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Unusual Deactivation in the Asymmetric Hydrogenation of Itaconic Acid

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Dedicated to I. Ojima.

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Abstract: During the asymmetric hydrogenation of itaconic acid with rhodium solvate complexes of the type $[Rh(PP)(MeOH)_2]$ BF_4 (PP = DIPAMP, MeDuPHOS) a deactivation with increasing substrate concentration is observed. It is shown that this inhibition phenomenon is due to the *in situ* formation of an inactive rhodium(III)-alkyl complex. Two crystal structures of single crystals of the responsible complexes (**1**) and (**2**) support the deactivation pathway.

Keywords: asymmetric catalysis; hydrogenation; phosphane ligands; rhodium

Introduction

Itaconic acid and its derivatives can effectivelly be transformed by enantioselective hydrogenation into methyl succinates,[1] which are also pharmaceutically interesting compounds.[2] However, in contrast to α-[3] and β-dehydroamino acid derivatives,[4] only a few mechanistic investigations exist.[5]

In 1978, the formation of substrate complexes from itaconic acid and the cationic Rh(I) solvate complexes with BPPM {*N*-(*tert*-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine} and PPPM {*N*-pivaloyl-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine)} as ligand was firstly investigated by Ojima using NMR spectroscopy.[6] Temperature-dependent investigations on catalyst-substrate complexes from itaconic acid and the Rh/BPPM, Rh/BZPPM {*N*-(benzoyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine} and Rh/DIPAMP {1,2-bis[(2-methoxyphenyl)-(phenyl)phosphino]ethane} systems were also described by Achiwa and Brown.[7] The authors concluded from NMR data that the substrate coordinates to the metal *via* three centers: the C=C double bond, and the α- and the β-carboxylate oxygen. Brown et al. furthermore observed a decolorization of the solution over time for the Rh/DIPAMP/itaconic acid system in methanol,[7b] which encouraged the authors' assumption of two coordinated carboxylate functions.

The influence of basic additives, mainly triethylamine, on the selectivity and activity of the hydrogenation of itaconic acid has been described several times with different results.[6,8,9] For DIPAMP[8c] and the aryl-substituted BCPM {*N*-(*tert*-butoxycarbonyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine} ligand,[10] it was reported that selectivity and activity increase with decreasing substrate concentration. Utilizing the PHIP methodology, the reversibility of the asymmetric hydrogenation of itaconic acid with [Rh(Ph-β-glup-OH)(COD)] BF_4 [Ph-β-glup-OH = phenyl-2,3-bis(*O*-diphenylphosphanyl-β-D-glucopyranoside)] could be proven.[11]

Initial studies in our group on the hydrogenation of itaconic acid with the Rh/DIPAMP catalyst in methanol surprisingly showed that conversions continuously decreased with increasing substrate concentration under otherwise identical conditions (Figure 1).

This preliminary finding suggested an apparent substrate inhibition.[12] The hydrogenation of 0.54 mmol of itaconic acid[13] with the DIPAMP-solvate complex [0.01 mmol catalyst in 15 mL MeOH at 25 °C and under normal pressure (standard conditions)] was fin-

