Mechanistic Insights into Anomalous Kinetic Behaviour in the Hydrogenation of a Substituted Nitrobenzene

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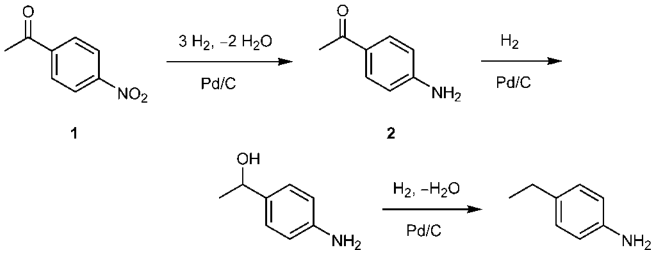
Abstract: Unusual rate behaviour in the Pd-catalyzed hydrogenation of 4-nitroacetophenone is rationalized in terms of a combination of two reaction mechanisms, one which dominates at high substrate concentrations and one which dominates at the low surface coverage of substrate found at the end of the reaction. Kinetic modelling yields substrate binding constants consistent both with literature values for the first mechanism and with this proposal for the second mechanism. This behaviour may be general for the hydrogenation of bulky substituted nitrobenzene molecules containing functional groups which can interact with the Pd surface.

Keywords: heterogeneous catalysis; hydrogenation; kinetic modelling; Langmuir–Hinshelwood kinetics; nitrobenzene; Rideal kinetics

Introduction

The hydrogenation of substituted nitrobenzenes is an important method for the introduction of nitrogen functionality into pharmaceutical intermediates. The reaction is usually carried out in a three-phase system employing supported transition metal catalysts such as Pd/C. We have recently reported different methods for the rapid selection of catalysts for such reactions, both in parallel screening[1] and in a one-pot protocol.[2] In the course of the former study, an unusual negative-order dependence on substrate was observed under certain conditions during the Pd/C-catalyzed reduction of 4-nitroacetophenone (Scheme 1).[1]

We report here on further observations of this phenomenon in the formation of intermediate product **2**. We propose a kinetic model whereby a shift in the predominant reaction mechanism occurs during the course of the reaction as the substrate concentration is depleted. This type of mechanism may be general for the hydrogenation of nitro groups on bulky multifunctional molecules, and the model suggests synthetic strategies for efficient and safe production in these cases.



Scheme 1. Sequential reduction of 4-nitroacetophenone.

Results and Discussion

The hydrogenation of 4-nitroacetophenone (**1**, Scheme 1) was carried out at 1 bar H_2 pressure and temperatures ranging from 20–80 °C using Pd/C catalysts in ethanol. Figure 1 shows reaction heat flow *vs.* time for a reaction carried out at 60 °C using an initial substrate concentration of 0.6 M and a substrate/Pd_{total} mole ratio of 300. As has been previously reported for the hydrogenation of nitrobenzene[2,3] and substituted nitrobenzenes,[1] the reaction proceeds with pseudo-zero-order kinetics in substrate for most of the reaction. However, towards the end of the reaction the rate was observed to rise before finally falling to zero as the substrate was depleted. This intriguing behaviour was observed at different temperatures and catalyst concentrations as shown in Figure 2. The extent of the rise in rate appeared to be greatest at lower temperature and higher catalyst concentration.

The observation of pseudo-zero-order kinetics is attributed to the strong binding of the organic substrate and non-competitive adsorption of hydrogen, known

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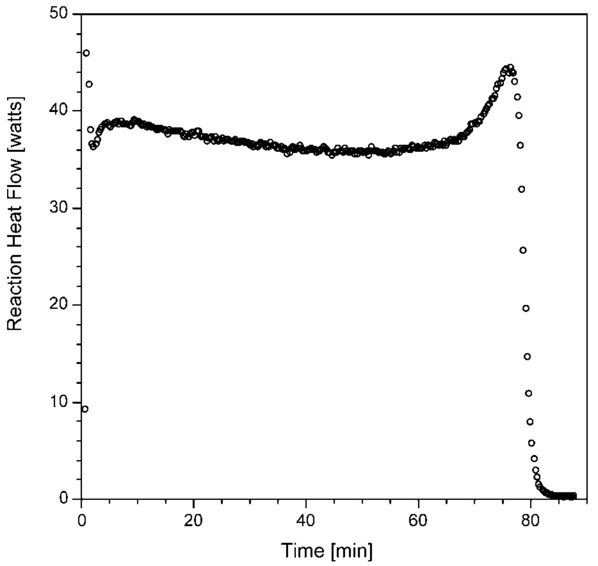


Figure 1. Reaction heat flow during the hydrogenation of 49.5 g of **1** (0.6 M in ethanol) at 1 bar and 333 K using 1.07 g of Pd/C.

