# Theoretical Study of Acid-Catalyzed Hydrolysis of Epoxides

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A theoretical study of propylene oxide acid-catalyzed hydrolysis was performed by investigation of the  $S_N1$  and  $S_N2$ -like mechanisms. By using chemometric tools, hierarchical cluster analysis (HCA), and principal component analysis (PCA), the MP2/6-311++G\*\* level of theory was selected from HF, MP2, and DFT as the best method to describe the geometry of the basic skeleton (oxirane). At this level of theory, geometry optimizations, vibrational frequencies, intrinsic reaction coordinate (IRC), and other thermodynamic calculations have shown that the borderline  $S_N2$  mechanism is more favorable than pure  $S_N2$  and  $S_N1$  mechanisms in the gas phase. In the  $S_N1$  mechanism, the existence of the typical carbocation was not observed, and furthermore, the possibility of epoxide conversion to a protonated aldehyde was indicated, even in the presence of a water molecule (nucleophile). The Chelpg charge distribution of the reactants, steric hindrance, synchronous bond breaking–formation and trajectory angle of nucleophilic attack are discussed for pure and borderline  $S_N2$  mechanisms. Solvation effect calculations indicate that the pure  $S_N2$  mechanism is more favorable than borderline  $S_N2$  mechanisms. This is discussed in terms of hydrogen bond formation.

# Introduction

Ethylene oxide or oxirane is the simplest epoxide, that is, a three-membered oxygen-containing ring. It is an extremely strained and reactive system which easily undergoes ring-opening, making it an important intermediate in many organic syntheses. These reactions can occur with a large variety of reactants over a wide range of reaction conditions.<sup>1–4</sup>

One of the most important reactions involving oxirane in biological and industrial applications is its hydrolysis.<sup>5</sup> From the biological point of view, the hydrolysis enables epoxide conversion into more soluble vicinal diols by metabolic pathways, in which the compounds formed are more easily excreted. The process is catalyzed by the enzyme epoxide hydrolase, which plays a key role in detoxification of living cells. Hydrolysis can also be used to convert epoxides into diverse species and chiral products in several industrial processes.<sup>1,5,6</sup>

Some of the first kinetic and mechanistic investigations on epoxide hydrolysis were carried out by Brönsted et al.<sup>7</sup> and Long and Pritchard.<sup>8,9</sup> In these experiments, three distinct kinetic mechanisms for the hydrolysis of oxirane in water were established, acid-catalyzed, base-catalyzed, and pH-independent hydrolyses. With respect to base-catalyzed and pH-independent mechanisms for asymmetric epoxides, experiments have shown that the water is added preferentially to the less sterically hindered carbon atom. This fact is consistent with the bimolecular nucleophilic substitution mechanism (S<sub>N</sub>2), where the breaking of the epoxide C–O bond occurs simultaneously with the formation of the covalent bond between the nucleophile and the epoxide.<sup>10</sup>

Regarding the acid-catalyzed hydrolysis,<sup>7–9</sup> there are two possible pathways. One is the well-known unimolecular nucleophilic substitution mechanism ( $S_N$ 1), where the breaking



Figure 1. Scheme of epoxide acid-catalyzed hydrolysis by  $S_N1$  and borderline  $S_N2$  ( $S_N2'$ ) mechanisms.

of the C–O bond brings a partial positive charge to the carbon atom (see Figure 1). This charge will be stabilized by electron donation (both inductive and hyperconjugative effects) from  $R_1$ , and in a later stage, the nucleophile (water) will attack this carbon atom. The other possibility is the  $S_N2$ -like mechanism in which the nucleophile is farther than usual from the site of attack and the driving force of the reaction is provided more by electron transfer from carbon to oxygen than by that from nucleophile to carbon. Under these conditions, when both partial bonds of the transition state (TS) are still longer than usual, it is reasonable to suppose that the central carbon atom carries a

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Figure 2. HCA dendrogram applied to experimental and optimized structural parameters obtained from different levels of calculations and basis sets for oxirane.

partial positive charge. This mechanism is referred to as "borderline  $S_N2$ " ( $S_N2$ ').

