Timing Is Critical: Effect of Spin Changes on the Diastereoselectivity in Mn(salen)-Catalyzed Epoxidation

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Received March 24, 1998

The pioneering studies by Katsuki and Jacobsen have led to a variety of chiral Mn(salen)-based catalysts which epoxidize alkenes with high enantioselectivity.[1] The synthetic utility of these catalysts has served as a stimulus for the elucidation of the mechanism of the reaction.[2] Three main proposals have been presented (Scheme 1): Isolated alkenes have been proposed to react in a *concerted* manner[3] (pathway A); conjugated alkenes have been proposed to react in a stepwise *radical process*[4] (pathway B); and one applicable to both substrate classes involves the reversible formation of a *manganaoxetane*[5] (pathway C). A radical intermediate is supported by the observed formation of trans epoxides in the epoxidation of cis alkenes.[4] No direct evidence exists that the radical intermediate also intervenes in the formation of the nonisomerized cis product.[6] The picture is complicated by the observation that modified Eyring plots of the selectivity show nonlinearities with some substrates,[5b] but not with others.[4b,c] Nonlinearities could be due to the presence of a reversibly formed intermediate or to competing reactions.[7]

The purpose of this study is to improve the understanding of how electronic effects influence the choice of reaction path. We have employed hybrid density functional methods[8] to investigate possible paths for the reaction between ethene and a simplified cationic oxo analogue **1** of [*N,N'*-bis(3,5-di-*tert*-butylsali-
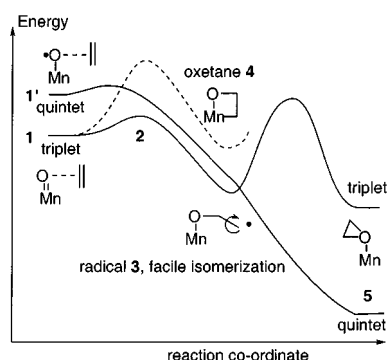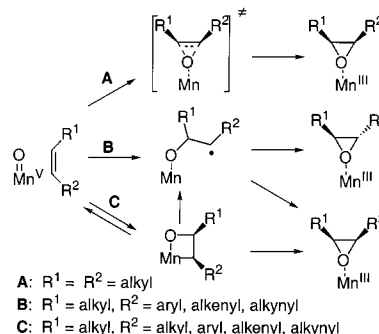
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(6) Reaction of styrenes substituted with hypersensitive radical clocks indicate that radicals are not intermediates in the formation of *cis*-epoxides, see: Linde, C.; Arnold, M.; Norrby, P.-O.; Åkermark, B. *Angew Chem., Int. Ed. Engl.* **1997**, *36*, 1723–1725.

(7) Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477–515. Eyring nonlinearities generally indicate that at least two TSs influence the reaction. Small changes in substrates or reaction conditions could easily render the breaks undetectable, and no conclusions can therefore be drawn from the absence of such breaks.

(8) B3LYP: Stevens, P. J.; Devlin F. J.; Chablowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98, 11623*. We used a (14s,11p,6d) primitive basis from Wachters, A. J. H. *J. Chem. Phys.*, **1970**, *52*, 1033. augumented by two p and one diffuse d function contracted to [6s,5p,3d]. On substrates and ligands we used the double-ζ basis set from Dunning, T. H.; Hay, P. J *Modern Theoretical Chemistry;* Plenum Press: New York, 1977.
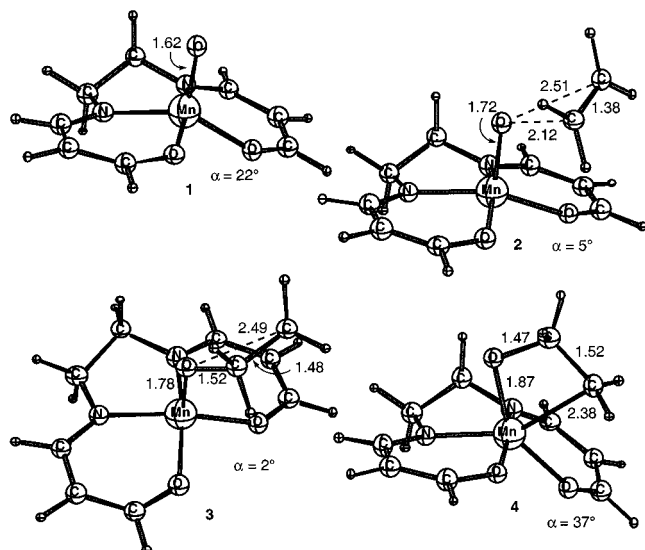
Figure 1. Schematic representation of the calculated reaction profiles.