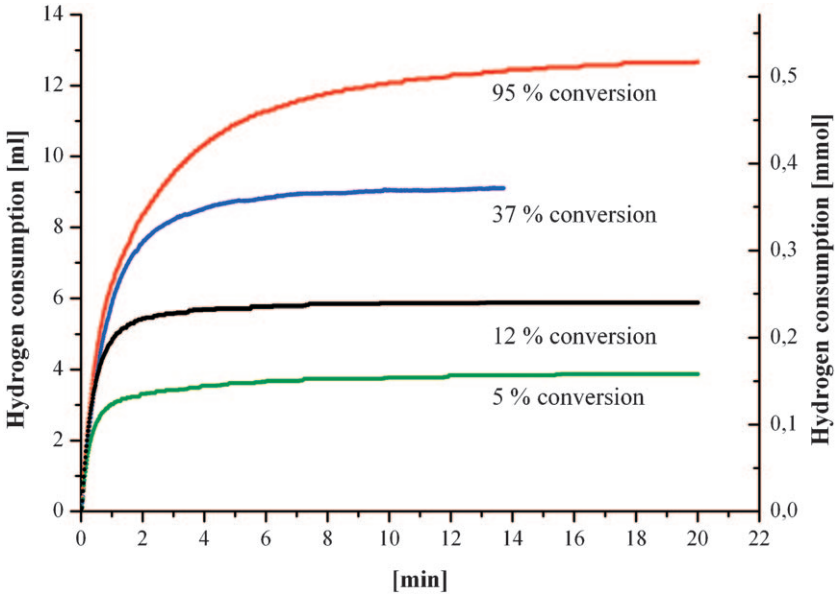

Figure 1. Hydrogenation of itaconic acid with [Rh(DIPAMP)(MeOH)$_2$] BF_4 (0.01 mmol cat., 15.0 mL MeOH, 25.0 °C, 1.01 bar total pressure): variation of substrate concentration [red = 0.54 mmol, (*ee* 76%), blue = 1.0 mmol, black = 2.0 mmol, green = 3.5 mmol (*ee* 85%)].

ished after only a few minutes with almost complete conversion. Increases of the substrate concentration showed that the achievable conversion continuously decreased. Increased dilution by variation of the solvent volume also led to higher conversions under otherwise identical conditions.

Although analogous experiments with Me-DuPHOS [1,2-bis(2,5-dimethylphospholano)benzene] showed complete conversion in all cases, the activity still decreased drastically with increasing concentration, of itaconic acid, see Supporting Information.

Therefore, the objective of this work was to identify the causes of the substrate concentration-dependent deactivation.

Results and Discussion

The investigation of the conversion of itaconic acid with [Rh(DIPAMP)(MeOH)$_2$] BF_4 at ambient temperature under an argon atmosphere showed that the solution decolorized within minutes from orange *via* yellow to almost colorless (an observation that was also made with Me-DuPHOS as ligand and during hydrogenations). Due to the fast transformation, the only state that could be investigated was the one in which the decolorization was already completed. In the ^{31}P NMR spectrum of the colorless solution two complexes were detected (Figure 2), which had significantly smaller P,P coupling constants in comparison

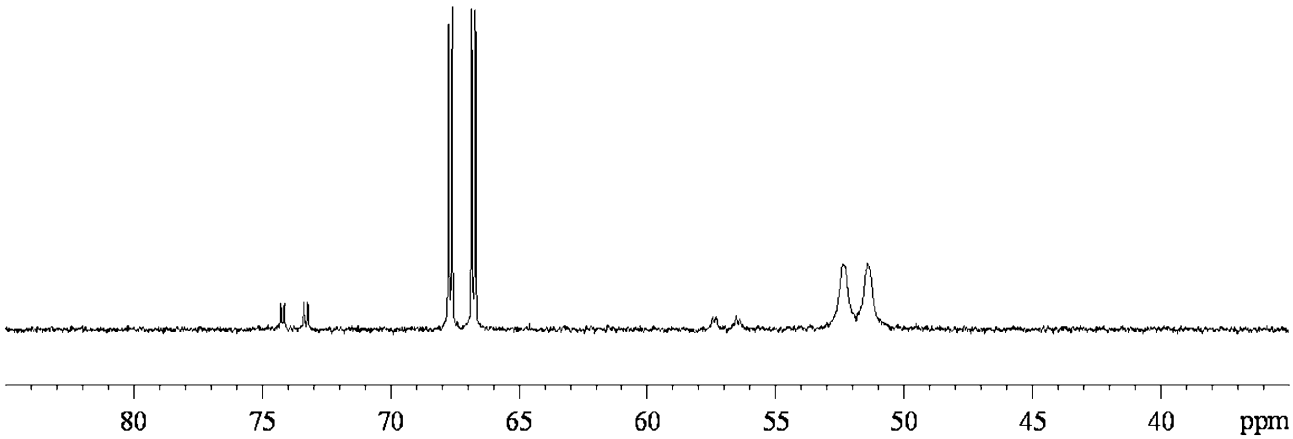

Figure 2. ^{31}P NMR spectrum of a solution of [Rh(DIPAMP)(MeOH)$_2$] BF_4 and itaconic acid (Rh:substrate = 1:40). The sample was measured 30 min after preparation under argon (colorless solution).

