Numerical Modeling of Differential Kinetics in the Asymmetric Hydrogenation of Acetophenone by Noyori's Catalyst

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Abstract: A combination of numerical integration of the rate equations and experimental measurement of the time-dependence of rates rather than concentrations is described for the analysis of the catalytic cycle by which Noyori's catalyst, trans-RuCl$_2$[(S)-binap][(S,S)-dpen], hydrogenates acetophenone. The method is simpler in practice than usual kinetic methods and yields furthermore rate constants for activation, dihydrogen cleavage, and hydride transfer to substrate under realistic catalytic conditions. The specific results for the asymmetric hydrogenation of acetophenone show that the turnover-limiting step changes from dihydrogen cleavage to hydride transfer if the H$_2$ pressure is increased, but also during the course of the reaction when the hydrogenation is performed under typical conditions.

Keywords: asymmetric hydrogenation, homogeneous catalysis, kinetics, ruthenium

Introduction

Even the simplest catalytic cycles involve kinetics more complex than can be easily handled by the usual tools for the extraction of rates. The typical approach to handling kinetics in catalytic cycles is to adjust process parameters, e.g., temperature, pressure, concentration, etc., to achieve a long enough period of time during which the reaction runs at steady-state in a regime where the rate law may be linearized. Experimentally, the measurable quantity is usually the decline of a reagent, the rise of product, or the generation of a physical effect, such as heat, that is proportional to turnover. While useful kinetics have been obtained by such an approach, there are inherent limitations. First and foremost is the necessity of adjusting the process parameters to enable linearity. One may be forced to work far away in parameter space from the regime where the catalytic reaction is actually used in practice. More fundamentally, however, the reaction itself, even at a fixed set of parameters, is dynamic with the turnover-limiting step, and accordingly the resting state in the cycle, changing with time and extent of turnover. This occurs because all steps in a catalytic cycle have the same rate at steady-state, with concentrations of each species continuously readjusting themselves accordingly to keep all the rates the same. Complicating the picture is the common situation in which the catalytically-active species is generated *in situ* from a precatalyst, which can lead to induction periods or other similar phenomena in catalysis. Lastly, experimental methods based on a measurement of the decline of reagents or the rise of product concentration can be difficult in very fast reactions. Recently, Boudart[1] has suggested that a better analysis of catalytic reactions can be achieved by what amounts to numerical integration of the equations corresponding to the elementary steps. While Boudart suggested that the elementary rate constants could be obtained by anything from a propitious guess through *ab initio* calculation to independent experimental measurement, his approach can be turned around in that the numerical integration of the system of differential equations corresponding to the elementary reactions can be used to determine the elementary rate constants by least-squares fitting. We report a kinetic investigation of the asymmetric hydrogenation of acetophenone by Noyori's catalyst,[2] *trans*-RuCl$_2$[(*S*)-binap][(*S,S*)-dpen] **1**, as a model study of the use of differential kinetics and numerical integration as an alternative to conventional kinetic methods. The study, with a simplified kinetic scheme for the catalytic cycle, provides both quantitative information in the form of rate constants, as well as a deeper intuitive understanding of the catalytic cycle.

Results

In all cases, hydrogenation was run to full consumption of acetophenone as determined independently by product isolation. Because of the exceedingly high activity of this class of hydrogenation catalysts, the catalyst concentration was reduced successively at constant pressure until the peak rate of hydrogen consumption became linear with catalyst concentration

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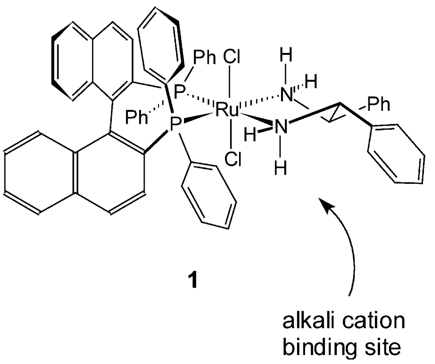

