Enantioselective hydrogenation of ethyl pyruvate with colloidal platinum catalysts: the effect of acidity on rate

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Platinum sols, prepared from H_2PtCl_6 in aqueous methanol, are, when modified by cinchona alkaloids, highly reproducible catalysts for the enantioselective hydrogenation of ethyl pyruvate. It is shown that the presence of HCl in the as-prepared sols has a marked effect on rate and reproducibility, and that removal of HCl by dialysis gives catalysts which display exceptional reproducibility and higher rates. The reliability of these colloidal catalysts will allow their use as a reliable test system both for precise rate studies, in the absence of possible support effects, of the various reaction parameters which affect catalyst performance in this reaction, and also for screening of alternative modifiers to cinchona alkaloids.

Keywords: colloidal platinum catalyst, modification by cinchona alkaloids, hydrogenation of ethyl pyruvate, acidity, reaction rates, enantioselectivity

1. Introduction

The use of modifying coadsorbates in heterogeneous catalysis is a promising method for the development of selective catalytic processes in organic synthesis. This approach is the heterogeneous analogue to the use of ligand effects (both steric and electronic) in the modification and optimisation of homogeneous molecular complex catalysts. One potential complication in the selection and evaluation of adsorbed modifiers in heterogeneous catalysis is the fact that traditional heterogeneous catalysts are often used as oxide-supported metal particles, and the adsorptive properties of the support may result in a competition for modifier molecules between metal sites and the support surface. The evaluation of modifiers is thus complicated by the presence of an adsorbing support.

Highly dispersed transition metals in colloidal suspension offer the possibility of studying the catalytic properties of small metal particles in the absence of solid supports, and as a prelude to the development of adsorbate modified metal colloid catalysts we have sought a colloidal catalytic metal which could serve as a test bed for modifier molecules, and a heterogeneously catalysed reaction in which such modifier effects could be studied. The reaction we have chosen is one in which such an effect is widely assumed to play an important role in a catalytic process, and that is the enantioselective hydrogenation of ethyl pyruvate to R- and S-ethyl lactate catalysed by supported platinum in the presence of cinchona alkaloids, such as cinchonidine or quinidine [1–6], and other chiral modifiers [7,8]. The evaluation of modifiers in this system is potentially complicated by the competitive adsorption of the modifier on both support and metal, a phenomenon which has been observed for this reaction [9]. The catalytic metal, platinum, is readily available in colloidal form by a number of preparative methods [10], thus giving access to colloidal support-free analogs to the supported Pt catalysts.

The selection of a preparation for Pt sols as test materials was complicated by the fact that particle morphology can be quite difficult to control in sol preparations, where preparation conditions can play an important role in determining both particle size and shape [11–13]. At the inception of this work we were aware of data suggesting that the performance in this reaction of platinum sols in the presence of cinchona alkaloids showed a strong dependence on the morphology of the catalyst particles, and that the colloidal catalysts were in some cases significantly less active than their heterogeneous counterparts [14]. Colloidal platinum prepared from platinum vapour was also less effective than the traditional Pt/Al_2O_3 catalysts [15]. However, recently published work by Duff and co-workers [13] has demonstrated that colloidal platinum may be prepared very reproducibly in the form of approximately equidimensional monodispersed particles, in a particle size range (30–40 Å) known to be effective in enantioselective ketoester hydrogenation [16], and so we chose this method to attempt to obviate any problems caused by irreproducible particle morphology. Our goal was to establish a colloidal catalyst system as a reliable test material for future modifier evaluation and mechanistic studies, but not to optimise the system for either e.e. or rate. Polyvinylpyrrolidone (PVP) was chosen as a stabilising agent to maintain the platinum particles in highly dispersed non-aggregated form, as used by Duff et al. [13] [1].

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[1] Recently a platinum sol has been prepared which is in fact stabilised only by dihydrocinchonidine [17], but the stabilising effect seems however to be unique to this alkaloid, limiting the utility of that system for the screening of other modifiers.

We report here results showing PVP stabilised colloidal platinum is highly active in catalysing the enantioselective hydrogenation of ethyl pyruvate. In particular, we show that the presence of variable concentrations of HCl, a side product form the colloid preparation, in the colloidal catalyst suspension causes a rate inhibition and irreproducibility prohibitive to useful kinetic analysis, but that when the colloid is purified by dialysis the resulting catalyst is highly reproducible and thus a promising test vehicle for evaluation of modifiers other than cinchona alkaloids.

