LETTER TO THE EDITOR

Comments on "Nature of Initial Transient Period During Enantioselective Hydrogenation on Pt and Pd" by T. Mallat, Z. Bodnar, B. Minder, K. Borszeky, and A. Baiker

INTRODUCTION

The asymmetric hydrogenation of α-keto esters with cinchona-alkaloid-modified Pt catalysts has received much attention in the literature as one of the few examples of efficient heterogeneous chiral catalysis (1, 2). Some of the peculiarities of this catalytic system still await resolution, although not for want of exhaustive experimental effort or lively discussion. Wells and coworkers (3) were the first to note an intriguing period of rising rate and enantioselectivity at the beginning of the reaction, and our group brought further attention to this phenomenon (4). Although the existence of this transient initial behavior is now generally accepted, a consensus concerning the fundamental reasons for this phenomenon remains elusive (5, 6). In our work, we noted that the initially rising reaction rate invariably reached a maximum at about 20% *conversion* of ethyl pyruvate for reactions carried out under a wide range of experimental conditions. This observation led us to propose that the transient period involves an as-yet-undefined link to the progress of the ethyl pyruvate reaction itself (4b).

Most recently the group of Baiker and co-workers (T. Mallat, Z. Bodnar, B. Minder, K. Borszeky, and A. Baiker) (1) has turned its attention to this phenomenon, calling for a re-examination of our proposal that the transient behavior is a "reaction driven" phenomenon. The purpose of this letter is to discuss their proposals and the data offered to support them, in the context of our own data and proposals.

DISCUSSION

The thesis of this recent paper is that the transient initial behavior may be traced to the presence of impurities in the system. The two hypotheses they present are considered in turn below, followed by a discussion of their comments concerning kinetic analysis.

(i) Hypothesis 1: Racemic Product Impurity in the Reactant

The authors suggest that some studies in the literature have reported spuriously low enantioselectivities at low conversions because they neglected to consider the presence of a small amount of racemic ethyl lactate product in the ethyl pyruvate substrate. One of our papers (4b) was specifically and erroneously cited in this context, and it is therefore important to clarify in this letter that our published work reports *corrected* enantioselectivity values (7). Since the transient behavior is clearly observed even in cases where this correction was made, this argument cannot be a general explanation, and the authors of Ref. (1) concede this fact. It should also be noted that a naïve analytical error in calculating enantioselectivity would provide no viable explanation of the observed transient behavior in *reaction rate*.

(ii) Hypothesis 2: Destructive Adsorption on Pt

A second suggestion is that the rise in enantioselectivity is due to the rapid and efficient removal of surface impurities to an increase in hydrogen surface coverage at the start of the reaction. They suggest that these impurities may arise from the destructive adsorption of either ethyl pyruvate or the alcohol solvent. The authors make a convincing case to show that hydrogen surface coverages can undergo significant changes as a function of catalyst pretreatment or reaction progress (8) under conditions where gas–liquid mass transfer is rate-limiting (9). We reported (4b), however, that identical rate and enantioselectivity behavior was observed in kinetically controlled reactions both for catalysts undergoing lengthy pre-exposure to hydrogen and for those given no pretreatment, suggesting that the transient is not caused simply by an initial hydrogen-assisted removal of surface impurities.

