

Jacobsen's Catalyst for Hydrolytic Kinetic Resolution: Structure Elucidation of Paramagnetic Co(III) Salen Complexes in Solution via Combined NMR and Quantum Chemical Studies

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Chiral salen metal complexes are of great importance as catalysts for enantioselective transformations. A special field, where Jacobsen's Co(III) catalysts are employed,¹ is their application for hydrolytic kinetic resolution (HKR), using water as a nucleophile for the ring opening of epoxides. Although it seems that association of epoxide with the salen complex is not responsible for enantioselection,^{2–4} a remaining crucial question is how selectivity is achieved: In a widely accepted proposal derived from kinetic measurements, the nucleophile consists of a — not observed — second catalyst species, which in turn would need to be able to differentiate between the two diastereomeric epoxide complexes.² Herein, we report an *in situ* solution NMR study of chiral salen Co(III) complexes combined with state-of-the-art density functional calculations of NMR shielding tensors for diamagnetic as well as paramagnetic systems.⁵ This sheds light on coordination as well as electronic and conformational properties of these compounds, which are essential for an understanding of the mechanism of this reaction.

Our investigation of the paramagnetic behavior of complexes of the type *R,R*-(salen)Co(III)X (with X = Cl, OAc, 3,6-difluorophenolate, OTs, SbF₆)⁶ revealed that Co(III) can change between a low-spin, hexacoordinated and a high-spin, pentacoordinated state, depending on axial ligands, solvent, and temperature (cf. Scheme 1):⁷ in noncoordinating solvents like dichloromethane (DCM), (salen)Co(III)Cl (**1**) shows a temperature dependence consistent with Curie's law,⁸ in agreement with observations made for square-pyramidal Co(III) complexes. Moreover, the magnetic susceptibility of **1** in DCM (χ_i at 298 K = 0.0310 mL mol⁻¹, $\mu_{\text{eff}} = 2.42$)⁹ is in the region for complexes with a spin quantum number 1, in line with paramagnetic, high-spin triplet Co(III) (d⁶). Figure 1a shows the spin-density distribution in open-shell **1**. The equilibrium between the paramagnetic and diamagnetic complexes can be observed for **1** in THF over a range of temperatures, yielding paramagnetic NMR spectra at increased temperatures (Figure 1b) and diamagnetic spectra at lower temperatures (~250 K).¹⁰

In more strongly coordinating solvents like pyridine, the NMR signals of **1** are those of a completely diamagnetic species. The observation of this spin-state transition is of special interest, since the coordination properties of THF and epoxides are comparable. Quantitatively, the fraction of paramagnetic species present at different temperatures, as well as association enthalpy and entropy, can be assessed from the fast equilibrium, taking into account Curie's law.¹¹

We were able to observe ligand exchange signals between both sides of the tetradentate ligand (for both aromatic and cyclohexyl

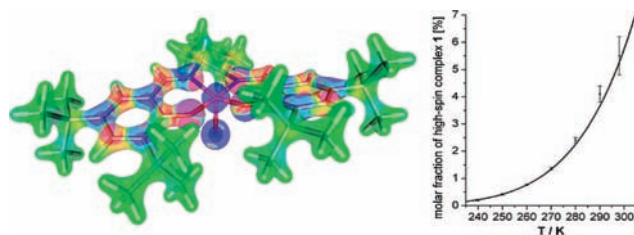
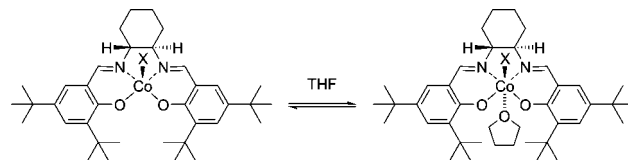


Figure 1. (a) Spin-density distribution⁵ in high-spin **1** (± 0.0003 au), mapped on an electron density surface (0.10 au); positive spin density is indicated in blue, negative spin density in red. (b) Molar fraction of the high-spin complex **1** in THF solution as a function of temperature.

Scheme 1. Equilibrium between Pentacoordinated, High-Spin (Paramagnetic) *R,R*-(salen)Co^{III}X Complex and Hexacoordinated, Low-Spin (Diamagnetic) *R,R*-(salen)Co^{III}X(THF) Complex



protons) through acquisition of ¹H–¹H NOESY spectra of **1** at 275 K in THF. This can only be explained by anion exchange¹² of the octahedral complex, confirming clearly the involvement of this paramagnetic Co(III) species and thus of the associated, facile spin-state transition.

Regarding the enantioselective step in HKR, understanding of the association of chiral salen complexes with chiral epoxides is of particular interest. We utilized pulsed-field gradient (PFG) NMR techniques¹³ to determine self-diffusion coefficients of (salen)Co(III)OAc (**2**)¹⁴ and styrene oxides in THF. Diffusion measurements proved that association constants of matching or mismatching epoxide enantiomers cannot play a decisive role in the selectivity of the HKR: only at temperatures below 250 K a notable degree of coordination is observable. For a detailed study of the association behavior, titration experiments with complex **1** and epoxide enantiomers were carried out in DCM. Coordination could be monitored in this way at rt, because of the strong paramagnetism of **1** under these conditions. While there is a measurable difference in chemical shifts for a given proton signal of the complex in the presence of equal amounts of either the *R* or the *S* epoxide enantiomer, the difference in the amount of epoxide–catalyst complex is only moderate: even at a ratio of 20 equiv of epoxide, only 16.5% associated complex exists in the case of the *S* enantiomer, and 13.9% for the *R* enantiomer. In agreement with results obtained for diamagnetic aziridine/(salen)Co(III) complexes,⁴ this is evidence for a somewhat stronger coordination of the matched