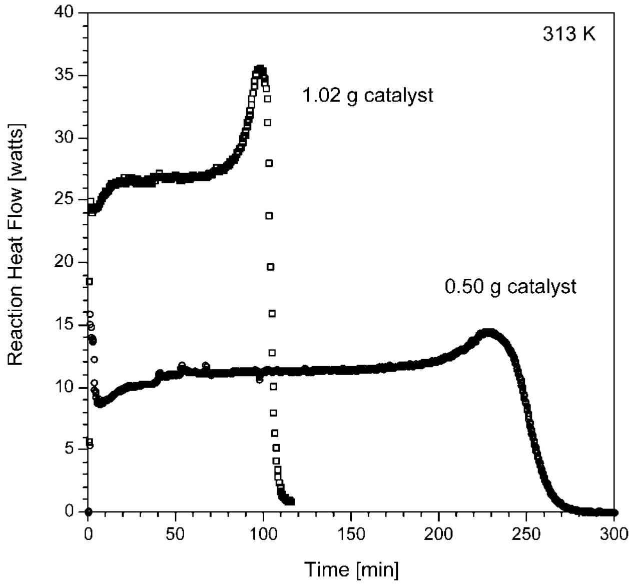


Figure 2. Reaction heat flow during the hydrogenation of 49.5 g of **1** (0.6 M in ethanol) at 1 bar and 313 K with different amounts of Pd/C.

as a Rideal mechanism.[4] The rate-limiting step in this case involves only one catalytic site. Thus hydrogen adds to the adsorbed substrate either directly from the solution phase or more likely as an "interstitial" surface species occupying surface Pd sites between those Pd ensembles which are large enough to accommodate the organic substrate, without perturbing substrate adsorption on those ensembles.[4] This is depicted in Scheme 2 (**A**). The corresponding rate equation is given in Eq. (1). The constant k_{cat} is a lumped parameter encompassing the intrinsic rate constant as well as the constant concentration of hydrogen. K_{eq} is the binding constant of substrate **1**.

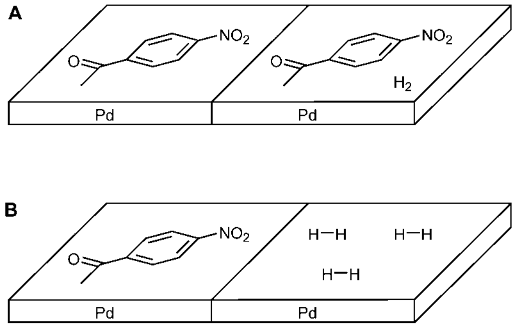
$$rate = \frac{k_{cat}[1]}{1 + K_{eq}[1]} \tag{1}$$

The Rideal rate equation predicts that pseudo-zero-order kinetics will be observed for strongly binding substrates at high concentrations of **1**. A transition from zero- to first-order kinetics should occur as the substrate concentration is depleted over the course of the reaction. In contrast to this expectation, the rising rate we observed at the end of the reaction indicatives *negative* order kinetics in substrate.

