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# Activation Parameters for Cyclohexene Oxygenation by an Oxoiron(IV) Porphyrin $\pi$-Cation Radical Complex: Entropy Control of an Allylic Hydroxylation Reaction

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Activation parameters for epoxidation and allylic hydroxylation reactions of cyclohexene with $Fe^{IV}O(TMP)^{\bullet+}Cl$ (**1**) were determined. Within the experimental temperature range, the epoxidation reaction was enthalpy-controlled (i.e., $\Delta H^{\ddagger} > -T\Delta S^{\ddagger}$), while the allylic hydroxylation reaction was entropy-controlled (i.e., $-T\Delta S^{\ddagger} > \Delta H^{\ddagger}$). An unexpectedly large contribution of the entropy term for the allylic hydroxylation reaction indicated that the free energy of activation, $\Delta G^{\ddagger}$, rather than the activation energy, $E_a$, should be used to discuss the reaction mechanism and chemoselectivity. The results of this study bring caution to previous density functional theory studies, in which the reaction mechanism and chemoselectivity are evaluated from calculated $E_a$.

Cytochromes P450 (P450) are very versatile catalysts, which activate molecular oxygen and catalyze hydrocarbon hydroxylation or alkene epoxidation with high stereoselectivity.[1,2] The reaction of P450 with cyclohexene yields a mixture of two major products: cyclohexene oxide (an epoxidation product) and 2-cyclohexen-1-ol (an allylic hydroxylation product).[3] Interestingly, the ratio of epoxidation to allylic hydroxylation products, i.e., the chemoselectivity, is changed by P450 isozymes and by mutation of a single amino acid near the proximal or distal side.[3] In addition, P450 model studies using synthetic iron porphyrin complexes showed that the chemoselectivity depends on various other factors, such as the nature of the porphyrin and axial ligands, solvents, and reaction temperature.[4−7] While these enzymatic and model studies suggest that chemoselectivity is dependent on the electronic structure of the reactive intermediate, oxoiron(IV) porphyrin $\pi$-cation radical species (compound **I**), it is not clear how compound **I** controls chemoselectivity. Recently, the reaction mechanism and chemoselectivity of P450 have been studied by theoretical calculations based on density functional theory (DFT).[8] In DFT studies, the reaction mechanism and chemoselectivity are predicted from the calculated activation energy, $E_a$, for epoxidation and allylic hydroxylation reactions of oxoiron(IV) porphyrin $\pi$-cation radical species. These studies are based on the assumption that the contribution of the entropy of activation, $\Delta S^{\ddagger}$, is much smaller than that of the enthalpy of activation, $\Delta H^{\ddagger}$. However, the validity of this assumption remains unproven because the activation parameters for epoxidation and allylic hydroxylation reactions of compound **I** species are yet to be determined. To better understand epoxidation and allylic hydroxylation reactions, the present study ascertained the activation parameters for epoxidation and allylic hydroxylation reactions of cyclohexene with compound **I** species,

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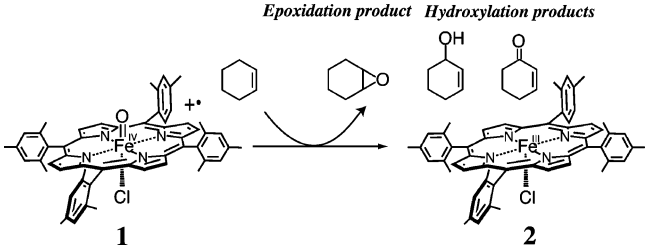


**Figure 1.** Epoxidation vs allylic C−H hydroxylation reactions of cyclohexene by **1**.

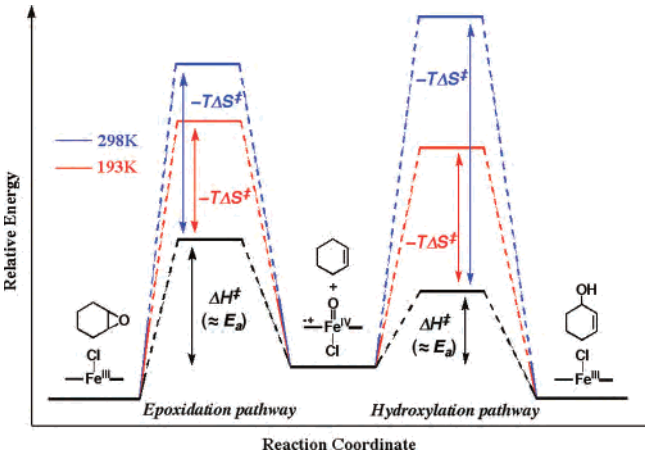


**Figure 2.** Diagram for cyclohexene oxygenation by **1**. The black lines show energy profiles with $E_a(\Delta H^{\ddagger})$. The red and blue lines show energy profiles with $\Delta G^{\ddagger}$ ($\Delta H^{\ddagger} - T\Delta S^{\ddagger}$) at 193 and 298 K, respectively.

