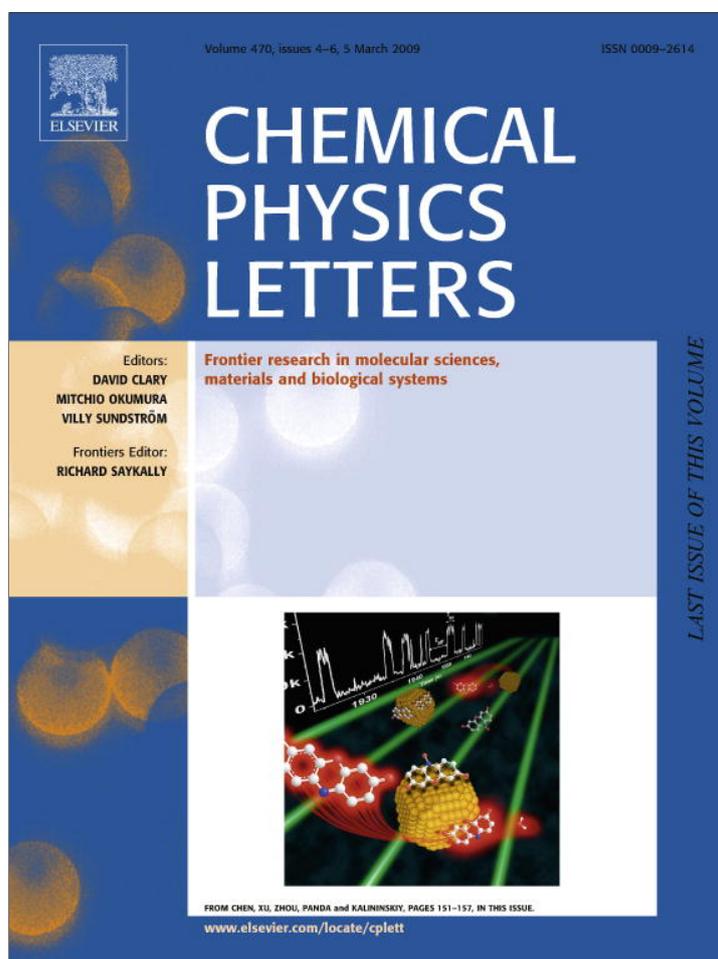


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Cooperative activation in ring-opening hydrolysis of epoxides by Co-salen complexes: A first principle study

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ABSTRACT

Density functional theory calculations were used to study the cooperative activations of the epoxide ring-opening hydrolysis catalyzed by the Co-salen complexes. We find that the activation energies of the reactions with two Co-salen catalysts are significantly lower than that of single catalyst. The cooperation effect comes not only from the simultaneous activation of both reactants but also from the cooperative charge transfer during the reactions. The transition states analysis indicates that the preferential reaction pathway is a S_N2 reaction, which explains the second order kinetic dependence on the concentration of the catalysts found in the experiments.

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1. Introduction

In catalytic organic synthesis, increasing evidences show that many reactions can be activated and/or promoted via the cooperative actions of the catalysts, which often leads to a higher activity [1,2]. The cooperation effects were attributed to the multicenters activation, and accordingly a series of multi-center and functional catalysts have been developed and applied in various organic synthesis reactions [3–6]. Though catalysts and corresponding synthesis procedures have been developed successfully, the details mechanistic understanding on the cooperative effects remains unclear. As a result, the utilization of the cooperation activations particularly in organic synthesis is hindered, and the microscopic mechanistic investigation on the cooperative activation is required.