More common than the Rideal mechanism for heterogeneous catalytic reactions is the Langmuir–Hinshelwood reaction mechanism.[4b] This mechanism assumes that the rate-limiting step in a multi-step catalytic reaction is a bimolecular elementary reaction between two surface adsorbed species in equilibrium with the fluid phase. This mechanism is depicted in Scheme 2 (**B**). The rate expression for this case may be written as shown in Eq. (2), where k_{cat}' and K_{eq}' have analogous meanings as defined for Eq. (1). Since two separate catalyst sites are involved, the rate expression exhibits a power of two in the denominator. In this treatment we have assumed that the binding constant for competitive hydrogen adsorption is much smaller than that for the substrate **1** at low coverage.

$$rate' = \frac{k'_{cat}[1]}{(1 + K'_{eq}[1])^2} \tag{2}$$

One rationalization for the observed rising reaction rate could be that the dominant mechanism for hydrogenation of **1** shifts from Rideal to Langmuir–Hinshelwood



Scheme 2. Schematic representation for (**A**) the Rideal model involving one catalyst site at a high surface covering of substrate **1**, and (**B**) the Langmuir–Hinshelwood model involving two adjacent catalyst sites at a low surface covering of substrate **1**.

kinetics as the concentration of **1** falls over the course of the reaction. The apparent zero-order kinetics observed through most of the reaction gives way to inverse order kinetics as the surface begins to accommodate hydrogen on sites that previously were blocked by the presence of the substrate, and the dominant reaction mechanism becomes the reaction of adsorbed **1** with adsorbed H_2 from these sites.

This proposal is supported by kinetic modelling of the reaction as the sum of the two separate rate processes. K_{eq} and K_{eq}' represent average binding constants for **1** at high and low surface coverages, respectively. In a system that obeys the assumptions of the Langmuir isotherm, these two values are equal. However, it is most commonly observed that heats of adsorption decrease with increasing coverage on non-ideal surfaces. Indeed, the binding constants are most likely not constant but are themselves functions of the substrate concentration. Various isotherms such as the Freundlich and the Tempkin isotherms have been developed to describe surface coverages in these cases.[4b] However, additional data, such as detailed measurements of the heat of adsorption, would be required in order to apply such models since they contain additional adjustable parameters. A simplified picture considers the two limiting cases of the rate expressions described in Eqs. (1) and (2) with constant but different heats of adsorption for high and low coverages. We also assume that the two reaction processes described by these two expressions operate independently, that is, there is no competition between a "strongly bound" site and a "weakly bound" site.[5] The observed reaction rate profile may be a combination of the rate expressions shown in Eqs. (1) and (2), with the former dominating at high concentrations of **1** and the latter dominating at the end of the reaction with low concentrations of **1**. Figure 3 compares the best model fit to this combined rate law with the experimental data. The individual rate profiles for the single-site and dual-site mechanisms are also shown. The values determined for the rate and equilibrium constants for each model are given in Table 1. The excellence of the fit lends support to the proposal that the mechanism shifts from predominantly Rideal to predominantly Langmuir–Hinshelwood kinetics over the course of the reaction. Consideration of the values for the equilibrium constants in Table 1 is also instructive. The model predicts that the adsorption equilibrium constant is *ca.* ten times smaller for the Rideal model than for the Langmuir–Hinshelwood model. This is in accordance with expectations that the binding strength at high surface coverage should be lower than at low surface coverage. A recent kinetic study of nitrobenzene hydrogenation over supported Pd and Pt catalysts reported Rideal kinetics and equilibrium adsorption constants around $7\,M^{-1}$,[3] in close agreement with the value of $5\,M^{-1}$ which we found for the single-site regime.

It is interesting to note that this kinetic behaviour was not observed for all Pd/C catalysts and was never observed in hydrogenations of the parent unsubstituted nitrobenzene. The catalyst exhibiting this behaviour had a Pd crystallite size of 7.5 nm as measured by X-ray diffraction line-broadening. It may be calculated that for a cuboctahedron crystallite of this size, more than 75% of the surface atoms are planar as opposed to edge and corner sites. Such planar sites could accommodate the larger bulk of the substituted molecule with multi-centred adsorption better than edge or corner sites could, since the ketone group may interact with the surface as well as the benzene ring and nitro group. This could accentuate the shift to stronger adsorption observed as the solution concentration of substrate decreases and the surface becomes less crowded. For the unsubstituted