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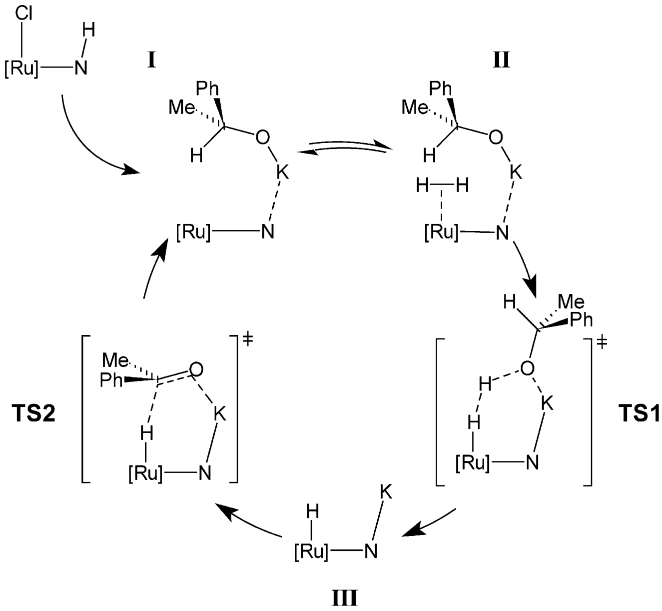
Scheme 1.

in order to ensure that the rate of hydrogen consumption reflected a chemical process rather than mass transport. It should be noted that a turnover frequency (TOF) in the neighborhood of 10,000 h^{-1} per molecule catalyst under the present conditions already makes the Noyori catalyst one of the most active homogeneous catalysts known, and that even higher turnover frequencies demonstrated[3] for these systems exacerbate the technical challenges for kinetic studies. Correspondingly high substrate-to-catalyst ratios (S/C) ranging from several thousand up to a few million mean that the catalyst is present in only μM to mM concentrations. Noyori recommended avoidance of glass reaction vessels to obtain high catalytic activities when using S/C > 5000.[3] We could confirm that a ratio of S/C = 4000, in our hands, could be used without significant problems due to either mass transport limitation or side reactions from the glass vessel, although at higher S/C ratios, repeated runs showed that the actual amount of catalyst in solution was much more difficult to regulate. Additionally, the 6.17 mL reaction solution in the 25 mm diameter reactor tube was stirred with a 38 mm long, vertically-oriented, magnetic stir-bar spinning at 1300 rpm so that the solution formed a thin, rapidly moving annular film extending several centimeters up the walls of the reactor tube. One should note that, when catalyst concentration is too high, i.e., when rate is not linear with concentration, or when stirring is inefficient, we find that the rate of H_2-transport from the gas phase into solution, or perhaps diffusion, becomes turnover-limiting.[4] The very efficient stirring is also needed to maintain good heat transfer needed for good temperature control. The hydrogenation of acetophenone is approximately 15 kcal/mol exothermic, which poses significant problems for isothermal kinetics in cases where the ketone is the solvent or a substantial fraction thereof.

Because the reductions proceed cleanly to completion, the areas under the curves should be the same, reflecting the complete hydrogenation of 10 mmol acetophenone in each case. Using the free volume of the reactor, the integrated areas under the curves for the three pressures, 1, 2, and 5 bar, correspond to consumption of 8.4, 8.5, and 8.1 mmol H_2, respectively. The difference arises from the initial equilibration period, during which time catalytic activity begins to appear. The actual amount of H_2 consumed, rather than 10 mmol, was therefore used in each of the fits.

The catalytic cycle previously proposed by this group[5] is shown in Scheme 2. The present catalytic system presents some interesting challenges as well as advantages. There are several potential species in the catalytic cycle, but the active species must be formed from an inactive precatalyst in a separate activation step. However, the active species are long-lived, as demonstrated by the exceedingly high turnover numbers that this class of catalysts has been shown to display.[3] The catalytic cycle shown in Scheme 2 can be modeled with a relatively simple system of coupled differential equations, including a separate activation step, which is assumed to occur through a first-order reaction leading into species **I** or its equivalent. Importantly, even if one does not accept the alkali cation cocatalysis,[5] i.e., if one assumes that a proton plays the role depicted for the potassium cation, the form of the mathematical description of the cycle remains unchanged. Species **I**, **II**, and **III** are the activated catalyst without dihydrogen, the dihydrogen complex, and the hydride, respectively. Ketone is consumed and alcohol released at the same points in cycles with or without an alkali cation cocatalysis, so the mathematical description of Scheme 2 by PowerSim is in fact more general than Scheme 2 itself.

