

(Salen)Mn(III)-Catalyzed Epoxidation Reaction as a Multichannel Process with Different Spin States. Electronic Tuning of Asymmetric Catalysis: A Theoretical Study

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The (salen)Mn(III)-catalyzed epoxidation reaction mechanism has been investigated using density functional theory (DFT). There is considerable interest in and controversy over the mechanism of this reaction. The results of experimental studies have offered some support for three different reaction mechanisms: concerted, stepwise radical, and metallooxetane mediated. In this paper, a theoretical examination of the reaction suggests a novel mechanism that describes the reaction as a multichannel process combining both concerted and stepwise radical pathways. The competing channels have different spin states: the singlet, the triplet, and the quintet. The singlet reaction pathway corresponds to a concerted mechanism and leads exclusively to a cis epoxide product. In contrast, the triplet and quintet reactions follow a stepwise mechanism and lead to a product mixture of cis and trans epoxides. We show that the experimentally observed dependence of isomer product ratios on electronic effects connected with the substitution of the catalyst ligands is due to changing the relative position and, hence, the relative activities of the channels with different cis–trans yields. Because the results and conclusions of the present work dramatically differ from the results and conclusion of the recent DFT theoretical investigation (Linde, C.; Akermark, B.; Norrby, P.-O.; Svensson, M. *J. Am. Chem. Soc.* **1999**, *121*, 5083.), we studied possible sources for the deep contradictions between the two works. The choice of the DFT functional and a model has been shown to be crucial for accurate results. Using high level ab initio calculations (coupled cluster-CCSD(T)), we show that the computational procedure employed in this study generates significantly more reliable numerical results. It is also shown that the smaller cationic model without a chlorine ligand that was used by Linde et al. is too oversimplified with respect to our larger neutral model. For this reason, using the cationic model led to a qualitatively wrong quintet reaction profile that played a key role in theoretical postulates in the earlier work.

Introduction

During the past decade, several methods of controlling the product specificity during epoxidation of unfunctionalized olefins have been developed.¹ One of the most important is the Jacobsen–Katsuki epoxidation. In these reactions, high enantiomeric excesses can be achieved, leading to several experimental studies to elucidate the reaction mechanisms and to discover the origin of the remarkable selectivity.²

It might be assumed that the electronic structure of the catalyst affects the mechanism of oxygen transfer and catalytic effectiveness of the reaction, while steric interactions between the catalyst and substrate are responsible for chiral induction. Neither aspect of such a simplified scheme has been fully understood, despite a number of experimental studies. Indeed, the results of experimental studies have offered some support for three different reaction mechanisms: concerted,³ stepwise radical,⁴ and metallooxetane mediated.⁵ This has led to conflicting views of the oxygen transfer process. The recent controversy

over the mechanism of the Jacobsen–Katsuki epoxidation makes this reaction a very attractive target for theoretical investigation.⁶ The process becomes even more puzzling in light of experimental data which suggest that isomer product distribution in the (salen)Mn-catalyzed asymmetric epoxidation reaction correlates directly with the electronic properties of the ligand substituents.⁷ Thus, it turns out that local processes on the metal active site result in both catalytic activity and isomer product ratios.

In this paper, a theoretical examination of the reaction suggests a novel mechanism that is consistent with major experimental observations. We describe the reaction as a multichannel process combining both concerted and stepwise radical pathways (Figure 1). In the framework of the proposed mechanism, it is possible to explain both the catalytic activity and the influence of electronic effects on enantioselectivity in the (salen)Mn-catalyzed epoxidation reaction.

- (1) (a) In *Comprehensive Organometallic Chemistry* II.; Wilkinson, G., Stone, F. G. A., Abel, E. W., Hegedus, L. S., Eds.; Pergamon: New York, 1995; Vol. 12, Chapter 11.1, pp 159–202. (b) Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189–214.
- (2) (a) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*, 1st ed.; Ojima, I., Ed.; VCH: New York, 1993; pp 159–202. (b) Jacobsen, E. N.; Finney, N. S. *Chem. Biol.* **1994**, *1*, 85. (c) Katsuki, T. *J. Mol. Catal. A: Chem.* **1996**, *113*, 87. (d) Dalton, C. T.; Rayn, K. M.; Wall, V. M.; Bousquet, C.; Gilheany, D. G. *Top. Catal.* **1998**, *5*, 75.
- (3) (a) Fu, H.; Look, G. C.; Zhang, W.; Jacobsen, E. N.; Wong, C.-H. *J. Org. Chem.* **1991**, *56*, 6497.

- (4) (a) Srinivasan, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309. (b) Finney, N. S.; Pospisil, P. J.; Chang, S.; Palucki, M.; Kinsler, R. G.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1720. (c) Linker, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2060.
- (5) (a) Norrby, P.-O.; Linde, C.; Akermark, B. *J. Am. Chem. Soc.* **1995**, *117*, 11035. (b) Hamada, T.; Fukuda, T.; Imanishi, H.; Katsuki, T. *Tetrahedron* **1996**, *52*, 515. (c) Linde, C.; Arnold, M.; Norrby, P.-O.; Akermark, B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1723.
- (6) (a) Cavallo, L.; Jacobsen, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 589. (b) Strassner, T.; Houk, K. N. *Org. Lett.* **1999**, *1*, 419.
- (7) Palucki, M.; Finney, N. S.; Pospisil, P. J.; Guler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 948 and references therein.

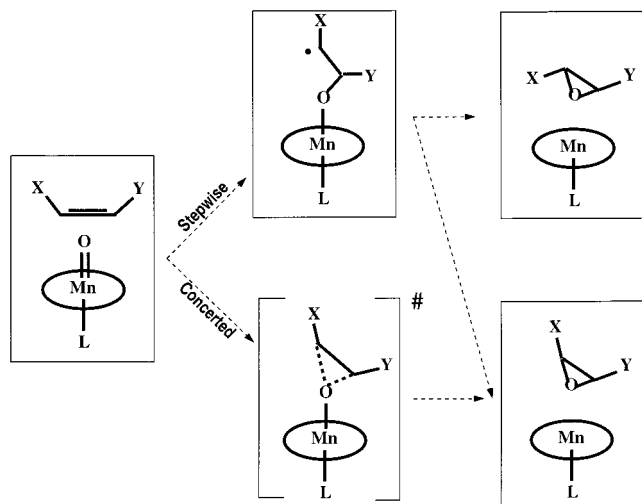


Figure 1. Schematic representation of the stepwise radical and concerted pathways.