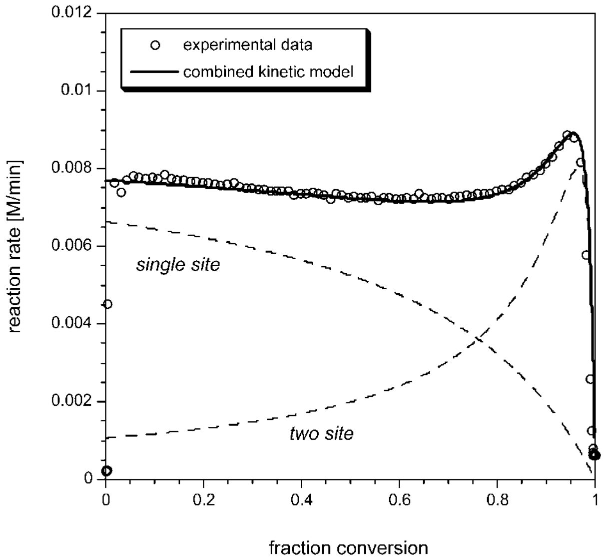


Figure 3. Kinetic modelling of the reaction shown in Figure 1. The single-site model corresponds to Eq. (1) and the dual site model corresponds to Eq. (2). Rate and equilibrium constants are given in Table 1.

Table 1. Rate and equilibrium constants from best fit of the data in Figure 1 to Eqs. (1) and (2) as shown in Figure 3.

Model	Parameter	Value
Single-site [Scheme 2 (**A**), Eq. (1)]	K_{eq} (M^{-1})	5 ± 0.9
	k_{cat} $(L\,mol^{-1}min^{-1})$	0.046 ± 0.005
Two-site [Scheme 2 (**B**), Eq. (2)]	K'_{eq} (M^{-1})	50 ± 2.1
	k'_{cat} $(L\,mol^{-1}min^{-1})$	1.594 ± 0.056

nitrobenzene, by contrast, the rate of reaction by the Langmuir–Hinshelwood mechanism never competes effectively with the Rideal mechanism even at very low substrate concentration.

The magnitude of the rise in rate was greater for lower temperatures and higher catalyst concentrations. In our cases the ultimate rate reached values up to *ca.* 35% greater than the initial rate, although for a short duration. Such a phenomenon could have implications for both safety and efficiency in hydrogenation reactions. Simply monitoring initial rates could lead to erroneous conclusions about requirements for heat removal. Conversely, this phenomenon suggests that higher productivity could be achieved by operation in a semi-batch mode in which the substrate concentration is metered in slowly to keep the reaction in the high-rate regime observed at low substrate concentrations.

Conclusion

An anomalous rising reaction rate observed at high conversions in the hydrogenation of 4-nitroacetophenone is attributed to a shift between two reaction mechanisms which have different catalyst surface site requirements. A fit of the experimental data to a kinetic model combining the two mechanisms helped to provide insight about binding constants and the nature of the catalyst-substrate interaction. The data also suggest protocols for safer and more efficient hydrogenation in the presence of such a phenomenon.

Experimental Section

Reactions were carried out at constant hydrogen pressure and temperature using a 10 wt % Pd/C catalyst (Johnson Matthey 82798, dry). The substrate to catalyst molar ratio was typically 300:1. Reactions were monitored in a reaction calorimeter (Mettler RC1) using a 1-litre jacketed glass vessel with a Hasteloy head and impeller shaft as described previously.[7] Reaction volumes were 500 mL. A reaction rate data point was obtained typically every six seconds over the course of the reaction. The reaction calorimeter is capable of minimizing and accounting for any heat losses attendant to the process under study. An energy balance around a batch isothermal reactor shows that, in the absence of side reactions or other heat effects, the measured heat flow is directly proportional to the reaction rate as shown in Eq. (3), where q(t) is the reaction heat flow (J s^{-1}), ΔH_{rxn} is the heat of reaction (J mol^{-1}), V is the reaction volume (L), and dC/dt is the reaction rate (M s^{-1}).

$$q(t) = \Delta H_{rxn} V \frac{dC}{dt} \tag{3}$$

Reactions were also monitored by FT-IR spectroscopy (Mettler-ASI ReactIR) and by hydrogen pressure uptake (Büchi). No intermediate nitroso or hydroxylamine species were observed in solution. Products were analyzed by gas chromatography during and after completion of the reaction. Selectivity was virtually 100% to product **2** in all cases.

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References and Notes

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