ARTICLE
Theoretical Study of the AlEt₃-Promoted Tandem Reductive Rearrangement of Epoxides

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The AlEt₃-promoted tandem reductive rearrangement reactions of epoxides was studied at B3LYP/6-31G(d,p) level. For the model compound α-hydroxy epoxides, two possible reaction pathways I and II were calculated. The main difference is the order of ethylene release and six- to five-member ring rearrangement. The ring contraction rearrangement in pathway I is the first step and this step is the rate controlling step with a free energy barrier of 116.62 kJ/mol. For pathway II, the ethylene release occurs first, and is followed by a six-member ring opening reaction which is the rate controlling step, and the barrier is 251.38 kJ/mol. The reason for such high barrier is that the ethylene release results in the following reaction being more difficult. The results show that pathway I (C−C rearrangement and then ethylene release) is more favorable, which is consistent with experimental results.

Key words: AlEt₃, Rearrangement, Density functional theory, Diol, Epoxide

I. INTRODUCTION

The epoxide-opening reaction is important in organic and biologic chemistry [1,2]. It has received much attention in organic and medicinal study due to its extensive occurrence in numerous biologically active natural products [1-3]. The epoxide-opening of chiral α-hydroxy and α-benzyloxy epoxides have been widely used in synthesis of natural products and chiral medicines, such as terpenes and steroids [4-10]. Since the first chiral α-hydroxy epoxides were synthesized by Katsuki and Sharpless in 1980 [11], chiral complexes have been studied extensively [5,12]. The ring-opening of α-hydroxy epoxides can produce 1,3-diol and 1,2-diol [5,13-16]. One important application is to synthesize a stereoselective group, 2-quaternary 1,3-diol with two quaternary carbon atoms [5,17,18]. The multifunctional 1,3-diol serves as a class of important building blocks required for the synthesis of many natural products, such as furanquinocin D, bryostatin 2 and ingenol [19-22]. Many promoters can promote the epoxide-opening. However, it is still a challenge to synthesize this kind of chiral compound with reasonable promoters. Recently a novel and highly stereoselective tandem rearrangement reductive reaction of α-hydroxy epoxide has been developed to construct a quaternary stereocenter and the hydroxymethyl attached to the carbon center using AlEt₃ promoter (see Fig.1) [13,14,23,24]. AlEt₃ was previously used as a catalyst for polymerization or alkylation reaction, which results in carbonyl formation as a byproduct. The 2-quaternary 1,3-diol yield is different with the different group R(H/benzyl, Bn). Tu et al. hypothesized that the reaction involves first, the C−C rearrangement and second, the ethylene release, basing the analysis on their experimental study (see Fig.2) [13].

To the best of our knowledge, no theoretical study has been reported for this important system. For these reactions, we take α-hydroxy epoxide as the model compound to study the AlEt₃-promote ring contraction rearrangement reaction. The reaction mechanism was investigated at Becke three-parameter hybrid functional combined with Lee-Yang-Parr correlation functional B3LYP/6-31G(d,p) level.

II. COMPUTATIONAL DETAILS

Stationary points along the reaction pathways, including both minima and transition states, were obtained by full geometry optimization with B3LYP/6-31G(d,p) [25,26] and confirmed by calculations of harmonic frequencies, which were also used to compute

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FIG. 1 AlEt₃-promoted tandem reductive rearrangement of the epoxides.
FIG. 2 The reaction mechanism of the AlEt₃-promoted tandem reductive rearrangement of the epoxides.

FIG. 3 The optimized geometries of substrate (RC1) and AlEt₃ at B3LYP/6-31G(d,p) level (bond length in Å).

FIG. 4 The calculated reaction pathway I is shown in Fig.4, and the corresponding structures of the stationary points with bond lengths are depicted in Fig.5. The CHELPG charges [28] and natural bond orders [29,30] at B3LYP/6-31++G(2df,p) level were computed to shed further light on the reaction pathways. All calculations were performed with Gaussian 03 [31]. The optimized geometries of substrate and AlEt₃ are shown in Fig.3.

III. RESULTS AND DISCUSSION

Based on the order of the two steps (C−C rearrangement and ethylene release), the mechanism of AlEt₃-promoted reductive rearrangement is proposed with two different pathways (see pathways I and II in Fig.2).

A. Pathway I: C−C rearrangement followed by ethylene release

The calculated reaction pathway I is shown in Fig.4, and the corresponding structures of the stationary points with bond lengths are depicted in Fig.5. The computed relative energies, enthalpies and free energies of all saddle points along pathway I are listed in Table I. The CHELPG charges and bond orders for the main change in the reaction process along pathway I are listed in Tables II and III.