At the same time that these calculations were being performed, Linde et al.⁸ used slightly different computational procedures to attempt to explain the experimental observation. This interesting theoretical study also emphasized the importance of various spin reaction pathways in the course of the reaction. Although in both works density functional theory (DFT) was used, and the chosen models look similar, the quantitative results are significantly different and produce qualitatively different pictures of the reaction.

In an attempt to resolve the deep contradictions between the two theoretical studies, we have performed a thorough comparative analysis of the methodologies used in both works. Two widely used DFT approximations have been applied to the study of the (salen)Mn(III)-catalyzed epoxidation reaction. Linde et al.⁸ performed their calculations in the framework of the hybrid density functional approximation B3LYP. We employed a generalized gradient approximation method with a Becke-Perdew (BP) exchange-correlation functional. Our model for salen uses bis(acetylacetonate) ethylenediamine (BAE) with the methyl groups removed⁹ (Figure 2a). Both salen and BAE have been used as model compounds for vitamin B12 and have shown similar properties.¹⁰ Our calculations are the first to use a neutral model of a Mn-oxo-salen complex with ethylene; Linde et al. used a simplified, cationic model without the chlorine ligand (Figure 2b).

The next section describes the theoretical methods used in this investigation and is followed by a discussion of the results. Possible sources of the differences between the theoretical study of Linde et al.⁸ and the results presented here (including differences in basis sets, density functionals, and salen models) are examined in this section. By comparing these calculational results with high level ab initio calculations and experimental observations, we show that the computational procedure employed in this study generates significantly more reliable results. Finally, we discuss our findings and show how they can be used to understand the electronic tuning of the asymmetric epoxidation reaction catalyzed by the (salen)Mn(III).

Method

Our investigation can be divided in two parts. The first part is the study of different reaction pathways for the neutral model depicted in

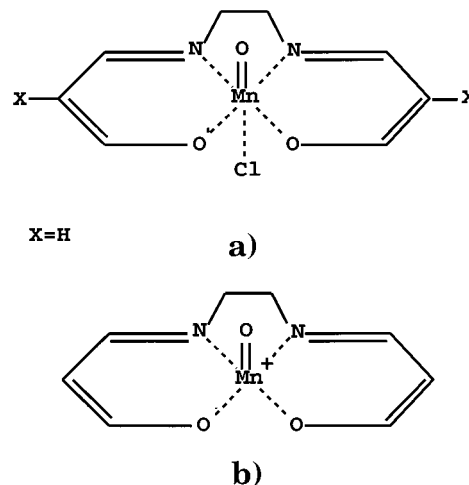


Figure 2. Models of the (salen)Mn catalysts used in the theoretical studies: (a) the neutral model (the present work); (b) the cationic model (Linde et al.⁸).

Figure 2a. The following methodological approach was used during this stage. All DFT calculations of the different reaction pathways were carried out using the DGauss program¹¹ as implemented in UniChem 4.0.¹² The calculations were performed using the DZVP basis sets, which are (621/41/1) for carbon, oxygen, and nitrogen atoms, (41) for hydrogen atoms, and (6321/411/1) for the manganese atom.^{13,14} The nonlocal corrections using the Becke exchange¹⁵ and Perdew correlation¹⁶ potentials have been obtained starting from the Vosko, Wilk, and Nuisair local potential.¹⁷ The convergence of geometry optimization is less than 0.001 hartree/bohr for the largest Cartesian energy gradient component. For every stationary point, an analytical Hessian matrix¹⁸ was calculated to prove the nature of the optimized structure. All open-shell calculations were performed using unrestricted Hartree-Fock (UHF) formalism.

In the second part of our work, where the reliability of the theoretical approximations and the models are examined, several other methods and basis sets are employed, in addition to BP DFT with the DZVP basis set. The B3LYP hybrid density functional method¹⁹ is used for comparative analysis with the BP DFT approach. The relative energy positions of the singlet, triplet, and quintet states have been tested using the coupled cluster method, which includes single, double,²⁰ and perturbatively connected triple excitations (CCSD(T)).²¹ Both B3LYP and CCSD(T) are used as implemented in the Gaussian 98 program.²² CCSD(T) calculations are done using two levels of approximation for the active orbital space. The frozen core orbital approximation (CCSD(T)_fc) corresponds to the standard option of the Gaussian program and excludes 1s orbitals of the second row atoms; 1s, 2s, and 2p orbitals of the chlorine atom; and 1s, 2s, 2p, 3s, and 3p orbitals of the manganese atom from the active orbital space. Our second approximation uses almost a full active orbital set (CCSD(T)_fu); only six very low-lying orbitals of the manganese atom (1s,2s,2p,3s) and the six highest energy

- (10) Hay, R. W. *Bio-inorganic Chemistry*; Ellis Horwood Limited: Chichester, U.K., 1984; pp 157-161.
- (11) Andzelm, J.; Wimmer, E. *J. Chem. Phys.* **1992**, *96*, 1280.
- (12) *UniChem*, V4.0; Oxford Molecular: Medawar Center, Oxford Science Park, Oxford OX4 4GA, U.K.
- (13) Sosa, C.; Andzelm, J.; Elkin, B. C.; Wimmer, E.; Dobbs, K. D.; Dixon, D. A.; *J. Phys. Chem.* **1992**, *96*, 6630.
- (14) Godbout, N.; Salahub, D. R.; Andzelm, J.; Wimmer, E. *Can. J. Chem.* **1992**, *70*, 560.
- (15) Becke, A. D. *Phys. Rev.* **1988**, *A38*, 3098.
- (16) Perdew, J. P. *Phys. Rev.* **1986**, *B33*, 8822.
- (17) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200.
- (18) Komornicki, A.; Fitzgerald, G. *J. Chem. Phys.* **1993**, *98*, 1398.
- (19) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B.* **1988**, *37*, 785. (c) Stevens, P. J.; Devlin, F. J.; Chabowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623.
- (20) Purvis, G. D.; Bartlett, R. J. *J. Chem. Phys.* **1982**, *76*, 1910.
- (21) Raghavachari, K.; Trucks, G. W.; Pople, J. A.; Head-Gordon, M. *Chem. Phys. Lett.* **1989**, *157*, 479.

