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Asymmetric Hydrogenation of Ethyl Pyruvate: Diffusion Effects on Enantioselectivity

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Marked shifts in enantioselectivity from ca. 20 to 60 ee% as a function of reactor agitation speed were observed in the hydrogenation of ethyl pyruvate over cinchona-alkaloid-modified Pt. Concomitant with this shift in enantioselectivity was a change in the observed kinetics from the zero-order substrate dependence typical of gas–liquid diffusion control to a positive dependence on substrate concentration, even for a series of reactions carried out at constant pressure. A strong relationship between the solution hydrogen concentration and this rate and enantioselectivity behavior was confirmed. For systems where enantioselectivity exhibits a positive dependence on hydrogen concentration, the intrinsic ability of a catalyst to effect asymmetric hydrogenation may be masked in a reaction carried out under conditions where gas–liquid diffusion is the rate-limiting step. © 1996 Academic Press, Inc.

INTRODUCTION

A significant number of investigations in the field of chiral heterogeneous catalysis have focused on the model system of cinchona alkaloid modified late transition metal catalysts for the hydrogenation of α-keto esters (1–20). Enantioselectivity in this system has been reported to be a function of a wide range of experimental variables, including reaction pressure (3, 8, 10) and temperature (13, 19), solvent (3, 5, 8), metal particle size and structure (4, 17), type of metal (14, 15, 18), and nature of the modifying species (10, 18). Less attention has been focused on the role that diffusion limitations may play in dictating enantioselectivity in this three-phase system (7, 19, 20). We recently reported that this catalytic system is one of several examples, in both heterogeneous and homogeneous asymmetric hydrogenation, where gas–liquid mass transfer control can result in a marked effect on enantioselectivity (20). The purpose of the present paper is to provide a detailed picture of the influence of competitive rate processes on enantioselectivity for the ethyl pyruvate/Pt/dihydrocinchonidine system, using reaction calorimetry as a kinetic tool.

BACKGROUND

While the effects of mass transfer processes on selectivity of multiphase catalytic organic reactions have been discussed, these studies have not focused particularly on asymmetric catalytic hydrogenation (21–25). The reactants in a hydrogenation reaction are present in two separate phases, and gas–liquid mass transfer appears as the first step in the sequence of diffusion, adsorption and reaction steps that characterize the overall reaction. In the description of a marked pressure dependence of enantioselectivity which has been observed in both homogeneous and heterogeneous catalytic hydrogenation of a variety of prochiral substrates, the implicit assumption in most work is that the solution is saturated with hydrogen under reaction conditions. However, this assumption is valid only when the reaction rate is very low compared with the maximum rate of gas–liquid mass transfer, a constraint easily violated under experimental conditions commonly employed to carry out these reactions (7). A more descriptive parameter is the concentration of molecular hydrogen in solution, $[H_2]$, which may be obtained from the hydrogen mass balance. In this balance, the change in hydrogen concentration in solution as a function of reaction time is set equal to hydrogen input across the gas–liquid interface minus consumption of hydrogen in the catalytic reaction:

$$\begin{aligned}\text{accumulation} &= \text{input} - \text{consumption}\\ \frac{d[H_2]}{dt} &= k_L a * ([H_2]^{\text{sat}} - [H_2])\\ &\quad -\eta * f\{[H_2]; [\text{catalyst}]; [\text{substrate}]\}. \quad [1]\end{aligned}$$

The hydrogen input rate is a function of the mass transfer rate coefficient, $k_L a$ (units of time^{-1}), and a concentration driving force, which is the difference between the equilibrium solubility of hydrogen at reaction conditions, $[H_2]^{\text{sat}}$, and the actual solution concentration, $[H_2]$ (both with units of moles/volume). The consumption term is in the general case a function of the catalyst, hydrogen, and

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substrate concentrations. In the absence of liquid–solid or internal diffusion control, the effectiveness factor, η, equals unity and the hydrogen consumption term is described by the intrinsic kinetic rate expression for the reaction. The present work shows that under typical operating conditions, a wide variation in $[H_2]$ is possible even for reactions carried out at a given constant pressure and that profound effects on enantioselectivity ensue when $[H_2]$ is significantly lower than $[H_2]^{sat}$.