Moreover, given that each step in the cycle is first-order in ruthenium complex, incomplete or inefficient activation changes the picture only insofar as a constant



Scheme 2.

multiplicative factor appears in each rate constant. The turnover limiting step and the resting state, as well as the mechanistic conclusions that derive from them, remain unchanged whether the absolute activation efficiency is 1% or 100%, although other work indicates that the absolute activation efficiency is not small.[6]

A further simplification arises if one presumes that the coordination of H_2, e.g., the step connecting **I** and **II**, is fast and reversible. It would constitute a preequilibrium which would allow the transformation of **I** to **III** to be treated as a single kinetic step in which the equilibrium constant for H_2 binding enters as a multiplicative factor with respect to the H_2 cleavage rate constant, giving an effective rate of dihydrogen heterolysis that is first-order in H_2. The relatively simple non-linear system nevertheless displays complex behavior characteristic of much more complicated catalytic cycles, which makes the asymmetric hydrogenation reaction catalyzed by **1** a suitable system to showcase the methodology.

Accordingly, the three kinetic parameters that are varied to produce the fit are the rate constant for activation $k_{\text{activation}}$, the rate constant for H_2 heterolysis $k_{\text{cleavage}}^{\text{effective}}$, and the rate constant for hydride transfer k_{transfer}.

$$\frac{\partial[\text{precatalyst}]}{\partial t} = -k_{\text{activation}}[\text{precatalyst}] \qquad (1)$$

$$\frac{\partial[\mathbf{I}]}{\partial t} = k_{\text{activation}}[\text{precatalyst}] - k_{\text{cleavage}}^{\text{effective}}[\mathbf{I}][H_2] + k_{\text{transfer}}[\mathbf{III}][\text{ketone}] \qquad (2)$$

$$\frac{\partial[\mathbf{III}]}{\partial t} = k_{\text{cleavage}}^{\text{effective}}[\mathbf{I}][H_2] - k_{\text{transfer}}[\mathbf{III}][\text{ketone}] \qquad (3)$$

$$-\frac{\partial[\text{ketone}]}{\partial t} = \frac{\partial[\text{alcohol}]}{\partial t} = k_{\text{transfer}}[\mathbf{III}][\text{ketone}] \qquad (4)$$

$$-\frac{\partial[H_2]}{\partial t} = k_{\text{cleavage}}^{\text{effective}}[\mathbf{I}][H_2] \qquad (5)$$

The actual equation to which experimental data are fit is Eq. (5). Although Eq. (5) explicitly contains only one rate constant and one of the ruthenium-containing species, the other concentrations are implicitly linked through constraints, e.g., the sum of [**I**], [**III**], and [precatalyst] must equal the total amount of original complex, or the rate of hydrogen consumption must equal the rate of alcohol production. In doing the fitting, we found that a simultaneous fitting of data from more than one pressure produced much smaller uncertainty bounds. Accordingly, the best fit rate constants, listed below, were obtained from the 1 and 2 bar runs.

As a check on the fit, the rate constants were then used to compute the curve for 5 bar total pressure – an extrapolation, not an interpolation.

$$k_{\text{activation}} = (1.366 \pm 0.4) \times 10^{-3}\ \text{sec}^{-1}$$
$$k_{\text{cleavage}}^{\text{effective}} = (4.307 \pm 1.0) \times 10^{2}\ \underline{\text{M}}^{-1}\ \text{sec}^{-1}$$
$$k_{\text{transfer}} = (4.271 \pm 2.0) \times 10^{0}\ \underline{\text{M}}^{-1}\ \text{sec}^{-1}$$