$Fe^{IV}O(TMP)^{\bullet+}Cl$ (**1**;[9] Figure 1). This study demonstrated that epoxidation is an enthalpy-controlled reaction, while allylic hydroxylation is an entropy-controlled reaction. The large contribution of the entropy term, $-T\Delta S^{\ddagger}$, to the free energy of activation, $\Delta G^{\ddagger}$, indicated that $\Delta G^{\ddagger}$, rather than $E_a$, should be used to predict reaction mechanisms and chemoselectivity.

The absorption spectrum of **1**, which was prepared by ozone oxidation of $Fe^{III}$(TMP)Cl (**2**) in $CH_2Cl_2$,[10] was changed to that of **2** with clear isosbestic points upon the addition of cyclohexene (Figure S1 in the Supporting Information). The clear isosbestic points indicated the absence of the accumulation of any reaction intermediate; moreover, the formation of the first transition state was the rate-limiting step for both the epoxidation and allylic hydroxylation reactions of cyclohexene oxygenation by **1**. Therefore, the activation parameters estimated in this study correspond to those of the rate-limiting steps.

The $E_a$ values for the epoxidation and allylic hydroxylation reactions of cyclohexene, estimated from an Arrhenius plot over temperatures ranging from 193 to 233 K (Figure S3 in the Supporting Information), were found to be 35.4 ± 1.7 and 20.9 ± 2.4 kJ $mol^{-1}$, respectively. Interestingly, the $E_a$ value for the epoxidation reaction was about 2-fold greater than that for the allylic hydroxylation reaction (Figure 2). This result is an inconsistency with DFT calculations for propene oxygenation, which predicted that $E_a$ for the epoxidation reaction was less than that for the allylic hydroxylation reaction.[8] According to previous DFT studies using $E_a$ values, the result of the present study, shown in Figure 2, leads to the conclusion that allylic hydroxylation is more favorable than epoxidation. However, this conclusion is erroneous because epoxidation is favored over allylic hydroxylation at room temperature.[4c]

To further analyze the cyclohexene oxygenation reaction, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values were estimated from an Eyring plot over temperatures ranging from 193 to 233 K (Figure S4 in the Supporting Information). The $\Delta H^{\ddagger}$ values for epoxidation and allylic hydroxylation reactions were estimated to be 33.6 ± 1.7 and 19.2 ± 2.4 kJ $mol^{-1}$, and the $\Delta S^{\ddagger}$ values were estimated to be −101.2 ± 6.7 and −169.1 ± 9.0 J $K^{-1}$ $mol^{-1}$, respectively. As expected from the equation $\Delta H^{\ddagger} = E_a - RT$,[11] the $\Delta H^{\ddagger}$ values were similar to the $E_a$ values. In contrast, the $\Delta S^{\ddagger}$ values for both the epoxidation and allylic hydroxylation reactions were large negative values, and the $\Delta S^{\ddagger}$ value for the allylic hydroxylation reaction was about 2-fold greater than that of the epoxidation reaction. The $\Delta S^{\ddagger}$ value for the epoxidation reaction was reasonable for a typical bimolecular reaction. However, the $\Delta S^{\ddagger}$ value for the allylic hydroxylation reaction was larger than that of a typical bimolecular reaction, approaching $\Delta S^{\ddagger}$ values observed for bimolecular reactions with a high degree of order in the transition state, such as the Diels−Alder reaction.[12]

The contribution of the entropy term, $-T\Delta S^{\ddagger}$, to the epoxidation and allylic hydroxylation reactions was unexpectedly large. $-T\Delta S^{\ddagger}$ became greater than $\Delta H^{\ddagger}$ at temperatures exceeding 114 K for allylic hydroxylation and 334 K for epoxidation. Within the experimental temperature range, for the allylic hydroxylation reaction, $-T\Delta S^{\ddagger}$ was approximately 2-fold greater than $\Delta H^{\ddagger}$ (entropy control). In contrast, the epoxidation reaction was enthalpy-controlled, but $-T\Delta S^{\ddagger}$ was comparable to $\Delta H^{\ddagger}$ at room temperature (Figure 3). Entropy-controlled reactions are uncommon but have been reported for hydrogen abstraction by a *tert*-butoxyl radical and rhodium(II) porphyrin (Figure 3).[12−14a]

In previous experimental and DFT studies, the reaction mechanism and chemoselectivity were discussed based on $E_a$ values.[7,8] These studies assume that, for the epoxidation and allylic hydroxylation reactions, $-T\Delta S^{\ddagger}$ values are much smaller than $\Delta H^{\ddagger}$ values, indicating enthalpy control. However, the results of the current study bring the results of these previous studies into question. The large contribution of the entropy term to both the epoxidation and allylic hydroxylation reactions indicates that the free energy of activation,

(9) $Fe^{III}$(TMP)Cl: chloroiron(III) *meso*-tetramesitylporphyrin. $Fe^{IV}O(TMP)^{\bullet+}$-Cl: chlorooxoiron(IV) *meso*-tetramesitylporphyrin π-cation radical.