2. Experimental

The catalysts under investigation were prepared using the method of Hirai et al. [18] as modified by Duff et al. [13], in which H_2PtCl_6 was reduced in aqueous methanol in the presence of polyvinylpyrrolidone under conditions of high ionic strength (i.e. at high H_2PtCl_6 concentrations). In a typical preparation, $H_2PtCl_6 \cdot 6H_2O$ (0.252 g, 0.487 mmol) was dissolved in a mixture of methanol (25 ml) and triply distilled water (25 ml) containing PVP (10 000 MW, 3.0 g) and heated under reflux for 75 min. A dark brown sol resulted, the UV/visible absorption spectrum of which showed no residual unreduced $[PtCl_6]^{2-}$. Three different PVP stabilised colloidal platinum catalysts containing 1.02, 0.98 and 0.96 Pt per ml were prepared under identical conditions. Subsequent dialysis, using cellulose dialysis membrane tubes (15 h), of the as-prepared sols was performed on solutions which had been dried under reduced pressure and redissolved in triply distilled water. The dialysed sols were then dried under reduced pressure. No change in particle size was observed after dialysis.

Catalytic hydrogenations were performed in a 500 ml cylindrical Fischer–Porter bottle (Andrews Glass, Vineland NJ) with a modified multiport head to allow gas inlet, liquid sample and return lines, liquid injection port (via septum), thermocouple and safety valve. A sealed magnetic drive overhead stirrer replaced the mechanical stirrer supplied with the head. Stirring was accomplished by a two-blade solid stirrer which extended over the diameter of the reactor. Gas was fed from a fixed volume reservoir at ca. 5 bar to the reactor, via a pressure reducing valve (Brooks) which maintained the reactor pressure of 1500 Torr with an error of ±0.2%. Four reservoirs with volumes of 75, 150, 500 and 1000 ml were available on the gas manifold, allowing flexibility in reaction scale. The consumption of gas in the reservoir, which was the reaction observable, and the constant reactor pressure were measured (±0.2%) using MKS Baratron pressure transducers and these, together with stirring speed and reactor temperature, were logged to a PC via an Analog Connection PC analog card and WorkBench PC software (Strawberry Tree Inc., Sunnyvale, California). Measured inputs were displayed in real time so that periodic visual checks could be made. Pressure measurements could be logged rapidly, for example every 0.1 s for gas–liquid diffusion measurements. During the catalytic process, data were logged at an appropriate rate to give 200–500 pressure measurements over the course of the reaction. Data quality was sufficient to allow direct rate determination without curve fitting of the pressure vs. time data. Rates were determined by differentiation of the pressure vs. time curve by measuring the slope over ±10 points from the 20th to the N-10th point in the set of N unsmoothed P vs. time data. In this way the initial rapid pressure drop (usually about 25 Torr) due to hydrogen dissolution was excluded from the rate measurements.

Gas–liquid diffusion measurements showed that for this reactor configuration adequate mass transfer coefficients for hydrogen into ethanol solutions of ethyl pyruvate were obtained at 1150 rpm, at which stirring speed the rate of hydrogen diffusion into the liquid phase exceeded the rate of consumption in the catalytic hydrogenation using as-prepared colloids by greater than a factor of at least forty, thus ensuring that the measured rates were unperturbed by gas–liquid mass transfer limitations [19].

Ethyl pyruvate (Aldrich), which was distilled immediately prior to use, was dissolved in dry ethanol (100 ml) to give a solution 0.22 M in the ester. The ester was hydrogenated by each of the three sols using approximately 10 mg Pt stabilised with 300 mg PVP (MW 10 000, Aldrich) at 24 ± 0.5°C, modified by 50 mg dihydrocinchonidine. PVP/Pt ratios were constant at 3%. Dialysed sols were used either at the same loading as for the as-prepared sols, or at 50% of that value. In the latter case the cinchonidine was reduced to 25 mg.

