methane. The diester **9** was isolated in 70% yield after chromatography (92% by ^{1}H NMR spectroscopy). The same experiment at 420 nm cleanly gave the diester **10** in 70% yield (70% by ^{1}H NMR spectroscopy). In other words, it was possible to perform a photochemical orthogonal deprotection of a bifunctional substrate.

In conclusion, we have shown that chromatic orthogonality is indeed possible, in both inter- and intramolecular cases. This new strategy could be successfully applied to orthogonal deprotection of bifunctional molecules and to wavelength-selective photorelease of compounds. We are currently investigating the possibility of adding a third dimension to the set, as well as testing applications in solution- and solid-phase organic synthesis.

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Rate Enhancement and Enantioselectivity of the Jacobsen – Katsuki Epoxidation: The Significance of the Sixth Coordination Site**

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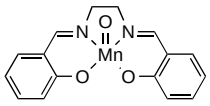
The oxygenation of olefins by high-valent transition metal oxo complexes is one of the most useful and elegant techniques for the functionalization of organic substrates. A breakthrough was the introduction of chiral manganese – salen catalysts by Jacobsen and co-workers,[1] with a similar system developed by Katsuki and co-workers.[2] The Jacobsen – Katsuki reaction is universally recognized as one of the most useful and widely applicable methods for the epoxidation of unfunctionalized olefins.[3, 4]

Despite the synthetic utility of this catalytic transformation, the origin of its high selectivity is not well understood. The key problems that mechanistic studies of the catalytic reaction cycle need to address are: 1) the nature of the oxygen-transferring species; 2) the mechanism of oxygen transfer to the olefinic substrate; and 3) the highly efficient stereochemical communication between catalyst and substrate. By electrospray tandem mass spectrometry, we were able to show that the reaction proceeds via an oxomanganese(v) complex as catalytically active species,[5] but the remaining questions are still open despite numerous experimental[6] and computational studies.[7]

Herein, we report on the results of a high-level computational study[8] of oxomanganese(v) – salen complexes of type **1** bearing different axial ligands. Axial ligation of the salen catalyst is known to have a favorable influence on the asymmetric induction. This has been explained by a shortening of the Mn–O bond length and a decrease of the reactivity of the oxo species upon axial coordination.[3d] We have recently shown experimentally that axial coordination of an *N*-oxide ligand at the oxomanganese(v) complex raises the oxygen transfer reactivity of the catalyst dramatically.[5d] The question arises why it is possible in this specific case of asymmetric catalysis to raise the



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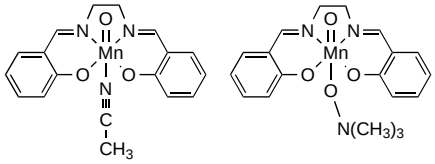
reaction rates as well as the enantioselectivities by axial coordination. We will show herein that the axial ligands have a profound effect on the conformation of the basal salen ligand, leading in the case of a strongly binding ligand to two steplike and one cup-shaped conformation.

In the absence of another ligand, the free binding site at the metal center is occupied by a solvent molecule. We studied this type of complexation for the case of the experimentally observed[5a,b] oxomanganese(v)–salen acetonitrile complex **2**.



2 **3**

To model the stronger binding *N*-oxide ligands commonly used as additives to enhance both reactivity and selectivity of the epoxidation,[3d, 9] we calculated the oxomanganese(v)–salen trimethylamine *N*-oxide complex **3**. All species were calculated by using the B3LYP hybrid functional in combination with a triple-zeta basis set. It was shown previously[5b, 7] that this functional yields qualitatively reasonable results, even though several of the species discussed here deviate significantly from the expected $\langle S^2 \rangle$ values.[10]

The structure of the oxomanganese(v)–salen complex **1** in its triplet and quintet state has been discussed previously.[5b] Contrary to the results of a recent study of a smaller model system,[7a] the singlet state of the oxomanganese(v)–salen complex, ^{1}**1**, is found to be 0.9 kcal mol^{-1} lower in energy than ^{3}**1** (Table 1). The axial Mn=O bond is calculated to be 0.05 Å shorter than in the previous studies, due to the larger triple-bond character, which needs a sufficiently flexible basis set for the description of the interaction of the 2p orbitals on the oxygen center with the $3d_\pi$ and the $3d_\delta$ orbitals on the manganese center.