EXPERIMENTAL

Materials. The organic substrate, ethyl pyruvate (Aldrich, >99%), and the solvent 1-propanol (Aldrich, 99.5%) were used without further purification at a substrate concentration of 1 *M*. Dihydrocinchonidine prepared by hydrogenation of cinchonidine (Aldrich) as described previously (17) was used in a concentration of 100 mg/liter. The catalyst employed in these studies was a 1 wt% Pt/Al_2O_3 (Precious Metals Corporation, prereduced, ca. 20% D). Reactions were carried out in 0.5-liter batches using 5.6 g catalyst.

Reactions. Catalytic reactions were carried out in a fully automated reaction calorimeter (Mettler RC1) using a 1-liter jacketed thick-walled glass vessel with a Hasteloy head and impeller shaft. This system is capable of minimizing and accounting for any heat losses attendant to the process under study. Reactions were carried out at 303 K and at constant pressure ranging from 135 to 685 kPa. Hydrogen was introduced to the liquid by drawing gas in from the head space through a hollow impeller shaft. Agitation speed was varied from 400 to 2000 rpm.

The energy balance for an isothermal reacting system shows that the heat flow is proportional to the reaction rate,

$$q_r = V_r \sum_i \Delta H_{rxn,i} \left(\frac{dC_i}{dt} \right), \qquad [2]$$

where q_r is the heat released or consumed by the reaction, V_r is the volume of the reactor contents, (dC_i/dt) is the reaction rate and $\Delta H_{rxn,i}$ the heat of reaction of the *i*th reaction. When the heat flow of a reaction is calibrated as described previously (19, 26), q_r gives a quantitative measure of the overall reaction rate. The overall heat of reaction is provided by integration of the heat flow curve.

Gas–liquid mass transfer coefficients, k_La, and hydrogen, solubilities, $[H_2]^{sat}$, were measured for a range of agitation speeds and pressures by a dynamic method as described previously (7, 19, 27). The solution concentration of hydrogen, $[H_2]$, may then be obtained as a function of time under a given set of reaction conditions by numerical integration of Eq. [1], with the reaction rate, determined from experimentally obtained heat flow curves, inserted into the term for consumption of hydrogen. Knowledge of the controlling regime for the consumption term is not required in order to use this experimentally determined rate data; however, without such knowledge, interpretation of these rate data in terms of kinetic rate expressions or diffusion constants is precluded.

The mass transfer rate of hydrogen is given in mol/liter/min. Since mass transfer is not a function of the catalyst concentration, comparison with catalytic reaction rates will be made on the basis of these units, using the rate measured for the contents of the batch reactor as an extensive variable. Catalytic reaction rates may be put on a site-specific basis by dividing by the moles of surface Pt present in batch reactor. For the catalyst concentration employed in this study, a heat flow of 1 W corresponds to a turnover frequency of approximately 0.25 s^{-1}.

Analytical measurements. Samples taken periodically as the reaction progressed were analyzed by gas chromatography (HP 5890 with autoinjector, FID detector) using Chiraldex B-TA column capable of separating the (*R*) and (*S*) ethyl lactate isomers as well as the unreacted ethyl pyruvate. The selectivity was expressed as the enantiomeric excess (ee%) of the (*R*) lactate using the relationship:

$$\text{ee\%} = \left| \frac{[R]-[S]}{[R]+[S]} \right| \times 100. \qquad [3]$$

RESULTS AND DISCUSSION

Table 1 summarizes the results of gas–liquid mass transfer measurements at 303 K for a variety of experimental conditions of pressure and agitation speed. A 100-fold increase in the mass transfer coefficient was observed as the agitation speed was increased from 400 to 2000 rpm. This was reflected in a concomitant increase in the maximum

TABLE 1

Gas–Liquid Mass Transfer as a Function of Agitation Speed[a]

Agitation speed (rpm)	Mass transfer coefficient, k_La[b] ($s^{-1} \times 10^2$)	Maximum gas–liquid mass transfer rate[c] r_{max} ($10^3 \times$ mol/liter/min)
400	0.48	3.5
480	1.97	14.2
510	3.32	23.9
575	6.24	44.9
750	14.1	102
2000	70.4	507

[a] Hydrogen mass transfer into 1 *M* ethyl pyruvate/propanol at 303 K and 580 kPa.

