A Re-Examination of Pressure Effects on Enantioselectivity in Asymmetric Catalytic Hydrogenation

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Abstract: Marked shifts in enantioselectivity in the asymmetric hydrogenation of several prochiral substrates were observed as a function of the availability of hydrogen to the catalyst in both heterogeneous and homogeneous catalytic reactions. The key kinetic parameter affecting enantioselectivity was found to be concentration of molecular hydrogen in the liquid phase, [H_2], rather than hydrogen pressure in the gas phase, and it was observed that under typical reaction conditions, [H_2] could differ widely from its equilibrium saturation value. It was demonstrated that the reported pressure dependence on enantioselectivity may in fact be reproduced ***at constant pressure*** for several systems by varying the rate of gas−liquid mass transfer. The general significance of the conclusions suggest that considerations of hydrogen diffusion limitations might be important in other asymmetric hydrogenation studies reported in the literature. For systems where enantioselectivity depends positively on hydrogen pressure, 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.

Introduction

In many chiral hydrogenation reactions, enantioselectivity has been shown to exhibit a marked pressure dependence. Examples include the homogeneously catalyzed hydrogenation of a wide variety of conjugated prochiral olefins with transition metal catalysts containing chiral phosphine ligands,[1−6] the hydrogenation of imines with soluble chiral titanocene catalysts,[7,8] and the heterogeneously catalyzed hydrogenation of α-keto esters over Pt surfaces containing chiral modifiers.[9] In addition, the role of pressure in dictating ultimate diastereoselectivity has also been noted in substrate-directed hydrogenation reactions of chiral substrates with achiral catalysts.[10] In most of these cases, detailed kinetic data are limited, and, as Noyori has noted,[1] the origin of this pressure effect has yet to be rationalized.

One particular case, the hydrogenation of α-acylaminoacrylic acid derivatives over [Rh(dipamp)]$^+$ by Landis and Halpern[3,4] has become a textbook example[11] both because of the elegance and exhaustive detail of the kinetic work and because of the striking conclusion that the major enantiomeric product resulted from the minor intermediate species. In those studies, spectroscopic and analytical data were used to propose a mechanism and develop rate laws for the (*R*)- and (*S*)- branches of the catalytic cycle. The observed effect of hydrogen pressure on enantioselectivity was then rationalized in terms of the different dependence on hydrogen concentration for the rate of formation of each product.

Recently, these data from Halpern's laboratory were recast by Boudart and Djega-Mariadassou[12] in terms of an example of kinetic coupling between elementary steps in a catalytic cycle, which can occur when the assumption of quasi-equilibrium between reactive intermediates and reactant or product molecules does not hold. They demonstrated that for the special case of two catalytic cycles occurring in parallel, as in the case of enantioselective reactions, the product selectivity may be affected by reaction conditions such as pressure if the elementary steps in one of the cycles are coupled to one another more strongly than are those in the other cycle.

The purpose of the present paper is to highlight another aspect of the kinetics of two- and three-phase catalytic systems that plays an important role in determining enantioselectivity but has received little attention in the literature. This work focuses on the relationship between gas-phase hydrogen pressure and solution concentration of molecular hydrogen during a hydrogenation reaction, and the importance of the latter in dictating enantioselectivity. In all of the work cited above, the measured variable of reaction pressure is used interchangeably with the concentration of molecular hydrogen in solution, [H_2], assumed to equal the equilibrium solubility of hydrogen, [H_2]^{sat}, at the temperature and pressure of the reaction. This assumption holds, however, only when the maximum rate of gas−liquid mass transfer under reaction conditions far exceeds the rate of hydrogen consumption by the catalytic reaction. Hydrogen pressure, which measures reactant concentration in a phase

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different from that in which the reaction occurs, is hence a less meaningful kinetic parameter than true solution hydrogen concentration.

