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Regioselective epoxide ring-opening using boron trifluoride diethyl etherate: DFT study of an alternative mechanism to explain the formation of *syn*-fluorohydrins

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ABSTRACT

Ring-opening of epoxides with boron trifluoride yielding *syn*-fluorohydrins was investigated using density functional methods (PBE) and two different basis sets (6-31G(d) and 6-311++G(2df,2pd), both in gas phase and simulating the bulk solvent using the PCM method. The only mechanism previously suggested for the formation of fluorohydrins from epoxides is an S_N1-like one. We propose in this work a new mechanism, in which bond breaking in the epoxide is coupled to fluorine transfer, yielding the fluorohydrine with retention of configuration through a single transition state.

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1. Introduction

Epoxides are widely used as building blocks in organic chemistry. They can be prepared efficiently, and their ability to undergo ring-opening reactions with different nucleophiles contributes to their synthetic value [1,2]. In particular, nucleophilic openings, mediated by hetero- or carbonucleophiles [3,4], of the homochiral three-membered heterocycles easily accessible via chemoenzymatic synthesis, are of great importance in the preparation of naturally occurring molecules [5–8]. Thus, the understanding of the mechanisms of reaction of these synthetic intermediates is an important task.

We have investigated the ring-opening reaction of epoxides under $BF_3{\cdot}OEt_2$ catalysis in the context of our research on the oligomerization of chiral cyclohexadiendiols derived from biotransformation of halobenzenes. The chemistry of BF_3 is defined by its exceptional Lewis acidity, which is induced by the intrinsic electron deficiency of the boron atom, a reason for which BF_3 is used extensively as a catalyst in organic chemistry [9]. Lewis acid-catalyzed rearrangement of epoxides to carbonyl compounds is a well-known reaction in organic chemistry, and has been studied extensively in the synthetic laboratory as well as computationally [10–14]. During our experiments on the epoxide ring-opening of (1*S*,2*S*,5*R*,6*R*)-3-chloro-5,6-oxi-1,2-*O*-isopropyliden-3-cyclohexen-1,2-diol (**1**), we found the surprising result that even in the presence of stoichiometric amounts of 4-methoxybenzylalcohol, BF_3 reacted as a nucleophile giving the diastereomeric fluorohydrins **2** and **3** as the main products (Fig. 1). No trace of the expected rearrangement product could be detected [15].

There is only limited information on the role of the $BF_3{\cdot}OEt_2$ complex as a fluoride source in the ring-opening of epoxides [16–20] to afford fluorohydrins. Halohydrins, in general, have considerable importance in organic synthesis because they can be employed for some useful synthetic transformations [21]. Fluorohydrins are the less common members of this type of compounds, and is mainly due to the scarcity of methods for its preparation. They are generally prepared through ring-opening of epoxides using inorganic fluorides [22,23]. We observed in our experiments that the epoxide-opening of **1** mediated by BF_3 produced the displacement exclusively at the allylic position, in agreement with all the information about the opening of this type of epoxides [5–8]. Fluoride ion acts as a nucleophile yielding both diastereomers in an approximately 1:1 ratio. This stereochemistry suggests an S_N1-type ring-opening step, leading to a cationic or zwitterionic species, which in turn reacts with the fluoride source. Thus, the mechanism suggested for the formation of

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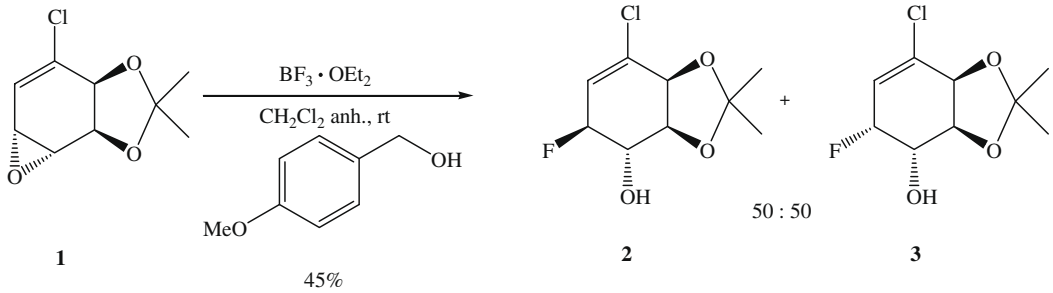

Fig. 1. Ring-opening of vinyl epoxide **1** with boron trifluoride diethyletherate.