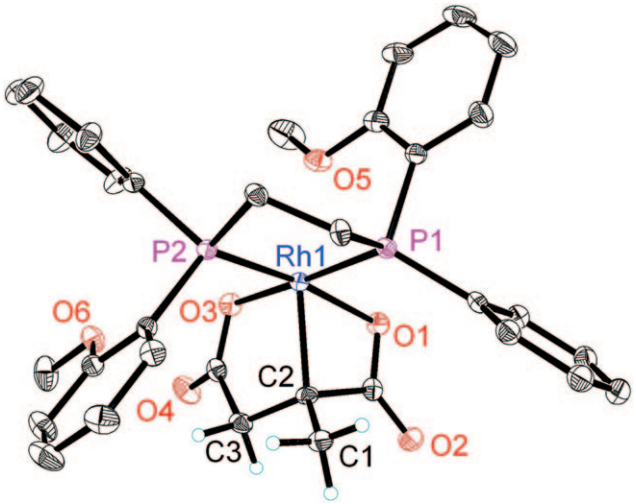

Figure 3. X-ray structure of (**1**) (ORTEP, 30% probability ellipsoids). Two molecules of methanol as well as the hydrogen atoms except for those on C1 and C3 are omitted for clarity.

to complexes with the dimethyl ester[5a] analogue indicating a different binding mode.

Although an isolation of the transient orange intermediate, which formed at first at ambient temperature succeeded neither at ambient nor at lower temperatures, single crystals could be isolated from the already colorless solution of [Rh(DIPAMP)$(MeOH)_2$] BF_4 and itaconic acid.

The X-ray structure (Figure 3), surprisingly, revealed that the substrate was not coordinated *via* the C=C double bond and one carboxylate oxygen as proven by X-ray analysis for dimethyl itaconate and comparable prochiral olefins with the DIPAMP catalyst[3c,4,5a,14], but instead *via* the two carboxylate oxygens and the quartenary carbon atom.[15] In this tridentate complexation that has already been described by Brown et al.[7b] the acidic functions of the substrate are deprotonated, the methylene group has been converted into a methyl through hydride transfer from the rhodium center and the tetrafluoroborate counterion is no longer present. Thus, complex (**1**) represents a neutral Rh(III)-alkyl complex, which had not been described in the literature before.[16]

^1H and ^{13}C NMR measurements of the single crystals of (**1**) dissolved in methanol confirmed the presence of the methyl group in complex (**1**) in agreement with the respective X-ray structure instead of the methylene group that is present in the free substrate, see Supporting Information.[17] The respective ^{31}P NMR spectrum showed that the usual equilibration to the assumedly diastereomeric complex of (**1**) was surprisingly not observed, see Supporting Information. Only signals of the "major complex" were detected in contrast to the ^{31}P NMR spectrum generated *in situ* (Figure 2). Thus it could be proven that the isolated single crystals of (**1**) correspond to the complex present in large excess in solution.[18]

Figure 4 shows the mechanism of the catalytic hydrogenation (*left*) – that can be accelerated by increasing the hydrogen pressure – along with the proposed deactivation pathway (*right*) leading to the formation of complex (**1**).

Initially, the substrate displaces two molecules of MeOH in the solvate complex in order to form bischelating diastereomeric substrate complexes. This type of intermediate was isolated and proven by X-ray structure for the analogue dimethyl itaconate[5a] and is the commonly observed species for α- and β-dehydroamino acid derivatives reacting with a Rh-bisphosphine solvate complex.[3,4] In the next step of the proposed deactivation pathway deprotonation of the β-carboxyl function follows. Consequently a basic ad-