A simplified description of the pathway followed by hydrogen from the gas phase to its incorporation into the product is given by the consecutive reaction network

$$H_2(g) \overset{k_La}{\leftrightarrow} H_2(l) \overset{k_{diss}}{\leftrightarrow} H^* \xrightarrow{k_{kin}} \text{product} \qquad (1)$$

where k_La, k_{diss}, and k_{kin} represent forward rate constants for each step, $H_2(g)$, and $H_2(l)$ represent gas and liquid-phase hydrogen concentrations, and H* represents an intermediate species associated with the catalyst. The relative rates of these steps determine the relative concentrations of the species shown, and it is only when k_La is very large compared to the other constants that the first step in the sequence can be assumed to be in equilibrium, and the solution concentration was assumed to be $[H_2]^{sat}$. Thus an additional rate process, that of hydrogen dissolution, must be considered in order to give an accurate general description of the concentration of hydrogen available for the catalytic reaction, which we will show has important implications for enantioselectivity.

This paper describes two examples of asymmetric hydrogenation studies from our laboratories, one heterogeneous and one homogeneous catalytic reaction, in which marked changes in enantioselectivity were observed for reactions carried out by varying the solution concentration of hydrogen even while maintaining the reaction vessel at ***constant hydrogen pressure***. Moreover, we demonstrate with the kinetic data from the classic study of Landis and Halpern[3] that it is possible to reproduce their observed variation of enantioselectivity with pressure, while holding hydrogen pressure constant and instead systematically changing $[H_2]$ by varying the gas−liquid mass transfer rate. The conclusion that the interplay of mass transfer and intrinsic kinetic rate processes may have a profound effect on enantioselectivity is of general significance for studies in this field, suggesting that careful scrutiny of the results of other catalytic hydrogenation reactions reported in the literature may be indicated.

Results and Discussion

Gas−Liquid Mass Transfer. The mass balance for hydrogen in the liquid phase during a batch catalytic hydrogenation reaction consists of a term for hydrogen input from the gas phase and a term for consumption of hydrogen due to the reaction:

$$\frac{d[H_2]}{dt} = k_La^*([H_2]^{sat} - [H_2]) - k_{kin}^*f\{[H_2];[\text{catalyst}];[\text{substrate}]\}$$

$$\text{accumulation} = \text{input} - \text{consumption} \qquad (2)$$

The hydrogen input term is equal to the rate of gas−liquid mass transfer, a function of the mass transfer rate coefficient, k_La (units of time^{-1}), and a concentration driving force, which is the difference between the equilibrium solubility of hydrogen at reaction conditions, $[H_2]^{sat}$, and the actual solution concentration, $[H_2]$ (both with units of mol/volume). The hydrogen consumption term is described by the kinetic rate law for the reaction, which in the general case is a rate constant k_{kin} (units depend on the rate expression) multiplied by some function of the catalyst, hydrogen, and substrate concentrations.

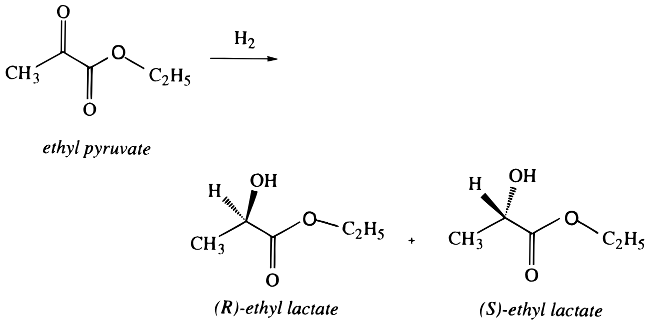
While k_{kin} is an intrinsic kinetic property of the catalytic system, k_La is strongly affected by characteristics of the reactor vessel, including agitation speed. The magnitude of $[H_2]$ during the reaction depends on the relative magnitudes of these two constants, and two extreme cases may be described. If the hydrogen consumption rate of the reaction is very high, so that the interfacial mass transfer rate is approached by that of the reaction's requirement for hydrogen, the solution becomes starved for hydrogen and $[H_2]$ approaches zero. The maximum observed rate is then dictated not by kinetics but by the driving force for mass transfer, r_{max}

$$r_{max} = \frac{d[H_2]}{dt} = k_La^*([H_2]^{sat}) \qquad (3)$$

with the variables defined as in eq 2. This equation describes the brief transient period which always occurs when hydrogen is first introduced to a solution, and, in the case of poorly stirred reactors, the condition of low $[H_2]$ may persist throughout the course of the reaction. On the other hand, if the consumption of hydrogen by the reaction is very slow, the input required to maintain a steady high concentration of hydrogen is small, and the solution concentration approaches its solubility limit, $[H_2]^{sat}$. The rate of change of hydrogen concentration in the solution is then dictated by the kinetics of the reaction. This case in fact represents the implicit assumption made in the literature discussed above.

