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Novel Contributions to the Mechanism of the Enantioselective Hydrogenation of Dimethyl Itaconate with Rhodium Complexes

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Itaconic acid and its derivatives such as dimethyl itaconate can easily be transformed into pharmaceutically interesting chiral methyl succinates via enantioselective hydrogenation.[1] In contrast to α-[2] and β-dehydroamino acid derivatives[3] mechanistic investigations concerning itaconates are hardly available. Investigations of the system Rh–dipamp/dimethyl itaconate (dipamp = 1,2-ethandiylbis[(2-methoxyphenyl)phenylphosphine]) by Brown et al. resulted in the detection of only one species in the ^{31}P NMR spectroscopy at −45 °C. From the rather large P–P coupling constant of 40 Hz they concluded the coordination of the C–C double bond and the β-carboxy group to the rhodium center.[4] Line-shape analysis of ^{31}P NMR spectra of the substrate complexes of dimethyl itaconate with a Rh–bisphosphinite and an aminophosphine–phosphinite provided support for a significantly higher rate of the intramolecular interconversion between the diastereomers compared to the intermolecular conversion via the solvate complex.[5] For the Rh–DPPP complex (DPPP = 1,3-bis(diphenylphosphino)propane) the formation of the hydrido alkyl species was shown to be reversible in H/D exchange studies.[6] By means of the PHIP method catalyst–substrate dihydride complexes could be detected in the asymmetric hydrogenation of dimethyl itaconate with cationic rhodium(I)–bis(phosphinite) complexes.[7] Reetz and co-workers studied the mechanism of enantioselective hydrogenation of dimethyl itaconate with Rh complexes containing monodentate binol-based phosphites.[8] DFT calculations support the validity of the lock-and-key principle[9] which was already proven experimentally for one α- and several β-dehydroamino acid derivatives.[2b,3]

The present work provides mechanistic insights into the hydrogenation of dimethyl itaconate with [Rh(dipamp)-$(MeOH)_2$]BF_4.

The hydrogenation of dimethyl itaconate with [Rh-(dipamp)$(MeOH)_2$]BF_4 proceeds via the expected Michaelis–Menten kinetics. Independent of the substrate concentration average values of the pseudo-rate constant $k_2 = 83\ min^{-1}$ and the Michaelis constant $K_m = 1.66 \times 10^{-2}\ mol\,L^{-1}$ result, as well as an enantioselectivity of 91 % (see Supporting Information).[10]

The quite large value of the Michaelis constant demonstrates the stability of the catalyst–substrate complexes for the system [Rh(dipamp)$(MeOH)_2$]BF_4/dimethyl itaconate to be about three orders of magnitude smaller in methanol at 20 °C than the stability constant determined by Halpern et al. for the very same catalyst but with the prochiral olefin (*Z*)-methyl acetamido cinnamate ($6.8 \times 10^4\ L\,mol^{-1}$, derived from activation parameters of ref. [2a] versus $6.0 \times 10^1\ L\,mol^{-1}$).

The ^{31}P NMR spectra for different catalyst/substrate ratios taken at room temperature show only broadened signals of one catalyst–substrate complex. Even at a five-fold excess of substrate only 85 % of the rhodium are present as substrate complex. This confirms the low stability of the intermediates already derived from kinetic measurements.

By cooling the solution containing a five-fold excess of substrate the signals become sharper and the P–Rh and P–P couplings are accessible. Furthermore, an additional signal set appears, presumably the corresponding minor diastereomer (see Supporting Information).