It was found experimentally that the activity of the hydrolytic kinetic resolution of the epoxide ring-opening reaction on the Co-salen catalysts (Fig. 1) is enhanced significantly when the catalysts are prepared in form of the dimeric structures [7–10], polymer brushes [11] or spatially confined in nanocages [12]. Since the dimeric, polymer or spatial confined catalysts allow the reactants on the catalysts to meet more frequently, the origin of the enhanced activity is attributed unambiguously to the cooperative activation, and this system therefore provides an ideal model system for the cooperative activation mechanism study. We report here a detailed density functional theory (DFT) study on the epoxide (propylene oxide as the representative example, noted as PO) ring-opening hydrolysis catalyzed by the Co-salen complexes [13]. We find that the activation energies of PO ring-opening hydrolysis catalyzed by dual Co-salen complexes are significantly

lower than those of single Co-salen complex due to the cooperative activation of the C–O bond of the epoxide. Remaining of the Letter is organized as followed. Calculation methods are given in Section 2, and the main results are presented and discussed in Section 3, and followed by a brief summary finally.

2. Computational methods

All DFT calculations were performed with GAUSSIAN 03 program [14], and the exchange–correlation interaction were approximated by B3LYP [15–17]. The basis set of Dunning/Huzinaga valence double-zeta [18] were used for all atoms, except Co described by Los Alamos ECP plus MBS basis set [19–21]. Automated transition state (TS) searching based on synchronous transit-guided quasi-Newton methods was used to identify the TS [22], which are confirmed by the frequency analysis with one and only one imaginary frequency. After that, the reaction pathway was scanned using the intrinsic reaction coordinate (IRC) to make sure that the TS connects smoothly the reactants with the products [23,24]. During the structural optimizations, all atoms in the system are allowed to relax without any constraints.

The structure of Co-salen complex is shown schematically in Fig. 1, in which R_1 and R_2 represent the group of $C(CH_3)_3$, and X for Cl, I or OAc ($OCOCH_3$) [25]. The full Co-salen complex is considered except R_1 and R_2 are substituted by hydrogen atoms to save the computational costs. The X in the Co-salen complex is represented by Cl anion without the statement otherwise. PO, as one of the simplest asymmetric epoxide, is chosen as the prototype molecule for the epoxide ring-opening reactions. We note that high level quantum chemistry computation at CASPT3 is remained too expensive for exploring thoroughly the reaction pathways for the reaction perusing in the present study, where two full Co-salen

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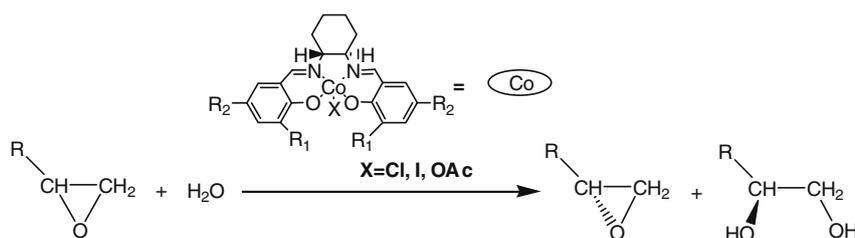


Fig. 1. Ring-opening hydrolysis reaction of the epoxides on the Co-salen catalysts.

complexes were considered explicitly. However, it was reported that the relative energetics from B3LYP (better than BP86 and BPW91) agrees generally with CASPT3 results [26,27]. On the other hand, our calculations show that the difference of the activation energy between single and dual catalysts (more than 60 kJ/mol) is significant larger than the possible error bar induced by B3LYP, which therefore has a little effect on the main conclusions of the present work. The accurate description of the activity on the different enantiomers, which is crucial to the chiral selectivity, requires higher level calculations. This is however not in the scope of the present work. Finally, it is noted that we do not consider the possible solvent effects in the present trend study.

The spin electronic states were examined carefully. Our calculations show that the ground state of the Co-salen complex is triplet with two unpaired electrons (multiplicity = 3), which is energetically favorable than that of the singlet (multiplicity = 1) by 12 kJ/mol and the quintet (multiplicity = 5) by 27 kJ/mol, respectively. After water or PO adsorption on the Co-salen complex (initial states) and the products (final states), the ground state of the adsorbed Co-salen complex is found to be the singlet, which is energetically favorable than the triplet state by about 30 kJ/mol. Accordingly, for the optimization of the transition states and activation energy calculations, only the singlet state calculations are considered and represented.