(8) Linde, C.; Akermark, B.; Norrby, P.-O.; Svensson, M. *J. Am. Chem. Soc.* **1999**, *121*, 5083.

(9) The name of our model BAE compound is chloro-4,4'-(1,2-ethanediyldinitrilo)bis(2-pentanonato)((2-)-N,N',O,O')-m-oxomanganese.

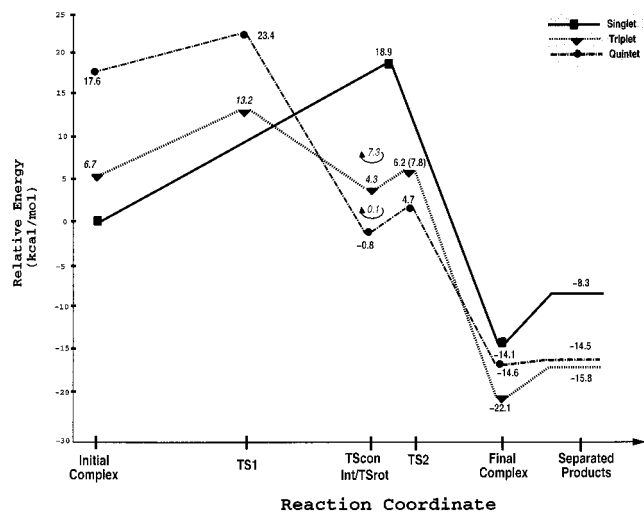


Figure 3. Relative reaction energies of the singlet, triplet, and quintet catalytic pathways calculated using the BP DFT functional with the DZVP basis set.

molecular orbitals are frozen. A number of calculations are performed with DZ and TZVP basis sets,^{13,14} which are H(41); C, N, O(621/41); Cl(6321/521); Mn(63321/531/41) and H(311/1); C, N, O(7111/411/1); Cl(73111/6111/1); and Mn((633111/51111/311), respectively. We also introduce (see the following text) the combination of the different basis sets for different shells of atoms in the Mn–salen catalyst. Such basis sets are denoted DZVPC and TZVPC. They are essentially DZVP and TZVP basis sets for all atoms, excluding hydrogen and carbon atoms; these latter atoms are treated at the DZ basis set level.

Results

Two possible reaction mechanisms, stepwise and concerted, have been considered (Figure 1). A third previously proposed reaction pathway,⁵ with the formation of the metallooxetane intermediate structure, was essentially ruled out in recent experimental work⁷ and did not receive support in a recent theoretical paper.⁸ Thus, the stepwise and the concerted mechanisms seem to be the most likely modes of oxygen transfer in the studied system.

Using the BP DFT approximation with DZVP basis set, we found three spin states (the singlet, the triplet, and the quintet states) to be important for understanding the catalytic activity of the manganese salen compound. For the optimized catalyst–ethylene complexes, the triplet and quintet states are the excited states and lie 7 and 18 kcal/mol above the ground singlet state, respectively (Figure 3). Charge distribution analysis shows that there is not any charge transfer between the manganese–salen compound and the ethylene molecule. The geometries of the catalyst and the substrate in the complexes are virtually the same as those for the separated compounds. Overall, the olefin–oxo interaction can be described as a weak electrostatic one.

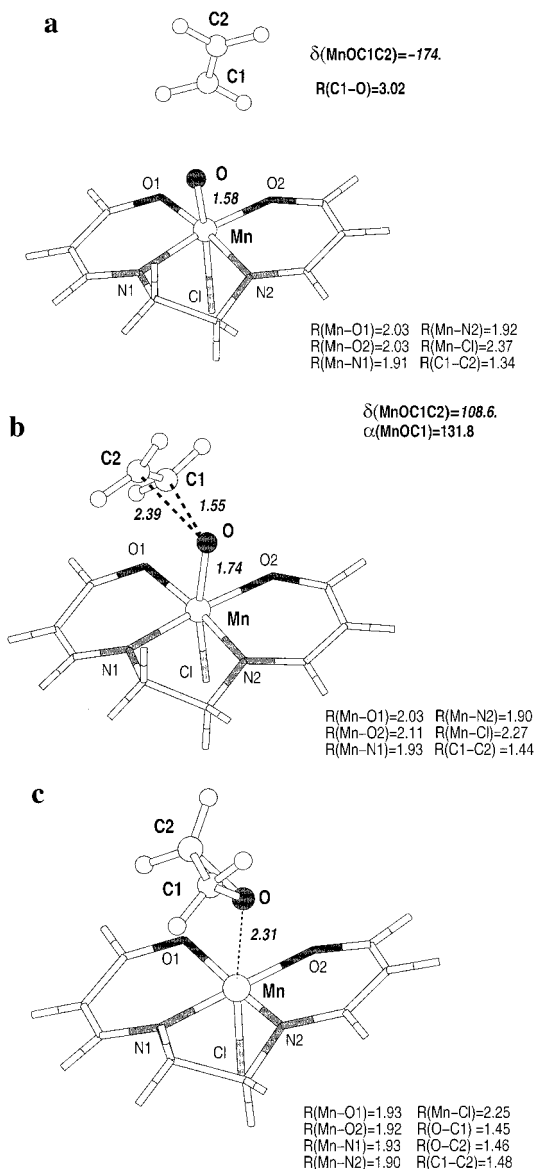


Figure 4. Optimized critical reaction structures for a concerted mechanism of the singlet state. Bond lengths are in angstroms, and bond angles are in degrees. The BP DFT approximation with the DZVP basis set is employed: (a) initial catalyst–ethylene complex; (b) concerted transition state (TScon) leading to the final products; (c) final catalyst–epoxide complex.

Despite the significant energetic gaps between the ground and excited states for the reactants, the triplet and the quintet states become more stable than the singlet for the reaction products. Because of different energetic stabilizations of the different spin states along the reaction coordinate, several crossings between different spin reaction pathways can occur. The consideration of a complex picture of the investigated reaction as a multichannel process with a different spin state will be presented in the Discussion. In this section, we present our findings for each spin state reaction channel separately.

Singlet State Reaction Pathway. Both the concerted and the stepwise mechanisms have been considered for the singlet state. Despite intensive searches on the singlet potential energy surface, we failed to find a stable intermediate structure. This indicates that only a concerted pathway is feasible for this spin state. The structures of the initial complex, the concerted transition state (TScon), and the final complex are depicted in Figure 4. The energetic reaction profile can be found in Figure 3.

