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Theoretical Study on the BF_3-Catalyzed Meinwald Rearrangement Reaction

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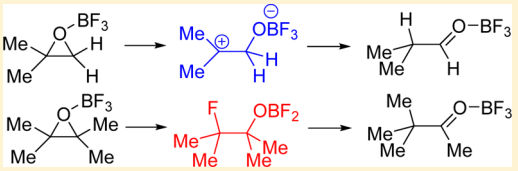
Supporting Information

ABSTRACT: The mechanisms of the BF_3-catalyzed Meinwald rearrangement reactions of five epoxides in dichloromethane solution have been studied at the M062X/6-311++G(2df,2pd) level. Accordingly, the Lewis acid−epoxide complex can react through several alternative pathways, though three phases (ring opening, C−C bond rotation, and hydrogen or alkyl group migration) are required in any path. In some cases, a concerted pathway (involving all three successive phases) is found. Otherwise, the reaction takes place through a reaction mechanism involving a zwitterion or a BF_3 addition compound (formed by fluoride transfer from the BF_3 moiety to the incipient carbocationic center generated by C−O bond rupture) or both as reaction intermediate(s). The BF_2-bound fluorohydrin yields the reaction product through a concerted process involving fluoride transfer from the C−F bond to the OBF_2 group and hydrogen or alkyl group migration, as first demonstrated in this work. Effects of a number of features (solvent effects, concurrent hydrogen/alkyl group migration, carbocation substitution, benzylic conjugation) are also discussed.

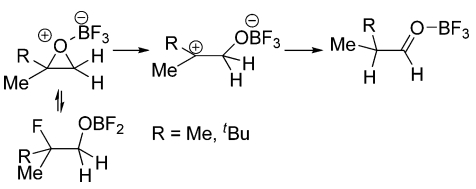


INTRODUCTION

The Meinwald rearrangement reaction allows the synthesis of aldehydes and ketones (especially those bearing one or several α substituents) by using epoxides as starting materials and Brønsted or Lewis acids as catalysts.[1] Interestingly, a plethora of mechanistic pathways depending on the catalysts and substrates have been proposed in several theoretical studies on that reaction. Thus, proton-catalyzed reactions can occur through either concerted (for oxirane)[2] or stepwise mechanisms involving a carbocationic reaction intermediate (for fluorooxirane,[2] benzene oxide,[2] and 2,2-dimethyloxirane).[3,4]

Lewis acid catalyzed Meinwald rearrangement reactions have been studied by Coxon et al. by using BF_3 as an acid model (analogously to other reactions, such as Diels−Alder,[5] allylboration,[6] electrophilic aromatic substitution,[7] and 1,3-dipolar cycloaddition).[8] Accordingly, a stepwise mechanism through a zwitterionic intermediate was inferred for the reactions of two structurally similar epoxides (2,2-dimethyloxirane[3] and 2-*tert*-butyl-2-methyloxirane),[4] the reversible formation of a BF_2-bound fluorohydrin being regarded as a competitive reaction in a dead-end pathway (Scheme 1).

Scheme 1. Mechanism Proposed by Coxon et al. for the BF_3-Catalyzed Meinwald Rearrangement Reaction



Unfortunately, the available information on the mechanisms of the Meinwald rearrangement reaction for a wide range of epoxides is relatively scarce. In order to illustrate the rich variety of plausible mechanisms, the most likely pathways for a BF_3-catalyzed reaction (according to our own results, see later) have been indicated with colored paths in Figure 1. Accordingly, the C−O bond rupture of the BF_3−epoxide complex generates a hypothetical zwitterion which can yield the final Lewis acid coordinated reaction product through different mechanisms. As a possibility, this species can surmount a conformational barrier through a TS bearing a nearly *syn*-periplanar C−C−C−C arrangement to generate a reactive conformer of the aforementioned hypothetical zwitterion, which undergoes hydrogen or alkyl migration, yielding the BF_3-coordinated reaction product in a concerted way (blue path).

The reactive conformer of the hypothetical zwitterion can lead to a reaction intermediate which undergoes a subsequent migration step (open red path). The zwitterionic intermediate can alternatively undergo a reversible fluoride transfer from the OBF_3^- group to the carbocationic center to yield a BF_2-bound fluorohydrin (closed red path). Such a BF_3-addition compound can act as a reactant reservoir, according to the experimental results for some Meinwald rearrangement reactions.[9]

The BF_2-bound fluorohydrin can also be formed through other mechanistic paths. Thus, the conformational barrier surmount for the initial hypothetical zwitterion can cause an approximation between the OBF_3^- group and the carbocationic