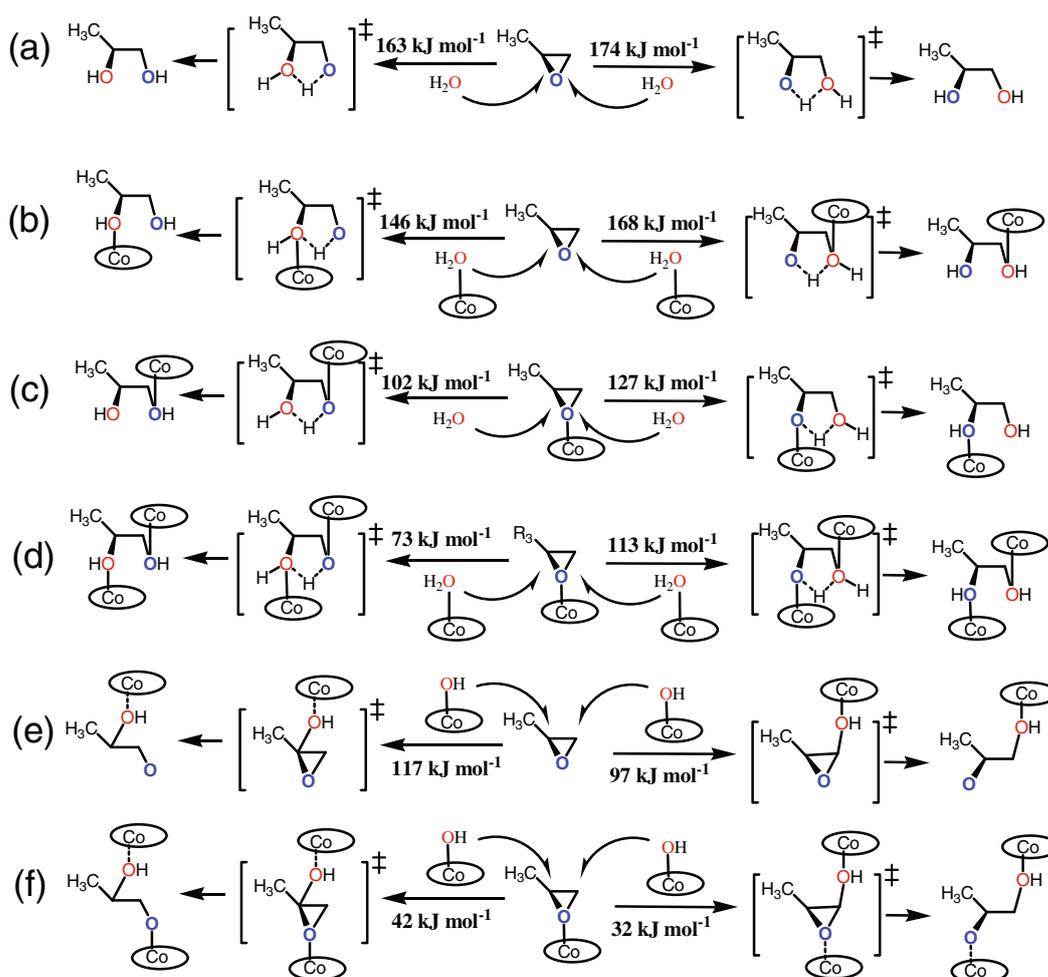


Fig. 2. Calculated reaction pathways for the PO ring-opening reactions and the corresponding reaction barriers: the reaction pathways between the PO molecules and the water without the complexes (a), one complex coordinated with water (b) and with PO (c), two complexes separately on two individual reactants (d). The reaction pathways between the (salen)Co–OH and the PO molecules without Co-salen complexes coordinated (e), and with one complex coordinated (f). The right part corresponds to the reaction pathways via the PO's primary carbon atoms, while the left part for the reaction pathways via the PO's secondary carbon atoms.