[b] Measured as described in Ref. 19.

[c] Calculated from Eq. [4] with $[H_2]^{sat} = 0.012$ *M*, measured as described in Ref. 19.

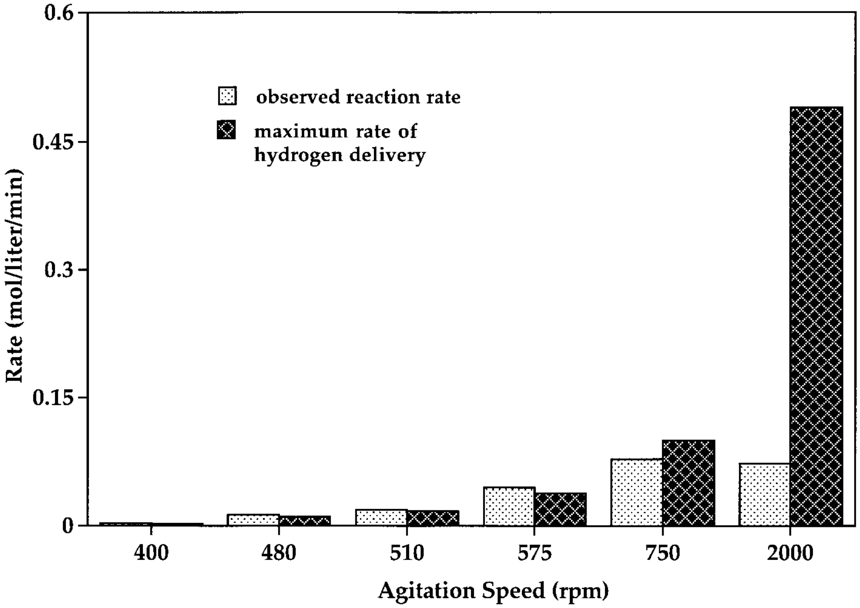

FIG. 1. Comparison of the maximum observed reaction rate (1 *M* ethyl pyruvate at 303 K and 580 kPa, 60 μmol Pt$_s$) to the maximum rate of delivery of hydrogen across the gas–liquid interface, as a function of the agitation speed.

rate of gas–liquid mass transfer, as calculated by

$$r_{\max} = \frac{d[H_2]}{dt} = k_L a * [H_2]^{\text{sat}}. \quad [4]$$

This rate represents the maximum driving force for mass transfer of H_2 across the gas–liquid interface and sets an upper limit to the rate at which hydrogen may be supplied to the catalyst for reaction. As a general rule, conditions under which the reaction is not governed by this mass transfer process require that the observed rate of the catalytic reaction be on the order of 10 times lower than the maximum mass transfer rate.

Figure 1 compares the observed rates for the hydrogenation of ethyl pyruvate at 303 K and at a constant pressure of 580 kPa to the calculated maximum mass transfer rates from Table 1 over the experimental range of agitation speeds. At lower agitation speeds the measured rate of reaction was clearly limited by the availability of hydrogen in the liquid phase, and only at the higher agitation speeds did the mass transfer rate approach the general rule for avoiding gas–liquid diffusion control discussed above.

