Asymmetric hydrogenation of methyl pyruvate using platinum carbonyl cluster supported on an anion exchanger as the catalyst

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Anionic platinum carbonyl clusters supported on quaternary amine functionalized cross-linked polystyrene, i.e., anion exchangers, are effective precatalysts for the hydrogenation of methyl pyruvate to methyl lactate. Kinetic data has been obtained for anion exchangers with different quaternary groups. Highest observed rate constant and enantioselectivity are obtained with cinchonine funtionalized resin. The kinetic data also indicates saturation kinetics. The decarbonylated used catalyst could be recarbonylated to give a material spectroscopically (infrared) equivalent to freshly anchored cluster.

Keywords: asymmetric, polymer-supported, heterogeneous, hydrogenation, catalysis

1. Introduction

Hydrogenation of methyl pyruvate ester, reaction (1), with cinchona-alkaloid-modified platinum catalysts is known to give methyl lactate with high enantioselectivity [1–3]:

$$\mathrm{MeCOCO_2Me} + \mathrm{H_2} \rightarrow \mathrm{MeCH(OH)CO_2Me} \qquad (1)$$

This reaction is called the Orito reaction after the name of its inventor, and in recent years has been studied in considerable detail [1,3–5]. We had shown that anionic carbonyl clusters could be supported on cross-linked polystyrene resin functionalized with cinchona alkaloids [6]. After decarbonylation supported platinum carbonyl clusters were bound to be effective catalysts for the Orito reaction. Here we report kinetic and other studies on these catalysts to address two questions. First, whether on the basis of an empirically derived rate law an insight into the mechanism of the reaction could be obtained. Second, could a trend in the kinetic data be observed on variation of the cation, i.e., the ligand environment, and if so, could this trend be correlated to the mechanism of enantioselection? Finally, we also wanted to see if on the basis of kinetic and IR studies some light could be thrown on the nature of the active catalysts.

2. Experimental

2.1. Physical measurements and materials

Chloroplatinic acid was purchased from Johnson Mathey, London. All the amines and the chloromethylated divinylbenzene cross-linked (20%) polystyrene were purchased from Fluka, USA. Infrared spectra were recorded on a Nicolet FT spectrophotometer.

Atomic absorption measurements were carried out on an IL 751 spectrophotometer. Microanalyses were carried out with a Carlo–Erba 1106 model C, H, N analyzer. The anionic carbonyl cluster $[\mathrm{Pt_{15}(CO)_{30}}]^{2-}$ and the amine 3,4-dihydroxy-N-benzylpyrrolidine were synthesized according to literature reported procedures [7,8]. Hydrogenation experiments were carried out in a Parr autoclave, USA. Conversion of methyl pyruvate to methyl lactate was monitored by gas chromatography (GC) using a SC-30 (mesh, 1000–2000) GC column and FID detector. Optical rotations were measured by using a JASCO polarimeter, model CT-10, Japan. All the solvents and organic compounds were thoroughly dried and distilled under nitrogen before use.

For the simulation studies, the differential equations were numerically integrated using fourth-order Runge–Kutta method [9]. The rate constants for different models were estimated by fitting the simulation results with experimental kinetic data. The fitting was done by adjusting the rate constants so that the sum of squares of the differences between the model predictions and the experimental data was minimum.

2.2. Functionalization of the polymer

A mixture of chloromethylated 20% DVB cross-linked polystyrene beads (1.0 g) and cinchona alkaloid (1.0 g) was stirred in a mixture of toluene (40 ml) and ethanol (40 ml) at 100 °C for 24 h. The polymer beads were filtered off, and washed successively with ethanol, chloroform, dichloromethane and ether and then dried under

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vacuum. Resins functionalized with other amines were prepared in a similar fashion. Repeated nitrogen analyses indicated the presence of one cinchonine group approximately per 75 monomeric unit of the polymer. This data is the average data for cinchonine groups that are present both in the bulk and on the surface. However, the high degree of cross-linking probably ensures that most of the functionalization occurs on the exposed surface of the rigid matrix.

