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Solvent effects in the kinetics of the enantioselective hydrogenation of ethyl pyruvate

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The influence of solvent on the kinetics of enantioselective hydrogenation of ethyl pyruvate by Pt/Al_2O_3/dihydrocinchonidine is reported. In a non-polar solvent, toluene, the reaction is approximately zero order in substrate at constant hydrogen pressure, while under the same conditions and at the same substrate concentration, in the polar solvents ethanol and propylene carbonate the reaction shows a first-order substrate concentration dependence. Fits to a Michaelis–Menten rate expression show that these differences are the expression of the relative magnitudes of the adsorption term in the rate expression, which in turn reflects the influence of the solvent on the adsorption–desorption processes which take place at the catalyst surface.

Keywords: enantioselectivity, hydrogenation of ethyl pyruvate, Pt/alumina catalyst, solvent effects, kinetics, solvent polarity

1. Introduction

We have a continuing interest in the characterisation of transition metal catalysts in colloidal form in the context of the relationship they bear to supported heterogeneous counterparts [1,2]. A particularly useful reaction for comparative studies of the two catalyst types is the enantioselective hydrogenation of α-ketoesters, because for this reaction both selectivity (enantioselectivity in this case) and rate are affected by several parameters, and so similarities and differences between the two types of catalyst can potentially be revealed with some sensitivity.

This catalytic system is particularly complex. In the most frequently investigated heterogeneous catalyst formulation, Pt/Al_2O_3, the chiral modifier, cinchonidine (or dihydrocinchonidine, which forms rapidly from cinchonidine under hydrogenation conditions), not only induces enantioselectivity in the hydrogenation of ethyl pyruvate to ethyl R-lactate, but also causes an increase in hydrogenation rate, and accelerations of between ×5 and ×100 have been reported. Similar effects have been reported for colloidal analog catalysts [1–3]. Many research groups, both academic and industrial, have conducted in-depth studies of the reaction since the initial work of Orito [4], and details of the various approaches, kinetic analyses and mechanistic postulates can be found in several recent authoritative reviews [5–8].

During our comparative study of the reaction rates induced by the colloidal and supported Pt catalysts, we noted reproducible differences in catalytic performance in two solvents, toluene and ethanol, differences which have been previously reported in the literature on this reaction. The rates of reaction were generally less in toluene than in ethanol at the same substrate concentration and hydrogen pressure, and toluene gave consistently higher optical yields (60–70%) than ethanol (35–40%). Previous studies of solvent effects in this reaction have focused on comparisons of optical yield between various solvents, and correlations have been made between enantioselectivity and solvent parameters such as acidity and basicity and dielectric constant [9,10]. Since enantioselectivity is only a function of the relative rates of production of the R- and S-products, both of the important parameters in the performance of catalysts for this hydrogenation are rate-derived, and both are affected by changes in solvent. A delineation the kinetic consequences of solvent effects should be important to the clarification of the surface chemistry involved in this catalytic system, which is not yet fully understood.

In this paper we explore the effect of solvent on the form of the kinetic rate curve for ethyl pyruvate hydrogenation catalysed by a standard 1% Pt/Al_2O_3 catalyst, using two polar solvents, ethanol and propylene carbonate, and a non-polar solvent, toluene. Specifically we focus on the potential effect of solvent on the adsorption–desorption equilibria at the catalyst surface. A subsequent paper will describe a comparison of these solvent effects for a colloidal platinum catalyst.

2. Experimental

1% Pt/Al_2O_3 was used as supplied by Precious Metals Corporation. Ethyl pyruvate (Aldrich) was distilled under reduced pressure and stored under dry argon at $-10\,^{\circ}C$ prior to use. Solvents were dried and distilled according to literature methods. Dihydrocinchonidine was prepared by hydrogenation of cinchonidine (Merck) at 2 bar hydrogen pressure using a 5% Pd/C catalyst, and recrystallised from ethanol.

