HYDROGENATION OF METHYL ESTER OF *Z*-α-ACETAMIDOCINNAMIC ACID CATALYSED BY RHODIUM-PHOSPHINE CARBOXYLATES*

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The title reaction has been studied using the *in situ* catalysts prepared from $[Rh(COD)Cl]_2$, $[Rh(COD)OOCCH_3]_2$ or Rh(COD)(acac) and a series of mono- and diphosphines. The use of (−)-N-acetylphenylalanine as a chiral carboxylato ligand gave catalytic systems with low asymmetric efficiency (optical yields from 5 to 10%). Kinetics of the hydrogenation catalysed by $[Rh(COD)OOCCH_3]_2 + (C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ or $P(n\text{-}C_4H_9)_3$ (Rh : P mol.ratio = 1 : 2) is reported.

Rhodium complexes containing carboxylato ligands are known to be efficient homogeneous catalysts. The earlier studies on their hydrogenation activity were briefly summarized by Nagy–Magos and coworkers[1]. Along with aliphatic and some aromatic carboxylic acids, their halomethyl derivatives were also examined. The interesting properties have been observed with the rhodium carboxylates containing L-tyrosine and N-phenylanthranilic acid which catalysed hydrogenation of aromatic[2] and some heterocyclic compounds[3] as well as disproportionation of cyclohexene and hydroformylation of 1-pentene[4]. Increasing interest in asymmetric hydrogenation, where especially for α-amino acid synthesis the chiral rhodium complexes are the most efficient catalysts[5], has initiated attempts at utilizing natural optically active carboxylic acids and derivatives thereof as the sole or an additional means of introducing chirality to these systems. This idea combined with the possibility of anchoring rhodium complexes through carboxylato ligand to an organic polymer led to prepare a copolymer of *S*-phenylalanine maleinimide with styrene. The rhodium complex attached to this optically active support showed, however, only low activity and enantioselectivity in hydrogenation of *Z*-α-acetamidocinnamic acid[6]. Also Wilkinson type catalysts containing benzylidene-*S*-alanine, both soluble[7] and immobilized on a polyaldehyde resin[8], were of inferior activity but exhibited high enantioselectivity (88 to 95%) in hydrogenation of methyl ester of *Z*-α-acetamidocinnamic acid. As far as

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the hydrogenation activity of rhodium carboxylates is concerned, promising results have been obtained[1] with rhodium-phosphine carboxylates prepared *in situ* from $[Rh(COD)(OOCCH_3)]_2$ and tertiary phosphines. The use of L-(+)-mandelic acid in place of acetic acid afforded chiral catalysts with moderate enantioselectivity for hydrogenation of the above methyl ester (max. 13% yield) for the complex with trimethylphosphine.

The present work reports on some complementary data concerning this type of catalysts with respect to the choice of catalyst precursors, phosphine ligands and kinetics of the hydrogenation.

EXPERIMENTAL

Rhodium complexes $[Rh(COD)Cl]_2$ (ref.[9]), $[Rh(COD)(OOCCH_3)]_2$ (ref.[9]), and Rh(COD).(acac) (ref.[10]) as well as ditertiary phosphines $(C_6H_5)_2P(CH_2)_nP(C_6H_5)_2$ ($n = 3, 4$) (ref.[11]) were prepared by the published procedures. The other phosphines were purchased from Fluka.

Methyl ester of Z-α-acetamidocinnamic acid was prepared from *Z*-methyl-4-benzaloxazolone by the reported procedure[12]. Methyl ester of (+)-N-acetylphenylalanine was obtained by the reaction of (+)-N-acetylphenylalanine with $SOCl_2$ in methanol[13] (79% chemical yield, m.p. 89–91°C, $[\alpha]_{546}^{29} = +120{\cdot}0°$, [*c* 1, $CHCl_3$]). (+)-N-acetylphenylalanine was prepared by asymmetric hydrogenation of *Z*-α-acetamidocinnamic acid according to the procedure proposed by Vilím and Hetflejš[14]. A suspension of 15 g (0·073 mol) of *Z*-α-acetamidocinnamic acid in 30 ml of benzene–ethanol (1/2 v/v) placed in a hydrogenation reactor was stirred under hydrogen for several minutes and then a solution of 1 mmol of $[Rh(COD)(+)\text{-DIOP}]^+ ClO_4^-$ in 15 ml of the above solvent was added. Hydrogenation was carried out at 25°C (hydrogen pressure 107 kPa). After all the acid had dissolved, the enantiomer formed in excess ((+)-N-acetylphenylalanine) began to precipitate. After the uptake of hydrogen stopped (conversion of the starting acid more than 98%), the precipitate was separated from the reaction mixture by filtration, washed with benzene–ethanol, cold diethyl ether and then dried *in vacuo* at 40°C, to give 75% chemical yield (11 g) of (+)-N-acetylphenylalanine ($[\alpha]_{546}^{25} = +55{\cdot}5°$, (*c* 1, C_2H_5OH, 98·5% optical purity)).