3. Results and discussion

The preparation of PVP stabilised platinum sols under conditions of high ionic strength is, as reported by Duff [13], a very reproducible preparative method, yielding approximately equidimensional, monocrystalline 30 Å colloidal platinum particles. The form and size of the particles were constant over ten independent preparations. A micrograph and particle size histogram of a representative sol is shown in figure 1.

The gross reaction descriptors for the enantioselective hydrogenation of ethyl pyruvate to R- and S-ethyl lactate, rate and enantiomeric excess, have been reported to be dependent on catalyst particle size [3,20,21], catalyst precursor and preparation method [16], on the modification protocol [4], on modifier structure [3], on catalyst pretreatment [22], on solvent [1,2,23], on modifier loading [5,9], on temperature [4] and on hydrogen pressure [4] (or more correctly dissolved hydrogen concentration [24]). Enantiomeric excess also varies with conversion [4,6,9]. Many of these variations in catalyst performance

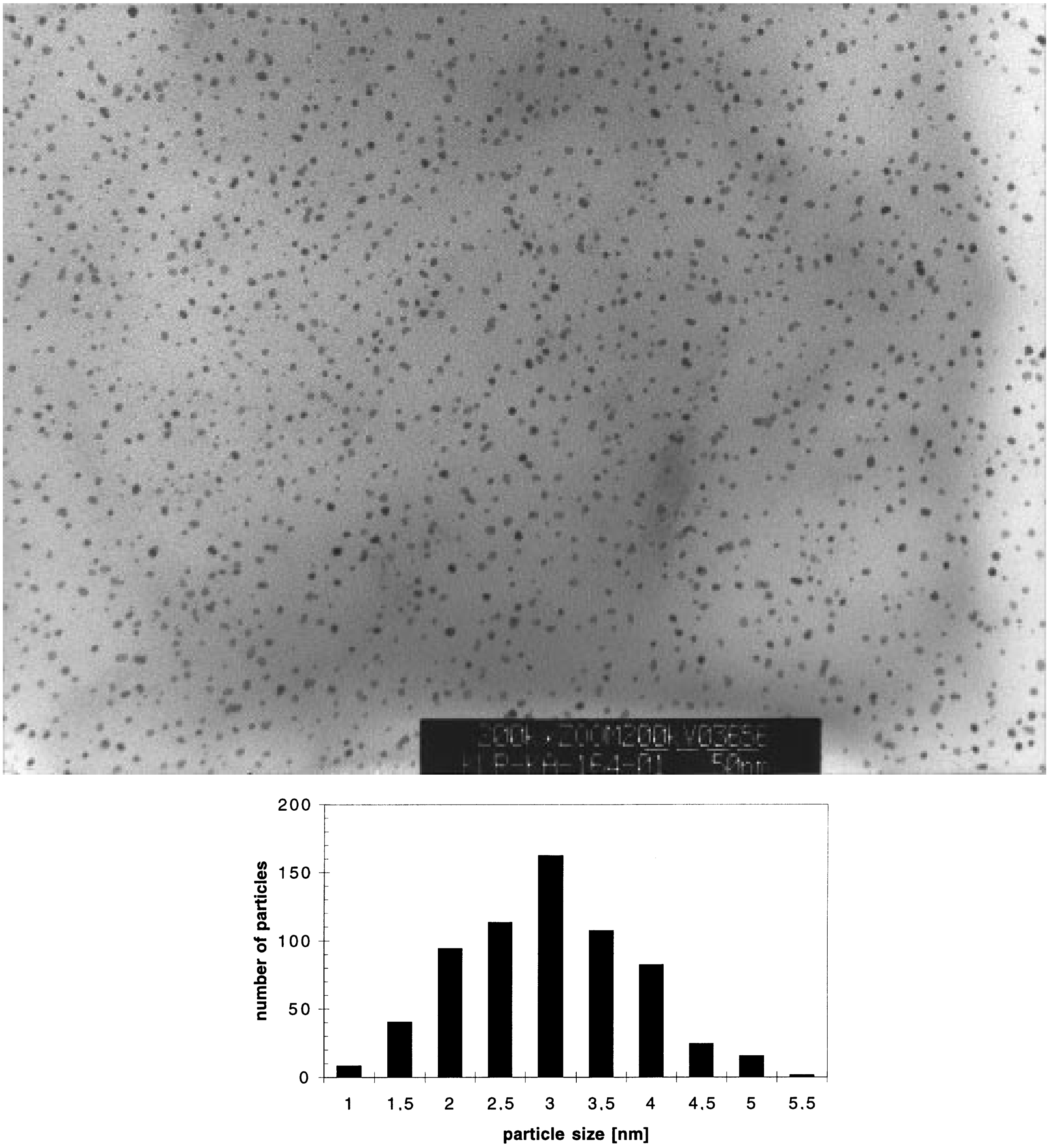

Figure 1. Transmission electron micrograph and particle size histogram of a PVP stabilised platinum colloid prepared from H_2PtCl_6 (see text).