(22) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.

The reaction starts from the initial complex (Figure 4a) in which the model catalyst and the substrate are separated from each other by 3 Å. Significant movement along the reaction coordinate toward the products is needed to come to the TS structure of the concerted mechanism (Figure 4b). This late (or productlike) TS structure is characterized by almost having one of the two carbon–oxygen bonds of the epoxide moiety completely formed ($R(\text{C1}-\text{O}) = 1.55 \text{ \AA}$). The second bond $\text{C2}-\text{O}$ is at the early stage of formation with a distance between C2 and O of 2.39 Å. The most significant geometrical change in the TS structure of the catalyst relative to the initial structure is an elongation of the $\text{Mn}-\text{O}$ bond by 0.16 Å. The TS structure leads directly to the product complex (Figure 4c). In the final complex, the oxygen of the epoxide compound is coordinated to the Mn(III) atom that virtually lies in the plane created by O1 , O2 , N1 , and N2 atoms. The interaction energy of the product complex is 5.8 kcal/mol.

The barrier corresponding to the concerted TS structure is 18.9 kcal/mol, and the reaction is exothermic by 14.1 kcal/mol. The concerted mechanism assumes that there is not any possibility for cis–trans isomerization in the course of the reaction. Thus, the singlet reaction channel exclusively yields cis epoxides.

Triplet State Reaction Pathway. It has been found that the reaction in the triplet spin state follows through a stepwise mechanism (Figure 5). In the first step of the reaction, the very early TS1 structure (Figure 5b) has geometrical parameters that are virtually unchanged relative to the geometries of the substrate and the catalyst in the initial complex (Figure 5a). The TS1 structure leads to the radical intermediate with a formed $\text{C1}-\text{O}$ bond ($R = 1.39 \text{ \AA}$) (Figure 5c). In this intermediate, the position of the C2H_2 of the ethene moiety corresponds to the rotation around the $\text{C1}-\text{C2}$ bond by 90° ($\delta(\text{HC2C1O}) = 177.8$) relative to that of the free ethene compound. The intermediate structure in which the ethene part of the catalytic complex closely resembles a free ethylene molecule is a rotational TS structure (Figure 5d). The radical intermediate can collapse into the epoxide product complex through two transition states: TS2_a and TS2_b (Figure 5e and f). Starting from the geometry of the radical intermediate, the TS structures can be obtained using clockwise or counterclockwise rotations about the $\text{C1}-\text{C2}$ bond and simultaneously forcing the C2 atom toward the oxygen of the catalyst from either the right or the left side. Because the radical intermediate structure is an intermediate configuration between cis and trans isomers, both transition states can lead to either cis or trans epoxide products. Moreover, because our small model does not take into account any possible steric interactions in the real catalyst, the probability of getting cis or trans product is the same, because clockwise or counterclockwise twisting of the intermediate is equally possible. TS2_a is calculated to be 1.6 kcal/mol lower in energy than TS2_b . We performed intrinsic reaction coordinate calculations to see what the product conformations TS2_a and TS2_b correspond to. It was found that the reaction pathway passing through the lowest TS2_a saddle point results in the final complex_a that is depicted in Figure 5g.

TS_b leads to the final complex_b that can be obtained from complex_a by rotation of the epoxide about the $\text{Mn}-\text{O}$ direction by approximately 180° .

The limiting step of the reaction in the triplet excited channel is the initial substrate attack on the oxygen of the catalyst. A modest amount of energy (6.5 kcal/mol) is needed to activate this step. The radical intermediate is more stable than the initial complex by ~ 2 kcal/mol and readily collapses (the TS barrier

is only 1.9 kcal/mol) to the product mixture of cis and trans isomers. The rotation of the ethene moiety of the intermediate around the $\text{C1}-\text{C2}$ bond is widely assumed to be responsible for cis–trans epoxide isomerization. Though such a rotation is energetically feasible (TSrot barrier is 3 kcal/mol) in our modeling, the nature of the intermediate offers an alternative way to get a mixture of cis and trans products. Our study reveals that the intermediate collapse to the cis and trans isomers is energetically more favorable than rotational changes in the intermediate.

Analysis of the spin density distribution shows that the unpaired electrons are localized on the metal atom in the beginning of the reaction and in the triplet TS1 structure. The picture is changed for the radical intermediate. In this structure, the unpaired electrons are delocalized, with one of them situated on the metal of the catalyst and another on the C2 atom of the substrate.

Quintet State Reaction Pathway. Many features of the quintet reaction channel are similar to those of the triplet reaction. First of all, the reaction in the quintet state also proceeds via a stepwise mechanism (Figure 6). Second, the first TS is a very early one and resembles the triplet TS1 (see Figures 5b and 6b). The quintet TS1 also leads to a radical intermediate structure (Figure 6c). In contrast to the triplet case, this intermediate does not have the C2H_2 ethylene group rotated about the $\text{C1}-\text{C2}$ bond. Thus, the quintet intermediate structure is qualitatively similar to the structure of TSrot in the case of the triplet reaction. At the same time, the rotational quintet TS (Figure 6d) structure is analogous to the triplet intermediate structure. The collapse of the quintet intermediate to the products proceeds through TS2 (Figure 6e). It is interesting to note that, in the salen–epoxide final complex (Figure 6f), the distance between the oxygen atom of the epoxides and the Mn atom is large (4.02 Å). This fact indicates that, unlike the singlet and the triplet cases, the epoxide is virtually not coordinated to the metal atom. From an energetic point of view, this leads to a final complex that is less stabilized with respect to separated products than in the case of other spin states (Figure 3).

The energy needed for the activation of the quintet reaction channel is approximately 6 kcal/mol, an amount that is comparable with the triplet TS1 barrier. The quintet state reaction pathway suggests only one way for cis–trans isomerization, that is, rotation about the $\text{C1}-\text{C2}$ bond in the intermediate. The corresponding TSrot barrier is found to be only about 1 kcal/mol, indicating virtually free rotation about this bond.

Reliability of the Theoretical Approximations and the Models. As mentioned in the Introduction, the results and conclusions of the present work differ significantly from the results and conclusions published in Linde et al.⁸ The main discrepancies include (but are not limited to) an ordering of the singlet, the triplet, and the quintet states for reactants and products and different qualitative reaction profiles for the quintet state.