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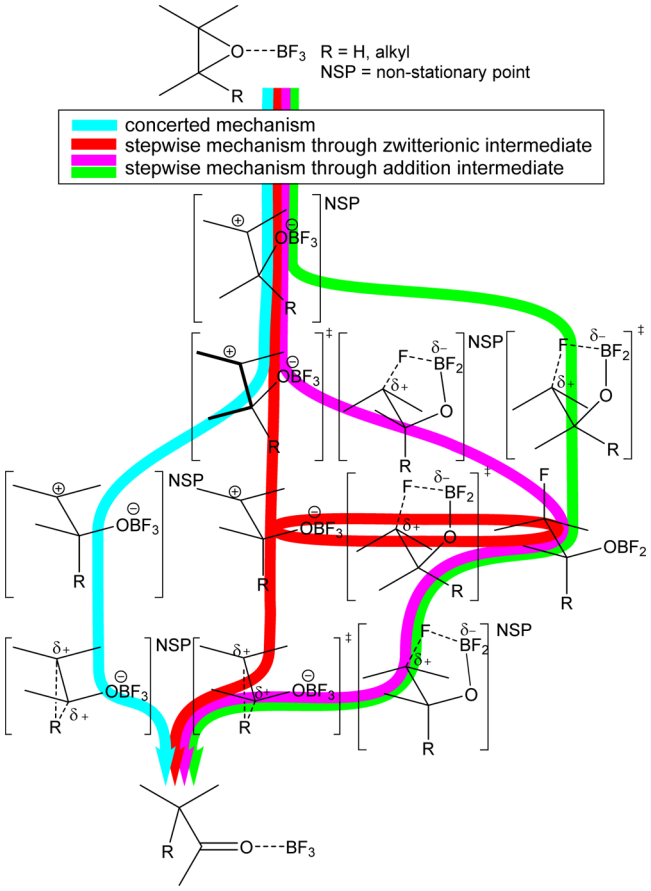

Figure 1. Schematic representation of the major mechanisms for a BF_3-catalyzed Meinwald rearrangement reaction.

center, favoring the fluoride transfer in a monotonic energy decrease (purple path). The BF_3-addition compound can undergo a concerted reaction involving fluoride transfer and hydrogen or alkyl migration to yield the final BF_3-coordinated reaction product.

In cases lacking a significant barrier for the C−C bond rotation of the initial hypothetical zwitterion, the energy maximum along the step involving the formation of the BF_2-bound fluorohydrin can be controlled by fluoride transfer (green path). Instead, the transformation of the reaction intermediate into the final BF_3-coordinated reaction product must take place in a way analogous to the purple path.

We want to gain here a general overview of the BF_3-catalyzed Meinwald rearrangement mechanism by means of a theoretical study, including for the first time stationary points optimized in a solvent model. In order to obtain general behavior patterns for the Meinwald rearrangement as a whole, we studied the reactions of five epoxides involving some interesting features: 2,2-dimethyloxirane (hydrogen migration), tetramethyloxirane (alkyl migration), trimethyloxirane (concurrent hydrogen/alkyl migrations), cyclohexene oxide (ring constraints), and phenyloxirane (benzylic conjugation). Such information would be useful for the rationale of the activity of epoxides in the presence of Lewis acids.

COMPUTATIONAL METHODS

The choice of theoretical method was based on the outstanding results of M052X/6-311++G(d,p) calculations on protonated epoxides,[10] though the M052X functional was replaced by M062X because of its increased accuracy.[11] Accordingly, all energy minima and transition states in the reaction mechanisms were initially calculated at the M062X/6-311++G(d,p) level in dichloromethane by using the polarizable continuum model (PCM). The connectivity between such stationary points in the corresponding mechanistic map was characterized at the same theoretical level by intrinsic reaction coordinate (IRC) calculations by using the Hessian-based predictor corrector (HPC) algorithm[12] (or the damped velocity Verlet method[13] for failed HPC calculations) by using 0.1 bohr steps along the reaction path until geometry convergence in both the forward and reverse directions. In many cases, IRC calculations revealed reaction steps in several stages, in such a way that the animation of the imaginary frequency of a TS is not an adequate criterion for predicting the fate of such a structure in the reaction mechanism.

In order to obtain a more accurate quantitative description of the reaction mechanism, all stationary points were recomputed at the M062/6-311++G(2df,2pd) level in dichloromethane solution. Energy minima and transition states (TSs) were characterized in dichloromethane by the correct number of negative eigenvalues (0 and 1, respectively) of the exact Hessian at that level. To the best of our knowledge, this is the first study on the Meinwald rearrangement reaction using optimized structures in a dielectric medium.

The methodology was tested for a large set of Meinwald rearrangement reactions in the gas phase. In particular, the results obtained for reactions catalyzed by proton (involving oxirane, 2,2-dimethyloxirane, and tetramethyloxirane) or BF_3 (involving 2,2-dimethyloxirane, tetramethyloxirane, trimethyloxirane, cyclohexene oxide, and phenyloxirane) were regarded. The corresponding results are included in the Supporting Information.

Kinetic isotope effects for the 2,2-dimethyloxirane + BF_3 reaction were calculated by means of the Bigeleisen−Mayer equation[14] by using the M062X/6-311++G(2df,2pd) analytical frequencies for the conveniently deuterium-substituted TSs optimized in carbon tetrachloride by using the PCM model at 273.15 K.

All calculations were carried out using the Gaussian09 program package.[15] Relative values for the sum of electronic and thermal free energies at 25 °C (calculated by using nonscaled frequencies) for all structures (included in the Supporting Information) were used in this paper for Gibbs free energy discussions on every system. Most significant structures have been represented in the figures by using CYLView.[16] Trivial structures for noncoordinated reactants or reaction products are not shown.