2.3. Synthesis of **1a**

To a green solution of $Na_2[Pt_{15}(CO)_{30}]$ (0.1 g) in methanol (15 ml), chloromethylated 20% DVB cross-linked polystyrene beads quaternized with cinchonine (1 g) was added and the mixture was stirred at 25 °C for 12 h under nitrogen. This resulted in a pale green solution and dark green beads of **1a**. The beads were filtered off, washed thoroughly with methanol and vacuum dried. Catalysts **1b** to **1g** were prepared by this general procedure using resins quaternized with different amines.

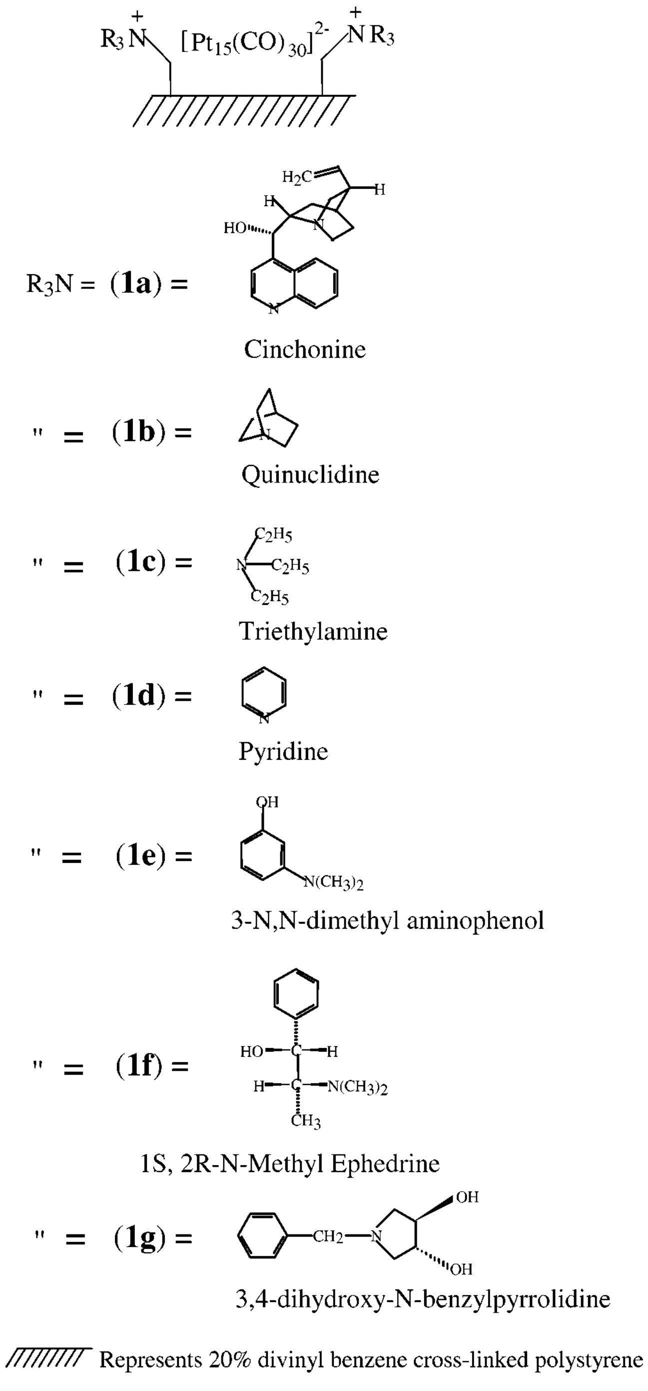
2.4. Decarbonylation of **1a**, kinetic studies and recarbonylation

For a typical catalytic experiment **1a** (0.1 g) was heated at 80 °C under vacuum for 4 h. The IR spectrum of a portion of the solid showed the total disappearance of the inorganic carbonyl bands. A methanol solution (5 ml) of methyl pyruvate (amount varying to give a concentration between 0.25 and 10 mol/l) in a glass vial with a small magnetic bar was placed in the Parr pressure reactor of 100 ml capacity. For a typical catalytic run four such vials could be placed inside the reactor. The reactor was charged with 500 psi of H_2 and the solutions in the vials were stirred magnetically at 25 °C for various lengths of time. The conversion of methyl pyruvate to methyl lactate was measured by gas chromatography and several independent optical rotation measurements gave the optical yield. For the recarbonylation experiment the catalyst was filtered off, dried and then left under a CO pressure of 500 psi for 6 h.