Scheme 1

A: R[1] = R[2] = alkyl
B: R[1] = alkyl, R[2] = aryl, alkenyl, alkynyl
C: R[1] = alkyl, R[2] = alkyl, aryl, alkenyl, alkynyl

cylidene)1,2-cyclohexanediamine]manganese(III) chloride, where only the inner frame work is kept.[9,10]

The calculations indicate that three different spin states are available to the oxomanganese(V) reactant; singlet, triplet, and quintet. The energy differences between these states are small; the triplet is the ground state with the singlet and quintet 6 and 11 kJ/mol, respectively, above. The oxo–manganese bond has close to triple-bond character in the singlet state, double-bond character (1.62 Å) in the triplet state **1**, and in the quintet state **1'** it has more single-bond character (1.71 Å). For the triplet state, one $3d_\pi$ and one $3d_\delta$-orbital (symmetry defined by the MnO moiety) are single-occupied. For the quintet state, the other $3d_\pi$-orbital and one $2p_\pi$-orbital of the oxo-group are single-occupied as well.[11,12]

On the product side, epoxide coordinated to manganese, the quintet state **5** is strongly favored (154 kJ/mol below the triplet state). As a consequence, a spin change could be expected along the reaction path, which has been investigated both for triplet and quintet intermediates and for some transition states. The calculated reaction profiles are schematically depicted in Figure 1 and the optimized structures **1–4** shown in Figure 2.

On the triplet surface an incoming ethene attacks the oxo group asynchronously even though the alkene is symmetric.[13] The structure of TS **2** for the first C–O bond formation is shown in

(9) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063–7064.

(10) Oxomanganese(V) was early postulated as the active species, but not until recently was direct proof found for its existence: (a) Feichtinger, D.; Plattner, D. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1718–1719. (b) Groves, J. T.; Lee, J.; Marla, S. S. *J. Am. Chem. Soc.* **1997**, *119*, 6269–6273.

(11) Calculations by Jorgensen et al. (Rasmussen, K. G.; Thomsen, D. S.; Jorgensen, K. A. *J. Chem. Soc., Perkin. Trans. 1*, **1995**, 2009.), using INDO calculations, have earlier shown that the ground state for a related Mn(V)O system is the triplet, 71 kJ/mol lower than the singlet. These calculations also show that the singlet has higher MnO bond order than the triplet.

(12) The reason for the small energy difference between the triplet and quintet states is the weak π-bond between the oxo group and the manganese center which in turn contributes to the high reactivity of the oxomanganese-(salen) complex.

Figure 2. Optimized structures (bond distances in Å). Oxo−manganese-(V) triplet **1**, TS for asynchronous addition of ethene to oxo−manganese-(V) triplet **2**, radical intermediate triplet **3**, manganaoxetane triplet **4**. The angle α is defined as the twist from planarity of the two N−Mn−O−C−C−C rings.

Figure 2. The barrier for a synchronous attack[14] lies 18 kJ/mol above TS **2**. The incoming ethene has a weak preference for an orientation parallel to the salen plane, the barrier for a perpendicular attack being 4 kJ/mol higher.[15] On the triplet surface, TS **2** leads to a free radical intermediate **3** with an sp^2-hybridized β-carbon. A manganaoxetane **4** with a weak Mn−C interaction was found 22 kJ/mol above **3**. The formation of **3** is also kinetically favored over **4** by 44 kJ/mol. The second C−O bond-forming step has a high barrier on the triplet surface (60 kJ/mol). The radical intermediate **3** is free to rotate since the barrier for rotation is much lower.[16] In addition there is no driving force from **3** to the coordinated epoxide **5** on the triplet surface since **3** and **5** are almost isoenergetic.

The quintet surface is much less complicated. In our theoretical model the ethene approach on the oxo ligand gives rise to a very early TS, 34 kJ/mol above the TS on the triplet surface (TS **2**). From the quintet TS, the reaction to epoxide product is monotonic and strongly exothermic. In the region of the first C−O bond-forming step, the quintet is close in energy to the triplet surface.

A pure quintet reaction cannot justify the experimentally observed selectivities since the alkene-to-oxo distance in the quintet TS is too long for steric interactions to exert any influence on the reaction. Moreover, in the beginning of the reaction the triplet state is energetically favored compared to the quintet. Our calculations also indicate that addition of ethene to the singlet oxo−manganese complex is endothermic with a high activation barrier. We therefore suggest the reaction to begin by alkene attack on the triplet surface, followed by spin change to the quintet surface which leads to the quintet epoxide product without a barrier.[17]

Electronic influence from the alkene substituents has been shown experimentally to affect the diastereoselectivity.[18] Accord-

ing to our interpretation of the calculations on ethene, vide supra, the timing of the triplet−quintet spin crossing might be affected by substituents resulting in a change in the cis−trans product ratio. We therefore performed preliminary calculations on 1,2-dimethoxy and 1,2-dinitroethene, as models for an electron-rich and electron-poor alkene, respectively.[19] The triplet−quintet energy difference for ethene is 37 kJ/mol in TS **2**, in favor of the triplet. For 1,2-dinitroethene this splitting is increased to more than 60 kJ/mol, but for 1,2-dimethoxyethene, the difference is only 12 kJ/mol. This suggests that the spin-crossing leading to quintet product should occur later on the reaction path for electron-poor alkenes, allowing C−C bond rotation before ring closure. Electron-rich alkenes will, for the same reason, yield more *cis*-epoxide since the spin transition will, to a larger extent, occur before the radical intermediate is formed.[20]