Single crystals for X-ray analysis were isolated from a solution of [Rh(dipamp)$(MeOH)_2$]BF_4 and dimethyl itaconate after slow diffusion of diethyl ether into the solution. Figure 1 shows the respective X-ray structure.[11,12] To the

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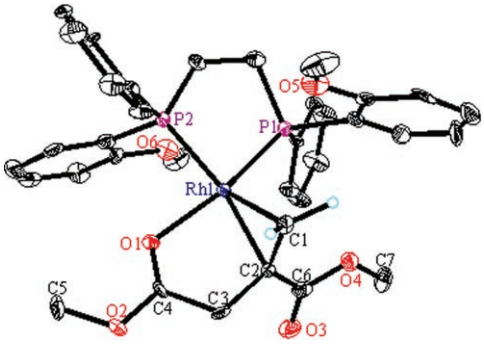

Figure 1. X-ray structure of the complex [Rh((*S*,*S*)-dipamp)(dimethyl itaconate)]BF_4 (ORTEP, 30% probability ellipsoids) One complex cation, both BF_4 anions and most hydrogen atoms are omitted for clarity. Selected distances and angles as well as details to the structure can be found in the Supporting Information.

best of our knowledge it is the first X-ray structure of a Rh–bisphosphine complex with an itaconic acid derivative.

The substrate coordinates via the C–C double bond and the β-carboxyl group, forming the larger of the two possible rings. The described coordination mode is thus similar to known X-ray structures of different α-[2c,13] and β-dehydroamino acid complexes[3] of the Rh–dipamp system.

Formal hydrogenation of the catalyst–substrate complex shown in Figure 1 would lead to the *R* product. Due to the fact that the hydrogenation yields the opposite enantiomer in excess the system seems to correspond to the major/minor principle[9] if the isolated complex can be assigned to the major substrate complex.

Due to the low solubility of the catalyst–substrate complex at low temperature a correlation of the isolated diastereopure single crystals to one of the ^{31}P NMR signal sets via freezing out the interconversion at low temperature is not possible.[2c]

However, also CD spectroscopy[14] does not lead to any result. Due to the low stability of the catalyst–substrate complex [Rh(dipamp)$(MeOH)_2$]BF_4 results, which thus disturbs the measurements with its own CD signals (see Supporting Information).

Solid-state NMR is an alternative method.[15] 100 mg of single crystals (0.12 mmol) of the substrate complex were isolated from a solution of Rh–dipamp solvent complex and dimethyl itaconate and powdered for the NMR measurements. The sample was proven to contain single crystals of equal sizes by X-ray powder diffractometry (Supporting Information) (see Supporting Information).

Interestingly, four different NMR signals (each is doublet due to heteronuclear (P–Rh) *J* couplings (c.f. Table 1)) are found in equal intensity ratios (Figure 2). Furthermore, a ^{31}P double quantum experiment (DQ) was carried out (Figure 3). In this spectrum two DQ pairs are found at DQ frequencies about 117 and 130 ppm (vertical axis) which are highlighted by the horizontal lines. This result shows that two P atoms with signals at $\delta = 71.0$ and 59.9 ppm are in close spatial proximity as well is the case for the P atoms with resonances at 66.4 and 51.1 ppm. These results are interpreted as two structurally slightly different molecules per unit cell (Supporting Information).

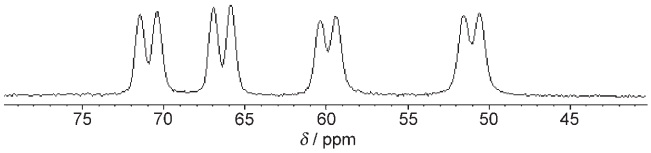

Figure 2. ^{31}P-CP/MAS NMR spectrum of [Rh(dipamp)(dimethyl itaconate)]BF_4.