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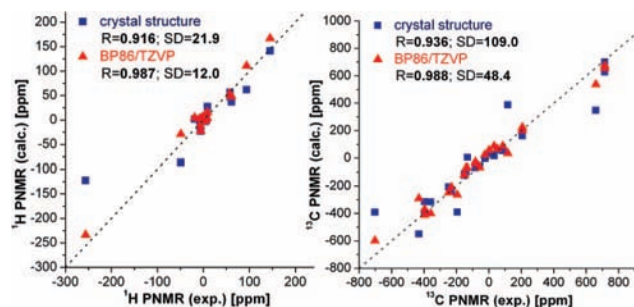


Figure 2. Computed vs experimental isotropic ^1H (left) and ^{13}C (right) NMR shifts of high-spin **1**. B3LYP/PCM results⁵ for the crystal structure (ref 15; blue squares) and for a BP86/TZVP optimized structure⁵ (red triangles), with extended basis sets.⁵ The dashed line indicates ideal agreement with experiment. “R” stands for correlation coefficients, “SD” for standard deviations.

enantiomer with the pentacoordinated complex. However, the small differences prove again² that the selectivity is not achieved at this point of the reaction.

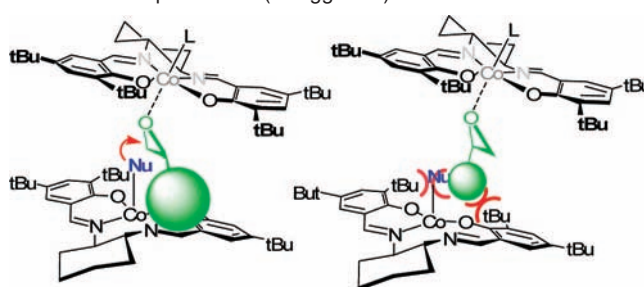
The titration allows a partial assignment of the paramagnetic chemical shifts of the Co(III) high spin complex. Together with quantum chemical calculations of structure and NMR shifts, the structure of the complex could be determined.^{5,15}

The BP86-optimized⁵ structure of the pentacoordinated high-spin complex reveals that the two “paddles” of the bulky aromatic groups are in a twisted and slightly stepped conformation. Similar conformations were also reported for the X-ray structures of non-Co salen complexes.¹⁷ Extensive asymmetry of pentacoordinated complex **1** is also evident from the large difference between ^1H and ^{13}C NMR shifts, respectively, of imine groups and ^{13}C shifts of aromatic C-3 carbon atoms (with attached *tert*-butyl group) on two different halves of the salen ligand.¹⁸ Interestingly, the crystal structure of the pentacoordinated complex itself,¹⁶ which shows a higher deviation of the calculated shifts (cf. Figure 2), does not exhibit such a pronounced twist, possibly due to packing effects. The optimized⁵ conformation of the octahedral low-spin complex in solution (THF) shows a much less distinctive stepping than the crystal structure recently published for low-spin Co(III) salen complexes coordinated with chiral aziridines.³ The much more pronounced asymmetry of the paramagnetic complex gives it a key role for the stereoselectivity of the HKR. While the epoxide is activated in an octahedral complex, the activated nucleophile may be a pentacoordinated, paramagnetic complex.

Together with the concept of a “head-to-tail” alignment of the catalysts¹ this provides an explanation for the observed stereoselectivity: an attack of the activated OH-nucleophilic complex on the “matched” epoxide complex, as depicted in Scheme 2, is sterically favored compared to an attack on the mismatched epoxide complex, which is rendered difficult by a hindered approach of the OH group toward the accessible side of the oxirane. Stereoselectivity is therefore induced by the pentacoordinated complex in two ways: it allocates space for the residue of the matched epoxide on the one side and (in the transition state) forces the second catalyst unit to a slightly staggered conformation on the other one. The octahedral catalyst complex thereby serves as a bulky “substituent” of the epoxide.

In HKR with chiral salen Co(III) complexes, attack of the nucleophile must take place in an enantioselective manner. Since both the dia- and paramagnetic complexes show matched conformations only in a “staggered” approach toward the “matched” epoxide, such an attack would account for the observed stereose-

Scheme 2. Proposed Matched (Left) and Mismatched (Right) Transition Complex of the (“Staggered”) Attack^a



^a The ring opening of the Lewis acid activated epoxide with the high-spin complex (activated nucleophile) is favored in the case of the R-epoxide.

lectivity. The existence of a paramagnetic, high-spin Co(III) complex also explains why no activated nucleophile complex could be observed until now. Work to elucidate the structure of this species and to apply the approach to paramagnetic epoxidation catalysts is currently underway in our laboratories. This involves also computational optimization of relevant transition states.

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Supporting Information Available: Experimental and computational details, NMR spectra of **1** in THF and CH_2Cl_2 , Curie law behavior of **1**, association enthalpy and entropy of **1** with THF and *S/R* styrene oxide, diffusion coefficients, NMR titration experiments, UV-vis spectra of **1–3**, optimized structures, and calculated energies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- See Tables S1 and S2 in the Supporting Information.

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