Thus the solution concentration of hydrogen during reaction depends on the relative magnitudes of the hydrogen input and consumption terms, and both pressure ($[H_2]^{sat}$) and mass transfer characteristics (k_La) as well as the intrinsic kinetic constant k_{kin} play a role in determining $[H_2]$. The examples given in this paper demonstrate how enantioselectivity may be influenced by this interplay of mass transfer and kinetic rate processes, even for reactions carried out at *constant hydrogen*.

Hydrogenation of Ethyl Pyruvate over Cinchonidine-Modified Pt/Al$_2$O$_3$. Enantioselectivity in the hydrogenation of α-keto esters to α-hydroxy esters over heterogeneous catalysts has been reported to be affected by a number of variables including hydrogen pressure, solvent, metal particle size and structure, and type of support.[9,13−17] In our studies of the hydrogenation of ethyl pyruvate to (*R*)- and (*S*)-ethyl lactate



we kept all of these variables constant, including hydrogen pressure, and instead varied the effective solution hydrogen concentration, $[H_2]$, by experimentally changing the gas−liquid

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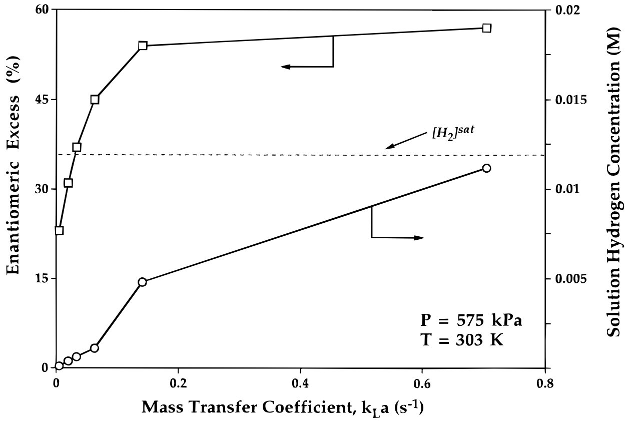


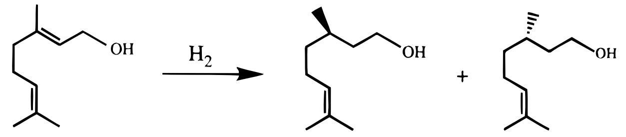
Figure 1. Enantioselectivity and solution hydrogen concentration at 50% conversion as a function of the gas−liquid mass transfer coefficient in a series of hydrogenation reactions of ethyl pyruvate over modified Pt/Al_2O_3 ***at constant pressure*** of 575 kPa and 303 K. $[H_2]$ was calculated from inserting rate data from calorimetry measurements (see Experimental Section) into eq 2.

mass transfer coefficient, k_La. For our reactor configuration, k_La was found to increase by more than two orders of magnitude by varying the agitation speed from 400−2000 rpm.

Figure 1 demonstrates that enantioselectivity and solution hydrogen concentration[18] varied as a function of the mass transfer coefficient k_La in these constant pressure reactions. Over a range of agitation speeds common in standard reaction systems, we in fact observed the spectrum of conditions encompassing the two extreme cases described earlier, with a rise in $[H_2]$ from nearly zero to a value approaching its solubility limit. Moreover, the enantioselectivity increased by almost a factor of three concomitant with the rise in $[H_2]$. This profoundly sensitive relationship between $[H_2]$ and enantioselectivity, even at constant hydrogen pressure, emphasizes the importance of direct knowledge of $[H_2]$ for rational kinetic interpretation of enantioselectivity.