RESULTS AND DISCUSSION

Rearrangement of BF_3-Coordinated 2,2-Dimethyloxirane. The calculated mechanism for the reaction of BF_3-coordinated 2,2-dimethyloxirane (**1**) in dichloromethane is shown in Figure 2. In a simple outline, BF_3-coordinated 2,2-dimethyloxirane (**1**) can undergo a ring-opening reaction through two alternative pathways (either *syn*, in a concerted step, or anti, via the addition compound **5**) to generate the folded zwitterion **4**. Such a species can undergo hydrogen migration through two alternative paths (either through a direct way or via the nearly C_s symmetric zwitterion **8**) to generate the BF_3-coordinated 2-methylpropanal **11**.

Although two types of ring-opening reactions (depending on which C−O bond is broken in the process) can be considered for the BF_3-coordinated epoxides, rupture of the most substituted carbon−oxygen bond was only considered along this study, analogously to other theoretical studies on the Meinwald reaction.[3,4,17]

Two diastereotopic methyl groups (*cis* and *trans*, depending on their position relative to the BF_3 moiety) can be distinguished in **1**. Since ring opening is coupled to C−C bond rotation,[3] two paths for the first step of the **1** reaction can be regarded, depending on the methyl group being approximated by the oxygen atom: *cis* (*syn* route) or *trans*

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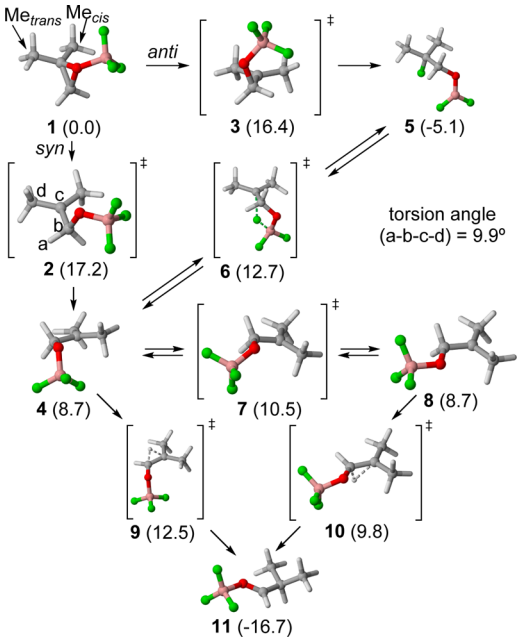


Figure 2. Rearrangement reaction of BF_3-coordinated 2,2-dimethyloxirane (**1**) in dichloromethane, according to DFT calculations. Relative Gibbs free energies (in kcal mol^{-1}) and a selected torsion angle are also shown.

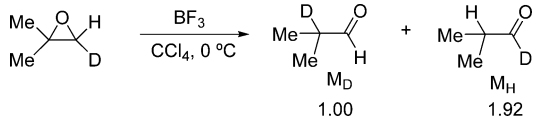
(*anti* path). The *syn* route takes place through TS **2**, which shows a nearly *syn*-periplanar C_{trans}–C–C–H_{trans} arrangement (9.9°), the imaginary frequency corresponding to C–C bond rotation. As a result of this step, the folded zwitterion **4** is obtained as an energy minimum in solution, in contrast with the lack of an authentic energy minimum in the gas phase (attributed by Coxon et al. to a calculation artifact).[3] Instead, the reaction of **1** along the *anti* pathway through TS **3** includes the fluoride transfer from the BF_3 group to the incipient carbocationic atom, thus yielding the BF_3-addition compound **5**. The formation of such a species is consistent with theoretical[18] and experimental[9,19] studies on the BF_3 addition to different epoxides. The different fate for complex **1** as a function of the sense of rotation of the C–C bond can be attributed to the motion of the OBF_3 group relative to the incipient carbocationic atom (moving away for the *syn* path; setting closer for the *anti* route).

Interestingly, that BF_2-bound fluorohydrin can also generate the zwitterion in the folded conformation (**4**) through fluoride transfer (involving TS **6**). Moderate activation barriers are found for both *syn* (17.2 kcal mol^{-1}) and *anti* (16.4 kcal mol^{-1}) paths, in contrast with the high barriers computed in gas phase reactions (32.0 and 25.4 kcal mol^{-1}, respectively; see the Supporting Information). The feasibility of such steps in solution can be attributed to the large stabilization by solvent–solute interactions for both TSs in a dielectric medium due to their large dipole moments (15.9 and 13.0 D, respectively, for the solvated structures).

Zwitterion folded conformer **4** can undergo C–O bond rotation with a very low activation barrier (1.8 kcal mol^{-1}) through TS **7** to yield the nearly C_s symmetric conformation **8**. The occurrence of two zwitterion conformers as intermediates in the reaction contrasts with Coxon's assumption on the participation of **8** as the only intermediate in solution.[3] Although both zwitterion conformers **4** and **8** can undergo hydrogen migration (through TSs **9** and **10**, respectively) to yield *anti* BF_3-coordinated 2-methylpropanal (**11**), a slight preference (by 2.0 kcal mol^{-1}) for the path occurring through the nearly C_s symmetric conformation **8** is found.