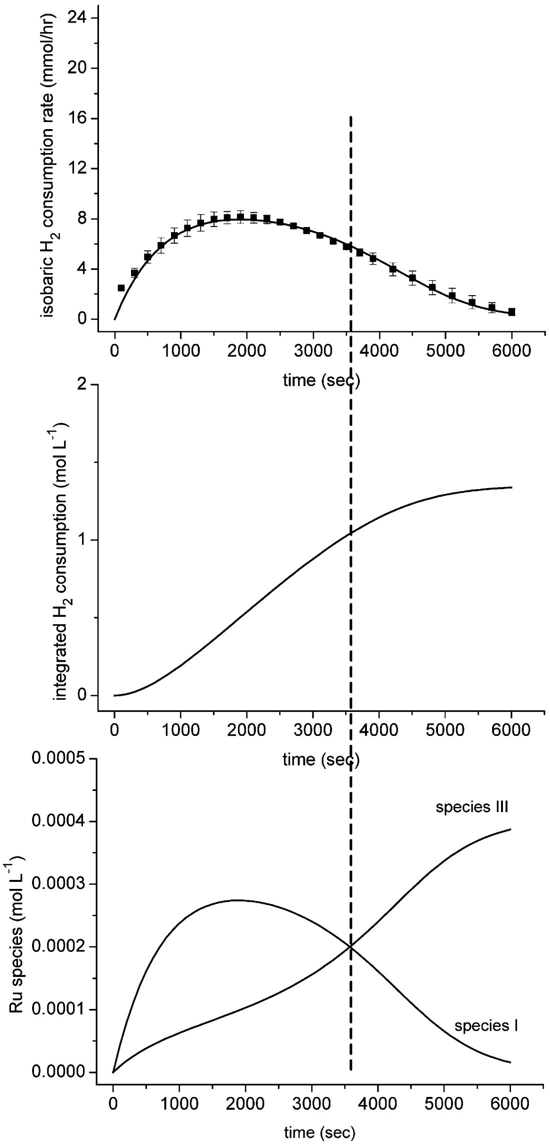


Figure 1. Experimental data for 1 bar total pressure with fit (upper panel), integrated H_2 consumption (middle panel) and concentrations of species in the catalytic cycle (lower panel). The dotted line indicates the point at which the turnover-limiting step in the catalytic cycle changes.

The experimental data with the fit (upper panel), the computed integrated H_2 consumption (which tracks product formation as well, middle panel), and the computed concentrations of species in the catalytic cycle (lower panel) are shown in Figures 1–3. It should be noted that the extrapolation of the 1 and 2 bar data to 5 bar gives a good fit only for the rising edge of the H_2

