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On the Chirality Transfer in the Epoxidation of Alkenes Catalyzed by Mn(salen) Complexes

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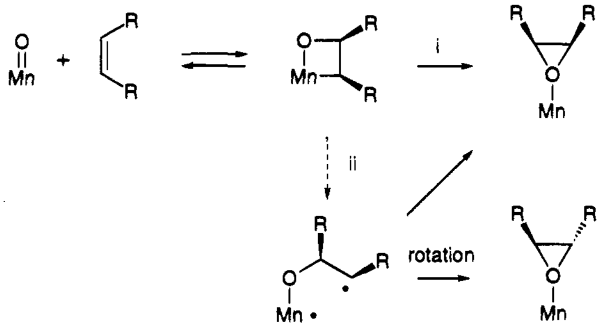
Manganese salens have been shown to be efficient catalysts for epoxidation of a wide variety of unfunctionalized alkenes.[1] Remarkably high enantioselectivities have been obtained for trisubstituted and *cis*-disubstituted alkenes using the Jacobsen and Katsuki type Mn^{III}(salen) complexes.[2]

Several mechanisms, both concerted and nonconcerted, have been proposed for the epoxidation reaction.[3−5] Most often a radical intermediate is invoked where an electrophilic oxomanganese species attacks the electron-rich double bond, forming a carbon radical intermediate. This intermediate would account for the *cis*−*trans* isomerization observed during the epoxidation of *cis*-alkenes since a rotation around the formed carbon−carbon single bond is possible if the lifetime of the radical is long enough. In the Mn(salen) system it has been possible to favor the selective inversion at one center of a reacting *cis* olefin yielding in essence the *trans* product with enantioselectivities sometimes higher than for the *cis* product.[1e,3c,6,7] It is clear that the forward reaction from a radical intermediate to epoxide has to be much faster than the reverse reaction back to alkene, since no isomerization of the starting alkene is detected.

Previous mechanistic models for chiral induction are based mainly on steric and electronic effects experienced by an approaching olefin but do not take into account the changes in conformational energy of the salen ligand along the reaction path.[1,2] Although the commonly postulated intermediate, a manganese−oxo complex, should have a slightly pyramidal conformation, it presents a fairly flat surface to the olefin. If a metallaoxetane is formed in the rate-determining step, as first suggested by Sharpless et al. for the chromyl chloride oxidation of olefins,[8] an octahedral or pseudo-octahedral intermediate would be formed. The formation of an oxetane would lead to considerable puckering of the salen ligand and creation of a chiral pocket. There is a recent report on formation of both an acac complex of Mn(III) and a dimeric Mn(IV) dioxo bridged complex which are octahedral with a salen-type ligand occupying three equatorial positions and one axial position.[9] We would therefore like to propose a mechanism including *reversible* formation of a metallaoxetane followed by irreversible rearrangement to bound epoxide (Scheme 1). The oxetane can follow two different routes to epoxide: either (i) direct rearrangement to *cis* epoxide or, when a stabilized radical can be formed; (ii) homolytic cleavage of the manganese−carbon bond with subsequent rotation around the carbon−carbon bond and collapse to the *trans* epoxide with retention at the O-carbon.[10]

Scheme 1. Postulated Mechanism for Mn(salen)-Catalyzed Epoxidation[a]



[a] Pathways leading to enantiomers are excluded.

Metallaoxetanes have been invoked to rationalize a number of different oxidations,[5,11,12] including epoxidations.[8,13,14] The metallaoxetane intermediates have generally not been detected, and their existence has been contested.[4,5] However, high-level quantum chemical calculations have shown them to be plausible, albeit high-energy intermediates.[12,13] As a model for the Mn(salen) catalyzed epoxidation of alkenes, an oxetane can be used to explain most of the experimental results published so far.

