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Asymmetric Hydrogenation of Ethyl Pyruvate: Relationship between Conversion and Enantioselectivity

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The hydrogenation of ethyl pyruvate over cinchonidine-modified Pt exhibited intriguing transient behavior at the beginning of the reaction, and a period of rising rate and enantioselectivity was linked to conversion of substrate for a wide range of reaction temperatures and initial substrate concentrations. A "reaction-driven equilibration" of the surface environment for optimal enantioselective catalysis was proposed for these reactions carried out under conditions where moderate enantioselectivities are observed. © 1996 Academic Press, Inc.

INTRODUCTION

The hydrogenation of α-keto esters with Pt catalysts containing chiral surface modifiers has received significant attention in the literature because it represents one of the few successful examples of asymmetric hydrogenation over a heterogeneous catalyst (1–16). Several important observations have been confirmed by different groups studying this system, although interpretation of the experimental phenomena remains the subject of vigorous discussion. First, the capability of cinchona alkaloid-modified catalysts to effect highly enantioselective hydrogenation appears to be a function of reaction variables including pressure and temperature as well as the characteristics of the catalyst. Second, the rate of reaction has been found to be significantly faster for the modified enantioselective catalyst system than for the unmodified catalyst producing a racemic product mixture. This observation led to the extension of the term "ligand-accelerated" kinetics (2) to this system, a term used by Sharpless and co-workers (17, 18) to describe significant rate increases observed in the homogeneous asymmetric dihydroxylation of olefins catalyzed by Os complexes with cinchona alkaloid ligands.

The cinchona-modified Pt catalyst system has also been shown to exhibit interesting kinetic behavior as a function of reaction progress. Wells and co-workers (11, 12) were the first to note a region of accelerating rate concomitant with rising enantioselectivity during the initial stages of the reaction of methyl pyruvate over cinchonidine-modified Pt.[4] Recently our group observed that enantioselectivity rose to a plateau near 10% conversion over a range of reaction temperatures representing a 50-fold difference in the reaction time required to reach this conversion level. This observation led us to carry out further detailed studies using reaction calorimetry as a kinetic tool to explore this intriguing relationship between enantioselectivity and conversion.

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 0.25–1 *M*. Dihydrocinchonidine was prepared by hydrogenation of cinchonidine (Aldrich) as has been described previously (14). The catalyst employed in these studies was a 1 wt% Pt/Al_2O_3 (Aldrich, prereduced). The catalyst exhibited a dispersion of approximately 20%, measured by pulse CO chemisorption using an Altamira Instruments AMI-1 temperature programmed system. The ratio of substrate : modifier : catalyst used in standard reaction conditions was 1 g ethyl pyruvate : 1 mg dihydrocinchonidine : 0.5 mg Pt_s. This gave the approximate molar ratios of substrate : $Pt_s = 17{,}000$ modifier : $Pt_s = 6$, and substrate : modifier $= 2900$. In experiments where the substrate and modifier concentrations were varied, these ratios varied accordingly.

Reactions. Catalytic reactions were carried out in a fully automated reaction calorimeter (Mettler RC1) using a 1-liter jacketed 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 263–323 K and at

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[4] We were remiss in Ref. (16) in neglecting to note that Wells' group had made this observation prior to that of our work.

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constant pressure of 580 kPa. Hydrogen was introduced to the liquid by drawing gas in from the head space through a hollow impeller shaft. Agitation speed was 1600 rpm. It was previously determined that the reaction was not controlled by gas–liquid mass transfer under these conditions of temperature, pressure, substrate concentration, and agitation speed (16). For the catalyst concentrations employed in this study, a heat flow of 1 W corresponds to a turnover frequency of approximately 0.5 s^{-1}.