When the rate of mass transfer became so high that $[H_2]$ approached $[H_2]^{sat}$, further increases in k_La caused no additional increase in the enantioselectivity. Pressure determines $[H_2]^{sat}$ (at a given temperature) and therefore may set the upper limit on enantioselectivity in this reaction for a given catalyst system. Under hydrogen-starved conditions, however, the rate-limiting step becomes equal to the rate of input of hydrogen to the solution, in which both the mass transfer coefficient, k_La, and the solubility, $[H_2]^{sat}$, play a role. From eq 3, therefore, one may predict conditions for obtaining identical rates, and hence identical values for $[H_2]$, in two extreme cases: for 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 1. Even for very different experimental conditions, similar gas−liquid mass transfer rates did indeed lead to similar $[H_2]$ concentrations when that rate was the controlling step. In addition, the enantioselectivities obtained under these very different pressures were identical, underscoring the importance of the actual solution concentration $[H_2]$ as the parameter dictating enantioselectivity in this system. When consideration is given to the variation in reactor configurations employed in studies of this catalytic system found in the literature, with the concomitant variation in k_La and hence $[H_2]$ values, one can begin to rationalize the wide range of reported enantioselectivities for this system.[9,12−17] In fact, unless results for this system are compared on the basis of $[H_2]$ rather than reaction pressure, it is difficult to interpret the role of other experimental variables such as solvent, metal particle size, or modifier characteristics. Further kinetic studies of this system will be published separately.[19]

Hydrogenation of Geraniol over $[RuCl_2(S)\text{-tolyl-binap}]_2\cdot NEt_3$. Enantioselective hydrogenation of allylic alcohols has been extensively studied by Noyori[1,2] using homogeneous Ru-(binap) catalysts where the enantioselectivity has been found to be strongly pressure dependent.



geraniol *(R)-citronellol* *(S)-citronellol*

For hydrogenation of geraniol,[2] the enantioselectivity to (*R*)-citronellol using a $[Ru(OCOCH_3)_2\text{-}(S)\text{-binap}]$ catalyst increased from 70 to 98% as the reaction pressure was increased from 4 to 100 atm (400−10 000 kPa). Hydrogenation of the *Z*-isomer, nerol, with the Ru(binap) catalyst of opposite absolute stereochemistry afforded a similar trend of pressure and enantioselectivity. Our studies of this reaction provide a second example of the sensitivity of enantioselectivity to actual solution hydrogen concentration under constant pressure conditions. Table 2 shows that the enantioselectivity in geraniol hydrogenation more than doubled with an order of magnitude increase in the mass transfer coefficient for reactions carried at 135 kPa. This increase in k_La also doubled the solution hydrogen concentration, effectively allowing it to reach its solubility limit, $[H_2]^{sat}$, at the temperature and pressure of the reaction.

Comparison of the last two entries in Table 2 with the first two demonstrates how k_La and $[H_2]^{sat}$ may each under different conditions be important in dictating enantioselectivity. When the magnitude of k_La was great enough so that mass transfer was no longer the limiting step, the enantioselectivity in geraniol hydrogenation increased from 57 to 90 ee% with a fourfold increase in pressure (and hence $[H_2]^{sat}$) for reactions carried out at constant k_La. Hydrogenation of nerol under identical conditions of rapid hydrogen mass transfer yielded 99 ee% (to (*S*)-citronellol). Interestingly, these high enantioselectivities[20] were observed under conditions close to the low pressure limit of Noyori's study,[1,2] where they reported 70% ee in both geraniol and nerol hydrogenation. This suggests that the lower pressure reactions described in ref 2 may have been carried out under conditions where the solution concentration of hydrogen was considerably lower than $[H_2]^{sat}$. Detailed kinetic studies of both experimental systems described in this paper will be published elsewhere.[21]

Analytical Treatment of Kinetic Data from the Hydrogenation of Methyl-(*Z*)-α-acetamidocinnamate with Rh-

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[18] The solution concentration was calculated by integration of eq 2 with the experimental reaction rate profile obtained from reaction calorimetry inserted in the hydrogen consumption term and experimentally determined k_La and $[H_2]^{sat}$ values inserted in the hydrogen input term (descriptions of the calorimetric and mass transfer measurements are given in the Experimental Section).

[19] Sun, Y.; LeBlond, C.; Wang, J.; Landau, R. N.; Blackmond, D. G. *J. Catal*. Submitted for publication.

[20] This result was obtained both for geraniol hydrogenation with the $[RuCl_2(S)\text{-tolyl-binap}]_2\cdot NEt_3$ catalyst) described in this paper and with the $[Ru(OCOCH_3)_2(R)\text{-binap}]$ catalyst described in ref 2 (in this case with 87% ee to the (*S*)-citronellol).