To gain further insights of the reactions, Mulliken charge analysis was carried out to study the variation of the charge transfer between Co-salen complexes and reactants from the initial states to the TSs. Compared to other methods, such as natural population analysis, electrostatic potential derived charge analysis and Merz–Kollman–Singh charge analysis, Mulliken charge analysis computes charges by dividing the orbital overlap evenly between the two atoms involved, which may be sensitive to how to define the boundary of atoms. However, the uncertainty becomes significantly smaller when the charge transfer between different groups or radicals are concerned. Indeed, these different methods give essentially the same results, as indicated in Ref. [28].

3. Results and discussion

The reaction pathways for PO ring-opening hydrolysis with water were investigated first. A number of possible reaction pathways were explored, and the main results are presented in Fig. 2a–d. The calculated activation energy of the reaction without Co-salen catalyst is 163 kJ/mol (left one in Fig. 2a). The barrier decreases to 146 kJ/mol and 102 kJ/mol when water and PO is activated separately by a Co-salen complex. This indicates that both reactants can be activated by the Co-salen complexes, and the activation effect is stronger on the PO molecules than the water molecules. More favorable reaction pathway can be visualized if both reactants are activated simultaneously by the individual Co-salen complexes (left part in Fig. 2d), as found by our calculations. Corresponding activation energy decreases dramatically to 73 kJ/mol.

From the above calculations, we can find that the water molecules prefer to react with the secondary carbon (left parts in Fig. 2a–d), and the corresponding activation energies are 10–40 kJ mol⁻¹ lowered than those of the primary carbon atoms (right parts in Fig. 2a–d). The preference of the reaction with the secondary carbon however disagrees with the fact of the preference on the primary carbon in the experiments [3,5]. Meanwhile, the experimental study [29] indicates that the epoxide ring-opening reaction proceeds via the nucleophilic (salen)Co–OH, and the ring-opening step is proposed to be the rate determining step. We therefore investigated the epoxide reaction with the (salen)Co–OH, and the identified reaction pathways are shown in Fig. 2e and f. In this context, we note that the (salen)Co–OH can be formed via the reaction between (salen)Co–OAc and activated

PO (coordinated with a salen complex), and the calculated activation energy is 44 kJ/mol. The small barrier indicates that the (salen)Co–OH can be generated easily. Once (salen)Co–OH is formed, it may react either with the PO molecules (unactivated) at barrier of 97 kJ/mol (right one in Fig. 2e), or with activated PO (coordinated with a Co-salen complex) at barrier of 32 kJ/mol (right one in Fig. 2f). After this, the final product diol is produced by a facile proton transferring, and (salen)Co–OH is regenerated to close the reaction cycle, as discussed in Ref. [29]. Calculated activation energies for the reaction pathways between the (salen)Co–OH and the primary carbon (right parts in Fig. 2e and f) are 10–20 kJ/mol lowered than those with the secondary carbon (left parts in Fig. 2e and f). This agrees well with the preference of attacking the primary carbon atoms found in the experiments [3,5], and confirm the epoxide ring-opening reaction via the nucleophilic (salen)Co–OH with the presence of the Co-salen complexes.

The variation of the calculated barriers can be rationalized by the change of the bond length of C–O in epoxide (initial state) to be broken, as plotted in Fig. 3. Compared to the isolated PO molecules, the bond length of C–O bond of PO coordinated with the Co-salen complex increases mainly due to the activation by the Co-salen complex. Additionally, the formation of the hydrogen bond between water/OH and PO molecules elongate the C–O bond further. As shown clearly in Fig. 3, the activation energies decrease with the increase of the C–O bond length of the PO molecules: the longer C–O bond, the easier broken. For the ring-opening reaction with water molecules, we find that the C–O bond length of the second carbon of PO (open square) is larger than that of the primary carbon, due to the electronic repulsion from the PO's CH₃ group. This indicates that the breaking of the secondary C–O bond is easier, as found indeed in our calculations. However, this does not hold true for the reaction pathway via (salen)Co–OH, where the longer secondary C–O bond (open triangle) corresponds to a higher activation energy than that of the shorter primary C–O bond (solid triangle). This comes from their distinct TSs during C–O bond breaking. For the later one, the (salen)Co–OH attacks the PO molecules from the backside of the epoxy oxygen accompanied by the inversion of the configuration. The influence of the steric hindrance becomes significant for the C–O bond breaking from the secondary carbon atom or the tertiary carbon atom because the presence of the extra alkyl groups.