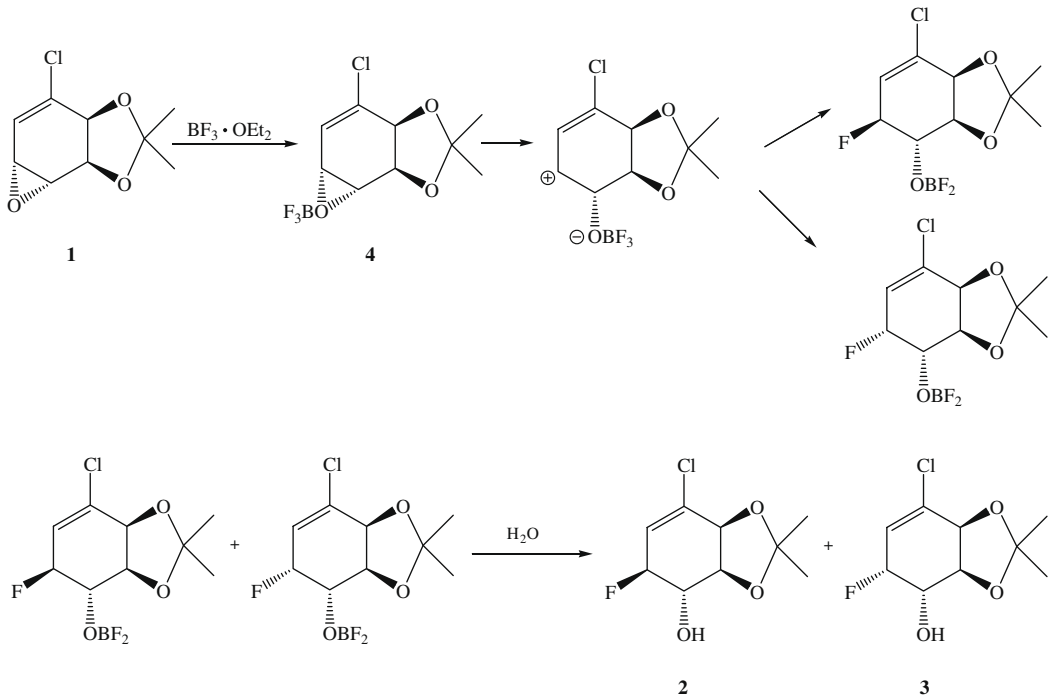

Fig. 2. Conventional mechanism proposed to explain the formation of *syn*- and *anti*-fluorohydrins.

diastereomeric fluorohydrins involves the cleavage of the epoxide ring aided by complexation with BF_3, giving a zwitterionic intermediate (Fig. 2). Subsequent transfer of fluoride anion to the cationic center would lead to a diastereomeric mixture of fluoroborates, which are further hydrolyzed to yield the corresponding fluorohydrins [18,19].

However, careful analysis of the experimental situation revealed an unexpected result. NMR monitoring of the reaction showed the preferential formation of the *syn*-isomer, as shown in Table 1.

The conclusion from our experimental observations was that *syn*-fluorohydrin is the main product of the reaction of **1** with $BF_3{\cdot}OEt_2$ in CH_2Cl_2, the *anti* isomer being formed in a smaller proportion. The *syn*-isomer seems to be unstable in the reaction conditions, but is not transformed into the *anti* isomer. Starting from isolated *syn*-isomer, the *anti*-one is not obtained, but decomposition is observed instead.

These findings prompted us to perform and in-depth computational study of the mechanism of this reaction. To the best of our knowledge, this is the first comprehensive computational study of the mentioned reaction at any level of theory.

Table 1
Isomeric ratio **2**:**3** determined by ^{1}H NMR performed in $CDCl_3$ at 30 °C.

Reaction time (min)	Ratio **2:3**
2	1:3.5
20	1:3
29	1:3
32	1:2
45	1:2
75	1:1.5

2. Theoretical approach

The complexes of BF_3 and (1*S*,2*S*,5*R*,6*R*)-3-chloro-5,6-oxi-1,2-*O*-isopropyliden-3-cyclohexen-1,2-diol (**1**), the intermediates and transition structures have all been studied at the density functional level [24], using the Perdew–Burke–Erzenhoff (PBE) potential [25,26]. Pople basis sets 6-31G(d) and 6-311++G(2df,2pd) were used as representative of small and medium/large one-electron basis sets [27–29]. Geometry optimization was performed on all the species considered until variation in the geometrical parameters was under 10^{-4} Å for all the Cartesian coordinates. Analytical second derivatives were calculated and used for determining the type of critical point on the PES. Charge analysis was performed using

both Weinhold's natural bond orbital (NBO) method [30–36] and by fitting of electrostatic potential (CHELPG) method [37,38]. Bulk effects of the solvent were accounted for by employing the PCM approach [39–42]. All calculations were performed using Gaussian03 [43].

3. Results and discussion

3.1. Gas-phase studies

It is currently accepted that the ring-opening of an oxirane is facilitated by the attachment of the Lewis acid to the oxygen atom in the epoxide; one of the carbon atoms is then attacked by the nucleophile [10,12,44]. Thus, we decided to examine first the complex of BF_3 and (1*S*,2*S*,5*R*,6*R*)-3-chloro-5,6-oxi-1,2-*O*-isopropyliden-3-cyclohexen-1,2-diol (**1**, Fig. 3a). There are several possible complexes, depending on whether BF_3 interacts with the oxygen of the epoxide or the oxygen atoms in the acetonide ring. Even when considering solely BF_3 on the epoxide oxygen two conformers are possible, one with the BF_3 species pointing toward the cycle and another pointing away. As expected, the lowest energy stationary point exhibits a BF_3 interacting with the oxygen of the oxirane ring and pointing away from the cycle (Fig. 3b). This complex reflects the interaction that facilitates ring-opening of the epoxide.

BF_3 must be transferred to the epoxide for the reaction to proceed efficiently, at least up to a concentration able to produce catalysis. Therefore, it is important to look to the different stability of $BF_3{\cdot}OEt_2$ and $\mathbf{1}{\cdot}BF_3$. Results with the different basis sets employed are shown in Table 2.

Looking to the equilibrium

$$\text{Diethyl ether} \cdot BF_3 + \mathbf{1} \rightarrow \text{diethyl ether} + \mathbf{4}$$

one gets a $\Delta(E + \text{ZPE})$ of 0.39 kcal/mol, a ΔH_{298} of 0.78 kcal/mol and a ΔG_{298} of −0.11 kcal/mol with the 6-31G(d) basis set, and −0.04, 0.22 and −0.04 kcal/mol with the 6-311++g(2df,2pd) basis set. Thus, the conclusion is that the process is slightly endothermic but spontaneous or nearly so, and complex **4** should be present in a similar concentration than that of the complex $BF_3{\cdot}Et_2O$. The Lewis acid would then be capable of helping the opening of the ring.