Introduction of a weakly binding ligand shows the following effects. Whereas no binding occurs in the singlet state, the solvent in the triplet state ^{3}**2** is weakly bound with a bond length of 2.46 Å (see Figure 1). This, and the fact that the partial charge on the manganese center in the three spin states of **1** is virtually identical, indicates that the solvent ligand is weakly bound by the p-donation of a free electron pair of the solvent into an empty orbital at the manganese center rather than by an electrostatic interaction as implied by previous studies using a chloride ligand complexed to the metal.[7b,c] This interaction is stronger in ^{5}**2**, leading to a bond length of only 2.23 Å. The effect of the ligand binding on the geometry of the manganese–salen moiety is relatively minor. The axial Mn=O bond is 0.02 Å longer than that in **1**. The metal center, which is positioned above the plane of the four basal heteroatoms in **1**, moves into the plane and the salen ligand is slightly distorted towards a steplike, transoid conformation.

The much stronger binding of the acetonitrile ligand in ^{5}**2** does, however, have a strong effect on the relative energies of the spin states. The already small energy difference between the triplet and the quintet states in **1** is almost completely overcome by the additional binding energy of the solvent ligand, leading to virtually degenerate triplet and quintet states in **2**.

These trends are even more pronounced for a stronger axial ligand as shown for **3**. While, in contrast to ^{1}**2**, the structure of a ligand-bound singlet state ^{1}**3** could be located, it is quite high in energy and was not considered further. The deviations from the planar structure and bond lengths of **1** are relatively small for ^{1}**3**. However, strong deviations from a planar structure were obtained for the triplet and quintet states ^{3}**3** and ^{5}**3**, leading to the *cis* and *trans* forms of ^{3}**3** and ^{5}**3** shown in Figure 1.

Table 1. Calculated relative energies and dihedral angles for singlet, triplet, and quintet states of **1**–**3**.

Compound	E_{rel} [kcal mol^{-1}]	$\langle S^2 \rangle$	Dihedral angle 1 [°][a]	Dihedral angle 2 [°][a]
^{1}**1**	– 0.9	–	175.8	170.3
^{3}**1**	0.0	2.0973	170.4	174.1
^{5}**1**	6.8	6.0545	175.1	173.3
^{1}**2**	–	–	–	–
^{3}**2**	0.0	2.2118	162.1	174.4
^{5}**2**	0.5	6.0523	170.0	175.6
trans-^{1}**3**	10.8	–	166.1	169.6
trans-^{3}**3**	0.0	2.8122	153.3	167.0
cis-^{3}**3**	1.5	2.8164	154.6	162.9
trans-^{5}**3**	3.0	6.0488	153.5	170.9
cis-^{5}**3**	3.9	6.0455	165.6	162.9

[a] Defined as angle between the plane of the phenyl ring and the plane of the four heteroatoms.

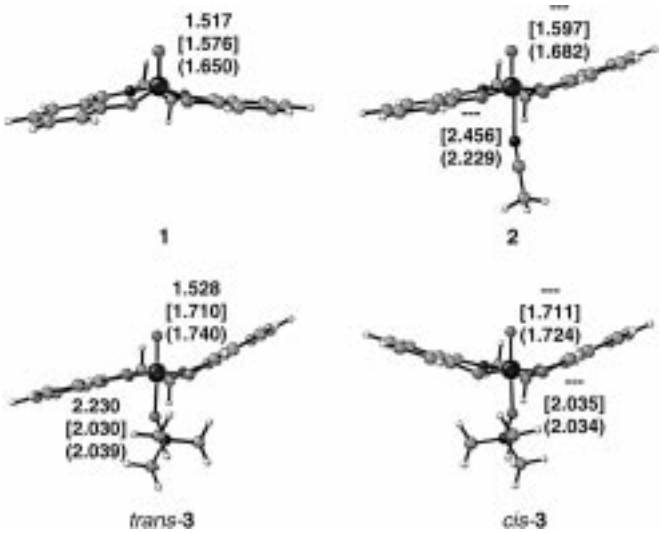


Figure 1. Structures of ^{3}**1**, ^{3}**2**, *trans*-^{3}**3**, and *cis*-^{3}**3** calculated at the B3LYP/6-311G* level. Bond lengths for singlet states are given without brackets, for triplet states in square brackets, and for quintet states in parentheses.