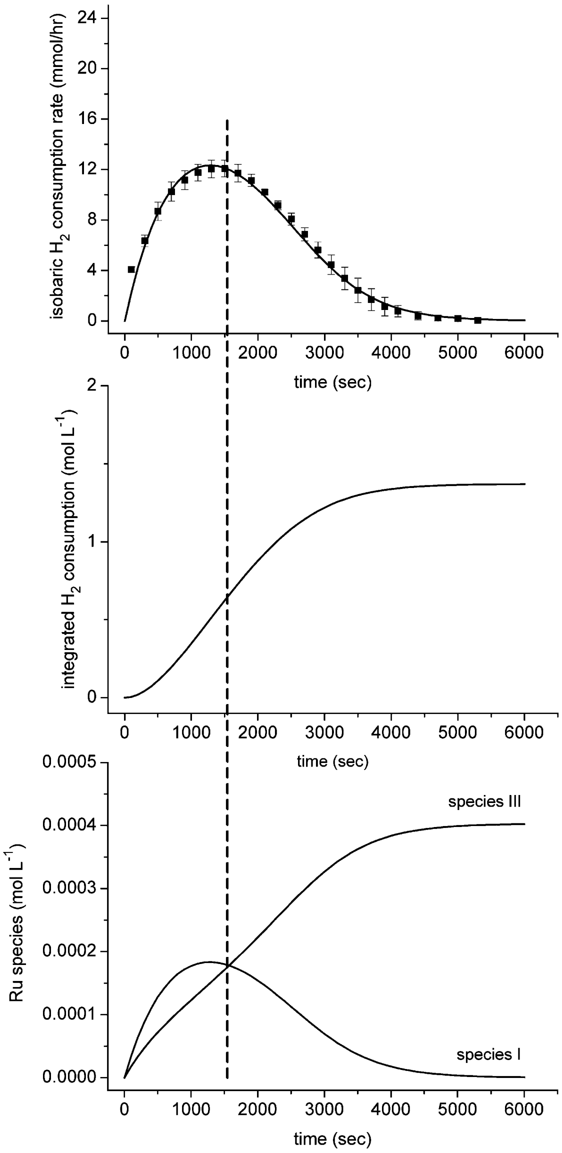


Figure 2. Experimental data for 2 bar total pressure with fit (upper panel), integrated H_2 consumption (middle panel) and concentrations of species in the catalytic cycle (lower panel). The dotted line indicates the point at which the turnover-limiting step in the catalytic cycle changes.

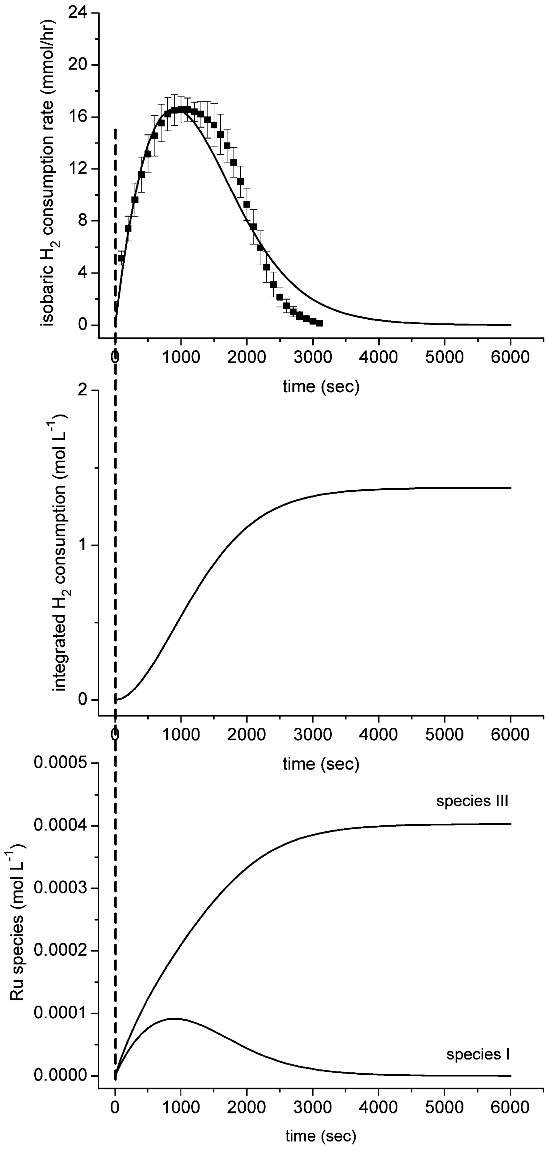


Figure 3. Experimental data for 5 bar total pressure with fit (upper panel), integrated H_2 consumption (middle panel) and concentrations of species in the catalytic cycle (lower panel). The dotted line indicates the point at which the turnover-limiting step in the catalytic cycle changes.

consumption curve up to the maximum. Given that the hydrogenation of a ketone to the corresponding alcohol is strongly exothermic, it is perhaps not surprising that, at the times of highest activity, heat transfer can become a problem. In that event, even the extremely efficient stirring and high surface area system used in this experiment may not suffice to keep the temperature constant. A rise in temperature would then lead to an artifactual increase in H_2 consumption rate. Nevertheless, the rising part of the curve and the maximum for 5 bar are well-modeled, with deviation in the expected direction only appearing subsequent to the point where the highest activity is found. Exploratory studies at even higher pressures show that this problem is indeed attributable to heat transfer and can be largely eliminated by reducing the catalyst concentration at constant substrate concentration, i.e., increasing the S/C ratio. In the practical implementation of the experiment, heat transfer problems do not appear in the present experimental apparatus as long as the peak H_2 consumption rate remains below 15 mmol/h.