3. Results and discussion

3.1. Kinetic studies

The "semi-combinatorial" approach of ion pairing of different quaternary chiral ammonium groups with anionic carbonyl clusters of different metals had enabled us to create a library of potential asymmetric catalysts. As already mentioned, for the Orito reaction ion pairing between $[Pt_{15}(CO)_{30}]^{2-}$ (**1**) and cinchonine or quinine gave the most effective catalytic system. We decided to vary the quaternary ammonium group to study the effect of such a variation on the rate. The designations of the catalysts with different quaternary ammonium groups are given in scheme 1. The designations are assumed on the principles of ion exchange and on the basis of electroneutrality. An alternative formulation that has one quaternary ammonium group and one sodium ion, the counter cation of **1** in the methanolic solution, may be ruled out since insignificant amount of sodium is detected by chemical analyses. A control experiment also establishes that there is no observable physical adsorption of the sodium salt of **1** on the unfunctionalized resin. Thus, physical adsorption especially after repeated washing with methanol may also be ruled out.



Scheme 1.

The initial rate of methyl pyruvate hydrogenation with **1a** as the catalyst shows an approximate linear dependence on the catalyst concentration. The reaction is therefore

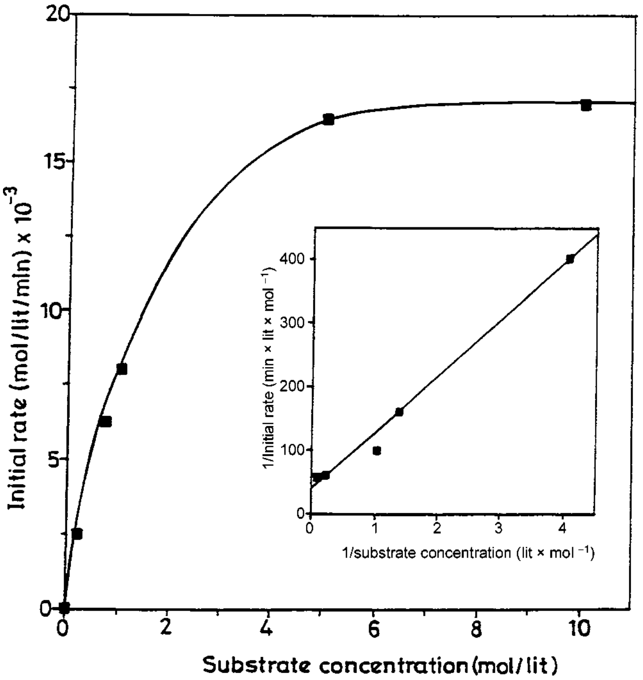


Figure 1. Plot of initial rate vs. substrate concentration with 100 mg of the polymer beads in 5 ml of methanol. Inset: plot of 1/initial rate vs. 1/[subs] with the same data points. All reactions carried out at 25 °C under a hydrogen pressure of 500 psi.

first order with respect to the concentration of the catalyst.

The order with respect to the concentration of the substrate is suggestive of saturation kinetics. With increasing substrate concentration the initial rate increases and then levels off (see figure 1). Also a double reciprocal plot, i.e., reciprocal of initial rate against reciprocal of concentration, gives a straight line (see figure 1, inset). Further evidence for saturation kinetics comes from simulation studies.

A large number of data points have been obtained at different time intervals with different initial concentrations of the substrate and catalyst. The extent of agreement of four kinetic models with the experimental data has been studied by a simulation method (figure 2). In the first three models the order of the reaction with respect to the concentration of methyl pyruvate is assumed to be first, second and half order, respectively. Although based on a smaller data set the half-order model had given [6] the best fit between experimental and predicted data points; with the larger data set the fit is found to be less than satisfactory.