The catalyst was used as received or was first pretreated *in situ* for 2 h under hydrogen at the temperature and pressure of the reaction, either in the solvent alone or with the modifier added to it. After catalyst pretreatment, reaction commenced with addition of the substrate to the vessel under hydrogen. Alternatively, the hydrogen was first replaced by Ar at atmospheric pressure before substrate addition, and the solution was stirred for 1 h prior to reintroduction of hydrogen. Product addition experiments were carried out by adding 0.4 *M* ethyl lactate at 60 ee% to the solvent/modifier/catalyst mixture and stirring under 580 kPa H_2 at the reaction temperature of 263 K for 1 h followed by degassing in Ar. Substrate (0.6 *M*) was then added and mixed for 75 min prior to commencement of the reaction with the reintroduction of H_2.

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

$$q_r = V_r \sum_i \Delta H_{\mathrm{rxn},i}\left(\frac{dC_i}{dt}\right), \qquad [1]$$

where q_r is the heat released or consumed by the reaction, V_r is the volume of the reactor contents, $(\sigma dC_i/dt)$ is the reaction rate and $\Delta H_{\mathrm{rxn},i}$ the heat of reaction of the ith reaction at the system temperature. When the heat flow of a reaction is calibrated as described previously (16, 19), q_r may be combined with the reaction stoichiometry to give a quantitative measure of the overall reaction rate.

Integration of the heat flow curve provides the overall heat of reaction. The fractional heat evolution (FHE) at any point in the reaction may then be used as a measure of the conversion of substrate:

$$\%\mathrm{conversion} = \mathrm{FHE} = \frac{\int_0^t q_r(t)dt}{\int_0^{t_f} q_r(t)dt}. \qquad [2]$$

Analytical measurements. Samples taken periodically as the reaction progressed were analyzed by gas chromatography (HP 5890 with autoinjector, FID detector) using a 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

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

In the case of product addition experiments, the ee% was calculated after subtraction to account for the added component. A small amount of ethyl lactate products (less than 1%) found in the ethyl pyruvate starting material was subtracted from the product concentrations before calculating the enantiomeric excess.

RESULTS

Reaction calorimetric monitoring of the rate of hydrogenation of ethyl pyruvate with cinchona alkaloid-modified Pt catalysts reveals interesting initial behavior, as shown in Fig. 1. Conversion and enantioselectivity from analytical sampling are also plotted for the same reaction. The heat flow data show a striking increase in rate at the beginning of the reaction, concomitant with the increase in enantioselectivity we have observed previously during this initial period. The rate reached a peak near 20% conversion, then decreased monotonically, indicating positive order dependence in substrate concentration, for the remainder of the reaction. This unusual rate behavior is more difficult to discern from the conversion vs time data also shown in Fig. 1. This initial rate and enantioselectivity behavior was also observed in reactions employing other solvents (methyl acetate) and other Pt catalysts (Pt/C).

Figure 2a shows that this link between rising ee% and conversion observed for the modified catalyst system was again observed in experiments where the initial substrate concentration was varied by a factor of four. The amount of catalyst was held constant in these experiments, and hence the substrate : $\mathrm{Pt_s}$ ratio also changed by a factor of four. The ee% followed identical behavior with respect to conversion in all cases, rising to a plateau between 10 and 20%

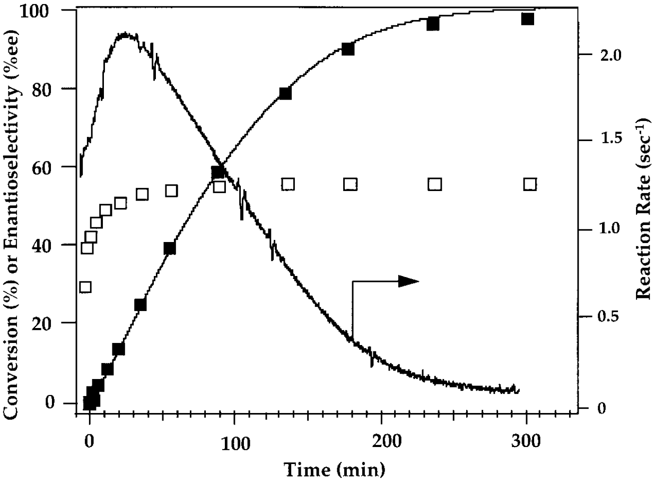

FIG. 1. Hydrogenation of 1 *M* ethyl pyruvate at 283 K and 580 kPa over dihydrocinchonidine-modified Pt as a function of time. Right axis solid line, reaction rate as measured by heat flow calorimetry; solid squares, conversion; open squares, enantioselectivity.