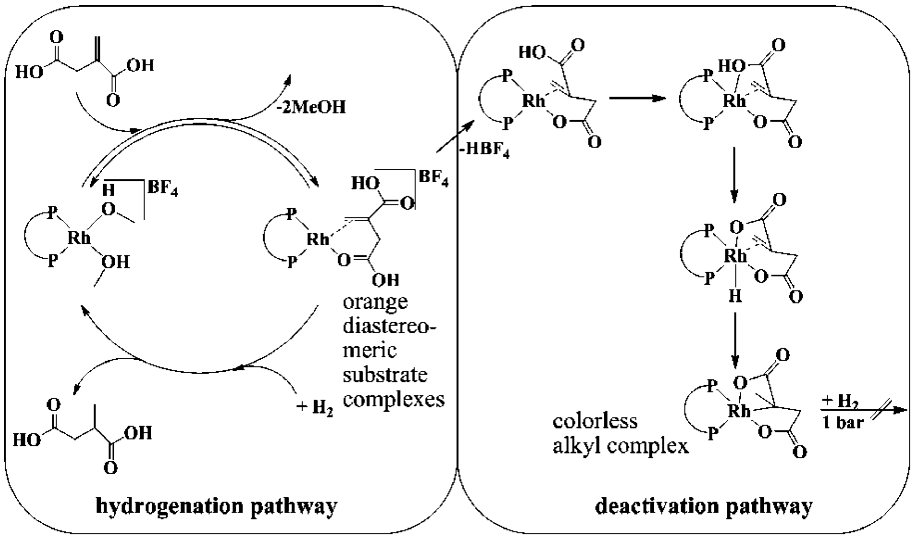

Figure 4. Reaction sequence for the usual hydrogenation and the deactivation pathway.

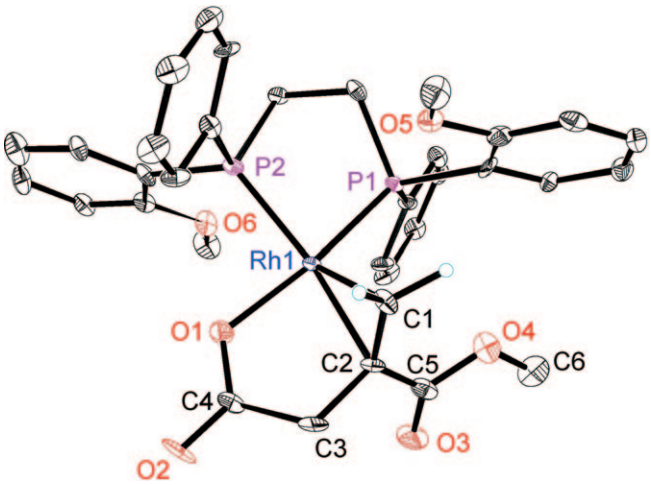

Figure 5. X-Ray structure of (**2**) (ORTEP, 30% probability ellipsoids). The hydrogen atoms except for those on C1 are omitted for clarity.[19]

ditive such as NEt_3 yields also complex (**1**) (NMR and X-ray).

The X-ray structure of a crystal obtained from a solution of [Rh(DIPAMP)$(MeOH)_2$] BF_4 and α-methyl itaconate (Figure 5) further supports this pathway.

Subsequently, the α-carboxyl function coordination is followed by a hydride transfer to the rhodium. Such a complex probably quickly converts into the respective Rh(III)-alkyl complex at ambient temperature.[20]

We postulate that the isolated complex (**1**) is not involved in the hydrogenation owing to the fact that the oxidative addition of hydrogen is formally impossible on a Rh(III) complex.[21] Indeed, addition of hydrogen to a methanolic solution of crystals of (**1**) only showed the signals of the Rh(III)-alkyl complex in the ^{31}P NMR even after 24 h. The solvate complex as result of the stoichiometric product formation was not detected. Also, the formation of product is not observed by ^{1}H NMR; the complex does not react with hydrogen under normal pressure.