Since the initial rate measurements indicate saturation (Michaelis–Menten) kinetics, a fourth model that assumes a rapid pre-equilibrium followed by the rate-determining step has been tried. This is found to give a significantly better fit than the half-order model. A typical fit is shown in figure 2. It may be noted that for a number of asymmetric *homogeneous* catalytic systems where high enantioselectivities are obtained, saturation kinetics are observed [10,11]. Such a rate law indicates a rapid pre-equilibrium between the catalyst, the substrate and a catalyst–substrate complex,

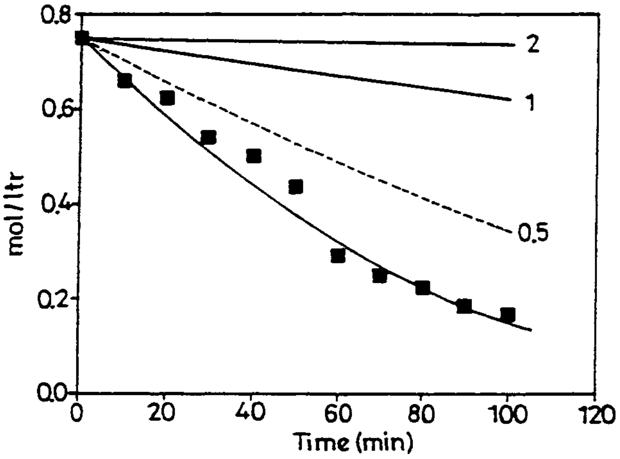


Figure 2. Fit of experimental data points with simulated conversion vs. time profile: (■) are the experimentally measured (100 mg polymer beads, 500 psi H_2, 25 °C, 0.75 mol/l of methyl pyruvate in 5 ml methanol) data points. The simulated conversion profiles are shown for rate $= k_{\mathrm{obs}}[\mathrm{subs}]^n$ ($n = 0.5$, 1 and 2) and saturation model (unlabelled), where rate $= k_{\mathrm{obs}}K[\mathrm{S}]/(1 + K[\mathrm{S}])$. For all the models $k_{\mathrm{obs}} = k[\mathrm{cat}]$.

followed by the rate-determining step. Our kinetic data is therefore indicative of a similar mechanism.

Two plausible mechanisms for enantioselection in the Orito reaction have been proposed. Molecular modeling suggests that on adsorption, regular arrays of cinchonine molecules are formed on the platinum crystal faces [12–14]. The chiral environment thus generated ensures that the transfer of hydrogen atoms from platinum to the carbonyl functionality is enantioface specific. The template model advanced in [13] to interpret the sense of the observed enantioselectivity, was later abandoned by these authors in favor of a 1 : 1 modifier–reactant interaction [15]. Another proposed mechanism invokes the concept of *ligand accelerated catalysis* (LAC), a phenomenon often observed in homogeneous catalytic systems [16,17]. Only a few of the potential active sites are modified by cinchonine adsorption. The rate of enantioselective hydrogenation on these sites is much higher than that of non-enantioselective hydrogenation at other sites [18]. Consequently high enantioselectivity is obtained even with a low level of cinchona loading. The support for this proposal comes from kinetic data. However, it is to be noted that the two proposals are *not mutually exclusive*. It is possible and likely that regular arrays of adsorbed cinchonine are formed on specific crystal faces where the rate of hydrogenation is much higher compared to unmodified faces.

Simple plots of conversion vs. time (figure 3, inset) indicate that the catalysts have noticeably different activities. With **1a** to **1g** as catalysts, under pseudo-first-order conditions with respect to pyruvate and dihydrogen concentrations, the initial rates have been measured. As already mentioned, plots of initial rates against catalyst concentration give reasonable straight lines (figure 3). From the slopes of these straight lines the observed rate constants are calculated. According to a recent literature reported protocol [19], the initial rates and the observed rate constants