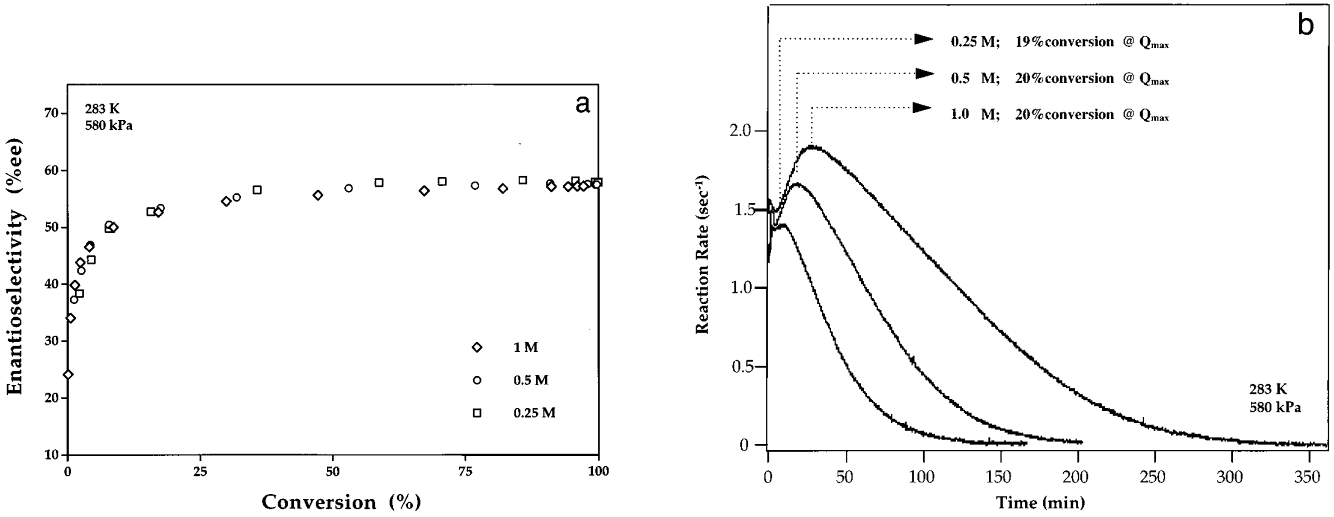

FIG. 2. Hydrogenation of ethyl pyruvate at 283 K and 580 kPa over modified Pt as a function of initial substrate molarity. (a) enantioselectivity as a function of conversion for 1 *M*, 0.5 *M*, and 0.25 *M* ethyl pyruvate; (b) reaction rate as function of time for 1 *M*, 0.5 *M*, and 0.25 *M* ethyl pyruvate. Arrows mark 20% conversion.

conversion, although this corresponded to a fourfold difference in concentration of the product, ethyl lactate, and a fourfold difference in the number of turnovers per catalyst site. The heat flow curves shown in Fig. 2b for these reactions show the same initial rising rate behavior for all substrate concentrations, with the peak in rate occurring in each case near 20% conversion.

Addition of ethyl lactate to the initial reaction mixture helped to explore the possible role of the product species in the initial reaction period. Reactions were carried out with a mixture of 0.6 *M* ethyl pyruvate and 0.4 *M* ethyl lactate (60 ee%). This represents a liquid-phase composition of the reaction mixture at a point after steady-state enantioselectivity was established. Figure 3 compares the results of this reaction at 263 K with that of the identical reaction without product addition. The presence of the product did not alter the trend of rising enantioselectivity and rising rate, which were identical in the presence and absence of product in the reaction mixture. Product addition served only to decrease the reaction rate, corresponding to the lower initial concentration of substrate.