The importance of prepurification of substrates and solvents is also stressed by the authors of Ref. (1). We have previously demonstrated (4b) excellent reproducibility in our results using as-received materials, and here we compare those data to results from the reaction carried out using purified substrate and solvent (Fig. 1). It is clear that even when the level of impurities in the purified ethyl pyruvate is below the GC-detectable limit, a maximum in reaction rate is still observed near 20% conversion, demonstrating that the transient rate behavior is not linked simply to impurities in the materials used.
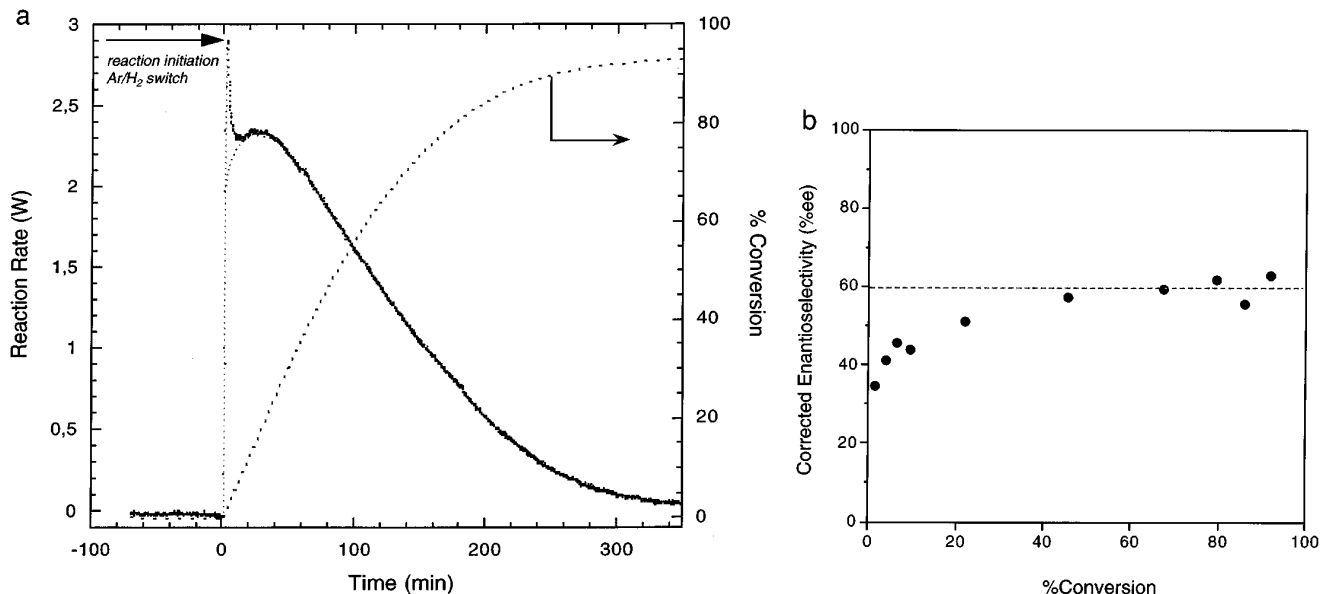
FIG. 1. Reaction rate and percentage conversion vs time for ethyl pyruvate (1 M in n-propanol) hydrogenation carried out at 283 K and 7 bar H_2 on a 1 wt% Pt/Al_2O_3 catalyst modified with cinchonidine (1×10^{-4} M). Prereaction distillation of the substrate and solvent using an 80 theoretical plate still resulted in 99.9% purity as monitored by GC.

Interestingly, a comparison between Ref. (1) and our published proposals reveals much common ground and even common terminology. Reference (1) describes the "development of the chirally modified surface" to reach "steady-state" conditions; our previously published proposal discussed the "equilibration of the chiral surface environment." The sole point of contention appears to be our suggestion that the approach to steady-state behavior is linked to the progress of the ethyl pyruvate reaction itself rather than to unrelated side reactions of adsorbed impurities. Because we observed excellent agreement between reaction rates measured by three independent techniques (heat flow calorimetry, hydrogen uptake, and analytical sampling) (10) which rely on different physical and chemical properties of the reacting system, this led us to discount an important role for side reactions of impurities in this case and caused us to search for other reasons for the observed transient behavior.

Indeed, this unusual behavior of *reaction rate*, and not only enantioselectivity, is a central feature of the experimental evidence for our proposals concerning this transient period; yet virtually no discussion of experimental reaction rate measurements, in their own studies or concerning our published work, is put forward in the paper by Mallat *et al.* (1). Their approach reflects the common practice in investigations in asymmetric catalysis of a nearly exclusive focus on the parameter of enantioselectivity, with very few groups reporting reaction rates as a function of time or reaction

progress (11). Using a direct, *in-situ* measurement of reaction rate, we were able to confirm this rate behavior under a wide variety of conditions. What we found was a striking link between the maximum in reaction rate and the *conversion* of ethyl pyruvate. The initial reaction rate reached a maximum at ca 20% conversion under a wide variety of conditions, including:

- 20 K variation in reaction temperature (over this temperature range, reaction times as disparate as 30 min to 3 h are required to reach the rate maximum at 20% conversion of substrate)
- fourfold variation in the concentration of ethyl pyruvate (corresponding to a fourfold difference in the number of turnovers per catalyst site to reach the rate maximum)
- catalyst pretreatment in hydrogen or in inert gas
- presence or absence of added ethyl lactate product.

None of the published observations (4) noted above was discussed in the paper by Mallat *et al.* (1), nor were experiments of their own reported under a similarly broad range of conditions (they report kinetically controlled reactions carried out at *one* reaction temperature, *one* H_2 pressure, *one* ethyl pyruvate concentration) in order either to corroborate or to challenge our experimental record. Their results do not shed light on a mechanism by which an impurity can cause an identical influence on the rate of the main reaction over such a wide array of reaction conditions.

If the approach to stable behavior of the working catalyst is not "reaction-driven," it nevertheless proceeds in virtual lockstep with the hydrogenation of ethyl pyruvate. There may be more than terminology at stake; the observations cited above may provide important clues to help further our understanding of this complicated catalyst system.

(iii) A Comment on Kinetic Analysis

The authors conclude that any kinetic or mechanistic analyses of these reactions carried out in alcohol solvents are questionable due to the proposed interference of impurities. Our results using *n*-propanol as solvent plead a different case. We have shown that the initial transient period is followed by perfectly constant enantioselectivity and well-behaved Michaelis–Menten kinetics (12) for the remainder of the reaction. Any influence on reactivity from surface interactions with alcohol solvents would thus appear to be confined to this initial period. This suggests that valid kinetic analysis may indeed be carried out based on the "equilibrated" surface after the initial transient period has ended.