Even though several experimental and theoretical works describing this system can be found in the literature,<sup>1,5-10</sup> the mechanism of epoxide acid-catalyzed hydrolysis is still not fully elucidated. Thus, the aim of this study is to give more insight into the acid-catalyzed hydrolysis mechanism of propylene oxide by inspecting the energy barriers from each of the mechanisms mentioned above through theoretical calculations.

The chemometric tools hierarchical cluster analysis (HCA) and principal component analysis (PCA)<sup>11</sup> have been shown to be very useful in selecting the best computational procedure for the systems under study.<sup>12,13</sup> In this work, they are applied to the analysis of internal coordinates, enabling selection of the best level of quantum chemical calculation between HF, MP2, and DFT and the most suitable basis set.

## Methodology

Experimental structural parameters of C<sub>2</sub>H<sub>4</sub>O, obtained by microwave spectroscopy,<sup>14</sup> were used as a starting point for geometry optimization. The complete geometry optimization was carried out employing ab initio molecular orbital calculations at the HF and MP2 levels and density functional theory (DFT) employing the functional B3LYP. The basis sets used were 6-NG, 6-N++G, 6-NG\*\*, and 6-N++G\*\*, with N equal to 31 and 311. The chemometric methods HCA and PCA were used to investigate which quantum chemical method and basis sets for geometry optimization would be the best in reproducing the experimental structural parameters.

After selecting the method and basis set, geometry optimizations and vibrational frequency calculations were carried out in order to describe the energy involved in the ring-opening mechanism of propylene oxide in acid-catalyzed hydrolysis. To confirm whether the transition states connect the right reactants and products, intrinsic reaction coordinate (IRC)<sup>15</sup> calculations were carried out by using the algorithm proposed by Gonzalez and Schlegel,<sup>16</sup> starting with the optimized transition-state structure and using a step of 0.100 (amu)<sup>1/2</sup> bohr. Electrostatic potential Chelpg partial atomic charges were also calculated.

Single-point aqueous solvation calculations were performed using a continuum description of the solvent (water,  $\varepsilon = 78.39$ ). The conductor-like polarizable continuum model (CPCM), which is particularly suited for highly polar solvents, like water, and the cavity definition given by the UAHF (united atom radii optimized for HF level of theory) were employed.<sup>17,18</sup>

All electronic structure calculations were carried out using the GAUSSIAN 03 program package.<sup>19</sup> PIROUETTE software<sup>20</sup> was employed for the chemometric data analyses.

#### **Results and Discussion**

**Chemometric Analysis.** The results obtained from HF, MP2, and DFT/B3LYP calculations using basis sets 6-NG, 6-N++G, 6- $NG^{**}$ , and 6-N++ $G^{**}$ , with N equal to 31 and 311, are presented in Table S1, available as Supporting Information. The structural data obtained were organized in matrix format, **X**(25,9), and column-wise autoscaled (mean-centered and scaled to unit variance). The dendrogram obtained by the linkage method incremental from HCA is shown in Figure 2.

The dendrogram in Figure 2 shows that the results from theoretical calculations are clustered in two main groups. The first is formed by subgroups A, B, and C, which correspond to HF, DFT/B3LYP, and MP2 calculations, respectively, without



Figure 3. Equilibrium between the propylene oxide stereoisomers.

polarization functions. The second cluster contains the subgroups D, E, and F, corresponding to HF, DFT/B3LYP, and MP2 calculations, respectively, with polarization functions. The scores plot obtained by PCA for the first three principal components, which accounts for 96.85% of the total information, allows clustering similar to that observed in HCA.

The subgroup F formed by MP2/6-311++ $G^{**}$ , MP2/6-311 $G^{**}$ , and MP2/6-31++ $G^{**}$  basis sets provides the best agreement between computed and experimental parameters. For this subgroup, the PCA scores plot indicated that MP2/6-311++ $G^{**}$  was the closest to experimental data, justifying the selection of this method and basis set for further calculations.