[21] We have recently observed that study of the hydrogenation of geraniol using these chiral phosphine catalysts is complicated by a separate kinetic consideration, the existence of a competitive isomerization reaction which can influence the ultimate enantioselectivity achieved. Nerol, the *Z*-isomer of geraniol, does not undergo this isomerization (Sun, Y.; LeBlond, C.; Wang, J.; Blackmond, D. G.; Laquidara, J.; Sowa, J. R. *J. Am. Chem. Soc.* **1995**, *117*, 12647.

Table 1. Hydrogenation of Ethyl Pyruvate over Pt/Al_2O_3[a]

pressure (kPa)	agitation (rpm)	$[H_2]^{sat}$ [b] (10^2 M)	soln H concn[c] $[H_2]$ (10^2 M)	mass transfer coeff[d] k_La (10^2 s^{-1})	gas−liquid mass transfer rate[e] (10^4 M s^{-1})	enantio-selectivity[f] (ee %)
580	575	1.26	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 at 303 K. [b] Measured as described in the Experimental Section. [c] Calculated using eq 2 in the text. [d] Measured as described in the Experimental Section. [e] Calculated from eq 3 in the text. [f] Measured at 50% conversion.

Table 2. Hydrogenation Allylic Alcohols over Ru(binap)[a]

substrate	pressure (kPa)	agitation speed (rpm)	$[H_2]^{sat}$ [b] (10^2 M)	soln H concn[c] $[H_2]$ (10^2 M)	mass transfer coeff[d] k_La (s^{-1})	enantio-selectivity[e] (ee %)
geraniol	135	200	0.33	0.15	0.0077	21
geraniol	135	1600	0.33	0.33	1.1	57
geraniol	525	1600	1.2	1.2	1.1	90
nerol	525	1600	1.2	1.2	1.1	99

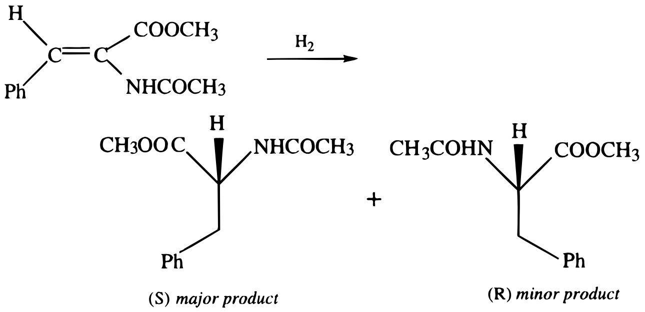
[a] 0.19 M solution of geraniol or nerol in methanol at 283 K with $[RuCl_2(S)\text{-tolyl-binap}]_2 \cdot NEt_3$. [b] Measured as described in the Experimental Section. [c] Calculated using eq 2 in the text. [d] Measured as described in the Experimental Section. [e] Measured at 30% conversion.

Table 3. Kinetic Constants from Ref 3 for the Hydrogenation of Methyl-(*Z*)-α-acetamidocinnamate with $Rh(dipamp)^+$

kinetic constants from eqs 4 and 5 (this paper)	kinetic constants as defined in ref 3[a]	values at 298 K from ref 3
k_a	k_2^{maj}	1.1 M^{-1} s^{-1}
k_b	$\dfrac{k_2^{min}K_1^{min}}{K_1^{maj}}$	59 M^{-1} s^{-1}
k_c	$\dfrac{k_{2b}^{min}}{k_{-1}^{min}}$	197 M^{-1}

[a] Kinetic variables defined according to the mechanism in Figure 2 of ref 3 where the constants found in the cycle forming the major (*S*)-product from the minor intermediate species is given the superscript {min}, and those from the cycle forming the minor (*R*)-product from the major intermediate species is given the superscript {maj}.