undoubtedly reveal mechanistic influences, but some seem difficult to correlate with recognisable catalyst properties or reaction conditions. For example, Blaser has reported a daunting variability in both e.e. and rate on simply changing the source of ethyl pyruvate, a difference which survives distillation of the material [25].

The primary reaction parameter we have focussed on is rate, and we had expected that by working with catalysts prepared by a reliable, reproducible colloidal synthesis method, and in the absence of a support, some of the variability would be removed. However, under apparently identical hydrogenation conditions the catalysts prepared from each of the three sols exhibited differing activities in ethyl pyruvate hydrogenation. Figure 2 (a)–(c) shows the rate of hydrogen uptake for the hydrogenation of 0.224 M ethyl pyruvate in 100 ml ethanol at 1500 Torr constant hydrogen pressure using ca. 10 mg Pt as a 3% PVP colloid in the presence of 50 mg

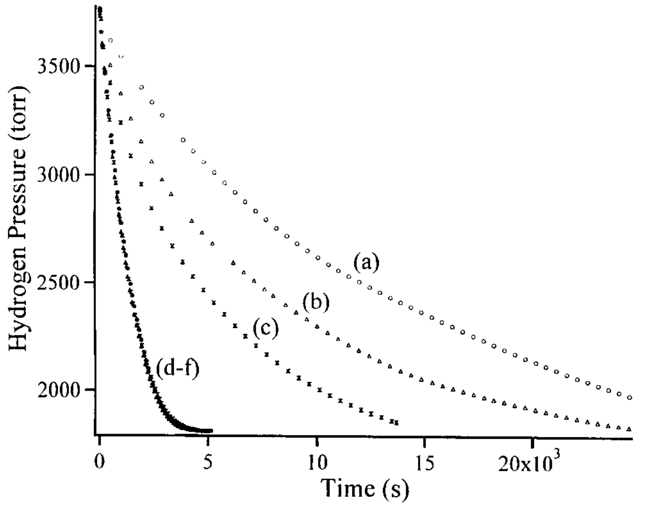

Figure 2. Hydrogen pressure vs. time curves for three colloidal platinum catalysed ethyl pyruvate hydrogenation reactions, before (curves (a)–(c)) and after ((d)–(f)) dialysis of the colloidal catalyst. (100 ml 0.22 M ethyl pyruvate in ethanol, ca. 10 mg colloidal Pt, 300 mg PVP, 50 mg dihydrocinchonidine, 24°C, 1150 rpm stirring speed).

Table 1
The effect of dialysis on the ethyl pyruvate hydrogenation activity of colloidal platinum. (100 ml 0.22 M ethyl pyruvate in ethanol, ca. 10 mg colloidal Pt, 300 mg PVP, 50 mg dihydrocinchonidine, 24°C, 1150 rpm stirring speed)

Pt sol	Pt_{tot} (mg)	Undialysed sols		Dialysed sols	
		$rate_{50\%}$ (mol ℓ^{-1} s^{-1})	$rate_{50\%}/Pt_{tot}$ (s^{-1})	$rate_{50\%}$ (mol ℓ^{-1} s^{-1})	$rate_{50\%}/Pt_{tot}$ (s^{-1})
(a)	10.2	1.0×10^{-5}	2.0×10^{-2}	9.1×10^{-5}	0.18
(b)	9.6	1.5×10^{-5}	3.0×10^{-2}	9.5×10^{-5}	0.19
(c)	9.8	2.5×10^{-5}	4.9×10^{-2}	9.5×10^{-5}	0.19

dihydrocinchonidine. In the pressure vs. time plots presented in figures 2 and 3, pressure measurements recorded every few minutes are used for visual clarity, although data were collected at a much higher rate. Reaction rates per total platinum atoms at 50% conversion (see table 1) varied from 2.0×10^{-2} to 4.9×10^{-2} s^{-1}, despite the apparently identical particle sizes of the colloidal metal in the three preparations. This degree of irreproducibility is unacceptable for our purposes in a test system.