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Hydrogenation catalysis

Catalytic hydrogenations were performed at 24 °C under constant 1500 ± 3 Torr hydrogen pressure in a 500 ml Fischer–Porter glass reactor, using a gas uptake manifold as described previously [1,2]. The progress of the reaction was monitored by precise pressure measurements with a pressure transducer, on a fixed volume gas reservoir connected to the reactor via a pressure reducing valve. During the catalytic reaction, data were logged at an appropriate rate to give >150 pressure measurements between 3500 and 1800 Torr with a precision of 5 Torr over the course of the reaction. Rates are determined by measuring the slope at each point on the hydrogen uptake curve over a ±10 point spread. After any change in reactor configuration (e.g., new stirrer geometry, changes in solvent or reaction volume) measurements of gas–liquid diffusion rates were carried out to ensure that catalytic hydrogenation rates were measured under kinetically controlled conditions [11,12]. In all experiments the catalytic hydrogen consumption rates were always slower than gas dissolution rates by a factor of 30.

The conversion of ethyl pyruvate and the enantiomeric excess of the product ethyl R-lactate were measured by gas chromatography (HP 6890-1; 25 m FS/20% TBCD/80% OV1701/N3108C). In all cases the reaction was carried out to completion, and a selectivity of >99% to ethyl lactate was obtained.

3. Results and discussion

In order to analyse the kinetic data obtained for the three solvents studied in the present work, we will use a rate law, equation (1), which is a simplified version of that derived by Blackmond and co-workers [12–15] from a steady-state model involving reversible adsorption of ethyl pyruvate and hydrogen and an irreversible hydrogenation step. The rate law derived in this way,

$$\frac{\mathrm{d[pyruvate]}}{\mathrm{d}t} = \frac{K_1\mathrm{[pyruvate]}}{1 + K_2\mathrm{[pyruvate]}}, \qquad (1)$$

allowed the hydrogen and substrate concentration dependence for the R- and S-branches of the reaction, and thus the dependence of e.e. on hydrogen concentration and conversion to be correctly predicted [15]. An alternative kinetic model for this system, which conforms to a Langmuir–Hinshelwood–Hougen–Watson model, has been proposed by Blaser et al. [16]. In this model reaction occurs between adsorbed species which are in fast equilibrium with their desorbed counterparts, and adsorption–desorption equilibrium is maintained throughout the reaction. These two approaches agree in many of their predictions, although some differences remain, specifically concerning the order of the reaction in hydrogen concentration. However, when reactions are performed at constant hydrogen pressure, the overall rate laws derived by Wang et al. and Blaser et al. reduce to the same classic Michaelis–Menten form, equation (1), and become kinetically indistinguishable.

In this expression K_1 is a lumped constant incorporating the rate constants for substrate hydrogenation and adsorption and desorption, and K_2 is a lumped constant including the equilibrium constants for adsorption and desorption of all relevant surface species. Although the detailed constituents of K_1 and K_2 differ in the two approaches, for the purposes of the present work each allows an equivalent description of K_1, essentially a kinetic term modified by inclusion of adsorption equilibrium, and K_2, an adsorption term. For gas–solid reactions K_2 reflects the strength of adsorption (and thus the adsorption–desorption equilibrium) on the catalyst surface of the gaseous molecules of the various species involved in the catalytic cycle. For reactions in the slurry mode, such as the one under study, the adsorption–desorption equilibrium is between solvated molecules and the (possibly) solvated surface, and so solvent effects will play a role in determining the value of K_2. The form of the rate vs. [pyruvate] curve defined in equation (1), in a given concentration range, will be most affected by the value of K_2, whereas the rate of the reaction will depend on both K_1 and K_2. For $K_2\mathrm{[pyruvate]} \ll 1$ the reaction will be first order in pyruvate, while for $K_2\mathrm{[pyruvate]} \gg 1$ the reaction will be zero order in pyruvate.

We will compare values of K_2 derived from the best fits to equation (1) for the experimental rate data obtained in toluene, ethanol and propylene carbonate.