Effects of the concentration and chemical state of the modifying species on catalytic behavior were also studied in a number of experiments. Figure 4 shows that the rate and ee% were identical whether cinchonidine or dihydrocinchonidine was used as modifier. Additionally, a

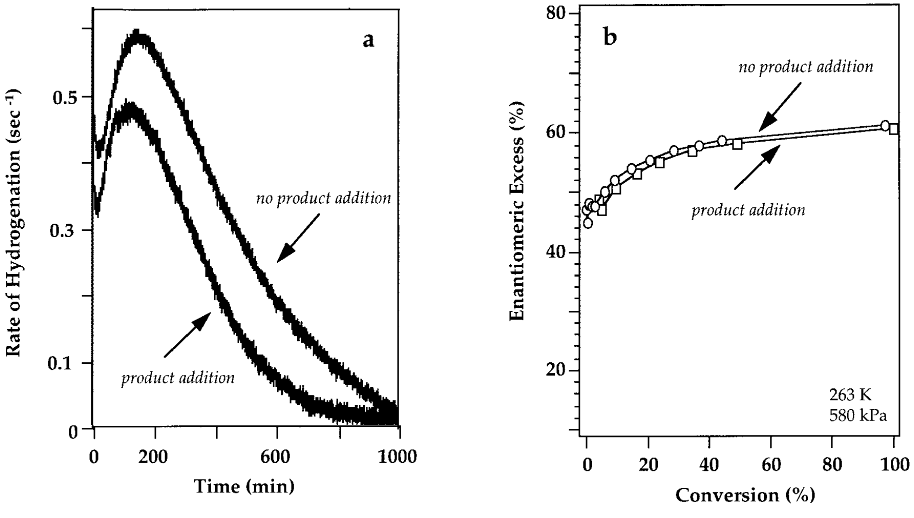

FIG. 3. Hydrogenation of 0.6 *M* ethyl pyruvate and 0.4 *M* ethyl lactate (60 ee%) over modified Pt at 263 K and 580 kPa. (a) Enantioselectivity as a function of conversion; the product added prior to the start of the reaction has been subtracted. (b) Reaction rate as a function of time.

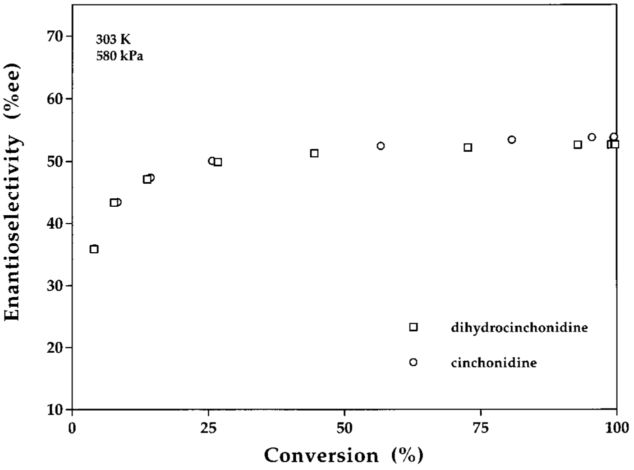

FIG. 4. Enantioselectivity and conversion vs. time for the hydrogenation of 1 *M* ethyl pyruvate at 303 K and 580 kPa over Pt modified by cinchonidine and by dihydrocinchonidine at 100 mg/liter.

similar initial period was observed for reactions carried out over a two order-of-magnitude difference in dihydrocinchonidine concentration, as shown in Fig. 5. At the lowest level of the modifier concentration, the enantioselectivity decreased slightly at high conversion, a characteristic which has been observed previously (3).

