LETTER TO THE EDITOR

Reply to Comment on "Nature of Initial Transient Period During Enantioselective Hydrogenation on Pt and Pd" by Donna G. Blackmond

INTRODUCTION

The enantioselective hydrogenation of ethyl pyruvate (EtPy) to ethyl lactate (EtLa) with chirally modified Pt has become popular topic in the past decade, a fact which is reflected by over 80 papers and reviews covering various aspects of this rather complex model reaction. An interesting facet of this reaction, which has been the focus of Blackmond and co-workers attention, is the behavior observed in the initial transient period (1, 2). The authors reported that the enantiomeric excess (ee) increased from a value close to zero and reached a plateau at ca 20% EtPy conversion. This behavior was attributed to a "reaction-driven equilibration of the surface environment."

In a recent paper (3) we investigated the nature of the initial transient behavior during enantioselective hydrogenation reactions over Pt and Pd using FTIR and electrochemical methods. Based on the results of this study and the wealth of available literature data we suggested that the observed transient behavior could also originate from impurities present in the system or generated by side reactions. Indeed, experimental conditions used by Blackmond and co-workers do not rule out this possibility.

In the preceding Letter to the Editor (4) Blackmond criticized certain points in our paper (3). We now address her four points of criticism which involve a wide variety of matters for consideration.

DISCUSSION

1. Racemic Product Impurity in the Reactant

First, we wish to point out that the work of Blackmond and co-workers was not erroneously cited in the context of racemic product impurity in the reactant. In the work cited by us (Ref. (24) in our paper (3)) the racemic product impurity was not taken into account by the authors. Although the impurity was accounted for in the kinetic investigation in a subsequent paper (Ref. (25) in our paper (3)), the authors never mentioned the faulty data evaluation in Ref. (24), thereby maintaining their contention that the optical yield is zero at very low conversion (Fig. 3 in Ref. (24) in (3)).

This omission prompted us to discuss the consequences of this impurity more extensively (3).

We never proposed that the transient behavior studied by Blackmond and co-workers can be fully traced to the racemic EtLa impurity in EtPy. However, we suggested (3) that the special interactions between (i) EtPy and alcoholic solvents (hemiketal formation) and (ii) EtPy, alcoholic solvents and Pt (destructive adsorption) cannot be disregarded when interpreting the observed transient behavior, as discussed below.

2. Destructive Adsorption of Ethyl Pyruvate and Alcoholic Solvents on Pt

2.a. We have shown by FTIR and electrochemical methods that CO and strongly adsorbed organic residues are formed during the initial adsorption of EtPy and short chain primary alcohols (e.g., ethanol, 1-propanol) on Pt (3). The coverage of surface Pt sites by these impurities reached astonishingly high values up to 0.79. FTIR model studies also indicated that the coverage by CO decreased considerably when the Ar atmosphere was substituted by hydrogen (Fig. 1 in Ref. (3)). Our observation in not a new discovery, rather it is an extension of a well-documented phenomenon in electrocatalysis (6–9 and references therein). It was also shown (10, 11) that hydrogen does not simply compete with the hydrocarbon fragments for the active sites, but it transforms them to more weakly adsorbed species, such as ethane and propane (from 1-propanol).

Blackmond (4) questioned our suggestion that hydrogen should play a major role in the initial transient behavior of EtPy hydrogenation by the (partial) removal of surface impurities. She raised two queries regarding our proposal:

(i) Blackmond and co-workers carried out their experiments in a reactor operated in the kinetic regime, whereas mass transfer was rate limiting in our case;

(ii) an *in situ* hydrogen treatment of the catalyst "for 2 h at the temperature and pressure of the reaction, either in the solvent alone or with the modifier added to it," as Blackmond and co-workers carried out the experiments (2), had no influence on the rate and ee of the subsequent reaction.