Interestingly, some experimental information on the hydrogen migration in this reaction has been obtained from kinetic isotope effects (KIE; see Scheme 2).[20] Thus, BF_3-catalyzed

Scheme 2. Experimental KIE on the BF_3-Catalyzed Meinwald Rearrangement Reaction of 2,2-Dimethyloxirane



rearrangement of 2,2-dimethyloxirane-3-*d* in CCl_4 at 0 °C yields a reaction mixture including two isotopomers derived from the migration of hydrogen (M_H) or deuterium (M_D). The calculated KIE in CCl_4 at 0 °C for TS **10** (M_H/M_D = 2.348) is somewhat larger than that of Coxon (M_H/M_D = 2.068 at the B3LYP/6-31G* level in the gas phase),[3] though qualitatively consistent with the experimental value (M_H/M_D = 1.92).[20] Numerical discrepancies between calculated and experimental KIE values may be related to the large variations in the TS geometries depending on the solvent properties (e.g., calculated C–C–O–B torsion angles for TS **10**: 108.3° in CCl_4, 165.5° in CH_2Cl_2).

Rearrangement of BF_3-Coordinated Tetramethyloxirane. Results for the reactivity of BF_3-coordinated tetramethyloxirane (**12**) in dichloromethane are shown in Figure 3. As a glimpse, BF_3-coordinated tetramethyloxirane **12** can react through two alternative pathways (*syn* and *anti*) through two different reaction intermediates (zwitterion **15** and BF_3-addition compound **16**, respectively), which can undergo methyl rearrangement to yield BF_3-coordinated pinacolone (in either *syn* (**19**) or *anti* (**20**) conformation, respectively).

The concurrence of *syn* and *anti* pathways, where the *syn* route (through TS **13**) yields zwitterion **15**, is analogous to the result obtained for the reaction of **1**. Zwitterion **15** can undergo methyl migration through TS **17** to yield *syn* BF_3-coordinated pinacolone (**19**). Interestingly, no minimum energy could be found in the gas phase for **15** (see the Supporting Information), presumably due to the large charge separation in such a species (15.9 D in solution). Evidently, full optimization of the structures in a dielectric medium is required for the characterization of the Meinwald rearrangement reaction mechanism, as done here for the first time.

Complex **12** can also react along an *anti* path through TS **14** to yield the BF_3-addition compound **16**. Such a reaction intermediate can undergo methyl migration through TS **18** to generate the *anti* conformer of BF_3-coordinated pinacolone (**20**), more stable than the *syn* form (**19**) by 5.3 kcal mol^{-1}. It must be remarked that this is the first work predicting the concerted rearrangement reaction of a Lewis acid addition compound (here, **16**) to yield the corresponding coordinated carbonyl compound.

The role of the Lewis acid–epoxide addition compound as an intermediate in the Meinwald rearrangement reaction of **12** is consistent with experimental results on the reaction of tetramethyloxirane with $NbCl_5$, leading to the corresponding chlorohydrin, whereas the reaction with NbF_5 yielded pinacolone.[22] On the other hand, the predicted alkyl migration

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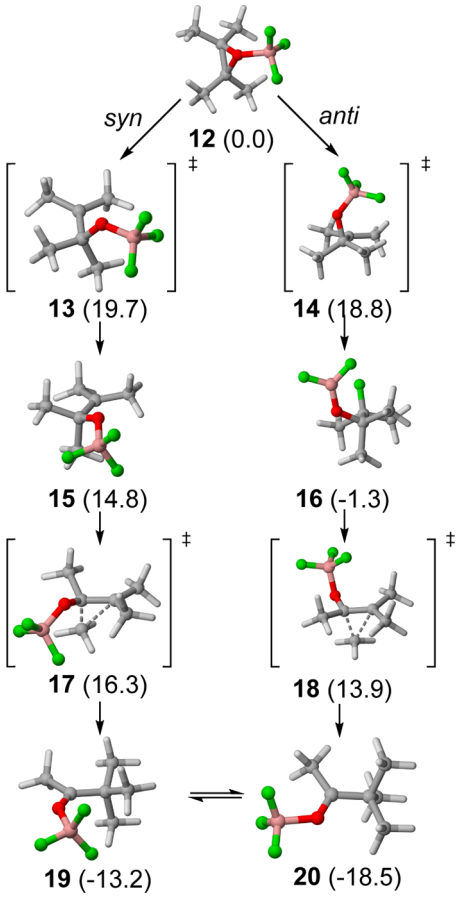

Figure 3. Rearrangement reaction of BF_3-coordinated tetramethyloxirane (**12**) in dichloromethane, according to DFT calculations. Relative Gibbs free energies (in kcal mol^{-1}) are also shown.

is consistent with experimental results on BF_3-catalyzed reactions on tetrasubstituted oxiranes.[21]

Rearrangement of BF_3-Coordinated Trimethyloxirane. The mechanistic route map for the BF_3-catalyzed reaction of trimethyloxirane in solution (Figure 4) can be outlined in a few statements. Therefore, both BF_3-coordinated trimethyloxirane invertomers (*exo* (**21**) and *endo* (**22**)) can undergo ring opening through two alternative ways (*syn* and *anti*). For both invertomers, the *syn* way involves a concerted rearrangement to generate a BF_3-coordinated carbonyl compound (involving hydrogen shift for **21** to lead to BF_3-coordinated 3-methylbutanone **36**; involving methyl migration for **32** to yield *syn* BF_3-coordinated pivalaldehyde **38**). Instead, both *anti* paths involve the formation of a zwitterion (in a different conformation depending on the initial trimethyloxirane−BF_3 invertomer), which can yield the final reaction product through a rearrangement step (BF_3-coordinated 3-methylbutanone **36** through hydrogen shift; BF_3-coordinated pivalaldehyde **37** through methyl migration).