Detailed analysis (Mulliken charge transfer) show that the cooperation activation comes from not only the individual activations on both reactants by the Co-salen catalysts but also the cooperative charge transfer during the reaction from the initial states to the TSs. For example, for the reaction between the nucleophilic (salen)Co–OH and the PO molecule (without Co-salen catalysts coordinated), there is overall 0.19 electron transferred from the (salen)Co–OH to the PO molecule (Fig. 4a). When the PO molecule is coordinated and activated by the Co-salen complex, most of the charge on the PO molecule transferred from the (salen)Co–OH at the TSs is transferred to the Co-salen complex coordinated with

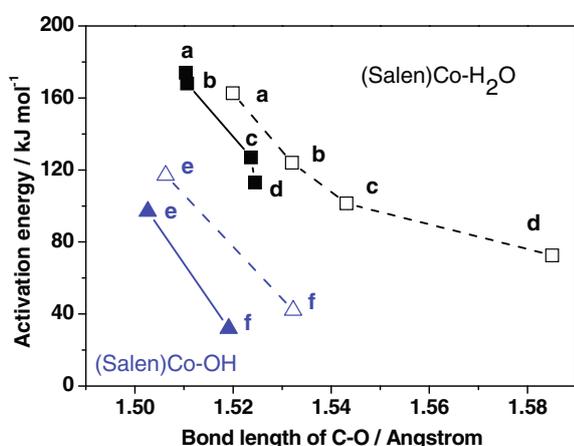


Fig. 3. The relationships between the activation energy and the bond length of PO's C–O bond to be broken at the initial states. The square (triangle) represents for the reaction via the Co-salen activated water (–OH), while the solid (open) symbol for the reaction via the primary (secondary) carbon. a–f represent for the different reaction pathways indicated in Fig. 2.

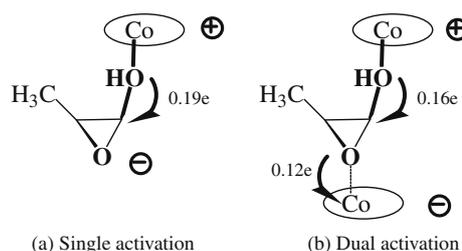


Fig. 4. Calculated Mulliken charge transfer during the reaction from the initial state to the transition state. The left (right) one corresponds the reaction between the (salen)Co–OH and the PO molecules without (with) Co-salen catalyst coordinated.

the PO molecule at another side, and the PO molecule is neutralized with overall 0.04 electrons only (Fig. 4b). The total energy of the system at the TSs is stabilized by the cooperative charge transferring, which lowers the reaction barriers, and the activity increases, correspondingly.

The significantly lower barriers for the PO ring-opening reaction with (salen)Co–OH (32 kJ/mol, right part in Fig. 2f) than the reaction with (salen)Co–H₂O (73 kJ/mol, left part in Fig. 2d) indicates that the previous reaction pathway is a kinetically favorable one, which would correspond to the ring-opening hydrolysis of epoxides catalyzed by the Co-salen complexes found in the experiments [5–12]. As a consequence, one Co-salen complex is responsible for the activation of the epoxide and another Co-salen complex is for the stabilization of the anionic nucleophile (OH[−]). The microscopic picture identified here supports strongly the mechanisms proposed by Nielsen et al. [29] and McClelland et al. [30] based on the structural and kinetic studies. This reaction process is similar to the normal base catalyzed hydrolysis, where OH[−] as nucleophile to attack PO from the backside. In normal base catalyzed hydrolysis, OH[−] is stabilized by water in the base environment. In Co-salen catalyzed epoxide hydrolysis reaction, OH[−] is stabilized by the Co-salen complex. As discussed in above, no H⁺ cation are produced continuously during the reaction, and the (salen)Co–OH is regenerated at the end of the reaction. Therefore, the whole reactions can proceed well in the neutral environment. In this context, we note that the OH[−] radicals is highly active: according to our calculations, the reaction barriers between the PO molecules and OH[−] radicals are almost barrierless. By varying the basicity of the medium, the activity can be changed. The higher activity results typically in the lower selectivity. Higher selectivity is more important for the reactions considered here (although not studied explicitly), where the Co-salen catalysts show reasonable activity.