3.1. Non-polar solvent: toluene

In figure 1 is shown a typical hydrogen uptake curve obtained in toluene using the standard conditions chosen for this study (0.22 M ethyl pyruvate, 1500 Torr hydrogen, 24 °C, 500 mg 1% Pt/Al_2O_3). The final e.e. of ethyl lactate was 58%. A point-by-point derivatisation of the conversion vs. time data gives the time-dependence of rate, shown on the left-hand axis of figure 1. The corresponding rate vs. [pyruvate] curve is shown in figure 2, with a fit to equation (1); $\mathrm{d[EP]}/\mathrm{d}t = 0.0019\mathrm{[EP]}/(1+34\mathrm{[EP]})$. An identical hydrogenation but using 1.0 mg dihydrocinchonidine gave a

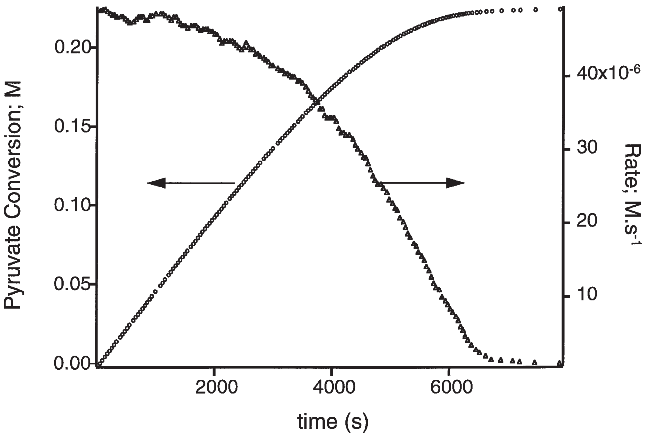

Figure 1. Ethyl pyruvate hydrogenation: 1% Pt/Al_2O_3 catalyst, toluene dispersion (0.22 M ethyl pyruvate in toluene, 100 ml; 500 mg catalyst, 25 mg dihydrocinchonidine; 1500 Torr reactor pressure, e.e. 58%).

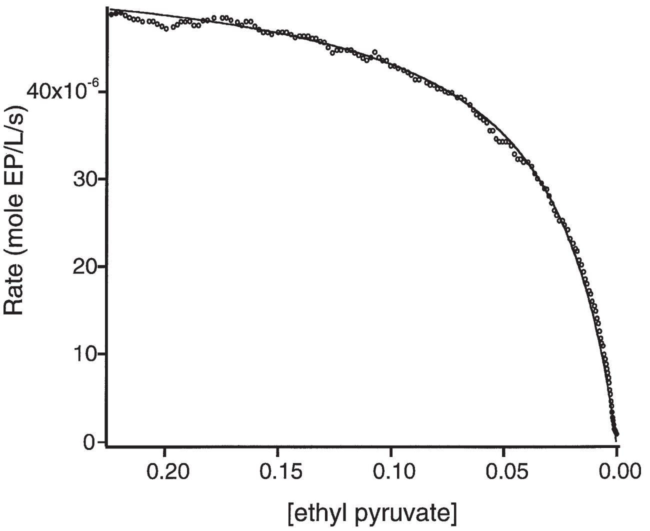

Figure 2. Rate vs. [ethyl pyruvate] in toluene, as in figure 1 (rate (50%) = 4.4×10^{-5} $\mathrm{M\,s^{-1}}$; e.e. = 70%).

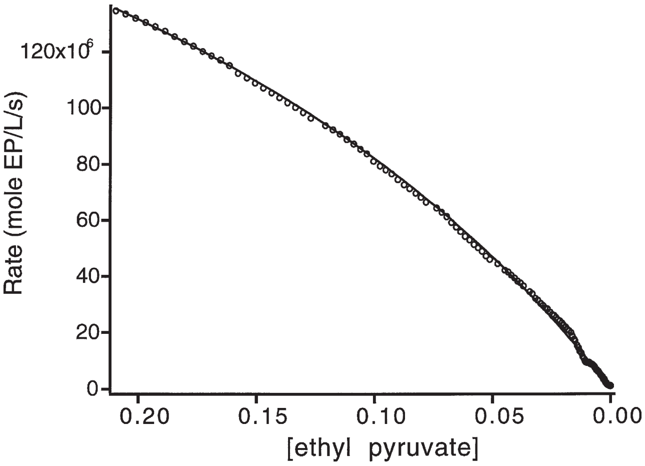

Figure 3. Ethyl pyruvate hydrogenation: 1% Pt/Al_2O_3 catalyst, ethanol dispersion. Conditions as in figure 1 (rate (50%) = 1.0×10^{-4} $\mathrm{M\,s^{-1}}$) (final e.e. 43%).