The data in Fig. 1 imply that the rate-controlling step in the hydrogenation of ethyl pyruvate switched from gas–liquid mass transfer either to another diffusion step or to the intrinsic kinetic regime as the agitation speed was increased. This is even more clearly demonstrated in Fig. 2, where rate curves are given for the full course of the reaction of ethyl pyruvate for the experimental conditions of Fig. 1. With no change in reaction pressure or temperature, increases in agitation speed resulted in a rate increase of over an order of magnitude, as well as a change in the form of the rate expression exhibited by the catalytic system. At low agitation speeds, and hence low values of $k_L a$, the reaction rate appeared to be zero order in ethyl pyruvate; however, the rate gradually assumed a positive substrate dependence as the gas–liquid mass transfer coefficient increased.[4] Under gas–liquid diffusion control, the reaction rate has no dependence on substrate concentration, being dictated only by the rate at which hydrogen can be delivered across the gas–liquid interface, which is first-order in hydrogen concentration (see Eq. [4]).

These data highlight an important concern for kinetic studies of hydrogenation reactions. Observation of zero-order substrate dependence in catalytic reactions is often ascribed to “saturation kinetics,” or a preequilibrium in the step of substrate adsorption, which suggests that if the surface coverage of substrate θ_{sub} is constant over the course of the reaction, the kinetic reaction rate will not depend on the bulk fluid concentration of substrate. In the present case, such an interpretation of the zero-order rate dependence observed at the lower agitation speeds would obviously be incorrect.

Observations similar to those described above have also been made in our laboratories for one Pt/C and two different Pt/Al_2O_3 catalysts at various substrate : catalyst ratios, for reactions carried out in propanol and methyl acetate

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[4] We recently described a phenomenon of rising rate at low conversion (Ref.28); this is nearly masked in the present case due to the reaction conditions employed. At 2000 rpm, the peak in rate observed between 10 and 20% conversion occurred within 2 min of the start of the reaction. In the case of the lower agitation speeds, diffusion control prevented observation of a peak in the rate curve.

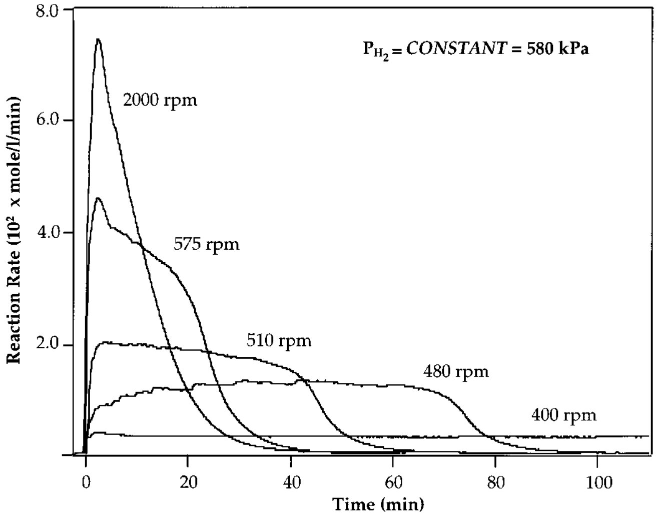

FIG. 2. Reaction rate curves as a function of time and agitation speed for the reactions shown in Fig. 1 (1 *M* ethyl pyruvate at 303 K and 580 kPa, 60 μmol Pt_s).

solvents, and for reaction temperatures and hydrogen pressures over the ranges 263–323 K and 135–700 kPa, respectively.

While investigations of the interplay between gas–liquid mass transfer and other rate processes, as well as methods for determining the rate-controlling step, have been discussed extensively using a wide range of catalytic applications as examples (22, 23), the importance of these concepts and the extent of the implications for enantioselectivity in complex organic reactions are just now being brought to light (20). Figure 3 demonstrates that hydrogen availability to the catalyst influenced not only reaction rate and observed reaction order, but also had a profound effect on enantioselectivity in this reaction. Over the range of agitation speeds studied, the enantioselectivity increased from 20 to 60%, even while carrying out the reactions at a constant overall hydrogen pressure (filled circles in Fig. 3).