Hydrogenation experiments were carried out in an apparatus described earlier[15]. Rhodium catalysts were prepared *in situ* in the hydrogenation reactor under hydrogen atmosphere by mixing solutions of the starting Rh complex and tertiary phosphine in benzene–methanol (1/1 v/v) under stirring. After activation of the catalytic system by hydrogen for 15 min (the period determined by preliminary experiments to give reproducible course of the hydrogenation), methyl ester of *Z*-α-acetamidocinnamic acid dissolved in the same solvent system was added. The hydrogenation was carried out at 30°C and constant hydrogen pressure 106·7 kPa (except for reaction rate-hydrogen pressure dependences). In all the experiments, the initial rate of hydrogen uptake was used to evaluate the activity of catalyst systems and to determine kinetics of the hydrogenation.

When (+)-N-acetylphenylalanine was used as a chiral ligand, the hydrogenation product was isolated in the following way. The reaction mixture was evaporated to dryness, a pale yellow residue was dissolved in a minimum volume of methanol, chromatographed on a silica gel column and eluted[16] with hexane-ethyl acetate (70 : 30). From the colourless fractions, the solvent was removed *in vacuo* and the optical rotation of the product was measured in chloroform at 29°C on Polamat A (Zeiss Jena, GDR) at $\lambda = 546$ nm. The optical yield of the reaction was determined by comparison with the rotation of the reference compound prepared by an independent route (see the synthesis of methyl ester of (+)-N-acetylphenylalanine described above).

RESULTS AND DISCUSSION

Nagy–Magos and coworkers[1] on the basis of comparison of the two rhodium-phosphine acetates prepared from ($[Rh(COD)OOCCH_3]_2$ and $P(C_6H_5)_3$ or $P(n\text{-}C_4H_9)_3$) with Wilkinson catalyst for hydrogenation of several olefinic substrates have concluded that both types behave similarly. An additional support for this conclusion is given by data in Table I, where the same trend in dependence on the structure of phosphines and only little difference in ITO values have been found by us for both dimeric catalyst precursors $[Rh(COD)Cl]_2$ and $[Rh(COD)(OOCCH_3)]_2$ in hydrogenation of methyl ester of Z-α-acetamidocinnamic acid. With chelating diphosphines, the overall reaction rate increases with increasing chelate ring size, in accordance to the effect of these ligands in cationic rhodium complexes (for recent discussion *cf.* ref.[17]).

Another precursor of efficient hydrogenation catalysts, Rh(COD)(acac), exhibits in this case only low activity. In general, the acac ligand can be displaced by non-coordinating inorganic acids to yield cationic rhodium complexes[18,19] and we have recently succeeded in preparing well defined *p*-toluenesulphonate rhodium-bisphosphine complexes by the same route[20]. It was thus of interest to test whether this procedure could be used to introduce carboxylato group. While in the case of acetic acid, the displacement is not quantitative and yields the catalysts with the little enhanced activity over the parent complex, but still inferior to the identical rhodium-phosphine acetates[21], data in the last column of Table I document that such a dis-

TABLE I

Hydrogenation of methyl ester of *Z*-α-acetamidocinnamic acid catalysed by the *in situ* rhodium-phosphine complexes. Ester concn. = $8{\cdot}33 \cdot 10^{-2}$ mol l^{-1}, pH_2 = 106·7 kPa, the ester/Rh molar ratio = 100, P : Rh molar ratio = 2 : 1, methanol–benzene (1 : 1 v/v), reaction temperature 30°C