The energies and most significant optimized geometric parameters for the epoxide **1**, complex **4**, diethyl ether and boron trifluoride diethyl etherate are reported also in Table 2. BF_3 interacts with a lone pair on the oxygen atom, both in the etherate and in the complex with **1**, adopting a pyramidal structure due to the transfer of electronic density from oxygen to boron, contrary to the perfectly flat geometry of the isolated Lewis acid. The C–O bond distances (d(O1C2) and d(O1C4) in Table 2 and Fig. 4) in boron trifluoride diethyl etherate are longer than the corresponding ones in diethyl ether, evidencing also the charge transfer from the oxygen to the Lewis acid. The B–O distances are shortened by 0.041 Å and 0.051 Å at the 6-31G(d) and 6-311++G(2df,2pd) levels, respectively, when passing from complex **4** to $BF_3{\cdot}Et_2O$. In addition, the BOCC improper angle flattens from 107.5° (ϕ(C4O11C3B25)) to 18.2° (ϕ(C2O1C4B16)) for the larger basis set. Those effects could be explained examining the interaction between fluorine atoms in BF_3 and hydrogen atoms in the ether or the epoxide. One of the fluorine atoms in complex **4** interacts with two hydrogen atoms on the same face of the epoxide. In $BF_3{\cdot}Et_2O$, the disposition of the methylenic hydrogens with respect to the fluorine atoms reduces the pyramidalization and shortens the B–O distance compared to complex **4**, in order to maintain F–H attractive interactions (Figs. 3 and 4).

The regioselectivity of the ring-opening of epoxides is dependent on the nature of the epoxide compound. Our experimental observations on vinyl epoxides such as **1** revealed complete regioselectivity, leading to the C3-opened product. This kind of selectivity can be justified from the effect of coordination in the geometrical features of the oxirane ring. Indeed, the theoretical investigation of **4** shows that the bond between the oxygen atom

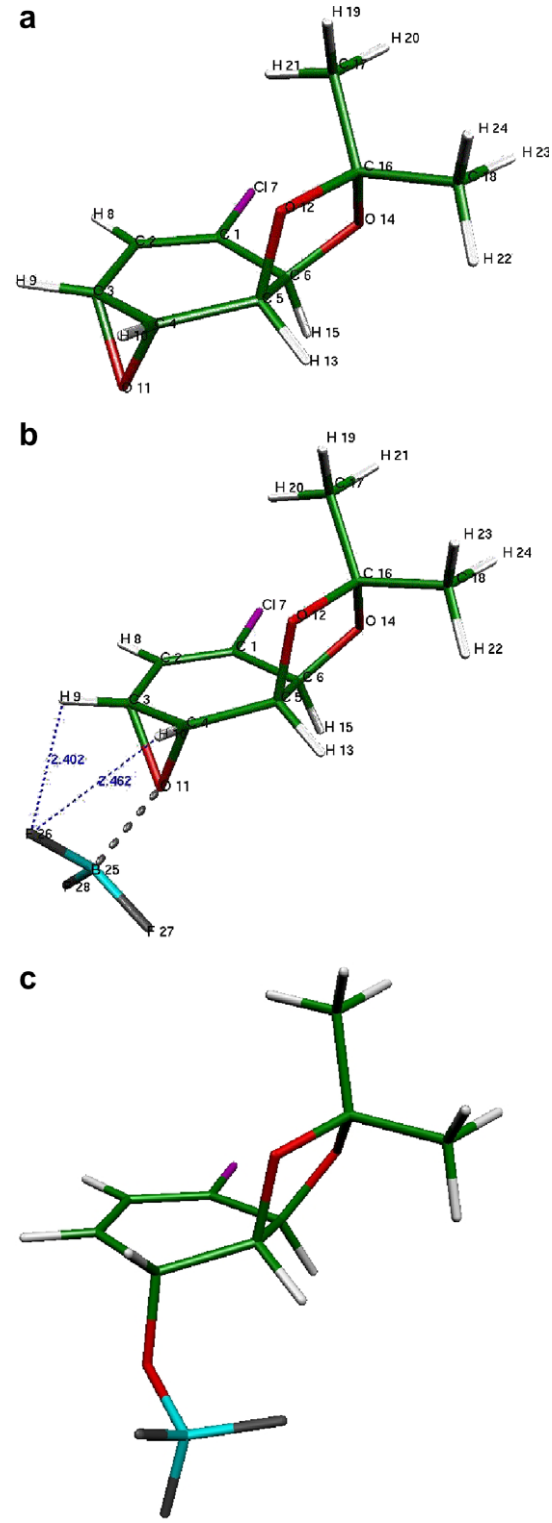

Fig. 3. (a) Structure of epoxide **1**. (b) Structure of the complex (**4**) of BF_3 with the epoxide **1**. (c) Structure of the hypothetical open-cycle zwitterion obtained at the semiempirical PM3 level. The numbering of the atoms helps in the identification of the geometrical parameters displayed in Tables 1–6.

Table 2
Electronic energies (ZPE corrected), standard enthalpies, free energies at 298.15 K (in hartrees), geometries and point charges derived from CHELPG and NBO analyses (the latest in parenthesis) for the species studied. Bond lengths are expressed in Å, bond and dihedral angles in degrees; numbering of the atoms as in Figs. 3 and 4.

