 1), especially with regards to the regioselectivity observed in the opening of the oxirane ring. The C3 halogen attack is always preferred to the C2 attack, due to kinetic effects. In fact, the computed energy difference between the proposed transition state structures shows that the C3 attack is the preferred one. The central role of the Li cation (which is linked to both oxygens of the starting compound) is well documented in the reaction profiles, pathways, and mechanisms speculated. For the energy differences in the TS, the NBO analysis indicates that the main contribution appears to be the X-H-O hydrogen bonding between the hydroxyl groups of the reactant and the incoming halogen nucleophile.

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Supporting Information Available: Atomic coordinates, energetic data, Mulliken charges, and dipole moments are collected for all the compounds involved in the reactions described. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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