Phosphine	ITO[a] (min^{-1})			
	$[Rh(COD)Cl]_2$	$[Rh(COD).(OOCCH_3)]_2$	Rh(COD)(acac)	Rh(COD)(acac) + AFA[b]
$P(n\text{-}C_4H_9)_3$	2·6	2·3	2·0	3·3 (8·3)
$P(C_6H_5)(C_2H_5)_2$	6·7	8·4	0·3	8·5 (6·0)
$P(C_6H_5)_3$	<0·1	<0·1	<0·1	<0·1 —
diphos[c]	0·6	1·4	<0·1	<0·1 —
prophos[c]	7·2	9·8	<0·1	6·5 (4·9)
buphos[c]	12·2	12·6	4·5	11·6 (10·8)

[a] Initial turnover (ITO) = mol H_2/mol Rh min; [b] AFA = (+)-N-acetylphenylalanine, used in mol. ratio to Rh = 1 : 1, the optical yields of methyl ester of (+)-N-acetylphenylalanine given in parentheses; [c] $(C_6H_5)_2P(CH_2)_nP(C_6H_5)_2$ (diphos, n = 2; prophos, n = 3; buphos, n = 4).

placement proceeds with (+)-N-acetylphenylalanine. The catalysts so obtained are comparable in their activity to the already mentioned rhodium-phosphine carboxylates. Similarly to the L-(+)-mandelate used as a chiral ligand by Nagy–Magos and coworkers[1] also here only low optical yields were obtained. Furthermore, both the activity and enantioselectivity of these systems did not depend on the Rh : acid ratio (tested in the range 1 : 1 to 1 : 4), indicating that the low asymmetric efficiency of the catalyst cannot be ascribed to the loss of the chiral ligand from catalytically active species, by dissociation or elimination processes. The same conclusion has been drawn by Nagy–Magos and coworkers[1] from the results obtained with L-(+)-mandelate.

It has been suggested by the authors[1] that the hydrogenation involves catalytically active hydrido complex $RhH_2(PR_3)_2(OOCR)$, which implicates the hydride pathway to products, the reaction of the complex with the ester being rate determining. We have expected that some data relating to this problem can be obtained by kinetic measurements. For these purposes we have chosen two rhodium acetato complexes with monodentate and bidentate phosphines ($P(n\text{-}C_4H_9)_3$ and $(C_6H_5)_2P(CH_2)_4.P(C_6H_5)_2$), prepared *in situ* by using $[Rh(COD)(OOCCH_3)]_2$ as catalyst precursors. The dependences of the initial rates of hydrogenation of methyl ester of Z-α-acetamidocinnamic acid (MAC) on catalyst and substrate concentration and hydrogen pressure are illustrated on example of $[Rh(COD)(OOCCH_3)]_2 + (C_6H_5)_2P(CH_2)_4.P(C_6H_5)_2$ system (Rh : P mol.ratio = 1 : 2) in Figs 1–3. The same situation has been observed also with $P(n\text{-}C_4H_9)_3$ (Rh : P mol.ratio = 1 : 2). Thus in both cases, the hydrogenation of MAC is first order in hydrogen and the ester and half an order in Rh_{Tot} concentration (Table II, Eq. (*1*)).

$$-d(MAC)/dt = k_1[H_2][MAC][Rh_{Tot}]^{0.5} \qquad (1)$$

This rate law indicates complex course of the reaction and its interpretation in terms of the mechanism of the hydrogenation seems unwarranted. The half order in the

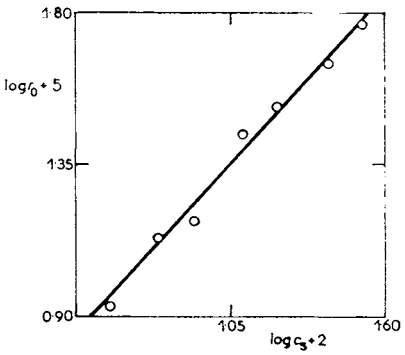

FIG. 1

Logarithmic dependence of the initial reaction rate (r_0) on the ester concentration (c_S) for the hydrogenation of methyl ester of Z-α-acetamidocinnamic acid catalysed by $[Rh(COD)(OOCCH_3)]_2$ + buphos (Rh : : buphos mol. ratio = 1 : 1). Catalyst concentration (c_K) = $1{\cdot}25 \cdot 10^{-3}$ mol l^{-1}, hydrogen pressure 106·7 kPa, the ester concentration (c_S) = $4{\cdot}2-33{\cdot}3 \cdot 10^{-2}$ mol l^{-1}, methanol–benzene (1 : 1 v/v), reaction temperature 30°C