Our calculations of the energies of a few representative oxetanes were performed using MacroModel/MM3*.[15] According to our model the preferred configuration around the octahedral metal depends on the conformational preferences of

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(10) An alternative explanation is heterolytic cleavage of the Mn−O bond, followed by rotation around the C−C bond and intramolecular S_N2-type attack of the oxygen on the Mn−C bond. The fact that addition of β-hydroxy quaternary ammonium salts greatly promotes formation of *trans*-epoxides (see ref 6) could be explained by coordination of the β-hydroxy group and brief stabilization of the alkoxy group as an ion pair with the quaternary ammonium group.

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(15) (a) MacroModel version 4.5: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440. (b) Allinger MM3 force field: Allinger, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 8551. The Mn parameters, which are not yet optimized, were obtained from X-ray stuctures of two published salen-type complexes, see ref 9, and from semiempirical calculations of an isoelectronic chromaoxetane on Iris Indigo machines using Spartan version 4.0 from Wavefunction, Inc.

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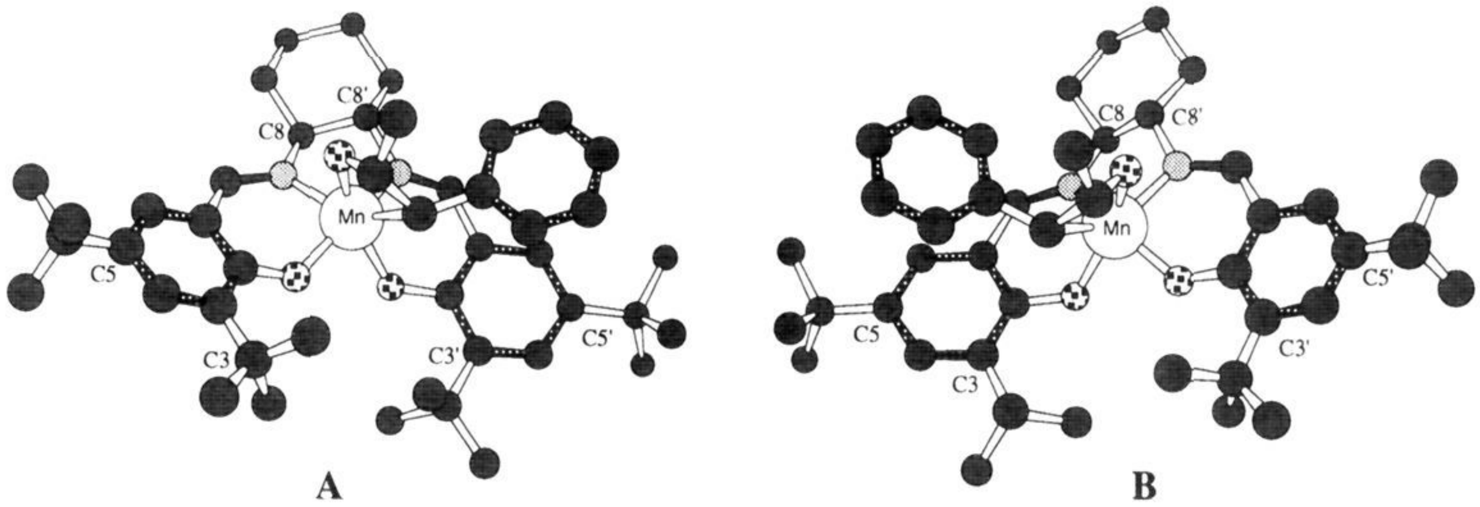

Figure 1. The two competing intermediate oxetanes found in the calculations for the epoxidation of *cis*-β-methylstyrene by (*S*,*S*)-**1** (**A** = major diastereomer, **B** = minor diastereomer). Hydrogens are omitted for clarity.