This level of calculation includes polarization and diffuse functions, which highlights the importance of electronic correlation to describe this system. This can be explained by the conjugation ability10 of the epoxide ring and its complex electronic structure.<sup>21</sup> The use of this type of basis set arises from the fact that oxirane is a strained system with atypical angles for the types of carbon found in it. Therefore, sufficient mathematical flexibility is necessary to adequately describe valence orbitals. Polarization functions include d orbitals for heavy atoms and/or p orbitals for hydrogen atoms, while diffuse functions allow the description of electrons located distant from the remaining electron density, including s and p functions with small exponents,<sup>22</sup> thus contributing to the mathematical flexibility of the basis set used. Furthermore, the level of theory and basis set selected seems to be reasonable for this kind of study (mechanism of reaction) since lower levels of theory and other basis sets do not describe well, or not at all, bond cleavage and formation, hydrogen bonds, intermolecular interactions, and other phenomena involving low electronic densities.

**Mechanistic Studies.** Once the method and basis set (MP2/ $6-311++G^{**}$ ) that best describes the oxirane experimental structure were selected, the energy involved in the hydrolytic epoxide ring-opening mechanism was studied using the oxirane derivative, propylene oxide.

Initially, propylene oxide protonation can occur at either side of the ring, leading to syn and anti stereoisomers (Figure 3). The calculations show that the anti species is more stable than the syn species by 0.2 kcal/mol. This small difference in energy suggests the existence of an equilibrium between the two stereoisomers. However, the transition-state structure for interconversion between the syn and anti forms, characterized by one imaginary frequency at 966i cm<sup>-1</sup>, has an activation energy barrier of 17.3 kcal/mol. This large barrier practically eliminates the possibility of interconversion between these stereoisomers.

On the basis of these results, the study of the epoxide ringopening mechanism was further investigated considering only the anti species.

As mentioned before, the epoxide ring-opening in an acid medium can occur by the  $S_N1$  or borderline  $S_N2$  mechanism  $(S_N2')$ . In the former, a C–O bond cleavage opens the ring and generates a carbocation that undergoes an attack by the nucleophile (Figure 1). The reaction rate is nucleophile-concentration-independent since carbocation formation is the slow step of the reaction. In the second mechanism, the nucleophile (water) attacks the more substituted carbon atom, and the cleavage of the epoxide C–O bond is considered more important than bond formation with the nucleophile (Figure 1), unlike the pure  $S_N2$  mechanism, where the nucleophile (water) attacks the less substituted carbon atom and the bond breaking occurs simultaneously with covalent bond formation. In  $S_N2$  mechanisms, the kinetics is nucleophile-concentration-dependent.

**S<sub>N</sub>1 Mechanism.** To fully understand the S<sub>N</sub>1 mechanism, calculations of IRC were performed. These calculations identified three transition states. Two were characterized by one imaginary frequency at 148i cm<sup>-1</sup> (TS1) and another at 204i cm<sup>-1</sup> (TS2), both of them connecting the protonated propylene oxide structure to protonated aldehydes (Figure 4a). The other transition state (TS3), characterized by one imaginary frequency at 177i cm<sup>-1</sup>, represents the transition structure for the degenerate hydride shift PROD2  $\rightarrow$  PROD2' (Figure 4b).

Profile reaction analysis, Figure 4a, demonstrates that the mechanism consists of two distinct and interdependent stages. The protonated ring is opened in the first stage, and in the second, the hydride migrates from  $C_1$  to  $C_2$ , forming the protonated aldehyde. Similar results were reported by Coxon et al.<sup>23</sup> using the MP2/6-31G\* level of theory. The profile in Figure 4b shows that the displacement of the methyl group occurs on the side opposite to hydride migration, connecting two degenerate states for the protonated aldehyde.