total Rh concentration is unexpected and could be tentatively explained by the rhodium carboxylate dimer (likely in the form of solvate) being predominant species in the solution (Eq. (*A*)) giving with hydrogen the already suggested catalytically active complex[1] (Eq. (*B*)).

$$[Rh(COD)(OOCCH_3)]_2 + 2\,P{-}P \xrightarrow[fast]{+4H_2} [Rh(P{-}P)S_2(OOCCH_3)]_2 + \\ + 2\,\text{cyclo-}C_8H_{16} \qquad (A)$$

TABLE II

The reaction orders to reaction components obtained by the method of initial reaction rates for the hydrogenation of methyl ester of *Z*-α-acetamidocinnamic acid (MAC) with [Rh(COD).(OOCCH$_3$)]$_2$ + buphos or P(n-C$_4$H$_9$)$_3$ *in situ* catalysts

Component	Reaction order	
	Rh-buphos (1 : 1)[a]	Rh-P(n-C$_4$H$_9$)$_3$ (1 : 2)[b]
MAC	0·9	1·0
Rh_{Tot}	0·5	0·5
H_2	1·2	1·1

[a] Figs. 1—3; [b] based on the results reported in ref.[21].

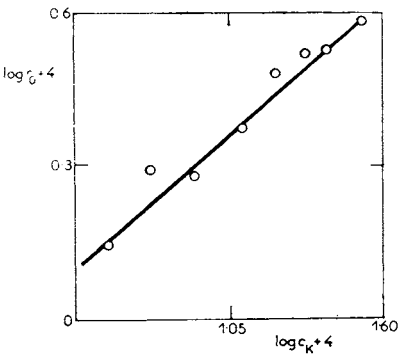

FIG. 2

Logarithmic dependence of the initial hydrogenation rate (r_0) on the catalyst concentration (c_K) (for reaction conditions see Fig. 1, $c_S = 1{\cdot}25 \,.\, 10^{-1}$ mol l^{-1}, $c_K = 4{\cdot}2-33{\cdot}3 \,.\, 10^{-4}$ mol l^{-1})

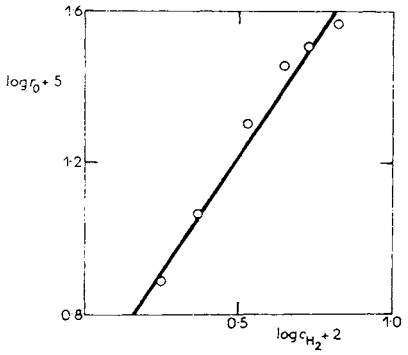

FIG. 3

Logarithmic dependence of the initial hydrogenation rate (r_0) on hydrogen concentration (c_{H_2}) (conditions as in Fig. 1, $c_S = 1{\cdot}24 \,.\, 10^{-1}$ mol l^{-1}, $pH_2 = 44{\cdot}8-164{\cdot}8$ kPa)

$$[Rh(P—P)S_2(OOCCH_3)]_2 + 2\,H_2 \overset{K_{eq}}{\rightleftharpoons} 2\,Rh(P—P)H_2(OOCCH_3) \qquad (B)$$

Then, if the equilibrium (*B*) is shifted far to the left $[Rh(P—P)S_2(OOCCH_3)]_2 \sim \sim [Rh_{Tot}]$ the monomeric dihydride concentration is given by the expression (*2*)

$$Rh(P—P)H_2(OOCCH_3) = K_{eq}^{0.5}\,[H_2]\,[Rh_{Tot}]^{0.5}\,. \qquad (2)$$

In the light of recent works[17] on hydrogenation of MAC catalysed by cationic rhodium complexes, where the olefin pathway is preferred for both Rh-monophosphine and Rh-diphosphine complexes, the behaviour of the Rh-carboxylate catalysts deserves further study.

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