To resolve the sharp contradictions between the two theoretical works, we performed a thorough comparative analysis of the methodologies used in both studies. Three factors that could lead to the discrepancies have been considered: using different basis sets, using different DFT functionals, and using different models. In this work, we present a brief summary of our findings. Further details will be forthcoming in a separate publication.

We found that only small variations in relative energies occur with different basis sets in the framework of the same DFT approximation. B3LYP calculations performed with our smallest

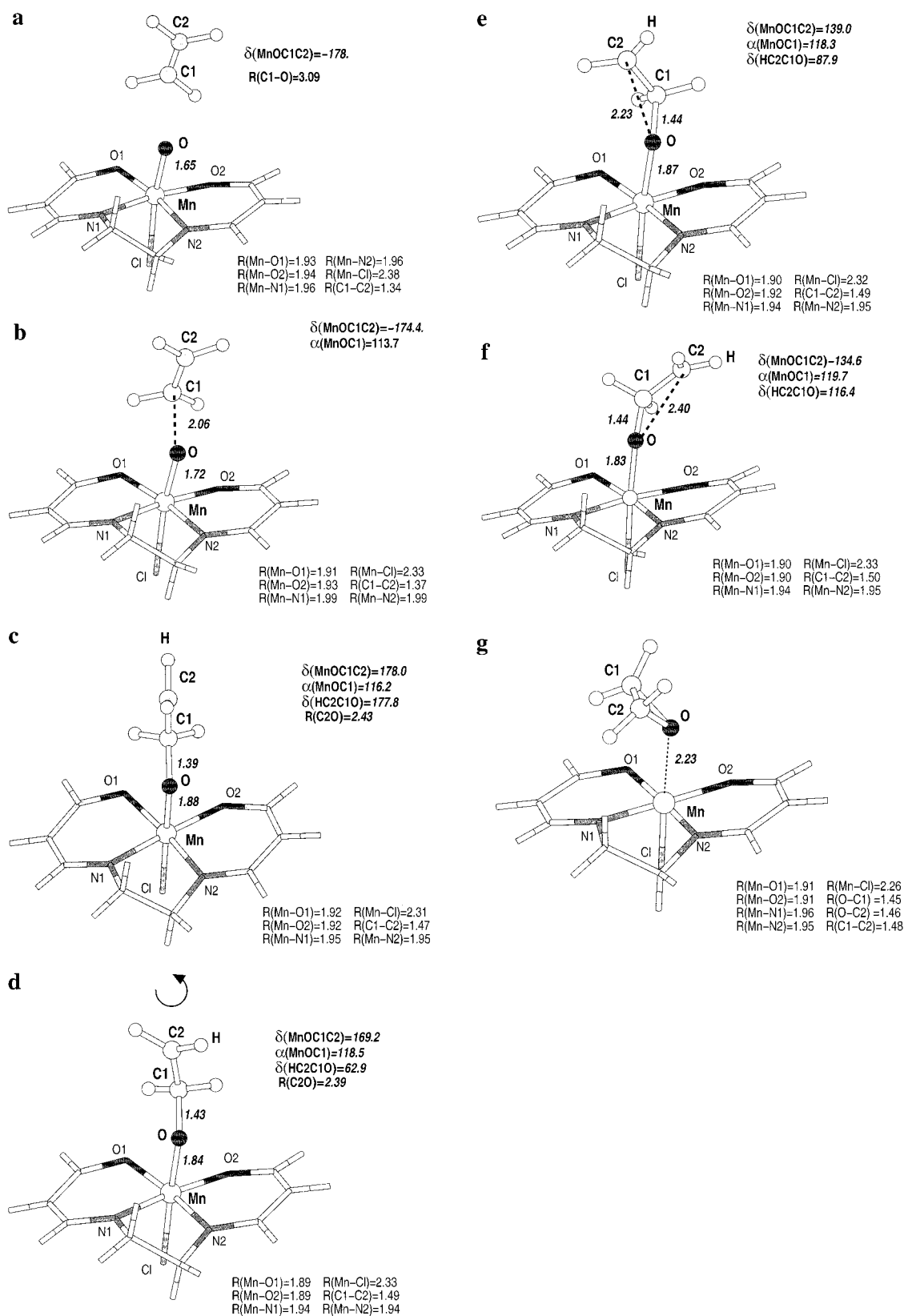


Figure 5. Optimized critical reaction structures for the stepwise radical mechanism of the triplet state. Bond lengths are in angstroms, and bond angles are in degrees. The BP DFT approximation with the DZVP basis set is employed: (a) initial catalyst–ethylene complex; (b) first transition state (TS1) resulting in the intermediate with a formed C1–O bond; (c) radical intermediate; (d) rotational transition state (TSrot) for the radical intermediate; (e) second transition state (TS2_a) leading to the final products; (f) alternative second transition state n(TS2_b, see text); (g) final catalyst–epoxide complex.

basis set DZ, which is similar to the DZ-like basis of Linde et al.,⁸ reproduces their conclusion that the energy differences

between all states are small (the maximum difference is 2.6 kcal/mol in ref 8 versus 4.6 kcal/mol with our corresponding