Species	Property	6-31G(d)	6-311++G(2df,2pd)
Diethyl ether	E + ZPE	−233.240476	−233.324317
	H(298)	−233.232778	−233.316557
	G(298)	−233.270496	−233.354375
	d(O1C2)	1.406	1.405
	d(O1C4)	1.406	1.405
	θ(C2O1C4)	112.7	112.9
Diethyl ether–BF_3	E + ZPE	−557.484026	−557.689576
	H(298)	−557.472474	−557.677743
	G(298)	−557.520557	−557.726783
	d(O1C2)	1.446	1.444
	d(O1C4)	1.448	1.444
	d(O1B16)	1.683	1.649
	d(B16F17)	1.364	1.361
	d(B16F18)	1.357	1.357
	d(B16F19)	1.357	1.356
	θ(C2O1C4)	116.9	116.2
	θ(C2O1B16)	113.8	116.7
	θ(C4O1B16)	116.4	119.8
	θ(O1B16F17)	103.8	105.0
	θ(O1B16F18)	102.1	102.7
	θ(O1B16F19)	102.5	103.0
	ϕ(B16O1C2C3)	157.2	118.9
	ϕ(B16O1C4C5)	78.8	67.7
	ϕ(C2O1B16F17)	62.9	62.3
	ϕ(C2O1B16F18)	−56.7	−57.0
	ϕ(C2O1B16F19)	−177.0	−177.5
	ϕ(C2O1C4B16)	24.9	18.2
1	E + ZPE	−1034.388576	−1034.606597
	H(298)	−1034.376178	−1034.594144
	G(298)	−1034.426320	−1034.644485
	d(O11C3)	1.440	1.437
	d(O11C4)	1.416	1.413
	q(C3)	0.15 (0.02)	0.20 (0.06)
	q(C4)	−0.12 (0.05)	−0.15 (0.09)
4	E + ZPE	−1358.631498	−1358.971917
	H(298)	−1358.614630	−1358.954984
	G(298)	−1358.676555	−1359.016964
	d(O11C3)	1.482	1.480
4	d(O11C4)	1.442	1.440
	d(O11B25)	1.724	1.700
	d(B25F26)	1.365	1.361
	d(B25F27)	1.349	1.348
	d(B25F28)	1.345	1.344
	θ(C3O11B25)	118.7	119.7
	θ(C4O11B25)	116.5	118.3
	θ(O11B25F26)	102.3	103.4
	θ(O11B25F27)	100.5	101.2
	θ(O11B25F28)	101.6	101.8
	ϕ(B25O11C3C2)	−143.1	−141.2
	ϕ(B25O11C4C5)	139.0	138.8
	ϕ(C4O11B25F26)	40.8	38.7
	ϕ(C4O11B25F27)	−78.2	−80.5
	ϕ(C4O11B25F28)	160.6	158.5
	ϕ(C4O11C3B25)	105.7	107.5
	q(C3)	0.23 (0.04)	0.27 (0.08)
	q(C4)	−0.17 (0.06)	−0.22 (0.11)

and the allylic carbon (C3O11) is weaker than the other oxirane bond (C4O11), as clearly seen by comparing the corresponding bond lengths. Coordination of BF_3 to the epoxide weakens both the C3O11 and C4O11 bonds with respect to the isolated epoxide, although not to the same extent. The oxirane ring in the isolated molecule **1** is not symmetric. At the 6-31G(d) level, the C3O11 bond (1.440 Å) is 0.024 Å longer than C4O11 bond (1.416 Å), while the difference increases to 0.040 Å in the complex **4**, leading to a less symmetric ring. These results suggest that interaction with the Lewis acid favors ring-opening at the allylic position. Thus,

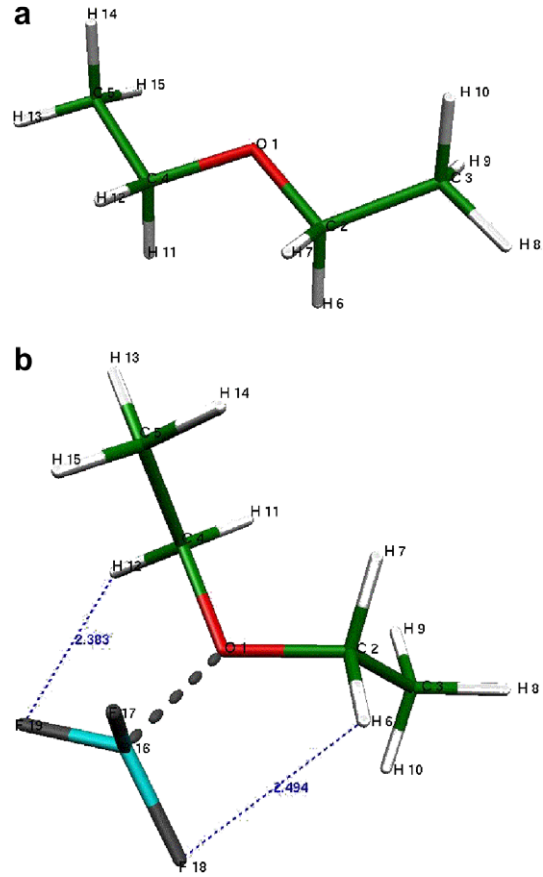

Fig. 4. (a) Structure of diethyl ether. (b) Structure of the complex boron trifluoride diethyl etherate. The numbering of the atoms helps in the identification of the geometrical parameters displayed in Table 2.

the presence of BF_3 increases the regioselectivity and facilitates the reaction with respect to the non-coordinated epoxides, in agreement with the experimental facts. The same trend is obtained when the larger basis set is employed.

Inspection of charge distribution in **4** reveals an inconsistency between the NBO and CHELPG results (Table 3). The most important difference is observed for atoms C3 and C4. C4 results slightly more positive than C3 in the NBO calculations (0.04 compared to 0.06 for 6-31G(d) and 0.11 compared to 0.08 for the larger basis set). Even though this charge distribution does not support a nucleophilic attack on C3, the difference is not really pronounced. Due to these results, we calculated also atomic charges fitting the electrostatic potential of the molecule (CHELPG method). CHELPG charges afford a much more positive C3 than C4 (0.23 compared to −0.17 for 6-31G(d) and 0.27 compared to −0.22 for the larger basis set). Considering then the CHELPG charges, the calculations support a C3-opening through a single nucleophilic attack. The inconsistency observed between these two different methods to determine atomic charges may suggest that the reaction is not charge-controlled, or that the NBO method breaks down in this case for an as yet unknown reason. CHELPG charges in the BF_3 complex, the transition state, and the product evolve consistently from a situation predicting attack at C3. We consider them more reliable than the NBO ones.

