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(Salen)Mn-Catalyzed Epoxidation of Alkenes: A Two-Zone Process with Different Spin-State Channels as Suggested by DFT Study

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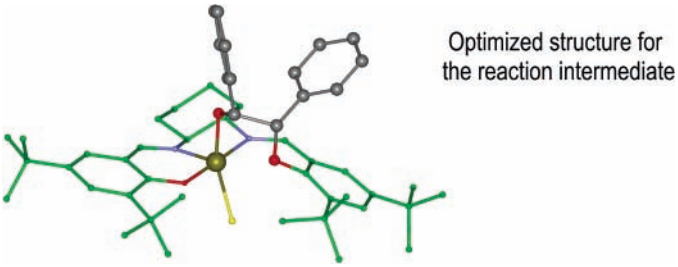
ABSTRACT



A novel (two-zone process with different spin-state channels) mechanistic picture for the Jacobsen–Katsuki reaction is presented that provides insight into the still elusive understanding of the epoxidation mechanism. For the first time, we show that the salen moiety of the catalyst can be explicitly involved in the epoxidation process.

Understanding the mechanism of the Jacobsen−Katsuki epoxidation reaction is of great interest from both a practical and a fundamental point of view. The ability of chiral (salen)-Mn complexes to catalyze enantioselective epoxidation of unsaturated alkenes is widely used in organic synthesis.[1] The detailed knowledge of the oxygen transfer mechanism by (salen)Mn synthetic mimics of enzymes is important for a better understanding of the biochemical processes involving the oxomanganese species.[2] Yet, despite extensive recent experimental[3] and theoretical investigations,[4] the Jacobsen−Katsuki epoxidation mechanism is still controversial.[5] This stimulates ongoing mechanistic studies and has recently led to the important finding that the epoxidation reaction is a multichannel process with different spin states and the possible crossing of potential energy surfaces.[4a,c,d] Spin-crossing effects have been shown to be critical for understanding many inorganic, organometallic, and bioinorganic reactions.[6] Though the importance of the consideration of

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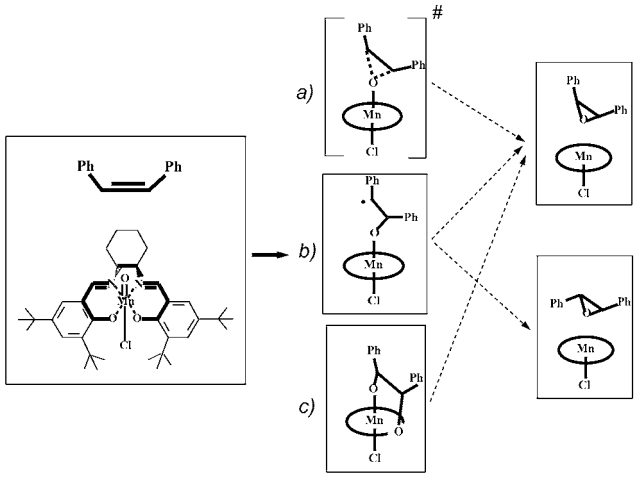
the Jacobsen−Katsuki reaction as a spin-forbidden process is indisputable, the results of the recent theoretical works [4a,d] that investigated the various spin reaction channels suggest different mechanistic pictures.

Linde et al.[4a] concluded that there is no radical intermediate on the quintet reaction pathway for the cationic model of the (salen)Mn catalyst. This precludes any cis/trans isomerization of the alkene and makes the quintet channel responsible for the diastereoselective epoxidation. However, contrary to this work, we and others were able to locate an intermediate on the quintet reaction pathway, first, for the neutral catalytic compound[4c,d] and, quite recently, for the cationic model as well.[7] Thus, the suggested "quintet" mechanism seems to be unlikely for this catalytic reaction. According to our proposed mechanistic scheme,[4d] it is the competition between the singlet and the triplet channels that influences the isomer ratio of the reaction product. The high activation barrier for the singlet concerted path, however, makes the approach vulnerable to criticism. In this communication, we report a new mechanistic scheme in the framework of our two competing channels approach with the energetically low-lying singlet channel. Three reaction

Scheme 1



mechanisms have been calculated (Scheme 1) using density functional theory.[8a,b] The concerted and the stepwise radical mechanisms (**a** and **b**) were already discussed in the literature.[3a−c,4a,c,d] The third mechanism with the five-member ring (FMR) intermediate (**c**), to our knowledge, has not been under consideration either for (salen)metal compounds or for the related porphyrin species. The unique feature of the proposed intermediate is a covalentlike bond that is created between the carbon atom of the substrate and the oxygen atom of the salen framework. We checked the feasibility of docking a bulky substrate to the catalyst and of formation of FMR intermediates by using in our DFT calculations the "real" substrate (*cis*-Stilbene) and the catalyst compound usually referred to as "Jacobsen's catalyst" (Scheme 1), instead of restricted models for the reactive species. The FMR intermediates were successfully optimized for the singlet, the triplet, and the quintet states, proving that the catalyst can accommodate the bulky substrate with the C−C bond roughly parallel to the plane. The corresponding optimized structure for the singlet FMR intermediate is shown in the abstract graphic (the qualitative pictures for the triplet and quintet intermediates are the same). We further calculated the reaction profiles for all three considered mechanisms (Figure 1). To make our investigation computationally feasible, a smaller model of the catalyst was used as shown in bold in Scheme 1.