Variations in catalyst pretreatment conditions were also investigated. Figure 6a compares conversation and ee% as a function of time for reactions using a catalyst reduced *in situ* prior to addition of the substrate and for a catalyst receiving no pretreatment. A reduction treatment time of 2 h was chosen to exceed that of the period of initial rising rate under these reaction conditions. Figure 6b shows the reaction rate from heat flow measurements for these two reactions. The period of rising rate and ee% was unaffected by the reduction treatment, with a slightly higher maximum in rate for the prereduced catalyst as the only difference. This observation was made both when the modifier was present during reduction and when it was added after reduction at the same time as the substrate. Hence, neither time of exposure of the catalyst to hydrogen, nor contact time between the modifier and catalyst, influenced the initial catalytic behavior. In addition, behavior identical to that shown in Fig. 6 was observed whether the substrate was added under hydrogen immediately after the reduction treatment or to an Ar-purged system followed by reintroduction of hydrogen.

The question of reproducibility in carrying out these reactions has been discussed in the context of the possible role of surface poisoning (or *in situ* removal of surface poisons), arising either from impurities present in the organic substrate or from reactions between the catalyst and solvent (20–23). Figures 7a and 7b show heat flow data from two reactions carried at different times under identical conditions, using different lots of solvent and substrate. The rising initial rate behavior was observed in both cases, and indeed, the rate throughout the the course of the reaction was nearly identical for the two experiments. In addition, Fig. 7c confirms that this unusual initial rate behavior was not observed in reactions carried out over the unmodified catalyst, where the rate followed a well-behaved positive order dependence on substrate concentration over the full course of the reaction. At a given reaction temperature, the reaction rate for the unmodified catalyst was lower by more than an order of magnitude, as has been noted previously (3, 11). The data shown in Fig. 7c are taken from a reaction at 303 K because the very low reaction rates obtained with the unmodified catalyst preclude accurate calorimetric analysis for reactions at lower temperatures.

An interesting point to note is that the solid lines representing conversion in Figs. 1 and 6a were determined not from a curve fit of the data points obtained from analytical sampling, but from integration of the heat flow data to give fractional heat evolution over the course of the reaction (as described under Experimental). Excellent agreement was thus exhibited between two independent measures of reaction progress.

DISCUSSION

Reaction calorimetry as a kinetic tool. The phenomenon of rising rate and enantioselectivity at the outset of the reaction was first noted by Wells and co-workers for the reaction of methyl pyruvate at 293 K over cinchonidine-modified EUROPT-1 (11, 12). Figure 1 provides remarkable further detail of this unusual initial rate behavior. Since the heat flow of a reaction is directly proportional to its rate, reaction calorimetry affords the opportunity of making direct kinetic measurements which are difficult to achieve by other methods. Measurements of concentration or conversion vs time give an integral measure of reaction progress, and the

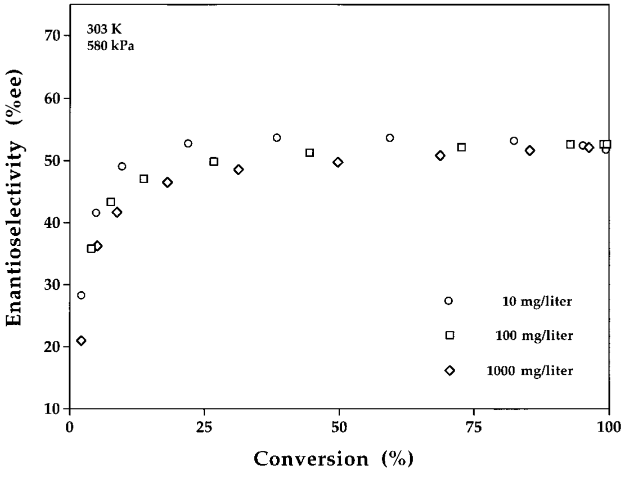

FIG. 5. Enantioselectivity and conversion vs time for the hydrogenation of 1 *M* ethyl pyruvate over modified Pt at 303 K and 580 kPa for three different modifier concentration levels.