With ^{31}P NMR spectroscopy it could be shown that the alkyl complex formation is indeed responsible for the aforementioned substrate concentration-dependent deactivation phenomenon. A colorless methanolic hydrogenation solution of itaconic acid and [Rh(DIPAMP)$(MeOH)_2$] BF_4, which did not consume any more hydrogen after approximately 2% conversion under normal pressure[22] was transferred into a 10-mm Young NMR tube under a hydrogen atmosphere and measured by NMR. A spectrum identical to Figure 1 resulted indicating that the solution only contained inactive Rh(III)-alkyl complex, see Supporting Information.[23,24]

Conclusions

The hydrogenation of itaconic acid with [Rh(DIPAMP)$(MeOH)_2$] BF_4 and [Rh(Me-DuPHOS)$(MeOH)_2$] BF_4 under 1 bar hydrogen pressure suffers from concomitant catalyst deactivation, which increases with increasing substrate concentration. Under decolorization itaconic acid formed complexes with both catalysts, which have significantly smaller P,P coupling constants in comparison to complexes with the dimethyl ester analogue. The X-ray structure of the complex isolated with the DIPAMP ligand, (**1**), revealed a terdentate binding of the substrate *via* both carboxylate groups and an Rh–C bond to the quarternary carbon atom of the previous double bond and a neutral Rh(III)-alkyl complex was formed. As expected, the Rh(III)-alkyl complex (**1**) is not hydrogenation-active under normal pressure and thus the cause of the observed deactivation. The formation of the Rh(III)-alkyl complex is a side reaction of the usual hydrogenation and dependent on many factors: ligand, hydrogen pressure, temperature and substrate concentration. In principle, this deactivation can be understood as an uncompetitive inhibition known from enzyme kinetics.

Experimental Section

All experiments were carried out under an argon atmosphere using standard Schlenk technique. Hydrogenations were performed as described in Ref.[25] Single crystals of (**1**) were isolated from a colorless solution of 0.01 mmol [Rh(DIPAMP)$(MeOH)_2$] BF_4 and 0.05 mmol itaconic acid in 1 mL MeOH that was layered with 5 mL diethyl ether. Single crystals of (**2**) were obtained from a solution of 0.015 mmol [Rh(DIPAMP)$(MeOH)_2$] BF_4 and 0.06 mmol α-methyl itaconate in 0.7 mL MeOH in a 10-mm Young NMR tube left overnight.

Acknowledgements

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[13] To exclude residual traces of oxygen in the substrate, the commercially available itaconic acid was recrystallized from anaerobic methanol prior to use.
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[16] The P,P couplings of the catalyst-substrate complexes of itaconic acid with DIPAMP and Me-DuPHOS were characteristically different from those of the comparable dimethyl itaconate which, in contrast, coordinated in a bidentate fashion,[5a] see Supporting Information.
[17] An H/D exchange *via* the free substrate with MeOH-d_4 was not observed, and supports an *irreversible* formation and a stable alkyl complex.
[18] The spectrum remains unchanged over several days and even heating until boiling of the solvent does not lead to the expected equilibration. Also in the ^{1}H NMR only signals of the major substrate complex are visible.
[19] CCDC 690298 and CCDC 696270 contain the supplementary crystallographic data (without structural factors) of (**1**)·2MeOH and (**2**) reported in this paper, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ; Fax:(+44)1223–336–033; E-mail: deposit@ccdc.cam.ac.uk. Further details can be found in the Supporting Information.
[20] Figure 4 clearly shows that the Rh(III)-alkyl complex can form under argon as well as under hydrogenation conditions.
[21] Taking into account the weak interaction of the OMe group of the ligand with the rhodium the complex would be an 18-electron species.
[22] If the hydrogen pressure is increased to 100 bar under otherwise identical conditions the hydrogenation is completed within 1 h.
[23] Hence, it is shown at the same time that apparently also the minor complex [$J_{P,P}$(minor) = 21.5 Hz, $J_{P,P}$-(major) = 20.9 Hz] is a non-hydrogenation active and probably the diastereomeric Rh(III)-alkyl complex.
[24] Since the measurement was carried out in non-deuterated methanol under a hydrogen atmosphere (the NMR tube contained a capillary with benzene-d_6 for the lock signal) hydride signals can be excluded.
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