For the preferential reaction pathway identified (right part in Fig. 2f), the (salen)Co–OH as the nucleophile attacks the PO's carbon (achiral) atom from the backside of the epoxy oxygen, which departs from the carbon atom simultaneously due to the repulsion from the nucleophile. At the TS, the carbon atom coordinates with both oxygen atom from nucleophilic OH and the epoxy oxygen atom of the epoxide to form a bipyramid structure (Fig. 5). In the

case of a chiral atom (for instance cycloalkene oxides) involved, the configuration inversion would be observed, as found in the experiment [7,31]. This shows that the corresponding reaction pathway is a substitution nucleophilic bimolecular (S_N2) reaction. As a S_N2 reaction, the PO ring-opening reaction would be a first order reaction with respect to the PO's concentration and a first order reaction to the nucleophile (OH) concentration. The overall reaction would be a second order reaction. Since both reactants are activated individually by a Co-salen complex, the PO ring-opening hydrolysis would show apparent the second order kinetics on the concentration of the catalysts, as observed in various epoxide ring-opening reactions [5,29,32]. The assignment of the epoxide ring-opening reaction as a S_N2 reaction accounts essentially the second order kinetic dependence on the concentration of the catalysts [7,12].

4. Conclusions

DFT calculations show that the PO ring-opening reaction on the Co-salen catalysts takes place mainly via the cooperative activations of individual reactants simultaneously by the separate catalysts. The present work provides a fundamental understanding of the origin of the cooperative effects in the catalytic reactions. According to the reaction mechanism identified, the PO ring-opening reaction takes place between the activated PO molecules and the nucleophilic (salen)Co–OH, and the reaction proceed as a S_N2 reaction. The nucleophile OH prefers to attack the primary achiral carbon atom of the epoxide, so the configuration inversion is not observed in the PO ring-opening reaction. Identification of the epoxide ring-opening reaction catalyzed by metal complexes as a S_N2 reaction may have wide implications on the study of the cooperative activations in the organic synthesis.

Acknowledgments

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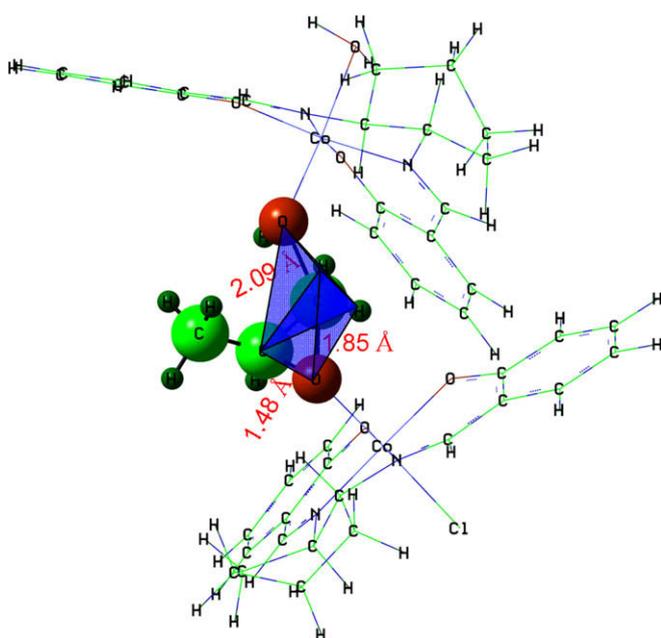


Fig. 5. The structure of the transition state for the preferential reaction pathway of the propylene oxide ring-opening reaction with the (salen)Co–OH.

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