Concerning point (i), Blackmond confused two different things. Our proposal for the positive effect of hydrogen is based on the FTIR model studies and the pertinent literature and not on the experiments performed in the batch reactor. On the contrary, the batch experiments, combined with the measurements of catalyst potential during reaction, were used to demonstrate the influence of mass transport on the surface hydrogen concentration in the initial period of EtPy hydrogenation (Fig. 2 in Ref. (3)).

With regard to point (ii), Blackmond's interpretation is rather astonishing. The reactant was added in their experiments after pre-exposure of the catalyst to hydrogen (2). However, the influence of the destructive adsorption of the reactant on Pt was completely ignored. Besides, the pretreatment temperature (ambient temperature) was inappropriately chosen, as will be discussed later.

2.b. The comment cited as Ref. (8) in the Letter to the Editor (4) is also erroneous and based on a misinterpretation of the results shown in Fig. 3 in our paper (3). In these experiments the initial transient period was monitored by measuring the catalyst potential during EtPy hydrogenation after two substantially different pretreatment procedures. In one case the Pt/alumina was prereduced in a hydrogen stream at 400°C and distilled EtPy was employed. The initial catalyst potential (145–150 mV) increased slowly and reached 220–230 mV after 2–3 h (i.e., at 40–60% conversion!). In the other case neither the catalyst nor EtPy was pretreated and the reaction mixture containing 1-propanol solvent was mixed for 2 h in nitrogen before introducing hydrogen (general procedure in Ref. (1)). Here the catalyst potential after introducing hydrogen was 220 mV (i.e., at 0% conversion!), and this value barely changed up to 80% conversion of EtPy. Consequently, in the initial transient periods of the two reactions (below 10–20% conversion) the catalyst potentials differed by up to 70 mV. For comparison, a change in the hydrogen pressure by a factor of 10 would shift the potential of *clean* Pt by only about 30 mV, according to the Nernst equation. This is a clear indication that different pretreatment procedures result in different surface concentrations of hydrogen and organic species in the initial transient period. It was also shown that the different surface state of Pt resulted in substantially different measure of ee throughout the reactions.

2.c. In the part of this section the role of impurities is discussed by Blackmond. Based on experiments carried out with purified or unpurified reactant and solvent, shown in Fig. 1 in her letter (4), it was proposed that the influence of impurities on the transient behavior is not important. This conclusion contrasts to our observations (3) and also the recent detailed studies by Blaser and co-workers (12), who demonstrated that distillation of EtPy purchased from eight different suppliers had a dramatic influence on both the reaction rate and the ee. Our observation shown in Figs. 3–5 in Ref. (3) provides a likely explanation to the apparent

discrepancy between Blackmond's and others' results. The destructive adsorption of 1-propanol during calibration of the calorimeter provides such a large amount of impurities on the Pt surface that other effects cannot be clearly observed.

Blackmond also refers to a previous experiment demonstrating the reproducibility of their results (2) and suggests on this basis that impurities cannot play an important role. We believe that the "two reactions carried out at different times under identical conditions, using different lots of solvent and substrate" (2) evidenced only that the supplier sold constant quality chemicals. In any case, it is rather astonishing to apply these experiments as evidence for the missing link between the presence of impurities in the system and the nature of the initial transient behavior.

Note that distillation of EtPy prior to use is especially efficient in separating the main component from nonvolatile impurities. In this respect, a GC detection of the impurity level, as suggested by Blackmond, is not a reliable method; HPLC or thin layer chromatography are more appropriate.

3. The Role of Reaction Rate in the Transient Period

3.a. Blackmond found an "excellent agreement between reaction rates measured by three independent techniques," and on this basis she proposed that side reactions and impurities could not play an important role in the observed phenomenon. Let us analyze the limitations of these methods, namely reaction calorimetry, hydrogen consumption measurement, and GC analysis, in following the real processes during EtPy hydrogenation in 1-propanol.