Bothe *exo* (**21**) and *endo* (**22**) invertomers are possible for BF_3-coordinated trimethyloxirane, the former being favored by 1.3 kcal mol^{-1}, presumably due to its lower steric hindrance. In turn, each invertomer can react through *syn* and *anti* paths. *syn* reaction paths for both invertomers **21** and **22** take place through concerted mechanisms. Imaginary frequencies for both TSs (**23** and **26**, respectively) correspond to C−C bond rotation, thus propitiating the approximation of a group (hydrogen and methyl, respectively) to the carbocationic

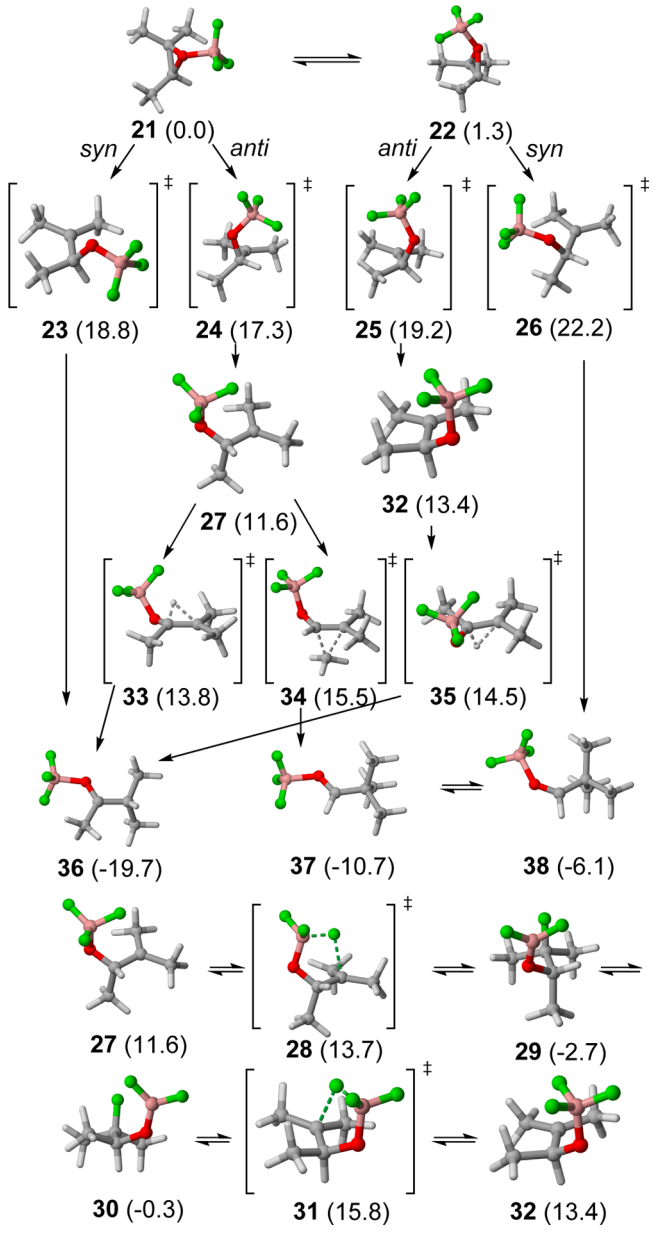

Figure 4. Rearrangement reaction of BF_3-coordinated trimethyloxirane in dichloromethane, according to DFT calculations. Relative Gibbs free energies (in kcal mol^{-1}) are shown.

vacant p orbital. As a consequence, the group migration is favored leading to the corresponding compound (*anti* BF_3-coordinated 2-methylbutanone **36** and *syn*-BF_3-coordinated pivalaldehyde **38**, respectively).

Instead, both *anti* paths lead to the formation of a common zwitterion in conformation **27** or **32**, which can interconvert through a BF_3-addition compound (**29**). Zwitterion **27** can also undergo the migration of a group (*syn*-hydrogen through TS **33** or *anti*-methyl through **34**) to generate the corresponding reaction product (BF_3-coordinated 3-methylbutanone **36** or *anti* BF_3-coordinated pivalaldehyde **37**, respectively). Instead, zwitterion conformer **32** can only undergo *anti*-hydrogen migration through TS **35** to yield **36**.