the chiral diimine bridge. If the plane containing the two imino groups is designated as equatorial then one of the phenolate oxygens is equatorial, whereas the other one is axial. Our calculations on the oxetanes formed from (*S*,*S*)-[*N*,*N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine]manganese(III) chloride (**1**) and *cis*-β-methylstyrene show that diastereomers **A** and **B** have the lowest energies (Figure 1). The local symmetry around the metal is changed between **A** and **B**, with different phenolate oxygens occupying the pseudoaxial position and with enantiomeric oxetane moieties. In both diastereomers, the oxetane substituents are pointing away from the C_3 or $C_{3'}$ *tert*-butyl substituents. The calculations show that **A**, which should give the observed major enantiomer (1*S*,2*R*)-1-phenylpropylene oxide, is more stable than **B** by ca. 10.5 kcal/mol.[2b,16] Introduction of *tert*-butyl substituents in positions C_5 and $C_{5'}$ leads to steric interaction with the phenyl substituents of **A** and **B**, which disfavors **B** over **A** by an additional 0.5 kcal/mol, in accordance with experimental data.[2b] The calculations also show that introduction of axial methyl substituents on the diimine bridge causes steric interference in **A** and lowers the energy difference between **A** and **B** by ca. 4.0 kcal/mol, again in qualitative agreement with experimental observations.[2b]

In the oxetane model, one of the substituents of a *trans*-alkene will always interfere with the C_3 and $C_{3'}$ substituents. Calculations show that this leads to a decrease in the energy difference between diastereomers **A** and **B**, leading to a fairly low expected ee.[1b,2d] This interaction rationalizes why *trans*-alkenes can be strongly susceptible to induction from chiral C_3 and $C_{3'}$ substituents, with very good ee's resulting from cooperative effects between the diimine bridge and the C_3 and $C_{3'}$ substituents.[2d] Chiral substituents at C_3 and $C_{3'}$ also affect the ee's for *cis*-alkenes. Our calculations reveal that, with certain groups (e.g., rotationally locked naphthyl substituents),[2h,i] the relative energies of **A** and **B** are strongly affected by the configuration of the C_3 and $C_{3'}$ substituents. However, for *cis* olefins the predominant influence seems to come from the configuration of the diimine bridge, with the C_3 and $C_{3'}$ substituents acting as matched or mismatched modifiers.[2d]

It has been shown that both enantioselectivity and alkene isotope effects increase in magnitude with increasing electron density on the salen ligand.[17,18] These observations have been interpreted in terms of a stabilization of the oxomanganese complex by electron-releasing substituents, moving toward a more product-like transition state according to the Hammond postulate.[17] The effects are nicely rationalized also within the framework of an oxetane mechanism. The stabilization of the oxomanganese species remains an important factor, but both enantioselectivity and isotope effects can be explained by a shift in the equilibrium in the addition step. With salen nitro substituents, the addition step is almost irreversible, and the only selectivity in the reaction arises from the addition of olefin to the oxo complex. In the rate-determining step, the olefin carbons have partial sp^2 character, leading to a low expected reverse isotope effect.[17] The selectivity is determined in a loose transition state without fully formed covalent bonds between the oxidant and the substrate, thus rationalizing the low ee. With a methoxy substituent on the salen ligand, the first step becomes more reversible and the selectivity is determined by the cooperative effects in two transition states for oxetane formation and rearrangement. The sp^3 hybridization of the oxetane carbons in the rearrangement step would rationalize the observed isotope effects if this transition state dominated the rate. Consequently, in a system which is electronically balanced to make the activation energies similar for the two transition states, it should be possible to observe nonlinear behavior in Eyring-type plots of the enantioselectivity–temperature relationship.[19,20]

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(20) During revision of this paper it came to our attention that nonlinear behavior has recently been observed in Mn(salen)-catalyzed epoxidation: Katsuki, T., Personal communication. This is a strong indication for a reversibly formed intermediate. Isomerization of the intermediate would result in isomerization of the starting alkene since the backward and forward reaction rates are equal at the inversion temperature.