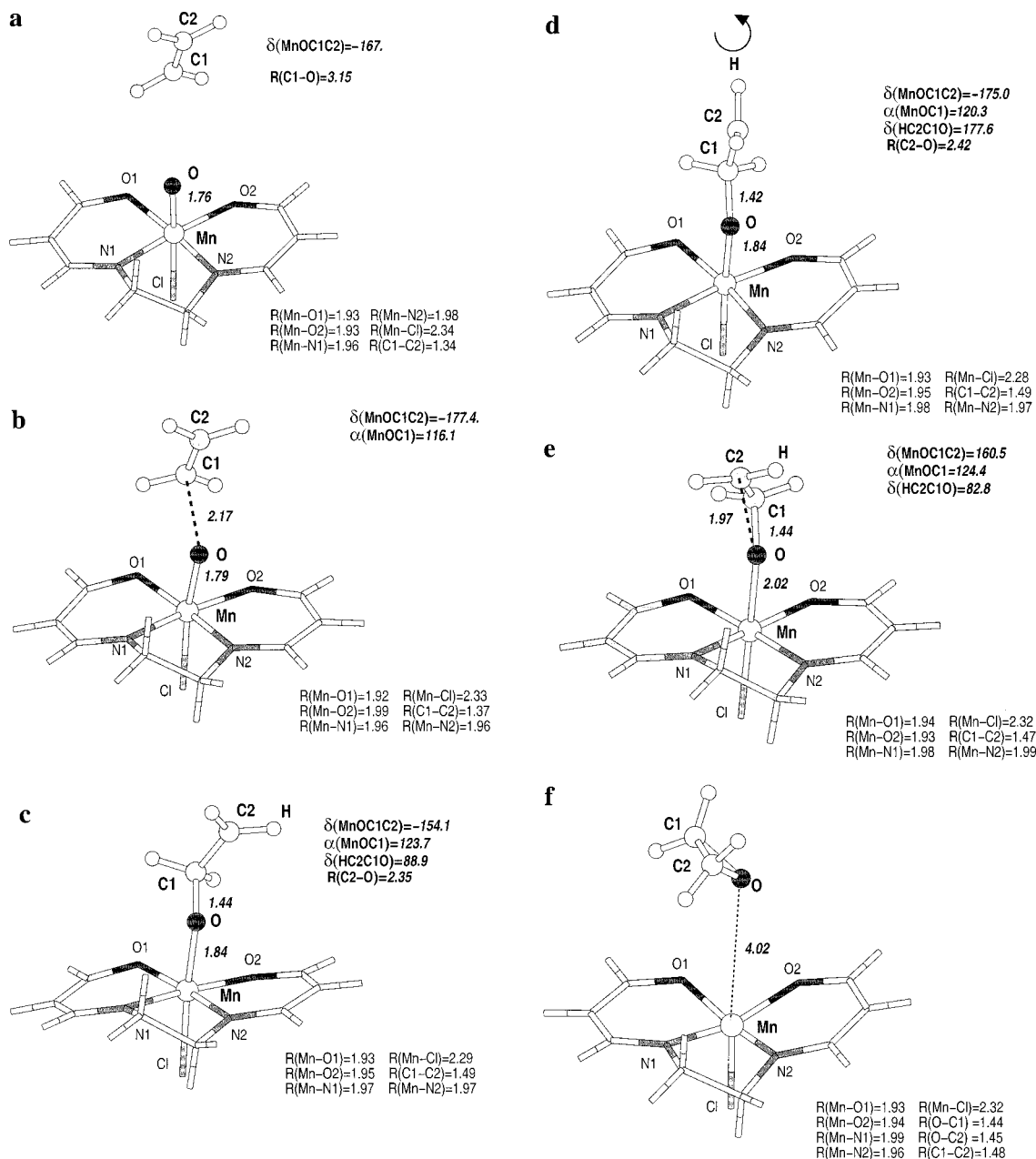


Figure 6. Optimized critical reaction structures for the stepwise radical mechanism of the quintet state. Bond lengths are in angstroms, and bond angles are in degrees. The BP DFT approximation with the DZVP basis set is employed: (a) initial catalyst–ethylene complex; (b) first transition state (TS1) resulting in the intermediate with a formed C1–O bond; (c) radical intermediate; (d) rotational transition state (TSrot) for the radical intermediate; (e) second transition state (TS2_a) leading to the final products; (f) final catalyst–epoxide complex.

basis set). Thus, we conclude that the contradictions between the two theoretical works cannot be a consequence of using different basis sets.

In this work, we determine which functional performs better in establishing the right energy relationship between different spin states in the particular case of this metallorganic system (Mn–salen catalyst model). A high level *ab initio* method (coupled cluster method (CCSD(T))) is used as a reference point to compare the performance of BP and B3LYP DFT functionals for the oxomanganese reactant. The CCSD(T) approach, while computationally expensive, is one of the most attractive choices to take into account electron correlation. As discussed in a recent paper by Schaefer and co-workers,²³ its accuracy is well-established for many chemical problems.

To make the CCSD(T) calculations more practical, some reduction of the size of the computational models and basis sets is made. First, the carbon–carbon bridge between the two nitrogen atoms (Figure 2) is eliminated by breaking the C–N bonds and saturating the cut nitrogen bonds with hydrogen atoms. This leads to a simplified neutral (SN) model and a simplified cationic (SC) model. The SN and SC models correspond to our model and the model considered by Linde et al., respectively. Second, we reduced the size of the basis sets for the SN and SC model compounds by treating the second shell atoms (carbons and hydrogens) with a small DZ basis set. We denote these basis sets as DZVPC and TZVPC (DZVPC_core and TZVPC_core), respectively. Preliminary results show that all of these simplifications only slightly influence the local electronic structure of the metal open shells and, therefore, the total picture of different spin state distributions would not be

(23) King, R. A.; Crawford, D. T.; Stanton, J. F.; Schaefer, H. F., III. *J. Am. Chem. Soc.* **1999**, *121*, 10788.

Table 1. Ab Initio and DFT Calculated Relative Energies (kcal/mol) for the Singlet (S), Triplet (T), and Quintet (Q) Spin States of the Simplified Cationic (SC) Mn–Salen Catalyst Model^a

	relative energy (kcal/mol)					
	SC:DZVPc model using the following methods			SC:TZVPc model using the following methods		SC:DZ model
	CCSD(T)_fc/ DZVPc BP	CCSD(T)_fu/ DZVPc BP	BP/ DZVPc BP	CCSD(T)_fc/ TZVPc BP	CCSD/ TZVPc BP	B3LYP/ DZVPc BP method
S	0.0	0.0	0.0	0.0	0.0	0.0
T	-4.0	+1.4	+12.7	+0.1	+5.6	-1.6
Q	+9.9	+17.3	+33.6	+16.1	+21.8	+5.0
singlet state total <i>E</i> (au)	-1716.0265	-1716.0981	-1719.6199	-1716.3089	-1716.510	-1719.1121

^a For the description of the model, see the text.