Acetic acid, which is offered by the authors as a clean, nonreactive alternative solvent, provides an interesting contrast. While reaction in acetic acid shows no dramatic initial transient period, neither does it exhibit the "steady-state" behavior described by the authors; instead, as their data show, enantioselectivity is observed to rise gradually over the course of the reaction (13). This suggests that a stable working catalyst surface never develops in the reaction carried out in acetic acid solvent. Kinetic analysis in such a system, where the ratio of the rates of two products changes with time, is problematic unless a mechanism for this unsteady-state behavior can be proposed. This suggests that alcohol solvents offer a better choice for valid kinetic modeling and analysis than do reactions carried out in acetic acid.

SUMMARY

The paper by Mallat *et al.* (1) supports our published conclusion that a stable, chirally modified catalyst surface develops after an initial transient reaction period in the Pt-catalyzed asymmetric hydrogenation of ethyl pyruvate in alcohol solvents. Their work focuses on enantioselectivity, while our observations emphasize that unusual reaction rate behavior is also a key feature of the initial transient period (14). The data provided in their paper do not encompass a sufficiently wide set of conditions either to prove or to reject the link we proposed between the transient period and conversion of ethyl pyruvate. The underlying reasons for such a relationship remain unexplained, and additional work on this intriguing phenomenon is needed and would

be welcomed. A proposal to re-evaluate our conclusions, however, must address the experimental record of reaction rate measurements over the broad range of conditions that led to these conclusions and should bear the burden of providing an alternate explanation for these observations.

REFERENCES

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6. Augustine, R. L., and Tanielyan, S. K., *J. Mol. Catal.* **112**, 93 (1996).
7. The Experimental section of our paper cited as Ref. (25) by Mallat *et al.* (Ref. (4b) in this letter) specifically notes that the subtraction of racemic ethyl lactate impurity was carried out. Figure 1 of that paper reproduced the reaction conditions of Fig. 1 in the paper cited as Ref. (24) (Ref. (4a)), showing that the subtraction was carried out although not specifically noted in Ref. (4a). It should also be clarified for readers that the authors of Ref. (1) present *uncorrected* enantioselectivity values in all data presented prior to Fig. 7 of Ref. (1).
8. The electrochemical measurements of catalyst potential under hydrogen shown in Fig. 3 in Ref. (1) show, however, that after 2 h in the reaction mixture the catalysts exhibit identical potentials, regardless of treatment history and whether hydrogen was introduced at the beginning or end of this 2-h period.
9. The conclusion in Ref. (1) that hydrogen surface concentration changes over the course of a diffusion-limited reaction supports our observation of similar changes in solution hydrogen concentration during diffusion-limited reactions (see Fig. 5 in Sun, Y., Wang, J., LeBlond, C., Landau, R. N., and Blackmond, D. G., *J. Catal.* **161**, 759 (1996)). However, extension of this interpretation of surface coverages to experiments carried out under kinetically controlled conditions is not straightforward.
10. Reaction calorimetry provides reaction rate calculated from the instantaneous heat release of the reaction. For an isothermal reaction in the absence of prominent side reactions, an energy balance shows that the instantaneous heat flow, q, is directly proportional to the rate of reaction, dC/dt, at any time during the reaction: $q = \Delta H_{rxn} V_r \, dC/dt$, where $\Delta H_{rxn} =$ heat of reaction and $V_r =$ volume of reactor contents. Monitoring *in-situ* hydrogen uptake provides reaction progress calculated from the reaction stoichiometry and the ideal gas law. GC analysis of the reaction solution gives compositional information as a function of conversion. Any contribution to the observed rate from side reactions must be negligible in a case, where these different methods give identical reaction rates, as we

showed in Ref. (4b) and also in LeBlond, C., Wang, J., Larsen, R. D., Orella, C. J., Forman, A. J., Landau, R. N., Laquidara, J., Sowa., J. R., Jr., Blackmond, D. G., and Sun, Y.-K., *Thermochim. Acta* **289**, 189 (1996).

11. A number of groups report initial rate values or define integral rate parameters, such as the time required to achieve a specific conversion or a specific number of turnovers. For a very recent report of detailed rate measurements in this reaction system see Kohler, J., and Bradley, J. S., *Catal. Lett.* **45**, 203 (1997).

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13. It may be calculated from Fig. 6 of Ref. (1) that the (corrected) *instantaneous* enantioselectivity increases by approximately 10% over the range of conversion shown.

14. A general conclusion of our work is the recommendation that reaction rate data receive more prominent consideration in any discussion of selectivity, since selectivity is a derived property of reaction rates.

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