(dipamp)$^+$. The hydrogenation of this α-amido prochiral olefin, studied extensively by Halpern's group[3,4] as noted earlier, leads to high selectivity to the (*S*)-enantiomer



These authors developed expressions for the rates of production of each enantiomer and determined kinetic constants for this system

$$\frac{d[R]}{dt} = k_a[H_2][Rh]_{tot} \tag{4}$$

$$\frac{d[S]}{dt} = \frac{k_b[H_2][Rh]_{tot}}{1 + k_c[H_2]} \tag{5}$$

where [*R*] and [*S*] represent concentrations of the two product enantiomers, $[H_2]$ is the solution concentration of hydrogen, $[Rh]_{tot}$ is the catalyst concentration, and the k_a, k_b, and k_c are lumped constants from ref 3 as defined in Table 3.

These detailed kinetic results afford us the opportunity to study the solution concentration of hydrogen under a range of typical reaction conditions. This was accomplished by inserting the above rate equations into the term for hydrogen consumption in eq 2 and solving the mass balance for solution hydrogen concentration.[22] $[H_2]$ was determined in this manner for reactions carried out at the arbitrarily chosen *constant* hydrogen pressure of 1000 kPa.[23] The mass transfer coefficient, k_La, was varied over the range 0.001−0.2 s^{-1}, similar to values found in our laboratory measurements over a range of typical reactor agitation speeds.[24] These $[H_2]$ values were then used to calculate the rates of (*R*)- and (*S*)- formation from eqs 4 and 5, and hence enantioselectivity, as a function of k_La.

Figure 2 confirms that a sensitive relationship between enantioselectivity and actual solution concentration of hydrogen also holds for this catalytic system. By varying the mass transfer coefficient k_La at constant hydrogen pressure, we were able to mimic the decrease in ee (95% to 75%) found by Landis and Halpern[3] when pressure was varied by an order of magnitude. Moreover, the rate of production of (*R*)- and (*S*)- products as a function of $[H_2]$ shown in Figure 3 looks strikingly similar to Figure 6 in ref 3, but in the present case the rate dependence was found at constant pressure, compared to the pressure variation from 0.3−10 atm employed in that work. This confirms that the "pressure effect" is more rigorously related to the availability of hydrogen in solution, terms which are not necessarily equivalent.

Figure 2 suggests that the implicit assumption that the solution was near $[H_2]^{sat}$ made in ref 3 is valid at 1000 kPa provided that the k_La value in that experimental system was 0.05 s^{-1} or greater, values which are within the capabilities of most small stirred autoclaves at moderately high agitation speeds; however, achieving good gas−liquid mass transfer in systems such as

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(22) The rate constants used in eqs 4 and 5 were those determined at 298 K in ref 3 (see Table 3). The reaction time chosen for the integration limit of the hydrogen mass balance was 100 s, which corresponds to conversions of between 30 and 60% over the pressure range studied in ref 3. Reaction time is arbitrary in the present case since in this kinetic model, which is zero-order in substrate concentration, $[H_2]$ remains constant with conversion of substrate. It should be noted, however, that reaction time becomes an important consideration for nonzero order substrate kinetics, in which case $[H_2]$ will vary with extent of reaction.

(23) 1000 kPa is approximately the high pressure limit of the study in ref 3, with a resultant $[H_2]^{sat}$ value of 0.025 M.

(24) Comparison of results obtained from different experimental apparatus on the basis of agitation speed alone is no more rigorous than, as discussed in the text, comparison on the basis of pressure. The mass transfer coefficient is a strong function of reactor characteristics (including reactor size, shape, fill level, mode of gas introduction, and type of impeller, in addition to agitation speed). These considerations render both pressure and agitation speed as less meaningful parameters than actual solution concentration of hydrogen in attempting to compare kinetic data from different laboratories.

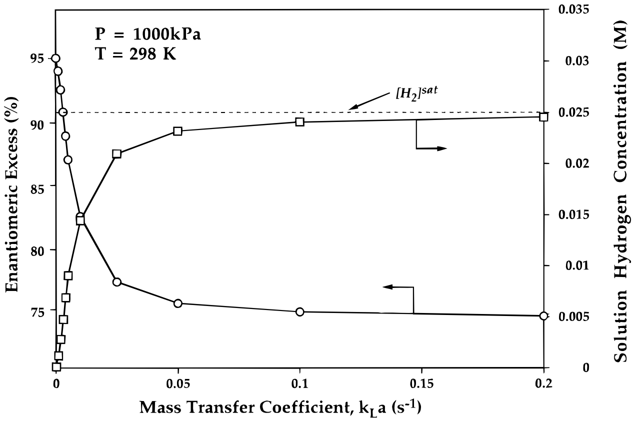

Figure 2. Enantioselectivity and solution hydrogen concentration at 50% conversion of substrate, as a function of the gas-liquid mass transfer coefficient ***at constant pressure***, using kinetic data for hydrogenation of methyl-(*Z*)-α-acetamidocinnamate with Rh(dipamp)$^+$ as described in ref 3. [H_2] was calculated from inserting rate expressions from eqs 4 and 5 (see text and Table 3) into eq 2.