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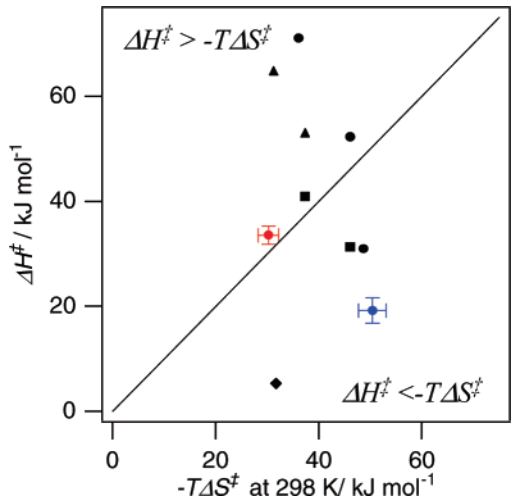


**Figure 3.** Plot of $\Delta H^{\ddagger}$ vs $-T\Delta S^{\ddagger}$ at 298 K for epoxidation (red circle) and allylic hydroxylation (blue circle) of cyclohexene oxygenation by **1** and for other related reactions. Black circles: Diels−Alder reactions.[12] Black diamond: *tert*-butoxyl radical and triphenylmethane.[13] Black squares: rhodium porphyrins and methane.[14] Black triangles: $KMnO_4$ or $CrO_2Cl_2$ and toluene.[15]

$\Delta G^{\ddagger}$, rather than $E_a$, should be used to discuss the reaction mechanism and chemoselectivity. In fact, temperature affected chemoselectivity of cyclohexene oxygenation: at 233 K, the major product of cyclohexene oxygenation by **1** was cyclohexene oxide, while at 193 K, it was 2-cyclohexen-1-ol (Table S1 in the Supporting Information). This temperature dependence of chemoselectivity cannot be explained by $E_a$ but only by $\Delta G^{\ddagger}$ because $E_a$ is independent of the temperature. The observed temperature effect on chemoselectivity of cyclohexene can be seen with $\Delta G^{\ddagger}$, as shown in Figure 2. Furthermore, reaction mechanisms also can be predicted by $\Delta G^{\ddagger}$ but not by $E_a$. In previous DFT studies, reaction mechanisms were predicted from $E_a$ values of possible reaction pathways. However, because of the large contribution of $-T\Delta S^{\ddagger}$, the reaction pathway having a higher $E_a$ value may be favored over a pathway with a lower $E_a$.

The difference in $\Delta S^{\ddagger}$ values between epoxidation and allylic hydroxylation was reasonable because the reactions proceed via independent pathways with different transition states.[4c] The large negative $\Delta S^{\ddagger}$ value for the allylic hydroxylation reaction suggested a highly ordered transition state, indicating that allylic hydroxylation occurs only when **1** and cyclohexene interact at a specific orientation. Allylic hydroxylation demonstrated a drastic kinetic isotope effect (Table S2 in the Supporting Information), suggesting involvement of C−H bond breakage in the transition state. Bond formation (orbital overlapping) between the oxo ligand of **1** and the allylic hydrogen may result in a highly ordered transition state for the allylic hydroxylation reaction, as indicated by the large negative $\Delta S^{\ddagger}$ value. In contrast, the $\Delta S^{\ddagger}$ value for the epoxidation reaction was typical for a bimolecular reaction. Furthermore, the epoxidation reaction did not show a kinetic isotope effect (Table S2 in the Supporting Information). The epoxidation transition state does not involve interaction of **1** with the C−H moiety of cyclohexene, and a complex with weak interactions, such as the charge-transfer complex, may form.

In summary, this study determined the activation parameters for cyclohexene oxygenation by **1**. Chemoselectivity of cyclohexene oxygenation by **1** was not controlled by the $E_a$ value but by the $\Delta S^{\ddagger}$ value, suggesting that previous DFT studies should be interpreted with caution. Additional studies investigating the porphyrin and axial ligand effects on activation parameters are being conducted using synthetic iron porphyrin complexes and heme enzymes by this research group.

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**Supporting Information Available:** Text containing experimental details for product analysis and kinetic analysis, Figures S1−S4, and Tables S1 and S2 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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