TABLE I The relative energies (ΔE), enthalpies (ΔH), and free energies (ΔG) of all saddle point along the pathway I (unit in kJ/mol).

<table>
<thead>
<tr>
<th>Species</th>
<th>ΔE (with ZPE)</th>
<th>ΔH</th>
<th>ΔG_gas-phase</th>
<th>ΔG_PCM</th>
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</thead>
<tbody>
<tr>
<td>RC</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>TS1-1</td>
<td>121.89</td>
<td>122.77</td>
<td>116.62</td>
<td>110.98</td>
</tr>
<tr>
<td>INT1-1</td>
<td>−49.70</td>
<td>−47.85</td>
<td>−57.10</td>
<td>−54.01</td>
</tr>
<tr>
<td>TS2-1</td>
<td>9.24</td>
<td>6.94</td>
<td>9.61</td>
<td>17.14</td>
</tr>
<tr>
<td>PC-1</td>
<td>−55.51</td>
<td>−66.88</td>
<td>−83.47</td>
<td>−67.46</td>
</tr>
</tbody>
</table>

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Firstly, AlEt₃ and α-hydroxy expoxide form a complex (RC), as shown in Fig. 4. The bond lengths of O₈−Al and O₇−Al are 2.077 and 4.317 Å, respectively. AlEt₃ coordinates with one O atom of the epoxy rather than two O atoms from the OH group, and the epoxy activates the O−C₃ bond and leads to its cleavage. The C₃−O₈ and C₂−O₈ bonds change from 1.447 and 1.433 Å to 1.481 and 1.454 Å, respectively. Through a transition state (TS1-1), a expoxide-opening intermediate (INT1-1) can be formed. The ethylene releases from intermediate INT1-1 and the product (PC-1) can be formed. PC-1 can produce the final product 1,3-diol after quenching with water. For TS1-1, the C₃−O₈ bond breaks, and the bond length changes from 1.481 Å to 2.337 Å. The corresponding bond order changes from 0.804 to 0.166, and the C₃−O₈ bond is almost cleaved in TS1-1. Meanwhile, the distance between C₁ and C₃ shortens to 2.445 Å, whereas it is 2.625 Å for RC. Comparing to RC, changes of the Al−O₈ and Al−O₇ bond lengths are obvious. They are 1.874 and 4.009 Å, respectively, which are 0.203 and 0.308 Å shorter than those in RC. The imaginary frequency associated with TS1-1 is calculated to be 222.5 i cm⁻¹, and the vibration model corresponds to the C₃−O₈ bond cleavage and the C₁−C₃ bond formation. Thus TS1-1 is the transition state that associates with RC and INT1-1. The rear-
The first increase and then decrease. In the meantime, the charges of C2, C3, and O8 have obvious change (see Table II). During the reaction, the charge on C2 changes from 0.19 ˚A longer than the general Al\(\text{Al}^+\) bond lengths have larger change. In this step, the charges of C2, C3, and O8 have obvious change (see Table II). During the reaction, the charge on C2 changes from -0.122e (RC) to 0.244e (TS1-1), and finally to 0.473e (PC-1). In the mean time, the positive charge on the C3 and the negative charge on the O8 first increase and then decrease.

The second step is the rearrangement product INT1-1 further releasing ethylene via TS2-1 with the barrier of 66.71 kJ/mol. For TS2-1, the interaction between Al and O8 makes C2 have one single electron. Thus H15 of the ethyl group can transfer from C10 to C2 more easily. The C2–H15 and C10–H15 bonds are 1.323 and 1.326 ˚A, respectively. The bond O8–Al is 1.839 ˚A, which is shorter than that in INT1-1 (2.050 ˚A). At the same time, one ethyl group is released from the AlEt\(_3\) group and transfers one hydrogen atom to C2. The Al–C9 bond length is 2.161 ˚A, which is about 0.19 ˚A longer than the general Al–C bond (1.985 ˚A in AlEt\(_3\)). For this step, the C2–O8 bond changes from double bond to single bond (bond length are 1.230, 1.310, and 1.415 ˚A for INT1-1, TS2-1, and PC-1, respectively) as the ethylene is released. The bond orders of C2–O8 are 1.690, 1.124, and 0.973 for INT1-1, TS2-1, and PC-1. The negative charge on O8 increases from 0.358e (INT1-1) to -0.573e (TS2-1) and to -0.707e (PC-1), and the charges on other atoms do not change much. At the same time, the O8–Al bond changes from 2.050 ˚A to 1.723 ˚A. Finally AlEt\(_2\) is released after quenching with water, and the expected 1,3-diol is formed.