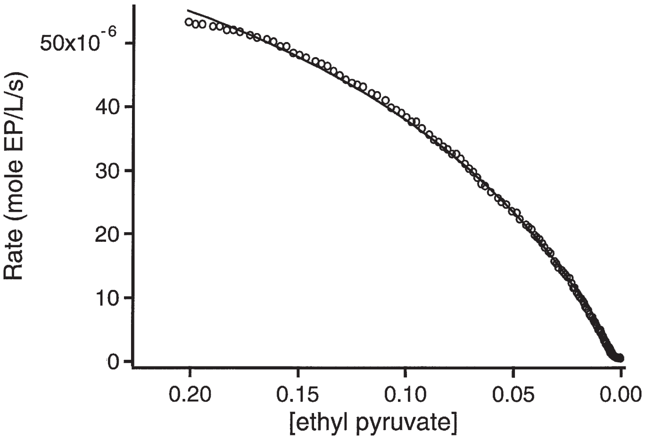

Figure 4. Rate vs. [ethyl pyruvate] in propylene carbonate (rate (50%) = 4.5×10^{-5} $\mathrm{M\,s^{-1}}$) (final e.e. 45%).

similar rate law ($\mathrm{d[EP]/d}t = 0.0024\mathrm{[EP]}/(1+39\mathrm{[EP]})$) and an e.e. of 70%. Over a series of five similar experiments in toluene values of K_1 and K_2 averaged 0.0028 ± 0.0009 and 37 ± 6.

3.2. Polar solvents: ethanol and propylene carbonate

The corresponding rate vs. [pyruvate] curve for standard conditions in ethanol and in propylene carbonate are shown in figures 3 and 4. The fit in figure 3 is to the rate law $\mathrm{d[EP]/d}t = 0.0014\mathrm{[EP]}/(1+4.7\mathrm{[EP]})$ (final e.e. 43%). Over a series of six similar experiments mean values for K_1 and K_2 were 0.0018 ± 0.0003 and 6.7 ± 2.0. In figure 4 are shown similar data for propylene carbonate with a fit to $\mathrm{d[EP]/d}t = 0.00064\mathrm{[EP]}/(1+6.8\mathrm{[EP]})$ (final e.e. 45%).

In the non-polar hydrocarbon solvent, toluene, the rate data approximate zero-order kinetics over the early part of the reaction due to a high value of the adsorption term K_2, despite the relatively low ethyl pyruvate concentrations used. In the cases of the two polar solvents, ethanol and propylene carbonate, the values of K_2, five to eight times lower than those found for the non-polar solvent, result in a positive order substrate dependence over the concentration range studied.

The differences in the adsorption terms between the two solvent polarities correlates with their solvating abilities for polar solute molecules. In the case of ethanol the interaction between ethyl pyruvate and the solvent may be complicated by the presence of the hemiketal, the formation of which is catalysed by both cinchonidine [17] and by alumina [18]. This possibility is eliminated in the case of the non-hydroxylic polar solvent propylene carbonate, in which we find a value of K_2 similar to that found in ethanol. We have also observed that the use of t-butanol, which cannot form a hemiketal, as solvent (but at 30 °C, compared to 24 °C under standard conditions), results in a fit to equation (1) with $K_2 = 12$. The formation of the hemiketal thus seems to play little role in determining the rate law followed during pyruvate hydrogenation. This is consistent with conclusions reached by previous workers who concluded that hemiketal formation is not significant in determining the enantioselective chemistry of this catalyst system [17].

Previously published data in studies of solvent effects have been a useful guide to the selection of solvents for optimizing optical yield [9,10]. The relative performance of catalysts in various solvents has been used as part of the evidence adduced to support postulated active site structures and mechanisms [9]. The beneficial influence of a low dielectric solvent has been demonstrated on the basis of comparative e.e. and rate data (although the preferred solvent, acetic acid, falls outside this correlation). In one study [9], based on a series of initial rate measurements at different substrate concentrations, no influence of solvent on the order in substrate concentration was observed. At the relatively high substrate concentrations which were used, from 2.3 to 9.8 M (neat ethyl pyruvate) zero-order kinetics in substrate concentration were observed in both