Discussion

Asymmetric reduction of ketones by Noyori's catalyst **1** was chosen as a test for the derivative kinetic methodology because, although the reaction is of significant practical importance, the mechanism is only just beginning to be studied quantitatively. Complex **1** exhibits exemplary characteristics which had not been adequately explained: exceedingly high activity as measured by substrate-to-catalyst (S/C) ratio, efficient cleavage of H_2 and reduction of ketones under mild conditions, and high chemo- and stereoselectivity.[2] Exploitation of these splendid properties in the asymmetric hydrogenation of ketones in a practical setting is desirable because, in contrast to the reduction of ketones catalyzed by ruthenium complexes that perform transfer hydrogenation, high concentrations of ketone, or even the neat ketone as solvent, may be hydrogenated completely to the corresponding alcohol. The starting point for any quantitative mechanistic explanation for the outstanding characteristics exhibited by **1** is kinetics, which for catalytic reactions can bring forth special problems. It should be mentioned that studies by Blackmond[7] have demonstrated that explicit kinetic modeling of catalytic reactions can bring important insights, although, in contrast to the present study, the modeling is done at the level of the rate equation rather than elementary reactions. The recently reported kinetic study by Morris and coworkers[8] yields rate constants and activation parameters for the hydrogenation of acetophenone by *trans*-RuH$_2$[(*R*)-binap][tmen] **2**, which differs from **1** in that the chiral diamine, dpen, in the usual catalyst is replaced by tetramethylethylenediamine, tmen. Furthermore, **2** is "preactivated" in that the dihydride is preformed; activation issues are avoided in this way so initial rate measurements may be done. Significantly though, the kinetics in that study were performed under conditions which led to the conclusion that the reaction is first-order with respect to H_2. As will be shown below, this cannot be universally assumed, especially given that the catalyst **2** was also used in preparative (not kinetic) runs.[8] Under these conditions the kinetic behavior is more complex, and is difficult to treat conventionally. Moreover, of the two kinetically important processes in the cycle, dihydrogen cleavage and hydride transfer to substrate, a rate constant was reported only for the former. Lastly, while the dihydride is isolable in the case of **2**, neither the monohydride nor the dihydride from **1** shows appreciable stability. That means that in any typical laboratory experiment or technical process, the dichloride **1** with *in situ* generation of the active species will be used. The need for activation makes the initial rate measurements in conventional kinetics impossible unless one can make activation so fast that the time is negligible on the scale of the overall reaction, which is ***not*** the case for **1**.

One may try to compare the rate constant for dihydrogen cleavage by **1** to that reported for **2**, acknowledging of course that the two complexes are not the same and that the former is measured at 50 °C in 2-propanol and the latter in the range 6–30 °C in benzene. Moreover, an increase in $k_{\text{cleavage}}^{\text{effective}}$ by **2** with additional *t*-BuOK was reported for **2** in 2-propanol but not in benzene. Taken together, the systems will not be comparable until more data is collected. Nevertheless, the present study shows how both kinetically important processes may be treated in a sensible way under conditions of high substrate concentration.