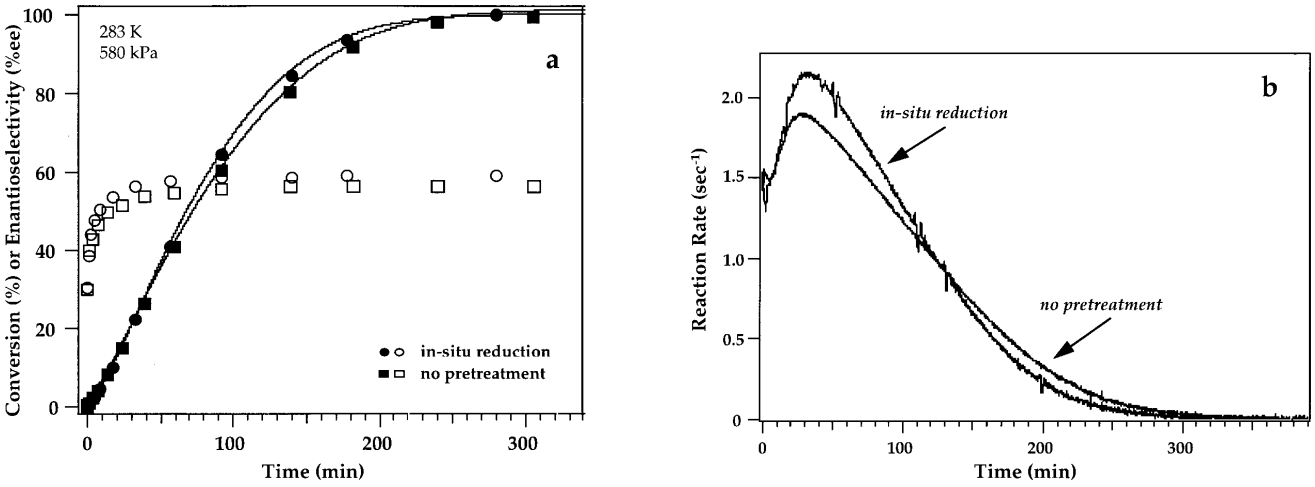

FIG. 6. Hydrogenation of 1 *M* ethyl pyruvate at 283 K and 580 kPa over modified Pt as a function of catalyst pretreatment. (a) Enantioselectivity (open symbols) and conversion (filled symbols) vs time: squares represent no catalyst pretreatment; circles represent *in situ* reduction in H_2 for 2 h at the temperature and pressure of the experiment followed by addition of substrate under Ar. (b) Reaction rate as determined by heat flow measurements for the experimental runs shown in Fig. 6a.

reaction rate may be obtained only from the derivative of such curves. Similar difficulties may arise with hydrogen uptake measurements, since reaction rate is directly proportional to hydrogen consumption only in the case of first-order reactions. When analytical sampling alone is used for rate measurements, sensitivity may be further hindered if discrete data points taken only every several minutes are used to describe rapidly changing rates. For example, the conversion data of Fig. 1 might lead one to assume a constant rate, or zero-order substrate dependence for this reaction. The increased sensitivity of the heat flow measurement shows that after the initial period of rising rate, the reaction exhibited a well-behaved positive order dependence on substrate concentration for the remainder of the reaction.