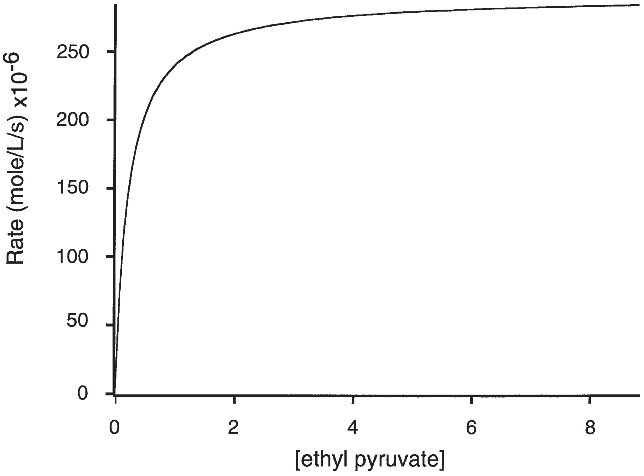

Figure 5. Rate vs. [pyruvate] calculated from the rate law in ethanol, $d[EP]/dt = 0.001363[EP]/(1 + 4.7[EP])$, extrapolated to neat ethyl pyruvate (8.9 M).

ethanol and toluene. A study conducted in ethanol with methyl pyruvate as substrate showed, after an initial period of increasing rate, zero-order substrate concentration dependence over 10–70% conversion, corresponding to a substrate concentration range of 3.4–1.1 M [19]. A recent report of extensive initial rate studies in toluene [16] showed rates which maximized at 2 M ethyl pyruvate, with a negative order in substrate concentration above this value. The authors point out that the range of ester concentrations used, 0.4–8.9 M, are of such a magnitude as to introduce changes in dielectric constant of the reaction medium, thus affecting the kinetics of the reaction.

The distinction we observe between polar and non-polar solvents in the present work becomes apparent when lower substrate concentrations, in a range which rates are a more sensitive function of concentration, are used. If, for example, we take the simplified rate law used to fit our ethanol and toluene data, with the values of K_1 and K_2 obtained, and extrapolate to neat substrate concentration (figure 5), it is clear that a zero-order substrate dependence in ethanol and between 2.3 and 8.9 M ethyl pyruvate is consistent with our results, as are the 3.4 M methyl pyruvate data. Higher order substrate–concentration dependencies have been reported in propanol at lower initial substrate concentrations, ca. 1 M [15], and if we assume that 1-propanol would show a K_2 value similar to ethanol, it is clear from figure 5 that in this concentration range a positive order in ethyl pyruvate would be expected. Thus reported substrate–concentration dependences which at first sight appear disparate become consistent with each other.

The results we present here demonstrate that the choice of solvent can have a significant effect on the kinetics of this reaction, and it is advantageous to establish a rate law for each solvent in comparative studies under conditions where distinctions can be made between the influence of solvent properties. The fact that the solvation of solutes has a measurable effect on the kinetics of the reaction makes it probable that the differences in e.e. observed between toluene and ethanol are related to solvation of one or more of the species involved in the adsorption equilibria which define the composition of the catalyst surface.

Table 1
Summary of kinetic constants K_1 and K_2 (equation (1)) and enantioselectivities from experiments in figures 2–4.

Solvent	K_1 ($\times 10^{-3}$)	K_2	e.e. (%)
Toluene	1.9	34	58
Ethanol	1.4	4.7	43
Propylene carbonate	0.64	6.8	45

Since cinchonidine is both a polar and an aromatic molecule, it is not unreasonable to assume that there will be differences in solvation of the modifier between polar and non-polar solvents, which may affect the adsorption equilibrium of the modifier on the catalyst surface. The presence of just such an effect was concluded by Blaser et al. [20] from measurements of the observation of a different dependence of optical yield on modifier concentration for a range of solvents.

Whether we remain with the commonly held assumption that modifier adsorption is a prerequisite for enantioselectivity and rate acceleration [5–8], or take the alternative view that a pyruvate–modifier complex forms in solution prior to adsorption and hydrogenation [21,22], it is clear that solvation of the modifier (or modifier–pyruvate complex) will differ significantly in ethanol and in toluene. A similar suggestion was made by Wehrli et al. [9] on the basis of optical yield and initial rate measurements. This difference in solvation may well have consequences for the enantioselectivity of this reaction, and contribute to the higher optical yield observed in toluene than in ethanol.

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