Conventionally, the formation of *syn*-fluorohydrins is explained by a two-step mechanism involving a zwitterionic intermediate where the negative charge on the oxygen of the opened ring is stabilized by the interaction with BF_3, and the carbon center adopts the local structure of a carbocation. The carbocationic center reacts

Table 3
Electronic energies (ZPE corrected), standard enthalpies, free energies at 298.15 K (in hartrees), relative energies (in kcal mol^{-1}) and point charges derived from CHELPG and NBO analyses (the latest in parenthesis) for the species studied with the basis sets 6-31G(d) and 6-311++G(2df,2pd). Bond lengths are expressed in Å, dihedral angles in degrees; numbering of the atoms as in Figs. 3 and 6.

Parameter	6-31G(d)			6-311++G(2df,2pd)		
	4	**5**	**6**	**4**	**5**	**6**
E + ZPE	−1358.631498	−1358.599993	−1358.645920	−1358.971917	−1358.944329	−1358.986907
H(298)	−1358.614630	−1358.583761	−1358.629110	−1358.954984	−1358.928040	−1358.969938
G(298)	−1358.676555	−1358.643724	−1358.690365	−1359.016964	−1358.944329	−1359.031961
Erelative	0.00	19.77	−9.05	0.00	17.31	−9.41
q(C3)	0.23 (0.04)	0.08 (0.10)	0.26 (0.16)	0.27 (0.08)	0.02 (0.20)	0.33 (0.19)
q(C4)	−0.17 (0.06)	0.26 (0.01)	0.26 (0.04)	−0.22 (0.11)	0.37 (0.03)	0.26 (0.09)
q(F26)	−0.34 (−0.54)	−0.37 (−0.56)	−0.33 (−0.49)	−0.39 (−0.53)	−0.46 (−0.55)	−0.38 (−0.48)
q(F27)	−0.32 (−0.52)	−0.33 (−0.53)	−0.31 (−0.48)	−0.41 (−0.52)	−0.42 (−0.52)	−0.36 (−0.47)
q(F28)	−0.32 (−0.52)	−0.36 (−0.53)	−0.24 (−0.37)	−0.39 (−0.51)	−0.44 (−0.54)	−0.30 (−0.38)
d(F26B25)	1.365	1.387	1.325	1.361	1.389	1.321
d(F27B25)	1.349	1.360	1.319	1.348	1.358	1.315
d(F28B25)	1.345	1.426	2.745	1.344	1.426	2.998
d(F28C3)	3.296	2.382	1.391	3.265	2.414	1.386
ϕ(F28B25O11C4)	160.6	74.2		158.5	72.6	

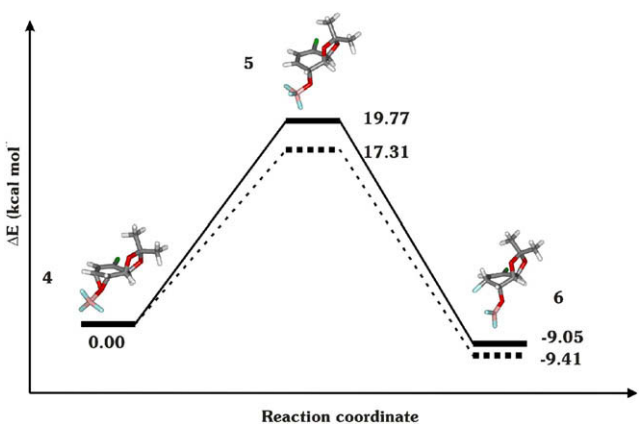

Fig. 5. Relative energies PBE/6-31G(d) (plain marks) and PBE/6-311++G(2df,2pd) (dashed marks) for the concerted ring-opening reaction of epoxide **1** with boron trifluoride in the gas phase.

with the nucleophile in another step, giving rise two stereoisomers. In our calculations, however, even though the coordination to the Lewis acid modifies the geometrical features of the oxirane ring, this interaction leads to complexes which retain the integrity of the ring. Indeed, despite all the attempts performed, a zwitterionic intermediate could not be found during the exploration of PES. More precisely, no critical point on the DFT PES was found where the oxirane ring was clearly open and the carbon center exhibits characteristics of a carbocation. Such a structure was found at the semiempirical level, though, and is depicted in Fig. 3c. Geometry optimizations at the DFT level starting from this geometry either in gas phase or incorporating the effect of the solvent employing the PCM method, failed to converge to any other structure than the closed-cycle **4**.

Therefore, we turned our attention to the possibility of an alternative mechanism instead of the classic S_N1-type. We performed an extended search of possible transition state structures, where the ring would open while the negatively polarized BF_3 moiety would interact with the positively polarized carbon atom. Only one structure was found and the calculated reaction pathway passing through it is shown schematically in Fig. 5.