We also calculated the PCM solvent effect: the barrier further decreases for TS1-1, for which the energy barrier is 110.98 kJ/mol. In contrast, the energy barrier increases from 66.71 kJ/mol to 71.04 kJ/mol for TS2-1. Because the solvent molecule THF can act with the promoter AlEt\(_3\), the explicit inclusion of solvent molecules in theoretical models can get better results [32], but because of the calculation difficulty, we did not calculate the solvent effect in this way. In this reaction process, the first step is reductive rearrangement reaction to form a stable five-member ring intermediate INT1-1, for which the relative free energy is -57.10 kJ/mol. The second step is the ethylene release reaction with a lower barrier of 66.71 kJ/mol. The ethylene release product is formed via TS2-1. The relative free energy of product is -83.47 kJ/mol. For this pathway, the energy barrier of the rearrangement step is highest and this step is the rate controlling step. Also, the energy

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**FIG. 5** The geometries of the stationary points along the pathway I at B3LYP/6-31G(d,p) level. bond length in unit of Å.
barrier is only 116.62 kJ/mol in gas phase.

B. Pathway II: ethylene release followed by C–C rearrangement

The calculated reaction pathway II is also shown in Fig.4 and the corresponding structures and important bond lengths of the stationary points are depicted in Fig.6. The computed relative energies, enthalpies and free energies of all saddle points along the pathway are listed in Table IV. The CHELPG charges and bonds orders for the main change in the reaction process along pathway II are listed in Tables V and VI.

Following the formation of reactant complex RC, the C3–O8 bond cleavage occurs with the concomitant ethylene release rather than reductive rearrangement. The free energy barrier is 119.71 kJ/mol for TS1-2. The Al–C11 bond length is 2.069 Å in TS1-2, which is 0.084 Å longer than that in AlEt3. The O8–Al and O8–C3 bond lengths are 1.838 and 2.207 Å, respectively. At the same time, the leaving group ethyl transfers one hydrogen atom to C3, and the corresponding C3–H16 bond length is 2.088 Å with the bond order being 0.069. The imaginary frequency for TS1-2 is 174.4i cm⁻¹ and the vibration model further indicates that this transition state associates the corresponding reactant and intermediate (INT1-2). For INT1-2, the Al–O8 and Al–O7 bond lengths are 1.782 and 2.061 Å, respectively. The relative free energy in gas phase for INT1-2+C2H4 is -190.02 kJ/mol, which is 132.92 kJ/mol more stable than that of INT1-1 along pathway I. Compared with INT1-1 along pathway I, the main difference is whether there is one hydrogen atom on the C3 atom. The hydrogen atom H16 on the C3 atom results in the following rearrangement reaction being difficult. For this step the charge changes on Al, C1, C2 and O8 are obvious, whereas the charges on other atoms do not change too much. The correspond-

![FIG. 6 The geometries of the stationary points along the pathway II at B3LYP/6-31G(d,p) level. Bond length in unit of Å.](image-url)
Thus it is more stable with the relative free energy different from that PC-1 along pathway I. For this PC-
diol is formed. Hence, PC-2 along pathway II is di-
chronously. Finally, the AlEt
Al
formed. The C1
and 1.174˚A, respectively. The distance between C1 and
C3
change. The C3
to 3.086˚A. The Al
bond length is 2.486˚A, which is longer than that in
INT1-2, TS2-2, INT2-2, TS3-2, and PC-2, respec-
tively, and the bond orders of O8
C2 bonds change with the ring con-
traction rearrangement. The bond order of Al–O8 de-
creases at first and then increases, whereas the change of bond order of O8–C2 is contrary. The bond or-
ders of Al–O8 are 0.377, 0.207, 0.193, 0.283, and 0.387 in INT1-2, TS2-2, INT2-2, TS3-2, and PC-2, re-
spectively, and the bond orders of O8–C2 in INT1-2, TS2-2, INT2-2, TS3-2, and PC-2 are 0.970, 1.431, 1.690, 1.124, and 0.973. This pathway includes three steps: the ethylene release, the six-member ring opening, and H migration/five-member ring formation. The free en-
ergy barriers for the three steps are 119.71, 251.38, and 143.96 kJ/mol, respectively. The barrier of the ethy-
lene release step is the lowest and the barrier of six-
member ring opening is the highest. Thus the second
step, the six-member ring opening reaction, is the rate-
controlling one.