We have shown earlier with UV and NMR studies (13) that in ethanol and methanol the major part of EtPy is present as a hemiketal. In ethanol the equilibrium was reached in 30 min, but only in 10 min when CD was also present (base catalysis (14)). Now we completed these experiments using 1-propanol. A 1 M propanolic solution of freshly distilled EtPy containing also CD (CD/EtPy = 0.1 wt%) was used for the measurement (0.25–1 M EtPy solutions with the same reactant/modifier ratio were used by Blackmond and co-workers for the catalytic runs (1, 2)). IR analysis of the CO and OH bands indicated a rapid transformation in the first 10 min, followed by a slower equilibration between the hemiketal and the free carbonyl compound (Scheme 1). About 40% of EtPy was present as its hemiketal after 45 min and the equilibrium was not yet reached.

Despite the significantly slower process in 1-propanol, compared to that in ethanol or methanol, after mixing EtPy and 1-propanol, hemiketal is also present, and the equilibration time is comparable to that necessary for the calibration of the calorimeter (approximately 2 h stirring of the reaction mixture under nitrogen (1)). A rough estimate of the heat of reactions indicates that the contribution of heat evolution due to the hemiketal formation cannot be neglected.
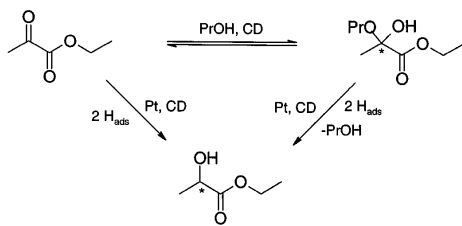
SCHEME 1. Possible reactions between ethyl pyruvate (**1**), 1-propanol and hydrogen over Pt, in the presence of cinchonidine.

Consequently, when using differential calorimetry for exploring the reaction kinetics this point needs to be considered.

It is not possible to detect the real amount of hemiketal during reaction by GC, as the equilibrium is shifted during analysis. Similarly, hydrogen consumption indicates the rate of reduction, but it cannot provide information on the amount of hemiketal.

3.b. An unusual increase of reaction rate at low conversion of EtPy was observed long ago in Wells' and our laboratories (S-type curve in the conversion dependence of hydrogen consumption (15, 16)). Accordingly, we have never disputed this fact itself, but we doubt that the maximum in the reaction rate would be strictly linked to ca 20% conversion of EtPy, independent of the reaction conditions, as proposed by Blackmond. Her suggestion was based on the "direct, *in situ* measurement of reaction rate," and the applied "wide variety of reaction conditions." The reliability of the rate determination by reaction calorimetry in alcoholic solvents has been discussed above. As concerns the reaction conditions, it is well established by now (12, 17) that the crucial parameters of the enantioselective hydrogenation of EtPy are (i) the structure and concentration of chiral modifier, (ii) catalyst pretreatment, (iii) surface hydrogen concentration (influenced by the hydrogen pressure, rate of mass transfer, etc.), and (iv) the chemical nature of the solvent. It is true that we did not change many parameters in our work (3), but we think that we focused on the important ones. For example, we demonstrated (3) that even the real (corrected) ee was below 10% at low conversion in 1-propanol, but it was close to 70% in acetic acid. We also discussed the striking effect of mass transport on the surface state of Pt and hence on the reaction rate and enantioselectivity. These remarkable effects indicate that under the optimum conditions for the enantioselective hydrogenation of EtPy (carefully purified catalyst and reactant, acetic acid solvent, high surface hydrogen concentration (18)) the nature and role of the initial transient period must be strikingly different from that reported by Blackmond and co-workers (1, 2).