Table 2. Ab Initio and DFT Calculated Relative Energies (kcal/mol) for the Singlet (S), Triplet (T), and Quintet (Q) Spin States of the Simplified Neutral Mn–Salen Catalyst Model^a

	relative energy (kcal/mol)		
	SN:DZVP model		SN:DZVPc model
	CCSD(T)_fu/DZVPc BP method	B3LYP/DZVPc BP method	BP/DZVPc BP method
S	0.0	0.0	0.0
T	+14.5	-8.1	+6.0
Q	+10.9	-9.4	+17.2
singlet state total <i>E</i> (au)	-2175.8944	-2179.5803	-2180.0605

^a For the description of the model, see the text.

changed in the simplified computational approach relative to a “standard” approximation.²⁴

Comparative analysis between ab initio and different DFT calculations has been performed for the simplified cationic model, and the results are presented in Table 1. Our highest level ab initio calculation (TZVPc CCSD(T)_fu) unambiguously suggests that the singlet state is the ground state for the oxomanganese reactant. The first excited level is the triplet which lies 5.6 kcal/mol higher in energy. The energy gap between the singlet and the quintet state is very large (21.8 kcal/mol). In contrast to these findings, the B3LYP DFT approximation with the DZ basis set (an approach similar to the one used by Linde et al.) predicts the triplet state to be the ground state with a small energy gap between the singlet and the quintet (5 kcal/mol in Table 1 and 1.2 kcal/mol in ref 8). Using the BP DFT approximation gives results qualitatively similar to the reference ab initio results. From the quantitative point of view, the BP DFT calculations suggest that the singlet is lower in energy than the triplet and the quintet by a greater amount than that predicted by the ab initio calculations: 12.7 versus 5.6 kcal/mol for the triplet and 33.6 versus 21.8 kcal/mol for the quintet. We, however, are encouraged by the fact that CCSD(T) ab initio calculations predict an increased stability of the singlet state with an increased level of calculation. In fact, increasing both the active orbital space (from the frozen core to the almost full space) and the basis set leads to widening the gaps between the singlet and other states. One can speculate that a more complete basis set could result in CCSD(T) numbers that come even closer to BP DFT calculations.

A big difference in the predictions of the BP and B3LYP functionals can also be seen in the neutral model (Table 2). B3LYP calculations suggest that the order of spin states is the quintet, the triplet, and the singlet, which is exactly the opposite of the results of the BP functional. The reference coupled cluster calculations show that the BP functional correctly predicts the

singlet to be the ground state, while the triplet and the quintet are excited states. We note, however, that in BP DFT calculations the triplet and the quintet are in reverse order with respect to the ab initio calculations.

As we already mentioned, our theoretical studies, like those of Linde et al., led to two qualitatively different profiles for the quintet state. We performed a number of additional calculations to see if using different DFT functionals can result in the qualitatively different reaction profiles. We first conducted an extensive search of the quintet potential energy surface of the cationic model, using both BP and B3LYP approaches with the aim of finding the intermediate structure. Similar to the results of Linde et al., no radical intermediate structure was found for the cationic model. For the neutral model, however, the geometry of the intermediate complex in the quintet state was easily obtained using the B3LYP method, starting from the geometry of the already optimized BP DFT structure. Thus, the existence or nonexistence of the quintet radical intermediate depends only on the type of model used in the calculations.

Discussion

An ordering of following the singlet, the triplet, and the quintet states for reactants and products plays a crucial role in the explanation of the Mn–salen catalytic activity.

Using the B3LYP approximation, Linde et al.⁸ found the triplet state to be a ground state for the reactant complex. This finding contradicts our prediction (BP approximation with DZVP basis set) that the singlet state is the lowest in energy. Even more striking differences in the results of the two theoretical studies are values of the energetic gaps between the different spin states of the reactants. Linde et al.⁸ predicted that all three spin states are pseudodegenerated with an energy difference between the lowest and the highest spin state of only 2.6 kcal/mol. In contrast to this observation, we found that the singlet ground state is significantly more stable than the excited triplet and quintet states (6.7 and 17.6 kcal/mol, Figure 3). The numerical discrepancies of two theoretical works lead to two qualitatively different pictures. In our case, the singlet reaction pathway plays a very important role explaining experimental

(24) Computed numbers of spin state relative energies for the simplified neutral model with the DZVPc basis set coincide with those of the original neutral model and standard basis set to less than 1 kcal/mol.

(25) The results of X = NO₂ and other substituent calculations will be published.

observations, while, in the earlier work,⁸ the addition of ethene to the singlet catalyst complex is considered an unlikely event.

As we have shown in the previous section (Tables 1 and 2), using the B3LYP DFT approximation leads to results that are qualitatively different from those obtained from high level ab initio calculations. The qualitative picture obtained using the BP DFT approximation is similar to that obtained from the CCSD(T) one, although the BP DFT results may need some numerical corrections. Overall, our results suggest that B3LYP calculations have a tendency to “overstabilize” the quintet state with respect to the singlet one. This is the reason for a large energetic gap between the quintet and the singlet states (by 40 kcal/mol) on the product side in the case of using the B3LYP approximation.^{6b,8} In our calculations (Figure 3), the splitting between the singlet and the quintet is not so pronounced, 7 kcal/mol. On the basis of the results for the reactant side, we believe that the BP method likely gives a more accurate description of the singlet–quintet separation.

One of the main conclusions of Linde and colleagues' work⁸ is that there is no intermediate structure on the quintet reaction pathway. Thus, a cis conformation of the reactant cannot be changed in this spin state. Therefore, the authors concluded that the spin change from the triplet to the quintet surface early in the reaction is responsible for the high yield of cis epoxides. Our calculations do not support this theory. We found the intermediate on the quintet reaction pathway and showed (see above) that the intermediate can yield both cis and trans epoxides. Our results suggest that the oversimplified cationic model used by Linde et al. is responsible for the “disappearing” of the quintet intermediate. We speculate that the cationic model may not be flexible enough to describe the wide changes in the electronic structure of the Mn atom in the course of the reaction (which starts with Mn(V) and ends with Mn(III)). For this reason, using the cationic model leads to qualitatively wrong results and one should exercise extreme caution when making conclusions on the basis of results obtained with this cationic model.

On the basis of the comparative analysis, we feel that the methodology used in this work gives a realistic description of the (salen)Mn(III)-catalyzed epoxidation reaction. As seen from the results of our calculations, the reaction can be considered as a three channel process with different spin states: the singlet, the triplet, and the quintet. Every reaction spin channel has distinguishing features, although the triplet and quintet reactions also reveal many similarities, including the same qualitative reaction profile that corresponds to a stepwise mechanism. The singlet reaction follows a concerted reaction pathway. There is only one late (productlike) TS structure on the singlet pathway that leads exclusively to the cis epoxide product.