The first step in the reaction is the transfer of the BF_3 moiety from the etherate to **1** generating **4** which will be in equilibrium with $BF_3.OEt_2$ as shown previously (Table 2). While in the S_N1 mechanism the reaction would proceed through C3–O11 bond

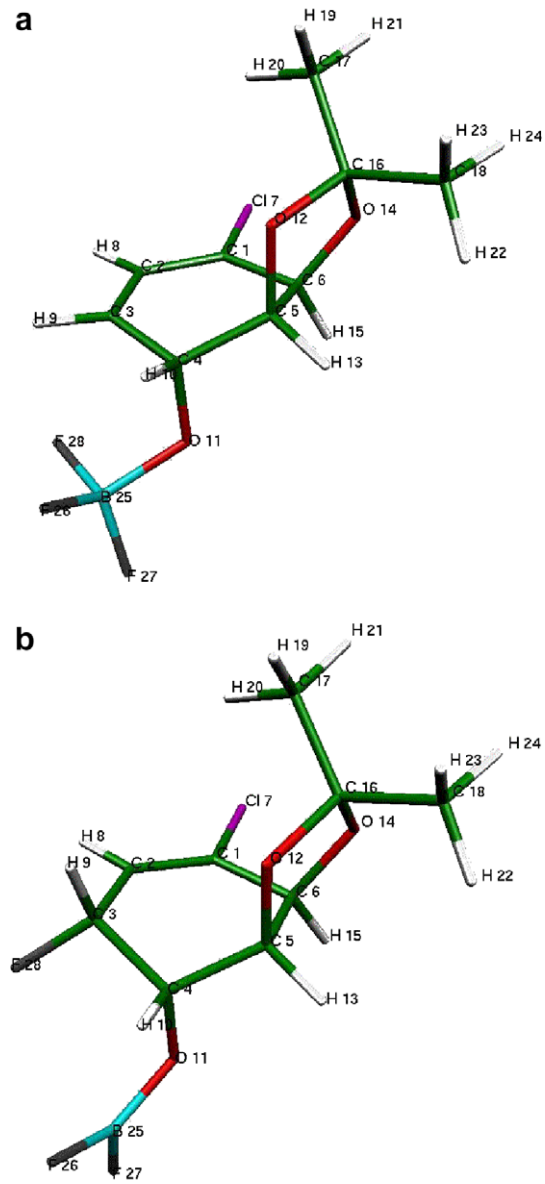

Fig. 6. Structure of the species involved in the formation of *syn*-fluorohydrin: (a) structure and atom numbering for the transition state **5**; (b) structure and atom numbering of the intermediate **6**.

breaking followed by rotation around the C4–O11 bond so that the BF_3 fragment would migrate away from the carbocation center giving a zwitterionic intermediate (see Fig. 3c), in the newly proposed mechanism the C4–O11 bond rotation couples with an O11–B25 rotation to reach the transition state **5**. Detailed geometries of the stationary points, as well as energies and point charges calculated with both basis sets, are included in Fig. 6 and in Table 3.

It was already pointed out that the C3–O11 bond in **4** is longer than the C4–O11 bond, in agreement with the experimental preference for allylic opening, which occurs concomitantly with rotation about the O11–B25 bond to give transition structure **5** (see Table 3). As a result of this rotation, the change in the dihedral angle ϕ (F28B25O11C4) positions atom F28 of BF_3 at a favorable location for intramolecular migration to the C3 carbon in a reaction that occurs with retention of configuration (the C3–F28 distance is 2.382 Å for 6-31G(d) and 2.414 Å for the 6-311++G(2df,2pd) basis sets, respectively). Propensity toward fluoride transfer is also observed in the important asymmetry of the B–F bond lengths of the fluoroborate residue, with a substantially longer one corresponding to the fluorine atom that is being transferred. Finally, the C3 local geometry in the transition state structure, reveals the important carbocationic character of this atom, which favors the final insertion of fluoride F28. Upon reaching the transition state, the reaction continues toward product **6** which is actually an intermediate that must undergo protonation in order to arrive to the final products: the *syn*-fluorohydrin **3** plus F_2BOH. This reaction must then proceed with trace amounts of water present in the reactive system coming both from the reactants and from the contact with the atmosphere.

3.2. Effect of the solvent

The effect of the CH_2Cl_2 solvent was mimicked including a dielectric field through the PCM method, using the experimental dielectric constant of dichloromethane. Geometry optimizations were repeated in all cases, to observe the changes induced by the solvent.

In the first place, it is interesting to observe how the solvent affects the equilibrium between the $BF_3{\cdot}Et_2O$ complex and **4**. Although the change is not tremendous, it is observed that the solvent tends to disfavor the displacement of the equilibrium toward the formation of **4**. In fact, the ΔG_{298} of −0.1 kcal/mol calculated in vacuum with the 6-31G(d) basis set is transformed into a +1.0 kcal/mol when the solvent is included, while with the larger basis set it changes from −0.04 kcal/mol in vacuum to +1.6 kcal/mol in dichloromethane. The energy values necessary to obtain these differences are collected in Table 4.

On the other side, the inclusion of the solvent has a beneficial effect in the structure of the BF_3-complexed epoxide in comparison to the isolated complex. In fact, as it is shown in Table 5, the asymmetry of the oxirane ring in the complex **4** is more pronounced in dichloromethane with respect to the calculations in gas phase. At the 6-31G(d) level, the C3–O11 bond is 0.050 Å longer than the

Table 4
Electronic energies (ZPE corrected), standard enthalpies, free energies at 298.15 K (in hartrees) for the species studied in dichloromethane.

Species	Property	6-31G(d)	6-311++G(2df,2pd)
Diethyl ether–BF_3	E + ZPE	−557.494208	−557.692144
	H(298)	−557.482691	−557.680387
	G(298)	−557.530772	−557.729100
1	E + ZPE	−1034.399660	−1034.611356
	H(298)	−1034.387218	−1034.598853
	G(298)	−1034.437622	−1034.649703
Diethyl ether	E + ZPE	−233.242885	−233.319808
	H(298)	−233.235172	−233.312538
	G(298)	−233.272921	−233.349958
4	E + ZPE	−1358.649225	−1358.980753
	H(298)	−1358.632441	−1358.963851
	G(298)	−1358.693877	−1359.026220

Table 5
Optimum bond lengths and point charges derived from CHELPG and NBO analyses (the latest in parenthesis) for the species studied in dichloromethane. Bond lengths are expressed in Å, numbering of the atoms as in Fig. 2. The lengthening with respect to the bond lengths in vacuum are given in parenthesis.