C. Comparison between pathway I and pathway II

For the two investigated pathways mentioned above, the main difference is the order of rearrangement and ethylene release. The six- to five-member ring reductive rearrangement reaction is the first step for path-
way I, and the H migration and ethylene release is the second step. However, the ethylene release is the first step along pathway II, and the following reactions are six-member ring opening, H migration and five-member ring formation. The rate-controlling steps are also dif-
ferent for the two pathways. The first step is the rate

### TABLE V

<table>
<thead>
<tr>
<th>Species</th>
<th>Al</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>O7</th>
<th>O8</th>
<th>C11</th>
<th>C12</th>
<th>H16</th>
</tr>
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<tbody>
<tr>
<td>RC</td>
<td>0.341</td>
<td>0.485</td>
<td>−0.122</td>
<td>0.245</td>
<td>−0.669</td>
<td>−0.214</td>
<td>−0.085</td>
<td>−0.030</td>
<td>−0.001</td>
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<tr>
<td>TS1-2</td>
<td>0.421</td>
<td>0.353</td>
<td>0.241</td>
<td>0.321</td>
<td>−0.626</td>
<td>−0.492</td>
<td>−0.188</td>
<td>0.083</td>
<td>−0.055</td>
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<tr>
<td>INT1-2</td>
<td>0.757</td>
<td>0.195</td>
<td>0.324</td>
<td>0.252</td>
<td>−0.595</td>
<td>−0.688</td>
<td>−0.028</td>
<td>0.025</td>
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<tr>
<td>TS2-2</td>
<td>0.366</td>
<td>−0.056</td>
<td>0.408</td>
<td>0.065</td>
<td>−0.541</td>
<td>−0.459</td>
<td>−0.022</td>
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<tr>
<td>INT2-2</td>
<td>0.509</td>
<td>0.102</td>
<td>0.473</td>
<td>0.113</td>
<td>−0.673</td>
<td>−0.439</td>
<td></td>
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<tr>
<td>TS3-2</td>
<td>0.357</td>
<td>0.094</td>
<td>0.116</td>
<td>0.225</td>
<td>−0.646</td>
<td>−0.503</td>
<td>0.104</td>
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<tr>
<td>PC-2</td>
<td>0.714</td>
<td>0.475</td>
<td>0.310</td>
<td>0.145</td>
<td>−0.687</td>
<td>−0.637</td>
<td>−0.023</td>
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### TABLE VI

<table>
<thead>
<tr>
<th>Species</th>
<th>Al–O7</th>
<th>Al–O8</th>
<th>Al–C1</th>
<th>O8–C2</th>
<th>O8–C3</th>
<th>C1–C3</th>
<th>C12–H16</th>
<th>C2–H16</th>
<th>C3–H16</th>
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<tbody>
<tr>
<td>RC</td>
<td>0.004</td>
<td>0.202</td>
<td>0.839</td>
<td>0.804</td>
<td>0.010</td>
<td>0.935</td>
<td></td>
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</tr>
<tr>
<td>TS1-2</td>
<td>0.003</td>
<td>0.326</td>
<td>0.970</td>
<td>0.166</td>
<td>0.011</td>
<td>0.865</td>
<td>0.000</td>
<td>0.069</td>
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<tr>
<td>INT1-2</td>
<td>0.196</td>
<td>0.377</td>
<td>0.007</td>
<td>0.970</td>
<td>0.029</td>
<td>0.009</td>
<td>0.002</td>
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<tr>
<td>TS2-2</td>
<td>0.123</td>
<td>0.207</td>
<td>0.294</td>
<td>1.431</td>
<td>0.003</td>
<td>0.009</td>
<td>0.864</td>
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<tr>
<td>INT2-2</td>
<td>0.043</td>
<td>0.193</td>
<td>0.478</td>
<td>1.690</td>
<td>0.001</td>
<td>0.006</td>
<td>0.867</td>
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<tr>
<td>TS3-2</td>
<td>0.042</td>
<td>0.283</td>
<td>0.438</td>
<td>1.124</td>
<td>0.053</td>
<td>0.661</td>
<td>0.164</td>
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</tr>
<tr>
<td>PC-2</td>
<td>0.194</td>
<td>0.387</td>
<td>0.006</td>
<td>0.973</td>
<td>0.963</td>
<td>0.907</td>
<td>0.001</td>
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</table>