Comparison between the paths for the rearrangement of both zwitterion conformers shows a preference for *syn*-hydrogen migration (TS **33**) in comparison with *anti*-methyl motion (TS **34**, by 1.7 kcal mol^{-1}) and *anti*-hydrogen shift (TS

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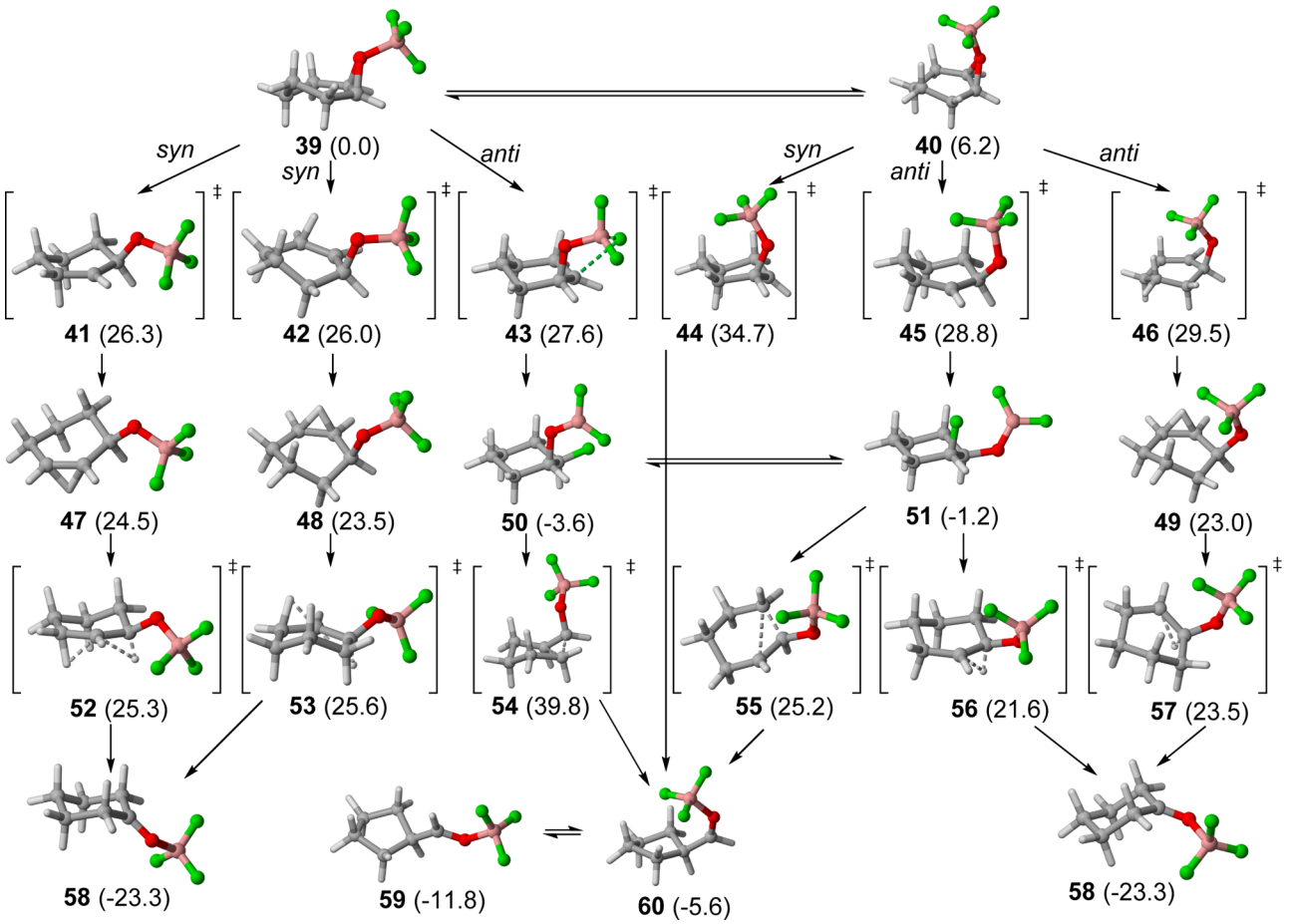

Figure 5. Rearrangement reaction of BF_3-coordinated cyclohexene oxide in dichloromethane, according to DFT calculations. Relative Gibbs free energies (in kcal mol^{-1}) are also shown.

35, by 0.7 kcal mol^{-1}). Comparison of these relative energies with gas-phase results indicates that the slight *syn*-hydrogen preference in solution is due to solvent effects (see the Supporting Information).

As the preferred mechanistic route for the reaction of BF_3-coordinated trimethyloxirane, *exo* invertomer **21** can undergo ring opening through TS **24** to generate zwitterion **27**, which can undergo a reversible reaction leading to the addition compound **29**. As the final reaction step, zwitterion conformer **27** can undergo *syn*-hydrogen migration to generate BF_3-coordinated 3-methylbutanone (**36**).