The number of kinetic studies of α-ketoestar hydrogenations is rather limited, but it is known that the enantio-

differentiation and the reaction rate, including the measure of rate enhancement observed in the presence of CD, are coupled. Using the wealth of knowledge gathered by now on EtPy hydrogenation (17), it is possible to find the appropriate range of important reaction parameters for a kinetic study. At first glance, Blackmond and co-workers tested a broader range of reaction conditions than we did, but they varied the parameters which are known to have little effect on the enantiodifferentiation, or choose the insensitive ranges of the parameters. For example, they:

—changed the temperature which provided at most 5–6% alteration in the ee (1), although it has been shown that around room temperature this parameter has barely any influence on the enantiodifferentiation (16);

—varied the EtPy concentration which resulted in alterations in ee barely exceeding the estimated analytical error (2);

—added EtLa product to the reaction mixture, which parameter has only minor influence on the ee, except a general negative effect on the reaction rate due to strong product adsorption, as has already been shown earlier (16);

—varied the CD concentration between 10 and 1000 mg/l, but it has been reported that this parameter has a marked influence on the enantiodifferentiation only below this concentration range (19);

—pretreated the catalyst in hydrogen at ambient temperature and found no influence on the catalytic performance, in agreement with the early observation of Orito *et al.* (20), who reported that only pretreatments at elevated temperatures ($\geq 250°C$) provided considerable ($\geq 20\%$) improvement in ee in methyl pyruvate hydrogenation.

To sum up, the missing variation of the maximum in the conversion dependence of reaction rate under a wide variety of reaction conditions would be a more convincing proof for the "reaction-driven equilibration," when the relevant ranges of influential parameters were also included in the studies. If the ee is barely influenced by the variation of reaction conditions, a similar effect can be expected for the rate acceleration, as—according to our present knowledge—the origin of enantiodifferentiation and rate acceleration is the same: the presence of the chiral modifier and its interaction with the reactant on the Pt surface.

4. Choice of Solvent for Kinetic Analysis

Based on our FTIR, NMR, electrochemical, and catalytic studies of the role of impurities and side reactions during EtPy hydrogenation we proposed (3) that acetic acid (or toluene) is a more suitable solvent than alcohols for the kinetic analysis of the reaction, with the further advantage of working around the optimum conditions (18). In her final comment, Blackmond refuses to accept this proposal with the argument that:

(i) in 1-propanol "the initial transient behavior is followed by constant enantioselectivity . . . for the remaining reaction," and

(ii) the reaction in acetic acid does not exhibit a "steady state" behavior as, according to Fig. 6 in our paper (3), the "instantaneous ee increases by ca 10% over the range of conversion shown."

This comment lacks any serious analysis of the data published. It is true that the ee was not constant in the reaction performed in acetic acid (Fig. 6 in our paper (3)), but the change was comparatively small: the largest difference in ee was only 6% (between 9 and 100% conversion). The likely explanation for the minor enhancement of ee with increasing conversion is the mass transport limitation in our reactor, as discussed above. Blackmond and co-workers demonstrated the significant influence of mass transport limitation on the enantioselectivity in 1-propanol (1, 21). Besides, an inspection of Fig. 1b in Blackmond's Letter to the Editor (4) or Figs. 3b and 5 in Ref. (2) indicates that the ee was not always constant in propanol above 10–20% EtPy conversion, even when the reactor was operated in the kinetic regime.

Finally, it should be noted that the change of selectivity with conversion is not an unusual phenomenon in heterogeneous catalysis. Many reactions show this behavior and it is rather astonishing to propose that this feature of EtPy hydrogenation would hinder a reliable kinetic analysis.

CONCLUSIONS

We have clearly demonstrated that the initial very low ee at low conversion is not an intrinsic feature of EtPy reduction, and the change of ee with conversion can easily be minimized by the appropriate choice of reaction conditions (3). The macroscopic observation of an initial transient behavior during the enantioselective hydrogenation of EtPy cannot be safely traced to a "*reaction-driven*" equilibration of the catalyst surface. We suggest that the observed phenomenon is the result of several superimposed effects which need clarification. Extremely important are the impurities and side reactions in the system, as discussed in Ref. (3) and in this Letter. Any interpretation of the observed macroscopic phenomenon has to take into account these effects, otherwise it remains purely speculative. It is impossible to explain the observed macroscopic phenomenon, as long as the interactions on the microscopic level are not properly understood. In this sense and in the light of the effects discussed we maintain our opinion that the interpretation of the phenomenon provided by Blackmond and co-workers needs re-examination.

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