For formation of the rearrangement product, there are two steps reactions from INT1-2 to PC-2. INT2-2 can be formed from INT1-2 via TS2-2 with a free energy barrier of 251.38 kJ/mol. The imaginary frequency for TS2-2 is 170.01 cm\(^{-1}\) and vibration model corresponds to the C1–C2 bond cleavage. In this reaction process, the action between Al and C1 is important to accelerate the C1–C2 bond cleavage. For TS2-2, the C1–C2 bond length is 2.486 Å, which is longer than that in
INT1-2 (1.546 Å), and the Al–O8, Al–O7, and Al–C1 bond lengths are 1.986, 2.20, and 2.116 Å, respectively. The six-member ring opening intermediate INT2-2 is formed. The C1–C2 bond length changes from 1.546 Å to 3.086 Å. The Al–O8, Al–O7, and Al–C1 bonds also obviously change with the C1–C2 bond cleavage. At the same time, the C3–O8 bond changes from single bond to double bond (from 1.405 Å to 1.231 Å).

The product PC-2 is formed via TS3-2 with a free energy barrier of 143.96 kJ/mol. The imaginary frequency is 396.41 cm\(^{-1}\). In this step, the main re-
actions are H migration and C1–C3 bond formation. From the optimized geometry of TS3-2, we can see this change. The C3–H and C2–H bond lengths are 1.745 and 1.174 Å, respectively. The distance between C1 and C2 is larger (3.370 Å), whereas the distance between C1 and C3 shortens (3.295 Å in TS3-2). The Al–O8, Al–O7, Al–C1, and C2–O8 bond lengths change synchronously. Finally, the AlEt\(_{2}\) group releases and 1,3-diol is formed. Hence, PC-2 along pathway II is dif-
f erent from that PC-1 along pathway I. For this PC-
2, the AlEt\(_{2}\) group is located between O7 and O8. Thus it is more stable with the relative free energy of \(-161.51\) kJ/mol, which is \(78.04\) kJ/mol more stable than that of PC-1 along pathway I.
controlling step for pathway I with a free energy barrier of 116.60 kJ/mol in gas phase. The rate controlling step for pathway II is the six-member ring opening reaction with a barrier of 251.38 kJ/mol. This is consistent with the idea that the six-member to five ring contraction requires the generation of an intermediate with (at least) partial positive charge on the appropriate carbon atom in the six-membered ring [33]. Once ethylene is lost and one hydrogen atom is donated to carbocation center, ring contraction becomes difficult. Thus the mechanism involving loss of ethylene first inevitably leads to the formation of 1,2-diol. Formation of 1,3-diol requires the carbon cation rearrangement to occur first, and the product carbon cation is then quenched by hydrogen donation and accompanied by loss of ethylene.

Due to the high free energy barrier (251.38 kJ/mol) for six-member ring opening reaction along pathway II, it is difficult for this step to occur at mild temperature. Hence the reaction requires high temperature in order to overcome the barrier. Actually, the sequential reactions along pathway II can not go through, and the expected product 1,3-diol can not be formed. The final product is the six-member ring 1,2-diol, which is formed by AlEt₃ release from INT1-2 after quenching with water. Thus pathway I is the more reasonable one. The free energy barrier discrepancy for TS1-1 and TS1-2 along pathways I and II is only 3.09 kJ/mol in gas phase and the barrier along pathway II is higher. The barrier discrepancy changes to 5.73 kJ/mol when the THF solvent effect is taken into account. Thus the reaction along pathway I is more favorable. Pathway I is the reasonable choice for the AlEt₃-promoted tandem reductive rearrangement of epoxides. This is consistent with experimental results.

IV. CONCLUSION

Detailed theoretical study on reaction mechanisms can help to shed light on reaction pathways. For the AlEt₃-promoted tandem reductive rearrangement of epoxides reaction, two possible reaction pathways were calculated at the B3LYP/6-31G(d,p) level. One pathway includes three steps, the six-member to five ring contraction rearrangement reaction and the hydrogen atom transfer/ethylene release. The other pathway includes three steps, the ethylene release first, then the six-member ring opening, and finally H transfer/five-member ring formation. The rate controlling step for the two pathways have different free energy barriers, which are 116.62 and 251.38 kJ/mol, respectively. The high free energy barrier for TS2-2 along pathway II will result in formation of the byproduct 1,2-diol via the AlEt₃ release after quenching with water from INT1-2. Hence pathway I is the more favorable one.

AlEt₃ offers one H to the reaction substrate as Lewis acid but also as the promoter to the ring contraction rearrangement. From the change of C2–O8 bond length and order, AlEt₃ is an important promoter to help the rearrangement. Due to the action between Al and O8, the charge distribution along pathway I is more favorable for the ring contraction rearrangement.

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