In contrast to the singlet reaction, the triplet and the quintet channels are characterized with early (reactantlike) TS structures that result in the radical intermediates which can collapse to a mixture of cis and trans epoxides. The main distinguishing feature between the triplet and the quintet channel is the way the radical intermediate transforms to the mixture of isomer products. The twisted nature of the triplet intermediates (Figure 5c) suggests that it can directly collapse to either the cis or trans isomer with equal probability. No additional rotation is required to get a trans epoxide. In contrast, the isomerization in the quintet channel needs the rotation about the C–C bond (Figure 6c) before the collapse of the quintet radical intermediate. Because the TS rotational barrier (~1 kcal/mol) is much lower than the TS barrier (~5 kcal/mol) corresponding to the collapse of the intermediate, we assume that a number of rotations can

occur in the quintet channel before the collapse. That should lead to equal amounts of cis and trans epoxides in the product mixture. Thus, in our restricted model, both the triplet and the quintet channels result in equal partitioning of cis and trans epoxides.

On the basis of the results of our calculations, the three reaction channels compete in order to contribute to the epoxide products (Figure 3). The quintet channel is characterized with the highest energy excited reactants, which makes the channel inactive in the first step of the oxidation reaction. However, the quintet intermediate lies lower in energy than the triplet, indicating that both the triplet and the quintet could contribute to the product isomers after the collapse of the radical intermediates. Because our modeling predicts a 1:1 ratio of cis and trans epoxide for each spin channel, the “combined” triplet/quintet reaction leads to an equal partitioning of the isomers as well. On the basis of the experimentally determined cis/trans product ratio of 6.3:1,⁷ however, we must account for the predominant production of cis epoxide. We suggest that the singlet reaction pathway must play a significant role in the overall reaction, because it leads to cis product exclusively.

Competition between the singlet and the triplet/quintet pathways offers a consistent explanation for the observed cis/trans partitioning. Even though the DFT estimated singlet activation energy is slightly higher than the triplet one, we believe that the activation energies coincide within the accuracy of our modeling. The reference high level ab initio calculations suggest that our DFT results may need some numerical corrections. Importantly, the suggested correction (see Table 2) would result in widening the gap between the singlet and the triplet reactants by 8 kcal/mol. Applying the suggested correction leads to an absolute energy of the triplet TS barrier which is higher than the activation energy needed for the singlet. Thus, overall, our computational results do not preclude the singlet channel to be the most competitive reaction channel. This fact would easily explain the experimentally observed predominant production of cis epoxide.

The description of the reaction as a process with competing channels that have different ratios of cis and trans products implies that any changes in the relative activation energies between the singlet and the triplet reaction pathways should influence cis–trans isomerization. Such shifting of the relative position of the singlet and the triplet TS barriers can be induced both by changing the electronic structure of the catalyst through ligand substitutions and by changing the substrate itself. The dependence of enantioselectivity for the catalyzed epoxidation reaction on the electronic properties of the catalyst and/or the substrate is a well documented experimental observation.⁷ Our preliminary calculations show that this proposed catalytic scheme allows for the effect of substituents. For example, substitution of X = H in our model (Figure 2a) by an electron withdrawing nitro group, X = NO₂, leads to decreasing the absolute singlet activation energy by 4.3 kcal/mol, while the absolute value of the triplet TS barrier lowers by only 2.6 kcal/mol. According to our catalytic scheme, the larger stabilization of the singlet pathway should lead to a higher yield of cis epoxide. That is in complete agreement with the experiment by Jacobsen and co-workers,⁷ thus providing, though indirectly, experimental support for our theory.

Finally, we would like to point out that the presented theoretical picture is likely a simplified version of the real catalytic action. This is due to the fact that our small model does not take into account the steric interactions between the side chains of the actual catalyst and the actual substrate that is

more bulky than model ethylene. One of the possible consequences of a more realistic system might be changing the "perfect" 1:1 ratio of cis–trans isomers for the triplet and the quintet channels.

Conclusions

On the basis of the results of a detailed DFT study, we introduce a novel mechanism for the (salen)Mn(III)-catalyzed epoxidation reaction. This mechanism is consistent with the major experimental observations, including the dependence of enantioselectivity on electronic effects. We describe the reaction as a process with competing channels having different spin states: the singlet, the triplet, and the quintet. The singlet reaction pathway corresponds to a concerted mechanism and leads exclusively to a cis epoxide product. In contrast, the triplet and quintet reactions follow a stepwise mechanism and lead to a product mixture of cis and trans epoxides. For our restricted model, we estimated this cis/trans product ratio to be 1:1. To account for the predominant production of cis epoxide, we propose that the singlet reaction is an active channel of the epoxidation process. Such a proposal leads to a consistent explanation of the experimental facts. We note that, although DFT estimations predict that the absolute activation energy for the triplet channel is slightly lower than that for the singlet, the activation energy for the singlet state likely will be the lowest among the channels after the numerical corrections of DFT estimations, as the results of coupled cluster *ab initio* calculations suggest.

In our catalytic scheme, the dependence of isomer product ratios on electronic effects connected with substitution of a substrate and/or a ligand of the catalyst can be easily understood. Such electronic effects should change the relative position and, hence, the relative activities of the channels with different cis–trans yields. Our preliminary calculations on catalyst ligand substitutions show that our theory explains electronic tuning of cis–trans isomerization of the product.

Because the results and conclusions of the present work dramatically differ from the results and conclusion of the recent DFT theoretical investigation,⁸ we studied possible sources for the deep contradictions between the two works. The choice of the DFT functional and a model has been shown to be crucial for accurate results. The B3LYP functional was used in Linde et al.,⁸ while our calculations employed the Becke–Perdew (BP) functional. Using high level *ab initio* calculations (coupled cluster-CCSD(T)), we show that the BP functional gives a realistic description of the relationship between the different spin channels involved in the reaction. In contrast, using the B3LYP approach in this particular catalytic system case results in a distorted picture of the spin state order. It is also shown that the smaller cationic model without a chlorine ligand that was used by Linde et al. is too oversimplified with respect to our larger neutral model. For this reason, using the cationic model led to a qualitatively wrong quintet reaction profile that played a key role in theoretical postulates in the earlier work.⁸ Overall, an analysis of the two theoretical methodologies shows that the theoretical approach used in this present work is more reliable. Further studies are needed to determine if our methodological findings suggest general recommendations for theoretical investigations of organometal-catalyzed reactions.

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