Comparing our results with those from Coxon et al.,<sup>23</sup> it is possible to observe that the basis set used in the present work better describes the importance of the hyperconjugative effect by a methyl hydrogen in stabilizing the transition states. This is demonstrated by the longer  $H_1$ - $C_3$  bond length (1.245 Å in TS1 versus 1.118 Å in structure 24 from ref 23 and 1.150 Å in TS2 versus 1.129 Å in structure 25 from the same reference) and the most compressed H<sub>1</sub>-C<sub>3</sub>-C<sub>2</sub> bond angle (64° in TS1 versus 101° in structure 24 from ref 23 and 86° in TS2 versus 96° in structure 25 from the same reference). Additionally, the preference for rotation of oxygen away from the more hindered face of the oxirane plane containing the methyl group was almost not observed. The factor that quantifies this preference (difference between transition-state energies) is 0.1 kcal/mol in the present work, while in ref 23, this value was 2.0 kcal/mol. Furthermore, structure 29 from ref 23 was flanked by a minimum where the eclipsing of the C-O with the adjacent CH was relieved by a change in the torsional angle of  $2^{\circ}$ . Differently, the corresponding TS3 structure (Figure 4b) connects the degenerate states for the protonated aldheyde as minima.

In Figure 4a, it is possible to observe some geometrical parameters for the mechanism via TS1. The average angle ( $a_m$ , sum of all angles around the atom divided by the number of angles) around C<sub>1</sub> changes from 108° in the TS1 to 120° in the PROD1, which agrees with a variation in the hybridization of this atom from sp<sup>3</sup> to sp<sup>2</sup>. Similarly, a change from sp<sup>2</sup> to sp<sup>3</sup> hybridization of C<sub>2</sub> is accompanied by a decrease in  $a_m$  from 120° in TS1 to 109° in PROD1. A shortening of the C<sub>1</sub>–O bond from 1.416 Å in TS1 to 1.267 Å in PROD1 shows the formation of carbonyl.

Figure 4a also features a more detailed profile of the reaction obtained by monitoring the changes observed in the molecular



**Figure 4.** (a) Reaction pathway for epoxide ring-opening by  $S_N 1$  mechanisms obtained by IRC (*r*, bond length in Å; *a* and  $a_m$ , angles in degrees; *d*, dihedrals in degrees). (b) Schematic energy profile for degenerate hydride shift.

geometry along the reaction path from the transition state (I) to the product (IV). Here, it is possible to visualize a similar species to TS1, however, with a conformation in which the  $O_1-C_1-C_2-C_3$  dihedral angle changes from -69° in (I) to 1° in (II). This structure was identified as a carbocation with the average angle of 120° at C<sub>2</sub>. Although the carbocation is identified on the potential energy surface (PES), it was not characterized as a minimum at the MP2/6-311++G\*\* level. This fact contradicts the  $S_N1$  mechanism (reaction steps), where the carbocation is the reaction intermediate.

According to Parker and Isaacs,<sup>10</sup> the epoxide ring-opening reaction in an acid medium can result in a rearrangement (1,2-hydride shift), producing aldehydes, although this should occur only in the absence of the nucleophile. To verify whether the

TABLE 1:	Variation of	of the Tota	al Energy	$(\Delta E),$	Zero-Point-	Corrected	Energies	$(\Delta E_{\text{ZPE}}),$	Enthalpy	$(\Delta H)$ , and	l Gibbs I	Free
Energy ( $\Delta C$	<b>G</b> ) along the	Reaction	Path <sup>a</sup>									

	$\Delta E^b$	$\Delta E_{ m ZPE}$	$\Delta H$	$\Delta G$
	S <sub>N</sub> 1 M	Mechanism		
$REAC \rightarrow TS1$	18.50 (37.96)	15.77	15.80	15.64
$REAC \rightarrow TS2$	18.35 (30.03)	15.00	15.41	14.47
$REAC \rightarrow PROD1$	-18.57 (-5.00)	-19.32	-18.97	-19.90
$REAC \rightarrow PROD2$	-18.20 (-3.71)	-18.49	-18.14	-19.20
	Pure S <sub>N</sub>	2 Mechanism		
$REAC \rightarrow TS$	7.85 (8.60)	7.87	7.19	8.98
$REAC \rightarrow PROD$	-3.84 (-16.06)	-1.70	-2.50	-0.26
	Borderline	S <sub>N</sub> 2 Mechanism		
$REAC \rightarrow TS$	6.65 (18.79)	5.92	5.59	6.75
$REAC \rightarrow PROD$	-6.82 (-19.29)	-4.87	-5.57	-3.75