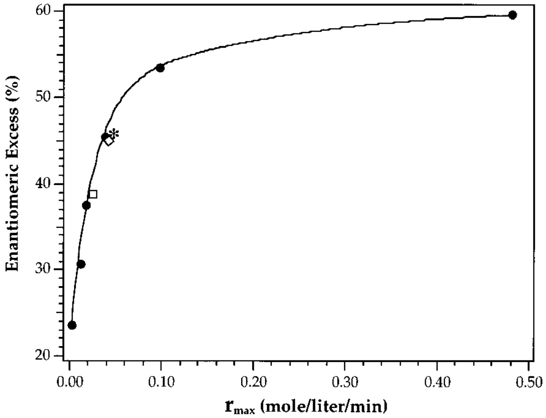

FIG. 3. Enantioselectivity at 50% conversion as a function of the maximum hydrogen delivery rate in ethyl pyruvate hydrogenation at 303 K; filled circles, from reactions shown in Figs. 1 and 2 (pressure held constant at 580 kPa; agitation speed varied from 400 to 2000 rpm); open square; 170 kPa, 750 rpm; diamond, 300 kPa, 750 rpm; star, 270 kPa, 780 rpm.

In a comprehensive study of mass transfer considerations, Blaser and co-workers (7) carried out studies of the effect of agitation speed on rate and enantioselectivity. For a range of k_La values similar to ours, they reported a threefold increase in rate and less than 10% increase in enantioselectivity. Changes in the rate dependence on substrate concentration were not discussed. This less pronounced effect on rate and enantioselectivity may be explained by the significantly higher pressures they employed in that work. At a given value of k_La, the higher hydrogen solubility at higher pressure affords a greater maximum hydrogen delivery rate and hence less influence from gas–liquid mass transfer on reaction kinetics. This suggests that the sensitivity of enantioselectivity to gas–liquid mass transfer characteristics is a more important consideration for studies carried out at low pressures. It also suggests that when a range of pressures is under study, care must be taken to ensure that the controlling step does not switch to gas–liquid diffusion as the pressure is lowered.

An additional practical point is highlighted by this work. For the reactor configuration employed by Blaser and co-workers (7), their data showed that k_La was proportional to the square of the agitation speed, while in our case a linear relationship was found. Hence comparison of data from different laboratories on the basis of stirring speed alone can be as problematic as comparison on the basis of pressure alone. Measurements of mass transfer coefficients and maximum gas–liquid mass transfer rates provide the most rigorous means of comparison between different experimental configurations.

The results of Fig. 3 and this discussion make it clear that without knowledge of the actual solution concentration of hydrogen, it is difficult to interpret the role of other experimental variables such as solvent, metal particle size, or modifier characteristics in dictating enantioselectivity in this system. Since mass transfer measurements are not routinely carried out to verify the regime of operation, and since a wide variation in reactor configurations have been employed in studies of this catalytic system (with concomitant variations in k_La and $[H_2]$ values), it is reasonable to consider gas–liquid diffusion control as one possible factor contributing to the wide range of enantioselectivities reported in the literature for this system.

Figure 3 shows, as did the work reported in Ref. (7), that when the gas–liquid mass transfer rate becomes high enough such that $[H_2]$ approaches $[H_2]^{sat}$, further increases in k_La cause no additional increase in the enantioselectivity. Pressure and temperature determine $[H_2]^{sat}$ and therefore these variables may set the upper limit on enantioselecti-

TABLE 2

Hydrogenation of Ethyl Pyruvate under Gas–Liquid Diffusion Control[a]

Pressure (kPa)	Agitation (rpm)	$[H_2]^{sat}$[b] $10^2 \times M$	Solution hydrogen concentration[c] $[H_2]$ $(10^2 \times M)$	Mass transfer coefficient[d] k_La $(10^2\ s^{-1})$	Gas–Liquid mass transfer rate[e] $(10^4 \times M\ s^{-1})$	Enantio selectivity[f] (ee%)
580	575	1.2	0.11	5.2	5.98	45
300	750	0.63	0.11	11.5	5.98	45

[a] 1 *M* ethyl pyruvate in propanol with Pt/Al_2O_3 at 303 K.

[b] Measured as described in Ref. 19.

[c] Measured at 50% conversion.

[d] Measured as described in Ref. 19.

[e] Calculated from the input term of Eq. 2.