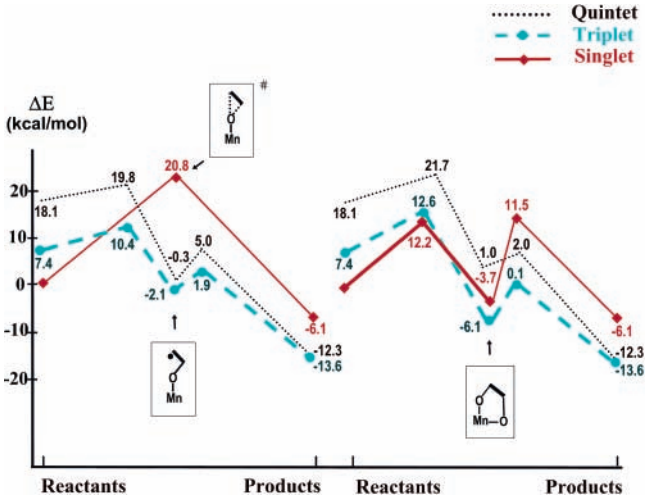


Figure 1. Competing channels of the Jacobsen−Katsuki reaction studied in this work. The singlet reaction pathways are shown in red, the triplet in blue, and the quintet in black. The left side profiles correspond to the stepwise radical and the concerted mechanisms as indicated. The right side drawings represent the profiles for the five-member ring intermediate mechanism. Feasible channels (the triplet for the TR mechanism and the triplet and the first part of the singlet channel for the FMR mechanism) are shown in bold.

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(8) (a) Becke−Perdue (BP) DFT approximation was used: Becke, A. D. *Phys. Rev.* **1988**, *A38*, 3098. Perdew, J. P. *Phys. Rev.* **1986**, *B33*, 8822. The Jaguar program with LACVP* basis (Jaguar 4.1; Schroedinger, Inc.: Portland, OR, 2000) was utilized for calculations that involved the complete model of the reaction: Jacobsen's catalyst plus the *cis*-Stilbene as the substrate. The Dgauss program (UniChem V4.0; Oxford Molecular: Oxford, UK) with DZVP basis was used to study the reaction profiles with the smaller model (see the text). (b) Using high level ab initio calculations (CCSD(T)), we recently showed (ref 4d) that the BP functional gives a realistic description of the relationship between the different spin channels involved in the studied reaction and is suitable for the reaction modeling. In contrast, using the B3LYP approach in this particular catalytic system case results in a distorted picture of the spin-state order. It was also pointed out that BP functional results may need some (likely, small) corrections since, on the product side of the reaction, the triplet and the quintet states are almost degenerated, although the quintet is known to be the resting state.

Several conclusions can be made from the presented profiles. First, the quintet reaction channel profiles for both the radical and the FMR paths reassemble the profiles of the corresponding triplet paths. The quintet surfaces also lie higher than the triplet ones almost all the way along the reaction coordinate, becoming energetically comparable with the triplet surfaces on the product side. Overall, our and others' results[7] suggest that the quintet channels are unlikely to play a special role in the considered reaction. Second, among the two mechanisms for the ground singlet state, the FMR intermediate mechanism needs significantly smaller activation energy than the concerted mechanism (12 kcal/mol versus almost 21 kcal/mol), indicating that only the first is feasible. For the FMR mechanism, the reaction starts in the singlet ground state. The spin changes for the triplet somewhere on the reaction path after the first transition state (TS) in the vicinity of the intermediate. Thus, there are only two channels, the triplet radical (TR) intermediate and the singlet−triplet FMR intermediate, that can compete with each other in the epoxidation process. Two-state reactivity has been shown previously to be of importance in other metal-catalyzed epoxidation processes.[6c−e] It should be noted that the practically coinciding activation energies for the TR and the FMR channels, 10.4 and 12.2 kcal/mol, respectively, and the low barriers for collapsing to the products, 4.0 and 6.2 kcal/mol, respectively, are the only common features for these reaction paths. The different nature of the corresponding intermediates, **2** and **4** (Figure 2), makes these channels