<sup>a</sup> Values are given in kcal/mol. <sup>b</sup> Energy variations in aqueous solution are given in parentheses.

presence of the nucleophile leads to a change in direction of the reaction path on the PES, calculations, starting from the structure of the carbocation (geometry II in Figure 4a) with a water molecule located in the vicinity of the positively charged carbon atom ( $C_2$ ), were carried out. The results show that even in the presence of a nucleophile (water), hydride migration followed by aldehyde production occurred instead of water coordination to the carbocation (data shown in Supporting Information).

The calculated energy barrier (in the gas phase) involved in the  $S_N1$  mechanism via TS2 was 18.4 kcal/mol. In their experimental work, Long et al.<sup>24</sup> reported the activation energy for this mechanism equal to 18.6 kcal/mol, which agrees very well with the results in the present work. Coxon et al.<sup>23</sup> obtained the value of 17.7 kcal/mol for the same system, using theoretical calculations at the MP2/6-31G\* level, while Shinoda et al.<sup>25</sup> obtained the value of 20.2 kcal/mol at the MP2/6-31G\*\* level. These facts show that the new results obtained in this work are much closer to the experimental data, indicating that the use of a chemometric approach to select the most suitable computational procedure based on structural data is superior to an arbitrary choice of theory level and basis sets. Other thermodynamic results are presented in Table 1.

This same reaction profile, when calculated at the HF/6- $311++G^{**}$ , presented an energy barrier of 7.9 kcal/mol and demonstrated the existence of a carbocation (1-methyl-2-hydroxyethyl cation) characterized as an intermediate. The detection of a carbocation by this method is possibly due to the absence of electronic correlation in the calculation which leads to an optimized product in the most sterically favored planar conformation.<sup>26</sup>

Similar results were reported in the literature. Nobes et al.<sup>27</sup> found that for protonated ethylene oxide, the 2-hydroxyethyl cation was characterized by a minimum when the HF/6-31G level of theory was utilized. This cation was not observed in the same way when polarization functions and electronic correlation were included in the calculations. The authors explained their findings due to the ease of rearrangement by a 1,2-hydride shift since it occurs without crossing an energy barrier. Méndez et al.28 studied the epoxide ring-opening of (1S,2S,5R,6R)-3-chloro-5,6-oxy-1,2-O-isopropyliden-3-cyclohexen-1,2-diol by boron trifluoride at the PBE/6-31G(d) and PBE/6-311G++(2df,2pd) levels. No critical point on the DFT potential energy surface was found by these authors, where the oxirane ring was opened and the central carbon exhibited characteristics of a carbocation. Hopmann et al.<sup>29</sup> also could not locate the carbocation in a system that simulated the catalytic mechanism of limonene epoxide hydrolase using a DFT/B3LYP approach. **Pure S<sub>N</sub>2 and Borderline S<sub>N</sub>2 Mechanisms.** For symmetrical epoxides, hydrolysis occurs, yielding only one type of product. On the other hand, in an experimental study carried out by Long and Pritchard<sup>8</sup> with unsymmetrical epoxides, hydrolysis with isotopic labeling in the  $H_2^{18}$ O molecule showed that the reaction was regioselective, with the possibility of formation of two types of products (diols). The first one, called normal, is that obtained from the nucleophilic attack on the less substituted carbon atom, and the second, called abnormal, is that resulting from nucleophilic attack on the more substituted carbon atom.<sup>10</sup> The preference for the formation of abnormal products in an acid medium has been known for a long time.<sup>8</sup>

Aiming to investigate theoretically the  $S_N^2$  mechanism, calculations of IRC were performed for the formation of both products, normal and abnormal. These calculations showed TSs characterized by imaginary frequencies at 476i and 366i cm<sup>-1</sup>, respectively, connecting the reactants, protonated propylene oxide and water, to their respective products (Figure 5). These frequencies correspond to C–O bond breaking and covalent bond formation with water, where configuration inversions at the carbon atom attacked by the nucleophile can also occur. All of these processes are features of a typical  $S_N^2$  mechanism.