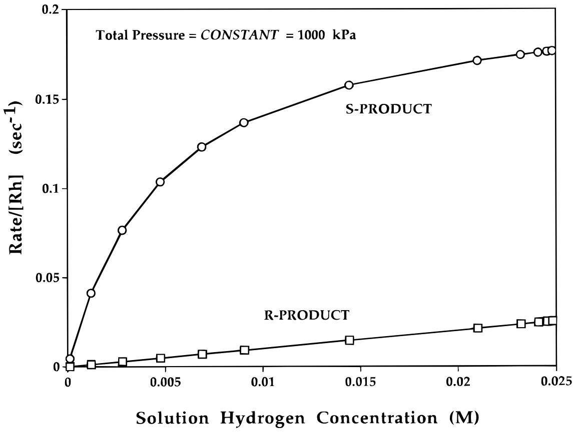

Figure 3. Rate of production of [*R*] and [*S*] enantiomers vs solution hydrogen concentration [H_2] at constant pressure using kinetic data reported for hydrogenation of methyl-(*Z*)-α-acetamidocinnamate with Rh(dipamp)$^+$ as described in ref 3. [H_2] was calculated from inserting rate expressions from eqs 4 and 5 (see text and Table 3) into eq 2. Kinetic data taken from ref 3.

shaker reactors or unstirred NMR tubes is problematic.[25] In addition, it is important to note that in studies of the effect of pressure on catalytic behavior, the rate-controlling process can change from gas−liquid mass transfer to kinetics over the range of pressures chosen for study, even without changing other parameters. At lower pressures, where the saturation [H_2] concentration is lower, consumption of hydrogen by the reaction may more readily deplete the solution of hydrogen, and higher k_La values are generally required in this situation to ensure operation outside of the gas−liquid mass transfer controlled regime.[26]

An interesting point to note in this system is that high selectivity to the (*S*)-product was favored by conditions in which the system is starved for hydrogen, and hence working in a diffusion limited regime could be beneficial in this case. In contrast, for the two experimental examples given above, high enantioselectivity was favored by high [H_2]. Not only may enantioselectivity be altered under conditions of poor gas−liquid mass transfer but also valid comparisons of different catalysts are precluded if the true kinetic behavior is masked by a rate-limiting diffusion step.

Conclusions

In this work we demonstrate that the interplay between mass transfer and intrinsic kinetic rate processes has the potential to effect marked shifts in enantioselectivity in the catalytic hydrogenation of prochiral substrates. We found that the pressure dependence of enantioselectivity cited in several examples of both homogeneous and heterogeneous asymmetric catalytic hydrogenations could in fact be mimicked ***at constant pressure*** by varying the rate at which molecular hydrogen is transferred from the gas into the liquid phase. This suggests that hydrogen pressure is a valid kinetic parameter only when efficient mixing allows the solution to approach its solubility limit for hydrogen, a condition frequently not met in typical laboratory apparatus. The solution concentration of hydrogen, rather than pressure, is the rigorous kinetic variable which should be considered in comparing studies carried out under different gas−liquid mass transfer conditions. A re-evaluation of the experimental conditions employed in studies reported in the literature suggests that the true kinetics, and hence the potential for high enantioselectivity, in a number of catalyst systems may in some cases have been obscured to rate-limiting diffusion processes.