Interestingly, a mixture of aldehydes and ketones (derived from alkyl and hydrogen migration, respectively) is usually obtained in experimental BF_3-catalyzed Meinwald rearrangement reactions of trialkyloxiranes, the major reaction product depending on the particular epoxide.[23] Nevertheless, the preference for hydrogen (instead of methyl) migration is consistent with experimental results on a number of $InCl_3$-catalyzed Meinwald rearrangement reactions involving different substrates.[24]

Rearrangement of BF_3-Coordinated Cyclohexene Oxide. The mechanism for the BF_3-catalyzed Meinwald rearrangement reaction of cyclohexene oxide in solution is gathered in Figure 5, where structures derived from the gauche$^-$ conformation of (1*R*,2*S*)-cyclohexene oxide are only shown. Such a reaction network can be summarized as follows. Both cyclohexene oxide + BF_3 invertomers (*exo* (**39**) and *endo* (**40**)) can react through several paths depending on the C−O bond broken in the process and the sense of rotation for the C−C epoxide bond (*syn* or *anti*). Both *syn* routes for invertomer **39** and one of the *anti* paths for invertomer **40** lead to the formation of a hydrogen-bridged carbocationic zwitterion (as a different stereoisomer, depending on the route), which can undergo hydrogen migration to yield BF_3-coordinated cyclohexanone **58**. Instead, some *anti* ways lead to the formation of a BF_3-addition compound (in a conformation depending on the initial invertomer), which rearranges (through methyl or hydrogen migration) to yield the corresponding reaction product. Finally, the *syn* route for invertomer **40** leads to the concerted formation (involving methyl migration) of *syn* BF_3-coordinated cyclopentanecarbaldehyde (**60**).

BF_3 can bind to either *endo* or *exo* lone pairs of cyclohexene oxide leading to invertomers **39** or **40**, respectively. The *exo* invertomer (**39**) is more stable than the *endo* analogue (**40**) by 6.2 kcal mol^{-1}, presumably due to the larger steric hindrance of the latter.

exo-BF_3-coordinated cyclohexene oxide (**39**) can react through three alternative TSs. In particular, two *syn* TSs (**41** and **42**) lead to the formation of zwitterionic hydrogen-bridged secondary carbocations (**47** and **48**, respectively). Both carbocationic zwitterions can undergo hydrogen migration (through TSs **52** and **53**, respectively) to yield BF_3-coordinated cyclohexanone (**58**). Instead, the *anti* pathway for **39** takes place through TS **43** to generate **50**, which undergoes a

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concerted rearrangement through TS **54** to finally yield *syn* BF_3-coordinated cyclopentanecarbaldehyde (**60**).

endo BF_3-coordinated cyclohexene oxide (**40**) can react through one *syn* route and two *anti* paths. The *syn* pathway leads to the concerted formation of **60**. Instead, the reaction through TS **45** generates the BF_3-addition intermediate **51**, which subsequently undergoes concerted rearrangement reactions involving *cis*-alkyl migration (through TS **55**) or *anti*-hydrogen shift (through TS **56**) to yield **60** or **58**, respectively. Finally, the reaction through TS **46** leads to carbocationic zwitterion **49**, which undergoes a hydrogen rearrangement through **57** to yield BF_3-coordinated cyclohexanone **58**.

The preferred pathway on cyclohexene oxide can be now inferred. Thus, **39** undergoes ring opening through TS **42** to generate carbocationic zwitterion **48**, which subsequently undergoes hydrogen migration through TS **53** to yield preferably BF_3-coordinated cyclohexanone **58**.

The participation of an addition compound as an intermediate in the cyclohexene oxide reaction allows explaining the experimental results of the reaction of cyclohexene oxide with magnesium bromide etherate, which led to *trans*-2-bromocyclohexanol at 0 °C but a *trans*-2-bromocyclohexanol/cyclopentanecarbaldehyde mixture at 60 °C.[25] The use of $InCl_3$ as a catalyst for the reaction of cyclohexene oxide also led to the formation of the corresponding chlorohydrin.[24] Instead, no reaction was found when $LiClO_4$ was used as a catalyst.[26] The major product from the experimental catalyzed Meinwald rearrangement reaction of cyclohexene oxide is highly dependent on the catalyst. Thus, cyclohexanone was obtained in the $AuCl_3/AgSbF_6$-induced reaction,[28] whereas cyclopentanecarbaldehyde was generated in the $Er(OTf)_3$-catalyzed process.[30]

Rearrangement of BF_3-Coordinated Phenyloxirane. The reactivity of phenyloxirane in the presence of BF_3 (Figure 6) can be summed up as follows. Both phenyloxirane+BF_3 invertomers (*exo* (**61**) and *endo* (**62**)) can react through *syn* and *anti* paths to yield a zwitterionic intermediate in two alternative conformations (either bearing (**71**) or lacking (**67**) an intramolecular C−H···O hydrogen bond). Such reaction intermediates can undergo hydrogen migration to yield BF_3-coordinated phenylacetaldehyde (in a *syn* conformation when derived from **67**; in an *anti* form if coming from **71**).

exo BF_3-coordinated phenyloxirane (**61**) is favored over the *endo* analogue (**62**) by 3.0 kcal mol^{-1}. Interestingly, two zwitterionic conformers can be formed as reaction intermediates, depending on the starting invertomer and the followed pathway. In particular, the zwitterion conformer bearing an intramolecular C−H···O hydrogen bond[27] (**71**) is formed through TS **64** (from **61**, *anti* path) and TS **66** (from **62**, *syn* route), whereas the hydrogen-bond-lacking conformation **67** is obtained through TS **63** (from **61**, *syn* path) and TS **65** (from **62**, *anti* route). Interestingly, both zwitterion conformers can interconvert through the BF_3-addition compound **69**.