As it can be seen in Figure 5, the nucleophilic attack on the less substituted carbon atom of the protonated propylene oxide (pure  $S_N2$  mechanism) is a process that has an energetic barrier of 7.85 kcal/mol, while the nucleophilic attack on the more substituted carbon atom (borderline  $S_N2$  mechanism) has an energetic barrier of 6.65 kcal/mol. The analysis of these results shows that the borderline  $S_N2$  mechanism is favored in the gas phase by -1.20 kcal/mol relative to the pure  $S_N2$  mechanism.

The results obtained here also suggest that for the ringopening, the charge distribution in the species (protonated propylene oxide) is more important than the steric features (usually very influential in bimolecular mechanisms) due to the preference for the borderline S<sub>N</sub>2 mechanism. In fact, the Chelpg charges for the reactants (protonated propylene oxide and water) presented the values +0.100 and +0.433 for C<sub>1</sub> and C<sub>2</sub>, respectively, that is, the charge on the more substituted carbon atom shows that it is more susceptible to a nucleophilic attack. Moreover, the borderline S<sub>N</sub>2 mechanism is not so sensitive to steric hindrance (by the methyl group) since the nucleophile is not so close when compared to what occurs in a pure S<sub>N</sub>2 mechanism (the pathway from the propylene oxide to the TS). As can be seen in Figure 5a, the distance  $C_1-O_2$  in the TS has value of 1.982 Å, while the distance  $C_2-O_2$  in Figure 5b is 2.159 Å.

Other geometrical parameters can be seen in Figure 5, especially the distance between the carbon atom attacked and



**Figure 5.** Reaction pathway for epoxide ring hydrolysis in acid medium obtained by IRC. (a) Nucleophilic attack on the less substituted carbon atom leading to the normal product (pure  $S_N 2$ ). (b) Nucleophilic attack on the more substituted carbon atom leading to the abnormal product (borderline  $S_N 2$ ) (*r*, bond length in Å; *a*, angles in degrees; *d*, dihedrals in degrees).

the oxygen atom (O<sub>1</sub>) in each TS. In the borderline  $S_N^2$  mechanism, this value is 1.940 Å, while in the pure  $S_N^2$  mechanism, it is 1.879 Å. This strengthens the greater importance of C–O<sub>1</sub> bond breaking in the borderline  $S_N^2$  mechanism and explains the larger charge separation in the TS. In the borderline  $S_N^2$  mechanism, the value of the O<sub>1</sub>–C<sub>2</sub>–O<sub>2</sub> angle is 145°, which corresponds to the trajectory of nucleophilic attack on the epoxide on the TS, while the O<sub>1</sub>–C<sub>1</sub>–O<sub>2</sub> angle is 155° in the pure  $S_N^2$  mechanism. This fact indicates that the former mechanism, when compared to the latter, differs more significantly from a typical bimolecular mechanism whose angle is close to 180° for the trajectory cited.<sup>26</sup>

Attention should be called to the fact that the trends presented in this work might not be observed when other nucleophiles are used as, for instance, halide<sup>30</sup> and formate anions,<sup>31</sup> in which other aspects such as size, polarity, and hyperconjugative effects must be considered.