The axial bond lengths in these four structures for ^{3}**3** and ^{5}**3** are very similar. The Mn=O bond in **3** is approximately 0.1 Å longer than that in **2**, whereas the manganese–ligand bond is approximately 0.42 and 0.2 Å shorter in the triplet and quintet state, respectively. The triplet–quintet gaps are with 3.0 and 2.4 kcal mol^{-1} for *trans*-**3** and *cis*-**3**, respectively, again small. Although these energy differences are on the order of the

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accuracy that can reasonably be expected from the method used, an analysis of the geometry suggests that the triplet–quintet gap is slightly larger than in the case of **2** because ^{5}**3** does not benefit from increased binding of the ligand in the quintet state. Steric repulsion cannot be the reason for the ligand bending as the bulky trimethylamine *N*-oxide ligand is far away from the salen moiety of the molecule. The energy difference between the *trans* and the *cis* conformer in ^{3}**3** and ^{5}**3** is only 1.5 and 0.9 kcal mol^{-1}, respectively. This indicates that the stronger bonding of the ligand corresponds to a weakening of the Mn=O bond.

These results provide a structural basis to test several of the hypotheses that have been put forward to explain the high degree of asymmetric induction by manganese–salen complexes. The calculated structures of the hexacoordinate complexes **2** and **3** support the hypothesis of a family of nonplanar, enantiomorphic conformations that are in rapid equilibrium. For both spin states of **3**, we find in addition to the *trans* conformation, which would be equivalent to the stepped conformation proposed earlier,[3a, 11] an energetically slightly higher *cis* conformation. As shown in Table 1, the distortion is stronger in the triplet than in the quintet state. These findings, together with the fact that the distortion from planarity correlates with the donor ability of the ligand, suggest that this effect is electronic rather than steric in nature.[12]

Further corroboration for the presence of nonplanar conformations of axially ligated oxomanganese–salen complexes comes from electrospray MS experiments with authentic epoxidation catalyst mixtures. When spraying an in situ mixture of Jacobsen's catalyst ((*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III)triflate), *p*-CN-*N*,*N*-dimethylaniline *N*-oxide, and iodosobenzene, the oxomanganese(v) complex, but no dinuclear μ-oxo-bridged manganese(IV)–salen complex were detected. This observation is in striking contrast to the behavior of solutions of the arene-unsubstituted salen complexes used in our previous studies, where conproportionation of oxomanganese(v) and manganese(III) complexes plays a crucial role for parking the catalyst in a more persistent form. Inspection of a model of the μ-oxo-bridged manganese(IV) complex with the arene-substituted Jacobsen ligand in a planar conformation shows no apparent steric overcrowding as a possible reason for the failure to observe the μ-oxo-bridged species. This leads us to the conclusion that in the case of salen complexes bearing sterically demanding substituents the existence of highly nonplanar conformations precludes the conproportionation to dinuclear μ-oxomanganese complexes.

trans-^{3}**3** can exist in two enantiomeric forms, which can be transferred into diastereomers with the help of chiral axial ligands (e.g. *N*-oxides).[13] While the *cis* conformation will be destabilized by the approaching olefin or the epoxide product, the *trans* conformation will be destabilized by a large axial ligand. This could potentially be the origin of the observed lower enantioselectivity obtained with bulky *N*-oxides.[13] The geometry of *trans*-^{3}**3** also suggests that a side-on approach of the olefin might most favorably occur from the salicylaldehyde ring rather than from the imine portion,[2b] which would be hindered by the axial substituents on the ethylene bridge.

In addition to the influence on the conformation of the salen, the axial ligand decreases the triplet–quintet gap and lowers the energy of the open-shell states, making the triplet the ground state of **2** and **3**. Contrary to an earlier proposal,[3d] stronger binding of the ligand leads to a weaker Mn=O bond, which should increase the reactivity for an oxygen transfer.

The importance of the triplet to quintet spin crossing, which has been shown to occur after the rate-determining transition state along the reaction pathway, has been pointed out earlier.[7a] Although an explicit calculation of the spin transition probability is not feasible for a system of this size,[14] it can be assumed that a decrease in the triplet–quintet gap leads to a stronger interaction between the states and a higher spin transition probability. This would lead to the drastic rate enhancement for epoxidation observed in the gas phase as well as in solution.

The results presented here provide new insights into the origin of the reactivity and selectivity of the oxomanganese(v)–salen complexes based on hybrid density functional calculations using triple-zeta basis sets on the complete chemical system. The effect of the axial ligand on the rate enhancement and enantioselectivity of the Jacobsen–Katsuki reaction should be quite general as all published epoxidation protocols contain potential axial ligands in the form of additives, counterions, or solvents. The structures obtained could help in the design of new and more effective asymmetric catalysts and additives for this and related reactions catalyzed by transition metal salen complexes.