A possible cause for this irreproducibility in activity with apparently identical catalysts is found in the fact that during the preparation of the platinum sols significant quantities of chloride, protons and formaldehyde were formed. For example, platinum particles of ca. 30 Å contain approximately 1500 atoms, and so a preparation from H_2PtCl_6 generates approximately 9 000 chloride ions per platinum colloid particle:

$$H_2PtCl_6 + 2CH_3OH \rightarrow Pt(0) + 2HCHO + 6H^+ + 6Cl^- \quad (1)$$

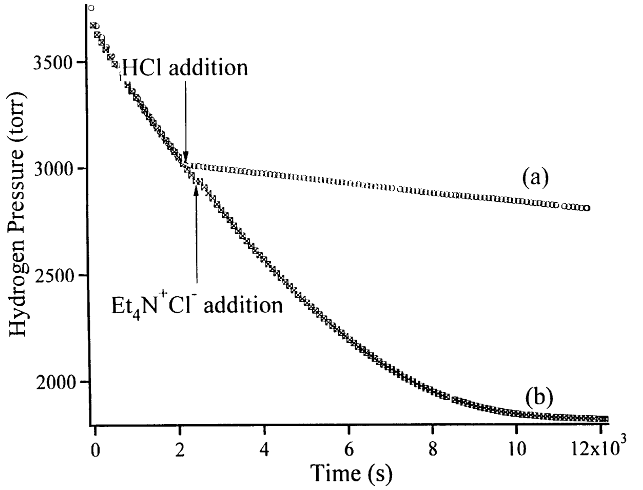

Figure 3. Hydrogen pressure vs. time curves for two colloidal platinum catalysed ethyl pyruvate hydrogenation reactions, showing the effect of adding (a) HCl and (b) $Et_4N^+Cl^-$ to reactions using catalysts which had been previously dialysed.

The standard sol preparation used in this study requires a starting H_2PtCl_6 concentration of approximately 10 mM, resulting in a chloride ion concentration of 60 mM, which, after the reduction of Pt(IV) to the colloidal metal, is in the form of HCl. The HCl can be lost during the reflux phase of the preparation in gaseous form, or removed during drying of the solid PVP/Pt product under reduced pressure. The extent to which the HCl is removed is not usually monitored and if, as seems probable, the removal is variable from preparation to preparation, this would result in a random residual concentration of HCl in the sol. Analysis of one of the dried sols used in this study gave a chlorine content of 2.57%, which can be compared with 3.15% expected if all the HCl initially present as $[PtCl_6]^{2-}$ had remained in the sol. Thus after reaction and work-up of the colloidal platinum > 80% of the HCl produced was retained. It seemed possible that variable concentrations of HCl in the catalyst might be the cause of the variable hydrogenation rate.

To test this hypothesis the specific Pt/PVP sols discussed above were dialysed over 15 h using a cellulose dialysis membrane. One such sol gave a chlorine analysis of 0.57% after dialysis, indicating 80% chloride removal and implying a similar lowering of acidity. The dialysed sols were then dried and redissolved in methanol for evaluation in the ethyl pyruvate hydrogenation reaction under identical conditions as before, thus allowing a direct comparison of catalytic properties to be made before and after dialysis for each of the three preparations. The results are shown in figure 2(d)–(f) and table 1. Using the same concentrations of platinum for each dialysed sol as had been used in the undialysed cases, the three colloidal catalysts which before dialysis had widely differing rates were faster by factors of four to eight, and had remarkably reproducible hydrogenation rates per total platinum atom, only varying from 0.18 to 0.19 s^{-1} (see table 1). The near identity of these rates is remarkable for three independent catalyst preparations, and is more reminiscent of rate reproducibility for molecular homogeneous catalysts than for heterogeneous catalysts. The similarity of the three measured hydrogenation rates is real, and not an artefact resulting from severely diffusion limited reactions showing identical rates of gas–liquid mass transfer, which at the same agitation speed would result in similar gas uptake rates for the three reactions [19]. Measurement of the gas–liquid mass transfer coefficient for the reactor, hydrogen pressure, liquid volume and composition used in this study gave a value of 0.6 s^{-1}, corresponding to maximum hydrogen dissolution rates at 1500 Torr of ca. 4×10^{-3} mol ℓ^{-1} s^{-1}, whereas the highest rates measured for the gas uptake for the dialysed catalysts were ca. 1.3×10^{-4} mol ℓ^{-1} s^{-1}, some thirty-fold slower than the calculated maximum gas–liquid diffusion rate. The absence of mass transfer limitations was confirmed by reducing the catalyst charge by half, which resulted in reduction of the observed rate by a corresponding amount, but the final e.e. was not significantly different. Increasing the agitation speed also had no effect on reaction rate.