Other thermodynamic results are presented in Table 1. It can be seen that in both mechanisms, the epoxide ring-opening reaction is exothermic with values of -2.50 kcal/mol for pure  $S_N2$  and -5.57 kcal/mol for borderline  $S_N2$  mechanisms. The Gibbs free-energy values point out that the borderline  $S_N2$ mechanism (-3.75 kcal/mol) is more spontaneous than the pure  $S_N2$  mechanism (-0.26 kcal/mol). Analysis of these results Theoretical Study of Acid-Catalyzed Hydrolysis of Epoxides

shows that the borderline  $S_N 2$  mechanism is preferred, confirming the experimental results obtained by Long and Pritchard,<sup>8</sup> where they reported that the abnormal product was favored in an acid medium.

**Solvent Effects.** The energy results for the reactions in aqueous solution are also shown in Table 1. As can be seen, the solvent drastically affects the energy variation in the REAC  $\rightarrow$  PROD pathway for all mechanisms. That is, the gas-phase results overestimate the stability of products in the S<sub>N</sub>1 mechanism and underestimate the stability of this species in the pure S<sub>N</sub>2 and borderline S<sub>N</sub>2 mechanisms. It is believed that this result is due to the fact that in the last two mechanisms, the existence of two oxygen atoms in PROD enables stronger interaction between these species and solvent through hydrogen bonds, stabilizing the system when the calculation includes the solvent effects.

It is known that solvent molecules can form hydrogen bonds with nucleophiles, which disfavors an effective nucleophilic attack on the reaction site. Thus, as can be seen in Figure 5, the distances between the nucleophile and epoxide in the TS (1.982 Å in the pure  $S_N2$  and 2.159 Å in borderline  $S_N2$  mechanisms) explain the higher energy barrier found for the borderline  $S_N2$  mechanism (18.79 kcal/mol) with respect to the pure  $S_N2$  mechanism (8.60 kcal/mol).

Through the results obtained when the solvent effect is considered, it is possible to conclude that the  $S_N1$  mechanism is the least favorable when comparing the energy barriers involved in the three mechanisms studied, followed by the borderline  $S_N2$  mechanism. On the other hand, the pure  $S_N2$  mechanism, contrary to what has been shown experimentally,<sup>8</sup> is favored.

## Conclusions

This study has enabled new and valuable insights into the acid-catalyzed hydrolysis mechanism of propylene oxide by means of IRC calculations.

The level of calculation used (MP2/6-311++G\*\*) was selected by means of chemometric tools, HCA and PCA, which were applied to internal coordinates. For this level of theory, it is shown that the  $S_N1$  mechanism has two TSs that connect the protonated propylene oxide to protonated aldehydes. The calculated energy barriers (in the gas phase) involved in this mechanism are 18.50 and 18.35 kcal/mol, which agrees very well with the experimental result (18.62 kcal/mol) reported in the literature. Although the carbocation was identified in the potential energy surface, it was not characterized as a minimum on the PES. This fact contradicts the  $S_N1$  mechanism, corroborating the idea that diols production by hydrolysis does not occur by this mechanism.

For the  $S_N^2$  mechanism of unsymmetrical epoxides, the acidcatalyzed hydrolysis is regioselective, resulting in different products from the nucleophilic attack on the more or less substituted carbon atom. Calculations reveal TSs that connect the reactants, protonated propylene oxide and water, to their respective products (normal and abnormal). In the gas phase, the pure  $S_N^2$  mechanism has an energy barrier of 7.85 kcal/ mol, while the borderline  $S_N^2$  mechanism has an energy barrier of 6.65 kcal/mol. These results show that borderline  $S_N^2$ mechanism is favored by -1.20 kcal/mol relative to the pure  $S_N^2$  mechanism and agrees with well-known experimental observations.

The energy variations in the REAC  $\rightarrow$  PROD pathway for all mechanisms are drastically affected by the solvent. Here, the pure S<sub>N</sub>2 mechanism, contrary to what has been shown

experimentally, is favored. The  $S_N 1$  mechanism is the least favorable, preceded by the borderline  $S_N 2$  mechanism.

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**Supporting Information Available:** Table S1 contains experimental and calculated internal coordinates values. PC1  $\times$  PC2 scores plot from PCA analysis and all stationary points obtained from theoretical calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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