The present experimental data concerning the kinetics of hydrogenation were quantified by the time dependence of the isobaric rate of H_2 consumption, which has the practical advantage over the more usual measurement of the rate of product appearance in that it is insensitive to transfer hydrogenation. However, the principal reason for the particular choice of metric is the improved sensitivity of the measurement to details of the mechanism. If one were to compare time development of the isobaric rate of H_2 consumption to the time development of product concentration, one sees that the former is the time derivative of the latter. In other words, if one were to integrate the isobaric H_2 consumption rate up to a specific time, one would get the product concentration at that time. Just as the derivative spectrum is more sensitive to the slight inflections and bumps in a microwave or ESR spectrum, the isobaric H_2 consumption rate should be inherently more sensitive to changes, for example, in the turnover-limiting step, than would be the kinetic conventional measurement. Furthermore, the rather easy isobaric H_2 consumption rate determination is amenable to measurement, with short time intervals, externally to the reaction solution. The need for very efficient stirring (for good mass transport) and the small volume (to reduce the absolute heat generation) puts the solution in the present experimental apparatus up on the sides of the vessel in a rapidly moving film. There is no convenient way to take aliquots from such a reaction, especially under pressure, and *in situ* spectroscopic probes, such as a ReactIR, are also incompatible with the physical arrangement. Thus, the measurement of isobaric H_2 consumption is very likely the most convenient means to obtain data of sufficient quality for reliable kinetics. A perusal of Figures 1–3 illustrates these points clearly. In each figure, the first panel shows the isobaric H_2 consumption rate, the second panel displays the amount of H_2 consumed, i.e., the integral of the consumption rate (which also measures product formation), and the third the time development of species **I** and **III** in the catalytic cycle depicted in Scheme 2. Given that a plot of the rise of the alcohol product would give the same plot as the middle panels of Figures 1–3, it is not difficult to see the advantage of the present method. The non-negligible activation period makes it problematic to choose the time at which a conventional rate measurement should begin. Moreover, even though all three pressures show curves in which an apparently linear region appears, examination of the lower panels shows that the turnover-limiting step can be changing in just that region as well. In the catalytic cycle, the most abundant species at any given time is the resting state of the cycle; the transition state following the resting state is turnover-limiting. For the simplified model in which the H_2 binding preequilibrium is subsumed into an effective rate constant $k_{\text{cleavage}}^{\text{effective}}$, there are only two possible resting states, **I** and **III**, and two possible turnover-limiting steps, $\mathbf{TS_1}$ and $\mathbf{TS_2}$, respectively. The bottom panels in Figures 1 – 3 show the concentrations of **I** and **III** as a function of time. In each case, there is a change of the resting state from **I** to **III** as hydrogenation proceeds to completion, meaning that the turnover-limiting step changes from H_2 cleavage to hydride transfer. For the lowest pressure, 1 bar, this changeover occurs when the reaction is nearly completed; for 2 bar, the change occurs near the halfway point; for 5 bar, the turnover-limiting step goes over to hydride transfer almost from the very onset. This is important because it means that, with realistic substrate concentrations, an increase in H_2 pressure brings little additional rate acceleration after only a few bars of pressure. Moreover, statements as to the kinetic order of the overall reduction with respect to either H_2 or substrate must be qualified, not only by the reaction conditions, but also by the extent of conversion. That this changeover occurs in the middle of the reaction under the pressure, temperature, and concentration conditions that one commonly finds for applications of **1** arises because the roughly two orders-of-magnitude difference between $k_{\text{cleavage}}^{\text{effective}}$ and k_{transfer} is almost perfectly balanced out (coincidentally) by the approximately two-orders-of-magnitude difference between the solution-phase concentration of H_2 and that of the ketone at the onset of hydrogenation. The temperature dependence, i.e., activation parameters, as well as the functional dependence of these parameters on externally-controllable variables such as alkali cation concentration will be the subject of further studies.

Conclusion

A differential kinetics method is introduced and demonstrated for the catalytic hydrogenation of acetophenone by Noyori's catalyst **1**. The method allows the determination of rate constants for all kinetically significant chemical events under conditions close to those employed in practice. Moreover, the numerical modeling of experimental H_2 consumption rates parameterizes a model from which further understanding of the catalytic cycle can be obtained.

Experimental Section

Noyori's catalyst **1** was prepared as previously described.[9] The activation of the catalyst by *t*-BuOK in 2-propanol follows the procedure in the literature. Hydrogenation of acetophenone at high concentrations, e.g., a few M ketone, with 1 – 5 bar H_2 at 50 °C is also the usual procedure. The actual concentrations used in this experiment are 1.613 M acetophenone, 0.403 mM catalyst **1** (S/C = 4000), 4.0 mM *t*-BuOK, and total pressure 1, 2, and 5 bar. On the other hand, the hydrogenation activity was quantified by the rate of isobaric H_2 consumption rather than product formation. Aside from avoiding any contribution to the kinetic analysis from transfer hydrogenation, which is a highly relevant issue for this catalyst family, isobaric H_2 consumption produces the derivative plots whose advantages were described above.