The cause of the lower rate for the undialysed sols was revealed in the following two experiments, in which either tetraethylammonium chloride or HCl was added to the reaction mixtures during ethyl pyruvate hydrogenation with previously dialysed sol catalysts (see figure 3). It should be noted that the colloidal catalysts used in these experiments were from separate colloid preparations, and so the coincidence of the two pressure vs. time curves in the initial stage of the hydrogenations (before either $Et_4N^+Cl^-$ or HCl addition) testify to the remarkable reproducibility of the dialysed sols in this notoriously capricious reaction. In these hydrogenations a dialysed sol was used under standard conditions until ca. 30% conversion was achieved. To one reaction a concentrated solution of HCl in ethanol was added, giving a chloride ion concentration equal to that which would be present if all the chloride liberated in the preparation of the catalyst charge were still present in the reactor as HCl. The effect on the rate of reaction was instantaneous and dramatic, as shown in figure 3 (a). The rate of reaction (30% conversion) per total platinum atom was reduced on HCl addition from 2.4×10^{-1} s^{-1} to 2.0×10^{-2} s^{-1}, a factor of twelve. However, when a similar experiment was performed by addition of a solution of tetraethylammonium chloride in ethanol to give the same chloride ion concentration as in (a), no change in rate was observed, as shown in figure 3 (b).

This result clearly shows that the original rate increase observed on dialysis of the as-prepared sols, shown in figure 2, is due to a lowering of $[H^+]$. This is in contrast to the reported rate enhancement in acidic solvents [2] found for alumina and silica supported catalysts, although in those cases the acidic component is usually a much weaker carboxylic acid. It was noted however that formic acid and trichloroacetic acid, both stronger acids than acetic acid, caused a significant decrease in rate except at low concentrations [2]. Protonation of one or both of the two nitrogen atoms in the cinchonidine molecule may well be involved in these observations, and the effect of HCl addition on the performance of the naphthylethylamine modifiers reported by Minder et al. [8] would be revealing in this context, as these molecules do not contain the second basic nitrogen found in the cinchona modifiers.

It is also remarkable that when the acidity of the colloidal catalyst suspension was reduced by dialysis, a *higher* rate was accompanied by a *lower* enantioselectivity. Over a series of nine experiments under standard conditions the predialysis colloidal catalysts spanned a range of 33–51%, with a mean of 43%, whereas over seven experiments with the corresponding dialysed sols the range was 32–36%, with a mean e.e. of 33%. The fact that rate and e.e. are affected in opposite directions by a change in pH is worthy of comment, although it should be recalled that a change of only 10% in e.e. in this range corresponds to an increase in yield of only ca. 5% of the R-enantiomer, hardly sufficient to allow detailed interpretation. Increases in rate and enantioselectivity are often assumed to occur in parallel in this system, but on the basis of the results reported here we suggest that the enantioselectivity and overall rate enhancement induced by cinchona modification of the catalyst can respond to reaction conditions independently in this reaction, in the present case to changes in pH. These phenomena are under continuing investigation in both the colloidal and supported platinum catalyst systems.

In summary, the dialysed colloidal catalysts described here have proved to be highly reproducible in rate and enantioselectivity under controlled hydrogenation conditions, and they thus provide a useful test system for a detailed study of both rate and enantioselectivity effects in the absence of possible support effects. Detailed rate and enantioselectivity studies are in progress using this colloidal platinum catalyst.

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