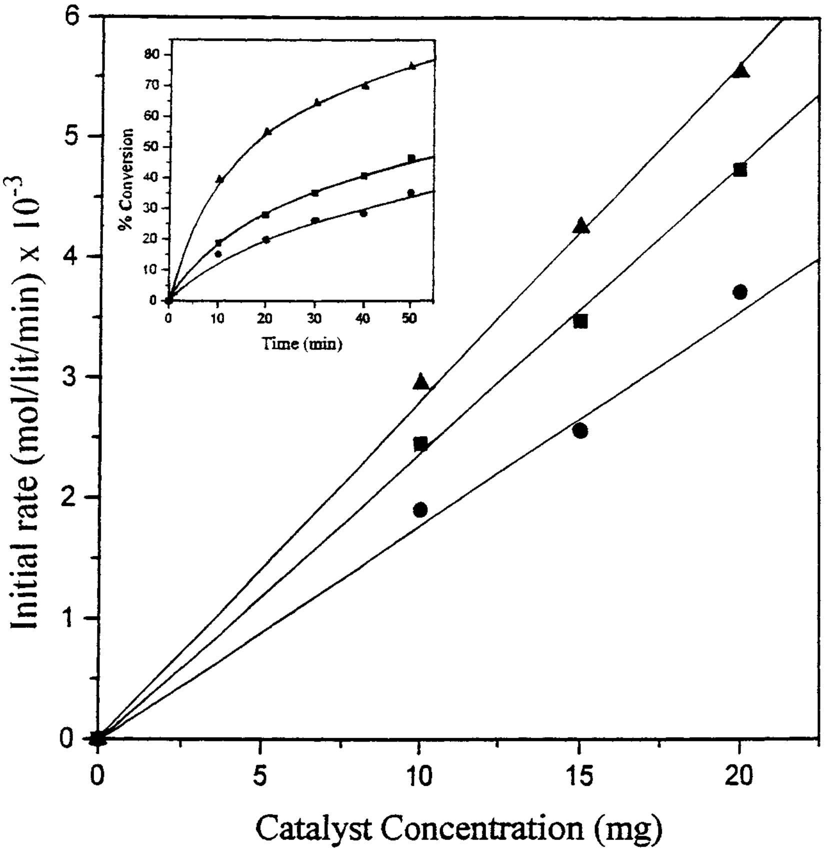


Figure 3. Typical plots of initial rate vs. amount of catalyst for three different quaternary ammonium groups: (▲) cinchonine, (●) pyridine, (■) N,N-dimethyl-3-aminophenol. All reactions carried out at 25 °C, 500 psi H_2 with 0.4 mol/l of methyl pyruvate in methanol (5 ml) and initial rate measured at 30 min. Inset shows plots of conversion vs. time for the same catalysts under the same conditions.

Table 1[a]

NR_3	$[(P)\text{-}CH_2NR_3]_2[Pt_{15}(CO)_{30}]$	k'_{obs}, ee[b,c]	k''_{obs}, ee[b,d]
Cinchonine	**1a**	300.5, 78	289.9, 74
Quinuclidine	**1b**	253.6, 0	248.3, 0
Triethylamine	**1c**	242.7, 0	235.7, 0
Pyridine	**1d**	236.5, 0	231.5, 0
N,N-dimethyl-3-aminophenol	**1e**	229.8, 0	221.0, 0
N-methyl ephedrine	**1f**	177.5, <10	169.0, <10
N-benzyl pyrolidine diol	**1g**	170, <10	160, <10

[a] All reactions were carried out at 25 °C under 500 psi of H_2, with methyl pyruvate 0.4 mol/l in methanol (5 ml). The values are with respect to platinum.

[b] The first number is the observed rate constant k' (min^{-1}) and the second number is the ee (%). For **1a**, **1f** and **1g**, the R enantiomer of methyl lactate is the major one.

[c] Initial rate measured on the basis of conversion after 30 min.

[d] Initial rate measured on the basis of conversion after 60 min.

have been measured at least at two different time intervals to add to the reliability of the kinetic data. These values, k'_{obs} and k''_{obs}, are given in table 1.

The literature reported values of initial rates for reactions catalyzed by oxide-supported platinum modified with cinchonine or dihydrocinchonine ranges from about 20 to 100 mmol/(min g). The cluster-based catalyst **1a** gives an initial rate of 1–10 mmol/(min g) of the polymer or 10–100 mmol/(min g) of platinum. On modification with cinchonine the rate of the oxide-supported platinum catalyst increases by a factor of about 20 [1,14]. With the cluster-based system such an absolute comparison is not possible since in the absence of quaternary ammonium groups the cluster cannot be anchored. However, both k'_{obs} and k''_{obs} are highest for **1a** where the quaternary ammonium ion is derived from cinchonine. For the other two chiral amines, i.e., catalysts **1f** and **1g**, lower rate constants and poor enantioselectivities are obtained. Similarly for **1a** to **1d**, the catalysts with achiral amines, lower k'_{obs} and k''_{obs} are obtained.