Parameter	**1** 6-31G(d)	**1** 6-311++G (2df,2pd)	**4** 6-31G(d)	**4** 6-311++G (2df,2pd)
q(C3)	0.18 (0.02)	0.22 (0.03)	0.26 (0.04)	0.28 (0.09)
q(C4)	−0.17 (0.04)	−0.18 (0.06)	−0.18 (0.06)	−0.21 (0.11)
d(C3O11)	1.446 (+0.006)	1.442 (+0.005)	1.503 (+0.021)	1.505 (+0.025)
d(C4O11)	1.420 (+0.004)	1.417 (+0.004)	1.453 (+0.011)	1.451 (+0.011)
Δ(dC3O11 − C4O11) in solvent	0.026	0.025	0.050	0.054
Δ(dC3O11 − C4O11) in gas phase	0.024	0.024	0.040	0.040

Table 6
Electronic energies (corrected for ZPE), standard enthalpies, free energies at 298.15 K (in hartrees), relative energies (in kcal mol^{-1}), bond lengths (in Å), dihedral angles (in degrees) and point charges derived from CHELPG and NBO analyses (the latest in parenthesis) for the species studied in dichloromethane. Numbering of the atoms is as in Figs. 1 and 4.

Parameter	**4**		**5**		**6**	
	6-31G(d)	6-311++ G(2df,2pd)	6-31G(d)	6-311++ G(2df,2pd)	6-31G(d)	6-311++ G(2df,2pd)
E + ZPE	−1358.638200	−1358.980753	−1358.620682	−1358.977621	−1358.646716	-1359.000254
H(298)	−1358.621415	−1358.963851	−1358.604480	−1358.961458	−1358.629865	−1358.983746
G(298)	−1358.682851	−1359.026220	−1358.664065	−1359.021167	−1358.691197	−1359.194101
Erelative	0.00	0.00	10.99	1.97	−5.34	−12.24
q(C3)	0.26 (0.04)	0.28 (0.09)	0.11 (0.10)	0.08 (0.22)	0.26 (0.15)	0.29 (0.17)
q(C4)	−0.18 (0.06)	−0.21 (0.11)	0.29 (0.01)	0.36 (0.04)	0.21 (0.03)	0.24 (0.03)
q(F26)	−0.34 (−0.55)	−0.37 (−0.54)	−0.39 (−0.57)	−0.47 (−0.55)	−0.34 (−0.49)	−0.37 (−0.54)
q(F27)	−0.35 (−0.54)	−0.39 (−0.53)	−0.37 (−0.58)	−0.43 (−0.54)	−0.33 (−0.49)	−0.36 (−0.49)
q(F28)	−0.34 (−0.54)	−0.38 (−0.53)	−0.38 (−0.55)	−0.45 (−0.48)	−0.26 (−0.38)	−0.31 (−0.37)
d(F26B25)	1.359	1.369	1.396	1.386	1.326	1.322
d(F27B25)	1.362	1.363	1.384	1.372	1.324	1.320
d(F28B25)	1.371	1.361	1.420	1.478	2.736	2.953
d(F28C3)	3.684	3.264	2.490	1.988	1.397	1.395
ϕ(F28B25O11C4)	162.1	158.4	62.6	40.4		

C4–O11 bond compared to 0.040 Å in gas phase. The difference is almost the same when the larger basis set is employed. Moreover, even though the oxirane ring in epoxide **1** is not symmetric in solvent media, the difference between both lengths, considering the errors, is equivalent to that obtained in gas phase. These results are in agreement with the experimental results. In dichloromethane, the complexation of the epoxide with boron trifluoride enhances the electrophilicity of the allylic center.

The geometries of the species involved in the proposed mechanisms were optimized in dichloromethane, and frequency calculations performed to characterize the stationary points. The energies and the most relevant parameters are collected in Table 6.

The opening of the epoxide at the allylic carbon occurs with rotation about the O11–B25 bond, as mentioned before. In dichloromethane, as well as in gas phase, the change in the dihedral angle ϕ(F28B25O11C4) positions the migrating fluorine atom close to C3. At the 6-311++G(2df,2pd) level, the C3–F28 distance is the shortest of those obtained in vacuum with both basis sets and in the solvent with the small basis set, resulting in a more favorable disposition for the reaction to occur. Inclusion of the solvent tends to favor the reaction, affecting the relative stability of the transition state. When the 6-31G(d) basis set is employed, the barrier decreases from 19.8 kcal mol^{-1} in vacuum to 11.0 kcal mol^{-1} in dichloromethane. At the 6-311++G(2df,2pd) level in gas phase the barrier is quite similar (17.3 kcal mol^{-1}) while in dichloromethane we obtained a very smaller one (2.0 kcal mol^{-1}). These observations lead to the conclusion that in the solvent employed, the transition state is easily reached, yielding the intermediate **6** which can then proceed to products.

4. Conclusions

A computational investigation on the formation of fluorohydrins from epoxides and boron trifluoride has been performed for the first time at the DFT level with two different basis sets and the inclusion of the solvation effects employing the PCM method.

Contrary to the conventional mechanism which proceeds through a carbocationic intermediate, we proposed an alternative concerted one, involving a single transition state without any intermediates. In this new mechanism, the rotation of the C4–O11 bond couples with an O11–B25 rotation to reach the transition state. The geometry of the transition state is suitable for a concerted intramolecular migration of fluorine F28 to the allylic carbon C3. These calculations explain the preferential formation of *syn*-fluorohydrin as observed experimentally.