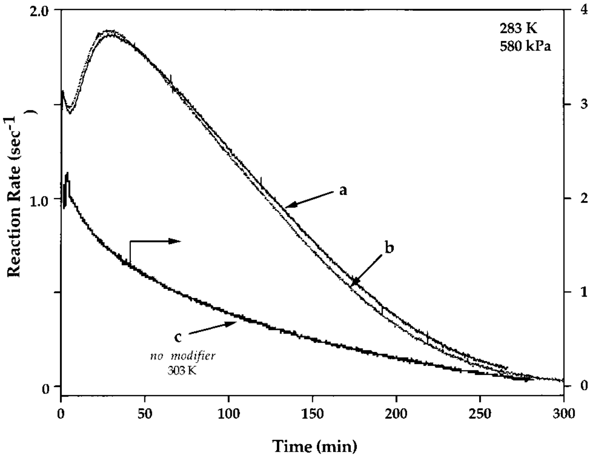

FIG. 7. Reaction rate as determined by heat flow measurements for the reaction of 1 *M* ethyl pruvate at 283 K, 580 kPa. (a) and (b) Two indentical experiments carried out with different lots of starting materials in order to demonstrate reproducibility. (c) shows reaction rate (×0.5) for the same reaction at 303 K over *unmodified* Pt.

The calorimetric data show that the accelerating initial rate and the rising enantioselectivity both correlate with the conversion level of the substrate and the presence of the modifier. Enantioselectivity is itself an integral property of the batch reaction, and the establishment of steady-state behavior ($d[R]/d[S] = 0$) actually occurs at a slightly lower conversion than is evident when the batch enantioselectivity is plotted vs conversion. Nonlinear relationships between rate and enantioselectivity are not uncommon (24); in fact, the homogeneous catalytic studies of Sharpless and co-workers in which the phrase "ligand-accelerated" kinetics was first employed found that the reaction rate reached a maximum at a higher concentration of cinchona ligands than that at which the enantioselectivity reached a maximum.

It is important to note the striking agreement between the calorimetric data and the data obtained from analytical sampling, two independent measures of extent of reaction. This emphasizes the power of reaction calorimetry as a kinetic tool. In addition, it assures us that in this case no extraneous reactions (and thus no contributions to q_r from extraneous heat flows) complicate the use of the technique or the analysis of this catalytic system. This result addresses questions concerning the formation of hemiketals between α-ketoesters and alcohol solvents (7). While we have also observed hemiketal formation in this system, manifested as a heat flow during the calibration period prior to commencement of the reaction, any significant contribution from this side reaction would have been apparent as a discrepancy between the conversion calculated from heat flow and that calculated from analytical sampling. Hence our conclusion, as was found in Ref. 7, is that the formation of hemiketals has little influence on the kinetics or enantioselectivity of this reaction.

The reproducibility of our experimental data, as demonstrated by the consistency of the data presented and specifically by the results shown in Fig. 7, also suggest that the combination of calorimetry and analytical measurements provide a sensitive means of monitoring both reaction rate and enantioselectivity over the entire course of the reaction, a critical concern in such a case where the reactive behavior changes dramatically as the reaction progresses.

Mechanism for catalysis on the modified surface. The link to conversion of substrate observed for both reaction rate and enantioselectivity in the initial period of reaction suggests that the progression of the hydrogenation reaction itself is the key to achieving the steady-state enantioselectivity and that a reaction-induced modification of the surface produces the sites which give the ultimate enantioselective performance. It is interesting to consider the concept of a reaction-driven formation of the site for enantioselective catalysis in the light of the of the seminal work of Jacobson *et al.* (17, 18) on asymmetric olefin dihydroxylation catalyzed by homogeneous Os complexes containing cinchona alkaloid ligands. They noted that the cinchona compounds caused both rate acceleration and increased enantioselectivity. In elegant kinetic studies, they reported that the ultimate enantioselectivity achieved was a function of the concentration of the chiral alkaloid ligand. In an analogous fashion, we might speculate that the induction period we observed is related to the dynamic “ligandization” of more and more Pt sites as the reaction progresses in a process clearly more complex than that of a simple adsorption–desorption equilibrium of the alkaloid modifier.