Thus there is a direct evidence for rate acceleration by cinchonine-derived ligand environment, i.e., LAC. It may be noted that in homogeneous systems both large (>100 times) and small (<2 times) effects of LAC on rates have been reported [20,21]. The magnitude of the effect seems to be dependent on the nature of the organic reaction, the metal ion and the ligand. In the present work though the effect of ligand environment on rate is clearly discernible, its magnitude is small.

3.2. Nature of the active catalyst

The IR spectra of the freshly supported cluster on resins with different quaternary groups are identical to that of free **1** in the inorganic carbonyl region. In other words **1** remains intact on the polymer surface and polymer anchoring does not lead to any spectroscopically observable structural change. This observation is in agreement with the earlier report [22]. Platinum and nitrogen analyses of the resin-supported clusters suggest the presence of approximately 1 mol of nitrogen per 75, and 1 mol of **1** per 150 monomeric units, respectively. The distributions of the quaternary ammonium groups and the anionic cluster molecules between the surface and bulk of the polymer matrix are not known. However, the molar ratio of total nitrogen to total **1** is 2 : 1. This value is consistent with the formulations shown in scheme 1.

As already mentioned, for optimum catalytic performance careful decarbonylation of the resin-supported clusters is necessary. This is effected by heating the resin-supported carbonyl clusters under vacuum (temperature ~80 °C), till the inorganic carbonyl absorption in the IR spectra completely disappears. Careful control of temperature is required since with higher temperatures the resin undergoes degradation while at lower temperatures insufficient decarbonylation gives drastically reduced rates in the subsequent catalytic reactions.

After use in a catalytic run, the **1a**-derived catalyst can be recarbonylated (CO pressure ~500 psi) to give a material that has an IR spectrum identical to that of freshly prepared **1a**. This is shown in figure 4. Many studies on de- and recarbonylation experiments with surface-anchored metal carbonyls have been reported in the literature [23,24]. Reversible decarbonylation has often been used as an indicator for the retention of molecular identity of a carbonyl complex on a support. To the extent reversible decarbonylation is a reliable criterion, on decarbonylation surface-anchored **1** does not seem to undergo an irreversible structural change.

In conclusion the two important results presented in this work are as follows. First, for the cluster-based systems kinetic data indicates that a catalyst–substrate complex is involved in the enantioselection process. Second, among the different quaternary ammonium groups the one derived from cinchonine is the most effective one both in terms of activity and enantioselectivity. Further studies directed towards a comprehensive characterization of the decarbonylated surface species are underway.

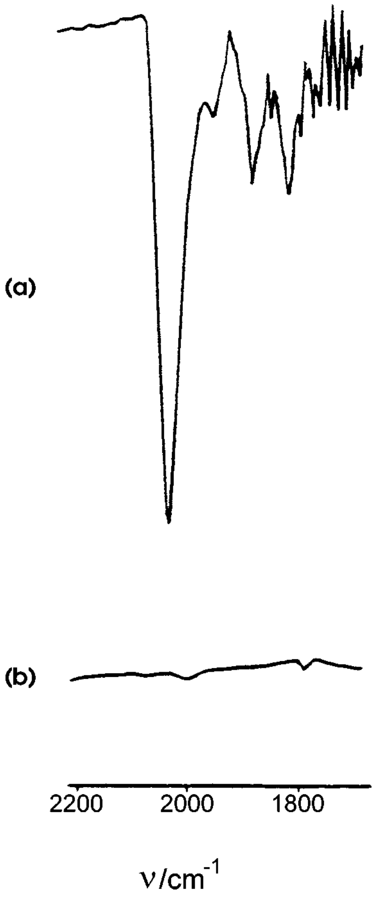


Figure 4. Infrared spectra of (a) freshly prepared **1a** and (b) decarbonylated **1a** after use in a catalytic run.

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