A heavy-wall borosilicate glass tube purchased from Aldrich (nominally 15 mL, 25.4 mm o.d.) was charged under Ar with the catalyst (2.5×10^{-6} mol, 1 equiv.), the base (2.5×10^{-5} mol, 10 equiv.), the substrate, acetophenone (10.0 mmol, 4000 equiv., 1.17 mL) and 2-propanol as solvent (5.0 mL). The total volume of the reactor including dead space in the manifold is 35 mL. No measurable pressure drop could be seen when an empty reactor was sealed with 5 bar H_2 over periods of time exceeding 60 min, indicating that the reactor was leak-free. After degassing by three freeze-pump-cycles, the reactor was pressurized with dihydrogen gas (1 – 5 bar H_2). The reaction mixture was saturated with H_2 during a period of 15 min under vigorous stirring at room temperature. A long stir bar (38 × 7 mm) oriented vertically in the reactor tube at 1300 rpm was used in order to obtain a vertical vortex. Absolute pressure in the reactor was measured continuously by an MKS Baratron capacitance manometer (model 122AA10000BB, range 100 – 10,000 Torr, accuracy ± 2%, linked to an MKS gauge controller PDR-C-1C). The solution-phase concentration of dissolved H_2 in 2-propanol at 50 °C was computed from the pressure using Henry's law and data from Brunner,[10] giving 0.00303, 0.00703, and 0.019 M for 1, 2, and 5 bar total pressure, respectively. At this point, the pressure vessel was sealed and set in a constant temperature bath. The (small) pressure drop in a fixed time period was recorded at 100 – 300 second intervals. The pressure in the vessel was otherwise kept at a constant level at all other times by connection to a gas reservoir at the desired pressure. After completion of the reaction (confirmed by termination of H_2 pressure drop) the mixture was passed through a short silica gel column. Solvents were removed by evaporation on a rotary evaporator and the product was purified by evaporation under reduced pressure (bp 83 °C at 13 mbar). The amount of conversion and enantiomeric excesses were determined using GC/MS [30 m × 0.25 mm Supelco β-*DEX* column, injector temperature 200 °C, FID detector 250 °C, linear temperature raise from 100 °C with 1 °C/min, t_r (min) = 13.7 (*R*), 14.4 (*S*)]. The complete measurement was repeated independently three times for each pressure; uncertainty bounds for the isobaric H_2 consumption rates are reported as one standard deviation.

Numerical modeling of the reaction was performed with PowerSim 2.5c (Powersim AS, P.O. Box 206, N-5100 Isdalstø, Norway) running on a 1.2 GHz Pentium III PC with Windows 2000 Pro operating system. The program provides a graphical interface for the construction of non-linear dynamic systems,[11] of which a catalytic cycle is a particular example, and then the numerical simulation of the system using a palette of integration techniques for the resultant coupled differential equations. The present integrations were done using a 4th-order Runge-Kutta method with variable step size. In each iteration of the fitting process, an error function consisting of the summed squared deviations of the computed curve relative to the experimental data points was calculated. Fitting of the elementary rate constants to the isobaric H_2 consumption curves was done in a two-step process. In the first step, a relatively coarse incremental grid search, comprising 560 runs, was done to localize the minimum in the error function and to establish uncertainty bounds in the fitted rate constants. Having found the general vicinity of the minimum, the error function was then minimized in the second step by a genetic algorithm[12] in which, for each generation, 25 random sets for the rate constants within preset bounds were generated and fed into simulations. From the 10 simulations with the lowest values of the error function, a new, narrower set of bounds for the rate constants was extracted. In the next generation, 25 new randomly selected rate constants within the narrowed bounds were run in the simulations, from which again the best 10 were selected. The process was repeated until self-consistent results were obtained, usually 20–50 "generations", meaning 500 to 1250 runs. Uncertainty limits on the rate constants were chosen to be those bounds for which the standard deviation of the fit did not exceed the standard deviation of the experimental data themselves (from replica runs). Because the uncertainty bounds are read from the incremental grid search, the bound on any single rate constant already includes compensatory effects of changes in the other rate constants. The bounds are accordingly statistically-grounded "worst-case" bounds. The fitting process described here is in fact a least-squares procedure, but it differs from the usual least-squares fitting routine in that it uses the genetic algorithm rather than, for example, the more common Marquardt-Levenburg[13] procedure. The grid search brings the advantage that uncertainty limits are automatically generated, and the genetic algorithm dispenses with the need to compute explicit (in this case numerical) first- and second-derivatives of the error function with respect to the rate constants.

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