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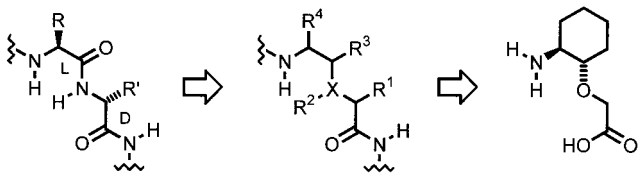
Cyclohexylether δ-Amino Acids: New Leads for Selectivity Filters in Ion Channels**

Hans-Dieter Arndt, Andrea Knoll, and Ulrich Koert*

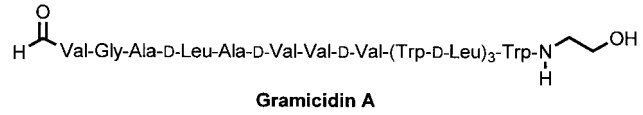
Biological ion channels are key molecules for cellular regulation and communication. They couple (bio)molecular events to electric signals.[1] This property of natural pore-forming substances has been utilized in engineering biosensors.[2] In order to use synthetic channel structures[3] as sensors or implants in biological systems, they have to meet requirements in two areas: ion selectivity[3e, 4] and gating.[5] We report here on novel oligomers made from δ-amino acids that led to H^+- and NH_4^+-selective ion channels.

On substituting the central amide bond of a dipeptide, a δ-amino acid is obtained (Scheme 1).[6] Besides offering structural diversity at four positions, a δ-amino acid allows incorporation of a heteroatom in the continuous backbone.[7] If one chooses an oxygen and constricts the degrees of conformational freedom with a cyclohexane ring, the ether amino acid (AA) **1** results.

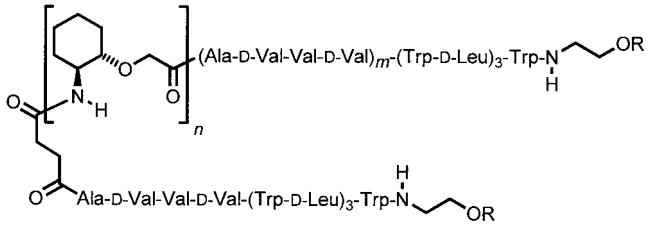


Scheme 1. From D,L-dipeptides to the stereoequivalent δ-amino acid **1**, a new building block for cation channels.

The selectivity filters of biological K^+ and Ca^{2+} channels are lined with backbone atoms.[8a,b] In the ion channel active, but weakly selective, $\beta^{6.3}$-helical dimer of the D,L-peptide gramicidin A (gA) only backbone amides are exposed towards the



Gramicidin A



2 (n = 2, m = 1)
3 (n = 4, m = 1)
4 (n = 6, m = 0)

R = tBuPh$_2$Si

interior.[8c] The incorporation of δ-AA **1** with its ether oxygens should offer additional binding sites for a cation in the lumen.[9] Our target compounds **2**–**4** were chosen by combining di-, tetra-, and hexameric δ-AA segments with functionally important sequences from gA to yield structures with the approximate total length of the gA dimer.[10, 11]

The synthesis of the compounds incorporating δ-AA **1** starts from cyclohexene epoxide **5**, which was transformed to the azido alcohol according to the method of Jacobsen and coworkers[12] (94% yield, 93% *ee* under optimized conditions, Scheme 2). Alkylation with *tert*-butylbromoacetate using phase-transfer catalysis[13] gave masked δ-AA monomer **6** (95%; R = tBu),[14] which was homodimerized to **9** via a mixed anhydride (R = COCMe$_3$; formed from **7** (step e in Scheme 2)). Dimer **9** could be obtained isomerically pure by crystallization (n-hexane/Et$_2$O (7:1), Figure 2). After elongation with a succinate building block, the resulting diester **10** was connected at both termini with the α-peptide **11**[11] to yield the target compound **2**. Compounds **3** and **4** were similarly synthesized (see Supporting Information).[14]

The compounds **2**–**4** were then examined for their ion channel forming activity.[15, 16] The compounds with tetra- and hexameric δ-peptide units, **3** and **4**, did not form detectable cation channels. But they induced short-lived proton channels when applied in concentrations above 100 nM (Figure 1a, b). Probably, a bottleneck conformation permits only protons to pass.[17]

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