The suggestion that the surface requires a certain ratio of concentrations of reactants, products, and perhaps reaction intermediate species to produce optimal enantioselective sites leads logically to attempts to design experiments in which such an equilibrated surface might be produced prior to the start of the reaction. The observation that addition of product did not influence the initial catalyst behavior may signify that such a simple experiment did not in fact provide a valid test of the hypothesis. While the product addition protocol quite accurately mimicked the bulk fluid concentrations in the reactor at 40% conversion, perhaps it did not mimic the *surface* of the catalyst at 40% conversion. One key reactant, hydrogen, was missing from the system. The surface processes occurring during the accelerated rate period, such as adsorption and dissociation of hydrogen, adsorption–desorption of substrate, intermediates, and products, as well as the reaction itself, must be taken into consideration, and a closer model to the working surface will be required to rationalize this phenomenon on the molecular level.

Various *in situ* reduction treatments of the catalyst demonstrated that preexposure to hydrogen at reaction temperature is insufficient to produce the sites required for the steady-state enantioselective catalysis. *In situ* reduction of cinchonidine to dihydrocinchonidine also occurred too rapidly to be considered an influence on the initial catalytic behavior. If adsorption of the modifier itself was related to the initial transient period, then changing its concentration or its contact time might have been expected to affect the catalytic behavior.

Our results also appear to dictate against simple explanations for the rising rate and enantioselectivity which invoke competitive kinetic processes such as the removal of a surface poison as the reaction progresses (11, 12). First, the kinetics of such a process would have to be identical to those describing the hydrogenation of ethyl pyruvate in order to explain the link between rising rate, enantioselectivity and conversion over a 50-fold range of observed rate constants. Second, this link to conversion is difficult to rationalize if the poison is an adventitious impurity in the substrate, since identical behavior was observed for a fourfold change in substrate concentration. The fact that the use of different types of solvents, including nonalcoholic solvents, did not affect the initial behavior suggests that the role of surface poisons from the solvent was not significant under these conditions. Other studies have reported effects on enantioselectivity of many of these variables, for reasons which are not clear but may be related to differences in experimental conditions and quality of starting materials found in different laboratories.

It has also been suggested that the enantioselective hydrogenation takes place through a substrate–modifier interaction in the bulk fluid phase rather than through interactions on the catalyst surface (5, 22). It is difficult to explain how this unusual catalytic behavior would be produced in an identical fashion for modifier : substrate ratios varying over two orders of magnitude. Furthermore, if the fluid phase is indeed most important in establishing the enantioselective behavior, it would be reasonable to predict that the product addition experiments described above should have altered the initial reaction behavior, since the experiment indeed mimicked fluid phase, if not surface, concentrations of species at a point well onto the plateau in enantioselectivity.

Finally, it is important to point out that the observations made in these experiments apply to the conditions of this work, and it would be unwise to extrapolate the results to those obtained under conditions far removed from these, such as the high pressure reactions which afford very high enantioselectivities. First, a simple arithmetic argument may be made to show that the existence of the same relationship of rising enantioselectivity to conversion, which we observed for our system ultimately attaining up to 60 ee%, is precluded for a reaction attaining very high enantioselectivity. The dilution effect of the lower enantioselectivity in the initial period dictates that any transient behavior must be concluded at very low conversions in order to produce an ultimate enantioselectivity over 90 ee%. Second, it is reasonable to assume that surface coverages of various species may be very different under high and low pressure conditions (25). However, results obtained under similar reaction conditions may be compared cautiously with the hope that perhaps what we learn under one set of conditions may ultimately lead to a more general understanding of the behavior of this complex catalyst system over a range of reaction conditions.

CONCLUSIONS

The phenomenon of a rising rate and increasing enantioselectivity in the initial period of the reaction of α-keto esters using cinchonidine-modified Pt catalysts was explored. The sensitivity of reaction calorimetric data helped to show that this phenomenon was linked to *conversion* over a wide range of reaction temperatures and initial substrate concentrations, rendering untenable simple kinetic explanations based on surface poisoning. A reaction-driven equilibration of the chiral surface environment is proposed, which appears to involve a more complicated process than simple adsorption of the chiral modifier.

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