According to Jacobsen et al. addition of a conjugated alkene to the oxomanganese species generates a radical intermediate in a rate-determining first C−O bond-forming step (Scheme 1, pathway B). The radical intermediate partitions between collapse and rotation/collapse to provide a mixture of *cis*- and *trans*-epoxides. In their model the formation of the two products is preceded by a common TS in the first step. This is in accordance with our results provided that the spin change occurs after the TS for the first C−O bond formation. On the other hand the barrier for ring closure on the triplet surface is too high (see Figure 1) to avoid a thermodynamic distribution of the product isomers via rotation around the C−C bond. In other words, only spin change before the formation of the radical intermediate can account for the high yields of *cis*-epoxides that can be achieved under optimized conditions.[6,21]

In conclusion, the concept of spin change can explain the diastereoselectivity in the manganese(salen)-catalyzed epoxidation of alkenes. It can also offer a basis for improved control of cis−trans isomerization and enantioselectivity.

(13) (a) Bernardi, F.; Bottoni, A.; Canepa, C.; Olivucci, M.; Robb, M. A.; Tonachini, G. *J. Org. Chem.* **1997**, *62*, 2018−2025. (b) Singleton, D. A.; Merrigan, S. R.; Liu, J.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 3385−3386.
(14) The two C−O distances were kept equal in the calculations of the synchronous attack.
(15) Structure **2** is proven to be a true alkene addition TS, whereas the perpendicular counterpart has two imaginary frequencies where the lower mode corresponds to a rotation to **2**. However, steric influences from a substituted salen ligand could affect this energy difference.
(16) From MM3-calculations on analogues, the barrier to rotation in the benzylic radical derived from styrene is estimated to 5−10 kJ/mol. Cis substitution lowers the barrier further.

(17) The spin transition probability can be calculated using the Landau−Zerner formula (LZ). Such calculations have recently been performed on the reactions of e.g., FeO⁺ (a) Danovich, D.; Shaik, S. *J. Am. Chem. Soc.* **1995**, *119*, 1773−1786. (b) Shaik, S.; Filatov, M.; Schröder, D.; Schwarz, H. *Chem.−Eur. J.* **1998**, *4*, 193−199. (c) Shaik, S.; Danovich, D.; Fiedler, A.; Schröder, D.; Schwarz, H. *Helv. Chim. Acta* **1995**, *78*, 1393−1407. (d) Mitchell, S.; Blitz, M.; Siegbahn, P.; Svensson, M. *J Chem. Phys.* **1994**, *100*, 423−433. In our case, such calculations are very difficult due to the size of the system. The fact that the triplet and quintet surfaces in this system are nearly parallell also makes it difficult to determine the exact crossing point. However, the fact that the surfaces are parallell and close in energy also indicates a high spin transition probability according to LZ formula.
(18) Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martínez, L. E. *Tetrahedron* **1994**, *50*, 4323−4334.
(19) The triplet-quintet energy differences for the substituted ethenes were calculated in the geometry of structure **2**.
(20) These results are in accordance with Jacobsen's findings that electron-poor alkenes give more isomerization than electron-rich alkenes, ref 18. We have also seen a similar effect: for example, *cis*-4,4′-dimethoxystilbene gives 84% *cis*-epoxide, while *cis*-4,4′-dinitrostilbene gives 96% *trans*-epoxide: Åkermark, B.; Norrby, P.-O.; Linde, C., manuscript in preparation.
(21) It is interesting that while the formation of the manganaoxetane **4** is kinetically disfavored compared to the radical route (see Figure 1) it is thermodynamically accessible on the triplet surface. Formation of a manga-naoxetane (Scheme 1, pathway C) would stabilize the cis orientation of the substrate substituents on the triplet surface before spin change. We have earlier suggested that the enantioselectivity in the reaction largely can be traced to an implicit twist of the salen ligand in the selectivity-determining step, see ref 5a. The suggestion has been contested on the basis of observed structures of planar Mn(III)−salen complexes, see: Pospisil, P. J.; Carsten, D. H.; Jacobsen, E. N. *Chem.−Eur. J.* **1996**, *2*, 974−980. A twist conformation is adopted upon oxidation to **1**, the angle between the aromatic rings being 22° in our model system. In TS **2** the angle is smaller (5°) but is likely to increase in the real system where the backbone and the bulky C3(C3′) substituents impose an inherent twist preference. Such a twist conformation is strongly suggested also by the results of Katsuki et al.: ref 5b and Hashihayata, T.; Ito, Y.; Katsuki, T. *Synlett* **1996**, 1079.