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References

[1] R.E. Parker, N.S. Isaacs, Chem. Rev. 59 (1959) 737.
[2] J. Gorzynski Smith, Synthesis. 8 (1984) 629.
[3] C. Xiong, W. Wang, C. Cai, V.J. Hruby, J. Org. Chem. 67 (2002) 1399.
[4] H.C. Kolb, M.G. Finn, K.B. Sharpless, Angew. Chem. Int. Ed. 40 (2005) 2004.
[5] T. Hudlicky, F. Rulin, T. Tsunoda, H. Luna, C. Andersen, J.D. Price, Isr. J. Chem. 31 (1991) 229.
[6] T. Nugent, T. Hudlicky, J. Org. Chem. 58 (1998) 985.
[7] T. Hudlicky, J. Rouden, H. Luna, J. Org. Chem. 58 (1993) 985.
[8] T. Hudlicky, J. Rouden, H. Luna, S. Allen, J. Am. Chem. Soc. 116 (1994) 5099.
[9] G. Prestat, C. Baylon, M.-P. Heck, C. Miokowski, Tetrahedron Lett. 41 (2000) 3829.
[10] J.M. Coxon, A.J. Thorpe, W.B. Smith, J. Org. Chem. 64 (1999) 9575.
[11] Y. Kita, Y. Yoshida, S. Kitagaki, S. Mihara, D.-F. Fang, A. Furukawa, K. Higuchi, H. Fujioka, Tetrahedron 55 (1999) 4979.
[12] J.M. Coxon, A.J. Thorpe, J. Org. Chem. 65 (2000) 8421.
[13] N. Hara, A. Mochizuki, A. Tatara, Y. Fujimoto, Tetrahedron: Asymmetry 11 (2000) 1859.
[14] K.A. Bhatia, K.J. Eash, N.M. Leonard, M.C. Oswald, R.S. Mohan, Tetrahedron Lett. 42 (2001) 8129.
[15] P. Saenz Méndez, R.E. Cachau, G. Seoane, O.N. Ventura, unpublished results.
[16] A. Bowers, H.J. Ringold, Tetrahedron 3 (1958) 14.
[17] A. Bowers, L. Cuéllar Ibáñez, H.J. Ringold, Tetrahedron 7 (1959) 138.
[18] T. Hudlicky, H. Luna, H.F. Olivo, C. Andersen, T. Nugent, J.D. Price, J. Chem. Soc. Perkin Trans. 1 (1991) 2907.
[19] N. Takaishi, H. Takahashi, Y. Inamoto, Tetrahedron Lett. 26 (1985) 2361.
[20] G. Islas-González, C. Puigjaner, A. Vidal-Ferran, A. Moyano, A. Riera, M.A. Pericàs, Tetrahedron Lett. 45 (2004) 6337.
[21] E.J. Corey, Tetrahedron Lett. 23 (1982) 4217.
[22] G. Haufe, J. Fluorine Chem. 125 (2004) 875.
[23] Y. Akiyama, C. Hiramatsu, T. Fukuhara, S. Hara, J. Fluorine Chem. 127 (2006) 920.
[24] R.G. Parr, W. Yang, Density Functional Theory of Atoms and Molecules, Oxford Science Publications, Oxford, 1989.
[25] J.P. Perdew, K. Burke, M. Ernzerhoff, Phys. Rev. Lett. 77 (1996) 3865.
[26] J.P. Perdew, K. Burke, M. Ernzerhoff, Phys. Rev. Lett. 78 (1997) 1396.
[27] W.J. Hehre, L. Radom, P.V.R. Schleyer, J.A. Pople, Ab Initio Molecular Orbital Theory, Wiley, New York, 1986.
[28] F. Jensen, Introduction to Computational Chemistry, Wiley, Chichester, West Sussex, England, 1999.
[29] J.B. Foresman, Æ. Frisch, Exploring Chemistry with Electronic Structure Methods, Gaussian, Inc., Pittsburgh, PA, 1996.
[30] J.E. Carpenter, F. Weinhold, J. Mol. Struct. (Theochem) 169 (1988) 41.
[31] J.P. Foster, F. Weinhold, J. Am. Chem. Soc. 102 (1980) 7211.
[32] A.E. Reed, F. Weinhold, J. Chem. Phys. 78 (1983) 4066.
[33] A.E. Reed, F. Weinhold, J. Chem. Phys. 83 (1985) 1736.
[34] A.E. Reed, R.B. Weinstock, F. Weinhold, J. Chem. Phys. 83 (1985) 735.
[35] A.E. Reed, L.A. Curtiss, F. Weinhold, Chem. Rev. 88 (1988) 899.
[36] F. Weinhold, J.E. Carpenter, in: The structure of small molecules and ions, Plenum Press, New York, 1988.
[37] C.M. Breneman, K.B. Wiberg, J. Comput. Chem. 11 (1990) 361.
[38] K.B. Wiberg, P.R. Rablen, J. Comput. Chem. 14 (1993) 1504.
[39] S. Miertus, E. Scrocco, J. Tomasi, J. Chem. Phys. 55 (1981) 117.
[40] J. Tomasi, M. Perisco, Chem. Rev. 94 (1994) 2027.
[41] S. Miertus, J. Tomasi, J. Chem. Phys. 65 (1982) 239.
[42] V. Barone, M. Cossi, J. Tomasi, J. Comput. Chem. 19 (1998) 404.
[43] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, B. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, A.J. Austin, R. Cammi, C. Pomelli, J. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malik, A.D. Rabuk, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, Gaussian, Inc., Pittsburgh, PA, 2003.
[44] B.N. Blackett, J.M. Coxon, M.P. Hartshorn, K.E. Richards, J. Am. Chem. Soc. 92 (1970) 2574.