Experimental Section

The heterogeneous catalytic hydrogenation of 1 M ethyl pyruvate (Aldrich, 98%) in *n*-propanol (Aldrich, 99%) was carried out over a 1 wt% Pt/Al_2O_3 catalyst (Precious Metals Corporation) with dihydrocinchonidine added as a surface modifier (prepared by hydrogenating cinchonidine, Aldrich). The substrate/Pt and Pt/modifier mole ratios employed were 1740 and 1.2 mol/mol, respectively. The homogeneous catalytic reaction of 0.19 M geraniol and nerol (Alfa, 99%) in methanol (Aldrich, 99.9%) was carried out over [$RuCl_2$(S)-tolyl-binap]$_2$·NEt_3 (Strem) using a substrate/Ru ratio of 1400 mol/mol.

Hydrogenation reactions were carried out in a reaction calorimeter (Mettler RC1) with agitation speeds of 200−1600 rpm. Reaction rates were measured by monitoring the calibrated heat flow of the reaction as described previously.[12] Briefly, the technique involves completing an energy balance around the reacting system. Equation 6 shows that for an isothermal, batch reacting system, the heat flow is proportional to the reaction rate

$$q_r = V_r \sum_i \Delta H_{\mathrm{rxn},i}\left(\frac{\mathrm{d}C_i}{\mathrm{d}t}\right) \qquad (6)$$

where q_r is the heat released or consumed by the reaction, V_r is the volume of the reactor contents, ($\mathrm{d}C_i/\mathrm{d}t$) is the reaction rate and $\Delta H_{\mathrm{rxn},i}$ the heat of reaction of the *i*th reaction. Automated data acquisition at 6-s intervals with an accuracy of better than 0.1 W afforded an extremely accurate measurement of reaction rate throughout the reaction.

Gas−liquid mass transfer coefficients and hydrogen solubilities in the reaction solutions were measured as described previously.[12,27] The substrate−solvent mixture in the absence of catalyst was charged to the reactor and degassed, and the reactor was pressurized and isolated under hydrogen (135−525 psi). Agitation was then commenced, and the pressure drop in the reactor was measured at a rate of 10 Hz. The mass transfer coefficient, k_La, is given as

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(25) An especially important concern is to insure that reactions carried out in apparatus for collecting spectroscopic data mimic the mass transfer characteristics of the same reactions completed in other apparatus used for collecting kinetic data.

(26) The ratio of mass transfer to kinetic rates may often be increased by changing other conditions, for instance by lowering reaction temperature or catalyst concentration, or, in systems which have a positive dependence on substrate concentration, working at lower substrate molarity.

(27) Deimling, A.; Karandikar, B. M.; Shah, Y. T.; Carr, N. L. *Chem. Eng. J.* **1984**, *29*, 140.

$$\left[\frac{(P_f - P_e)}{P_i - P_e}\right]\ln\left[\frac{P_i - P_f}{P - P_f}\right] = k_La{*}t \qquad (7)$$

where P_e is the equilibrium vapor pressure of the mixture at the temperature of the experiment, the initial and final pressures are P_i and P_f, and the pressure at any time t is P.

The total pressure decrease until equilibrium is established also yields the solubility of hydrogen in the solution under the conditions of the experiment. From these parameters the maximum rate of hydrogen delivery from the gas to the liquid may be determined by eq 3 given in the text where the $[H_2]^{sat}$ value is the solubility of hydrogen at the final pressure of the experiment.

The actual solution concentration of hydrogen, $[H_2]$, was determined by solving eq 2, given in the text, over a range of values of k_La. For the experimental studies of the hydrogenation of ethyl pyruvate and geraniol, eq 2 was integrated to give $[H_2]$ at different conversion levels. The reaction rate profiles determined from heat flow calorimetry were inserted in the hydrogen consumption term, and the k_La and $[H_2]^{sat}$ values corresponding to those conditions, measured as described above, were used in the hydrogen input term of eq 2. In these two experimental studies, product selectivity, reported as absolute enantiomeric excess, was measured by GC on a Chiraldex B-TA chiral column

$$ee(\%) = \frac{|[R] - [S]|}{[R] + [S]}100 \qquad (8)$$

In the example involving the hydrogenation of methyl-(*Z*)-α-acetamidocinnamate, the rate expressions and kinetic constants from ref 3 (given in eqs 4 and 5 and Table 3) were used in the hydrogen consumption term in eq 2, which was solved numerically for $[H_2]$ using $[H_2]^{sat} = 0.025$ M and k_La values in the range of those determined experimentally in our laboratories.

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