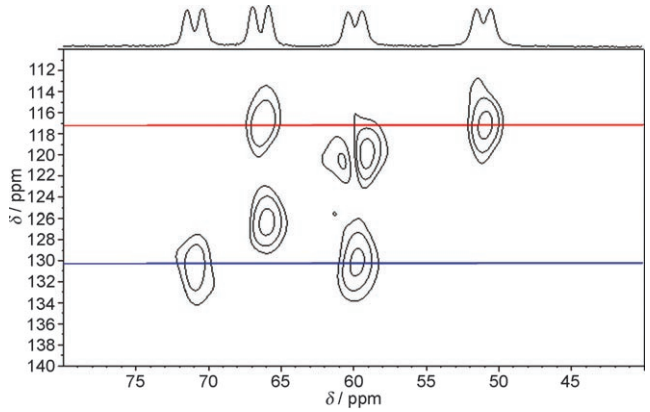

Figure 3. Double quantum experiment for homonuclear correlation of the ^{31}P NMR signals. Two DQ peak pairs at 117 and 130 ppm are found (marked by the horizontal lines) indicating spatial proximity of the respective sites. The remaining signals are single-quantum artifacts.

In Table 1 the chemical shifts and P–Rh couplings of the solid-state NMR measurement are compared with the data of the low-temperature NMR measurement at −80 °C.

Table 1. Comparison of the low-temperature NMR data of [Rh(dipamp)(dimethyl itaconate)]BF_4 in solution at −80 °C with the NMR data of the solid-state NMR measurement.

		P_{Maj1}^{low-T}	P_{Min1}^{low-T}	P_{Maj2}^{low-T}	P_{Min2}^{low-T}
Solution NMR	δ [ppm]	69.5	78.2	49.1	55.0
	J_{P-Rh} [Hz]	*174*	154	*154*	150
		P_{A1}^{solid}	P_{B1}^{solid}	P_{A2}^{solid}	P_{B2}^{solid}
Solid-state NMR	δ [ppm]	71.0	66.4	59.9	51.1
	J_{P-Rh} [Hz]	*171*	*171*	*159*	*159*

Due to the huge differences between solid-state and solution NMR, the chemical shifts are not qualified for a correlation of the solid-state NMR signals with either major or minor substrate complex. However, the analysis of coupling constants leads to pairs which match quite well: The coupling constants 171/159 Hz of the diastereopure substrate complex characterized by solid-state NMR correlate much better with the data of the major diastereomer in solution (174/154 Hz) than with the respective data of the minor substrate complex (154/150 Hz).

Thus, the experimental results prove that indeed the major substrate complex was isolated. Since it does not lead

to the main enantiomer formed during hydrogenation the major/minor concept should most likely be valid for the hydrogenation of dimethyl itaconate with [Rh(dipamp)-$(MeOH)_2$]BF_4.

In summary, dimethyl itaconate forms two diastereomeric catalyst–substrate complexes with [Rh(dipamp)-$(MeOH)_2$]BF_4, which are, however, significantly less stable than known Rh–dipamp complexes with α- und β-dehydroamino acid derivatives. X-ray analysis of the isolated substrate complex shows the coordination of the olefinic double bond and the β-carbonyl oxygen. The isolated complex leads to the minor enantiomer in hydrogenation and can be identified as major intermediate via solid-state NMR spectroscopy. Hence, the major/minor principle should be valid for the hydrogenation in methanol.

Keywords: asymmetric catalysis · hydrogenation · kinetics · reaction mechanisms · rhodium

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[9] In the lock-and-key principle the major enantiomer leads to the stereochemical main product. In case of the major/minor principle, however, the lower concentrated minor substrate complex dictates the stereochemical outcome concerning product formation dominantly by its tremendously higher reactivity.

[10] Already at 25 °C the hydrogen consumption cannot be measured without diffusion influence. H.-J. Drexler, A. Preetz, T. Schmidt, D. Heller, "Kinetics of Homogeneous Hydrogenations: Measurements and Interpretation" in *The Handbook of Homogeneous Hydrogenation* (Eds.: J. G. de Vries, C. J. Elsevier), Chapter 10, Wiley-VCH, Weinheim, **2007**, pp. 257–296.

[11] CCDC 670412 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[12] Two independent complex molecules per unit cell were found which differ only slightly in geometry, see Supporting Information.

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