Zwitterion conformer **67** can undergo hydrogen migration through two alternative TS's (**72** and **73**) to generate *syn* BF_3-coordinated phenylacetaldehyde (**75**). Instead, conformer **71** can undergo hydrogen migration through TS **74** to yield *anti* BF_3-coordinated phenylacetaldehyde (**76**), more stable than the *syn* analogue (**75**) by 0.9 kcal mol^{-1}. Formation of phenylacetaldehyde as the only reaction product of the phenyloxirane rearrangement is consistent with experimental studies involving the use of a number of catalysts (such as LiBr,[25] $LiClO_4$,[26] $Cu(BF_4)_2$,[29] and $InCl_3$).[24]

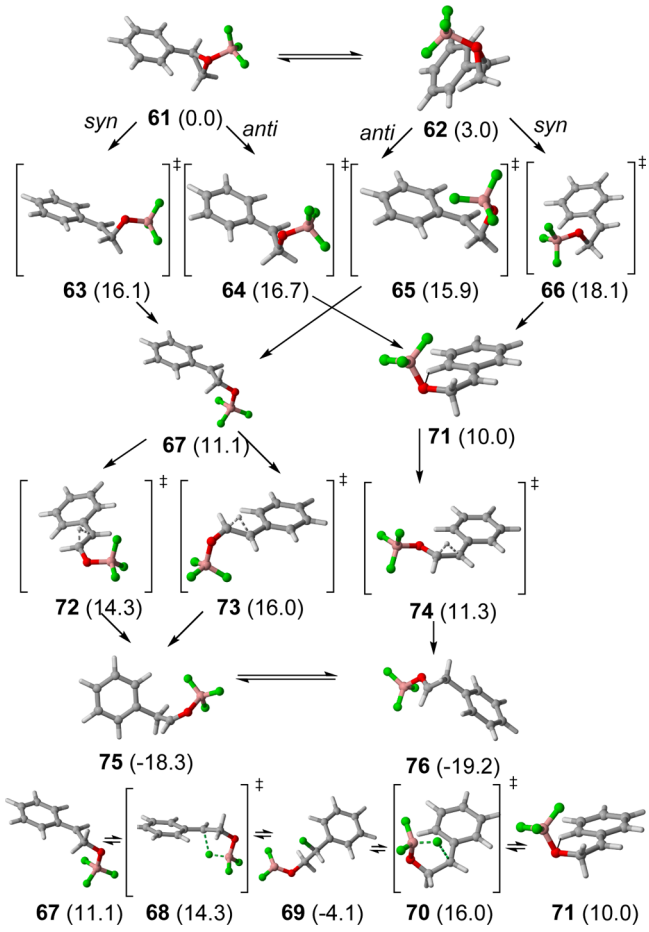

Figure 6. Rearrangement reaction of BF_3-coordinated phenyloxirane in dichloromethane solution, according to DFT calculations. Relative Gibbs free energies (in kcal mol^{-1}) are also shown.

CONCLUSION

A general rationale on the mechanism of the catalyzed Meinwald rearrangement reaction can be drawn from this theoretical study. At least three phases (ring opening, C−C bond rotation, and hydrogen or alkyl group migration) are required for any reaction of the Lewis acid−epoxide complex. No TS for mere ring opening could be located, presumably due to the monotonic energy raise induced by the C−O bond rupture. The main contribution to activation barriers in catalyzed Meinwald rearrangement reactions can be attributed to the C−O bond rupture, though the moderate activation barriers can be attributed to the stabilization in a polar medium because of the large dipole moments.

Some conclusions with synthetic interest can also be withdrawn. For example, an increase in the activation barrier induced by ring constraint may be applied to the selective rearrangement of epoxides derived from acyclic alkenes. Although both hydrogen and alkyl migration reactions are possible in many Meinwald rearrangement reactions, a hydrogen shift is usually preferred.

Nevertheless, some caution should be taken in the extrapolation of these mechanistic clues to real systems involving other catalysts or substrates. For example, experimental results can be highly dependent on the catalyst. Therefore, 1-methylcyclohexene oxide reacts in the presence of lithium bromide through an addition intermediate to yield a mixture of cyclopentane derivatives, whereas it reacts in the

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presence of lithium perchlorate to generate a mixture mainly composed of 2-methylcyclohexanone.[31]

The reactivity of Meinwald rearrangement reactions can be affected by other side reactions. Thus, the low yield obtained for the 2-*tert*-butyl-2-methyloxirane + BF_3 reaction[32] is due to the significant formation of an acetal by the reaction between the original epoxide and the ketone resulting from the Meinwald rearrangement.[33]

In any event, the influence of the epoxide structure in the reaction mechanism should be regarded for synthetic applications. The presence of reactive substituents can lower the reaction yields, as found for 2-nitrooxiranes in the presence of BF_3 leading to nitro, fluoro, and hydroxy ketones, as well as some dimer derivatives.[34]

■ ASSOCIATED CONTENT

Supporting Information

Text, figures, and tables giving the complete reference of Gaussian09 and results and discussion on Meinwald rearrangement reactions in the gas phase, as well as electronic and Gibbs free energies and Cartesian coordinates of all structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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