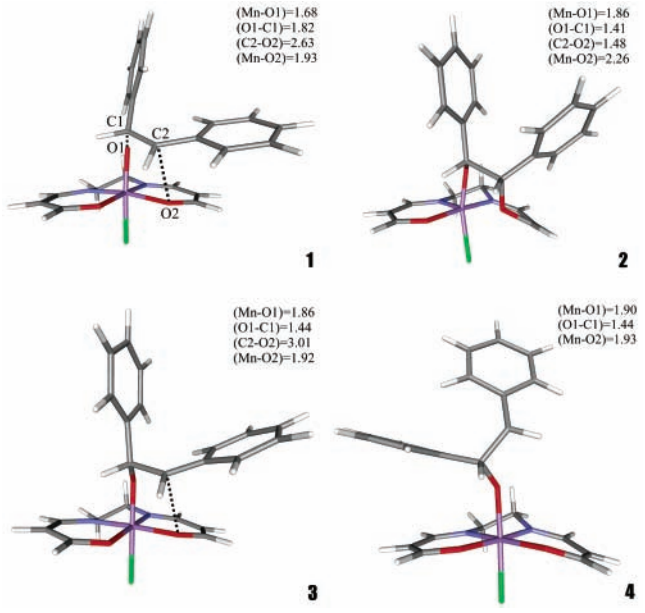

Figure 2. Optimized structures for some selected reaction critical points: TS1 structure **1** leading to the FMR intermediate **2**, TS2 structure **3** corresponding to the closing of the epoxide ring with simultaneous breaking of the temporary C2−O2 bond, and the triplet radical intermediate structure **4**.

qualitatively distinguished. The TR intermediate **4**, with unpaired electrons to be delocalized with one of them situated on the metal of the catalyst and another on the C2 atom of the substrate,[4d] allows rotation around the C1−C2 bond. This leads to the mixture of cis and trans species in the reaction products (Scheme 1) with the equilibrium shifted toward trans products.[3f] The FMR intermediate **2**, being attached to the oxidizing oxygen and the salen framework, lacks any opportunity for changing the stereo conformation of the substrate and collapses (TS2, **3**) to the products with an exclusively cis conformation. It is intriguing to speculate that chemical substitutions in the catalyst or in the substrate could lead to relative stabilization of one of the two channels and to the corresponding changes in cis/trans partitioning of the products. Indeed, our preliminary calculations[9] suggest that by using this approach it is possible to consistently explain experimental observations, including effects of substitution of the axial ligand[3e] and effects of electron-donating/electron-withdrawing substituents on the catalyst.[3c]

It is interesting to note that the reaction occurs in two different zones of the catalyst. In the case of the TR mechanism, the substrate interacts directly only with the oxidizing atom O1 and is situated in a "pop-up" position with respect to the catalyst plane, **4**. In contrast, the FMR intermediate forms bonds not only with O1 but also with the O2 atom of the salen moiety. That makes the reaction proceed in the close vicinity of the catalyst plane. All previously proposed mechanisms, including TR, are based on the assumption that the oxidizing oxygen and Mn are the only atoms directly involved in the chemical reaction. The role of the salen frame is assumed to be "auxiliary": to keep the proper oxidation state of the metal, to stabilize the catalyst as a chemical compound and to govern the stereo interaction between the catalyst and the substrate. For the first time, we show that the salen moiety of the catalyst can be explicitly involved in the epoxidation process. This observation may lead to evolution of our understanding of how to construct and modify the catalytic complexes capable of epoxidizing alkenes in a desirable fashion.[10]

Overall, the reaction proceeds on at least two different spin surfaces and spin-crossing effects could affect the reaction rate and many other properties,[6b,f] including diastereoselectivity.[6e] The reaction starts in the singlet ground state. The singlet state is concerted, and the TR processes occur in the "pop-up" position with, respectively, late and early TSs (R(C1−O1) = 1.55 and 2.06 Å).[4d] Because of the high concerted TS barrier, the reaction cannot proceed on the singlet spin surface and a spin change for the triplet should occur (likely at the vicinity of the early TS) to continue the reaction. The probability of the singlet−triplet spin changing for the FMR mechanism in the vicinity of the intermediate determines the lifetime of this intermediate

(9) Results will be published.

(10) Both TR and FMR channels should be considered to get an accurate quantitative estimation of the reaction characteristics. The recent theoretical study (Jacobsen, H.; Cavallo, L. *Chem. Eur. J.* **2001**, *7*, 800−806), which managed to qualitatively explain the reaction enantiomeric excess using direct attack on the oxygen only, may indicate that both channels have the same stereoselectivity-determining step with branching after that step to reach the different catalytic zones. Our modeling does not contradict that picture, since TR and FMR reaction critical point structures can be easily qualitatively superimposed by rotation around the C1−O1 bond.

because the ring closing is much faster on the triplet surface than on the singlet (TS barriers −6.2 and 15.2 kcal/mol, respectively). In contrast to the Cr−salen reaction,[6e] however, the lifetime of the intermediate does not influence the diastereoselectivity of the Mn−salen reaction since the nature of the FMR intermediate does not allow any izomerization.

In conclusion, we present an unprecedented (two-zone process with different spin-state channels) mechanistic picture for the Jacobsen−Katsuki reaction that provides insight into the still elusive understanding of the epoxidation mechanism. In the framework of this mechanism scheme, we report a new reaction pathway that starts in the ground singlet state, has a low activation barrier, and is responsible for the formation of *cis*-epoxide products with a high enantiomeric excess. Competition between this channel and the triplet radical one determines the cis/trans partitioning of product formation. It can be changed by substitutions in the substrate and/or in the catalyst. The first applications of such an approach for interpretation of the experimental data are encouraging and are in progress now.

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