[f] Measured at 50% conversion.

vity in this reaction for a given catalyst system under given reaction conditions. At lower agitation speeds, however, the role of k_La is more important. In the gas–liquid diffusion-controlled regime where the observed rate is given by Eq. [4], one might envision obtaining identical catalytic behavior for two extreme cases: first, a system exhibiting high $[H_2]^{sat}$ and low k_La (high pressure and poor gas–liquid mass transfer), or alternatively for a system with low $[H_2]^{sat}$ and high k_La (low pressure and good gas–liquid mass transfer). The results of two such experiments are shown in Table 2 and Fig. 4. For these different experimental conditions of pressure and agitation speed, similar gas–liquid mass transfer rates did indeed lead to strikingly similar rate curves when that rate was the controlling step. In addition, the enantioselectivities obtained under these different pressures were identical.

Other experiments varying both agitation speed and pressure were also carried out, with the results also plotted in Fig. 3. These data help to address the question of the contribution of another type of diffusion control, that of liquid–solid mass transfer. If diffusion through a stagnant film at the liquid–solid interface is the controlling step, then changing the agitation speed should change the thickness of this film and hence the surface concentration of hydrogen. Yet in all cases, the enantioselectivity was found to correlate only with hydrogen concentration in the bulk fluid.

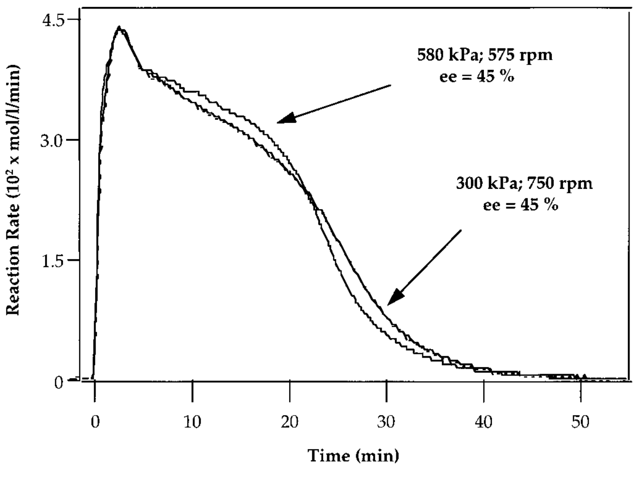

FIG. 4. Reaction rate as function of time for two sets of experimental conditions of pressure and agitation speed in the hydrogenation of 1 *M* ethyl pyruvate at 303 K: 580 kPa and 575 rpm; 300 kPa and 750 rpm.

The positive order dependence on substrate concentration observed in this system when gas–liquid diffusion was not controlling has another implication for understanding catalytic behavior. Figure 5a shows that a batch reaction commencing under conditions where hydrogen gas–liquid diffusion is controlling will eventually switch out of this regime as the substrate is consumed and, therefore, the reaction rate decreases. The sharp rise in solution hydrogen concentration mirrors the fall in rate with substrate consumption. This suggests a possible alternative explanation for similar observations found in the literature. For example, a severe retardation in rate and a switch from zero- to positive-order substrate dependence was observed near 65% conversion of methyl pyruvate over EUROPT-1 by Wells and co-workers (12) and was attributed by them to product inhibition (28). Behavior similar to what they report may be observed due to a change in the rate-controlling step as illustrated in Fig. 5a.

Even more interesting is the marked effect of this changing hydrogen concentration on enantioselectivity over the course of the reaction shown in Fig. 5b. The "incremental" enantioselectivity, calculated from the reaction products formed between two given reaction times, is plotted in Fig. 5b since it provides a more sensitive measure of changes occurring over the course of the reaction than does the more conventional "cumulative" enantioselectivity, which is an integral property of the batch reaction. The rise in incremental enantioselectivity as solution hydrogen concentration rises confirms the strong relationship between the two. This also confirms that enantioselectivity can be a dynamic variable and it makes a strong case for the necessity of monitoring reaction progress in order to follow such be-

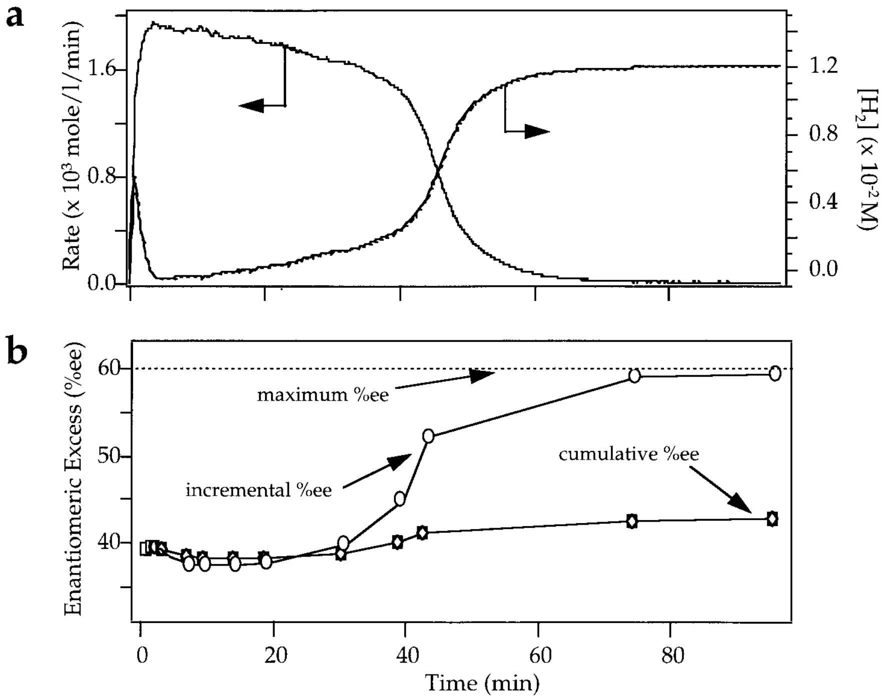

FIG. 5. Hydrogenation of 1 *M* ethyl pyruvate at 303 K, 580 kPa, 60 μmol Pt$_s$, and 510 rpm as a function of time. (a) Reaction rate and solution hydrogen concentration (b) Enantiomeric excess: cumulative %ee represents the integral enantioselectivity of the batch at any time; incremental %ee represents the instantaneous enantioselectivity at any time; maximum %ee represents the highest enantioselectivity achieved under these reaction conditions using maximum agitation speed (2000 rpm).

havior. A simple measurement of enantioselectivity either under initial conditions or at total conversion would present a misleading picture of the performance of this catalyst under the reaction conditions employed in this work.

Also shown in Fig. 5b is the maximum value for enantioselectivity which we have been able to achieve under these reaction conditions with this catalyst, given optimal gas–liquid mass transfer conditions. The fact that the incremental enantioselectivity, which measures the enantioselectivity at a given point in the reaction, approaches the value for the maximum ee% at high conversion (and high [H$_2$]), demonstrates that the system had no memory of the hydrogen starvation conditions experienced at the beginning of the reaction. As [H$_2$] increased with reaction progress to approach its saturation value, the ability of the catalyst to effect enantioselective hydrogenation becomes identical with that observed when the reaction was carried out with agitation sufficient to avoid gas–liquid diffusion limitations over the entire course of the reaction.

CONCLUSIONS

The interplay between gas-liquid mass transfer and other rate processes has the potential to effect marked shifts in enantioselectivity in the catalytic hydrogenation of ethyl pyruvate over cinchonidine-modified Pt. By varying the rate at which molecular hydrogen is transferred from the gas into the liquid phase, the reaction rate behavior shifted from the zero-order substrate dependence typical of diffusion control to a positive dependence on substrate concentration. Even more strikingly, a tripling of the enantioselectivity accompanied this transition of the rate-controlling step. These findings clearly illustrate the importance of assuring kinetic control in studies of this complex system if a rational interpretation of rate and enantioselectivity dependences is to be made.

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