Available online at www.sciencedirect.com
ScienceDirect
Journal of Catalysis 251 (2007) 246–248
JOURNAL OF CATALYSIS
www.elsevier.com/locate/jcat

Response to Letter to the Editor

In a recent paper in this journal [1] we discussed the dynamic nature of chiral modification of Pt, using the hydrogenation of ethyl pyruvate (EP) as a test reaction. The study in a continuous-flow reactor confirmed the dramatic effect of solvent on catalyst deactivation, which we examined in the light of former observations. Catalyst deactivation is a critical issue in evaluating the so-called "ligand acceleration," that is, the higher reaction rate over the chirally modified Pt surface compared with that on unmodified Pt [2]. There is considerable experimental evidence in favor of this concept, and rate acceleration is commonly considered linked to enantioselectivity [3–6].

Recently, another interpretation, suggesting that the origin of rate acceleration can be traced back to the suppression of side reactions by the chiral modifier [7,8], has been brought into the discussion. We believe that the chiral modifier induces enantioselection and intrinsic rate acceleration in the Pt-catalyzed hydrogenation of various activated ketones. Quantitative determination of the *intrinsic* rate acceleration has never been realized, due to the inherent difficulties connected with unknown surface coverage of modifiers and byproducts. Consequently, simple consideration of the *overall* rate behavior for interpretation of the intrinsic rate acceleration may lead to confusion. This is particularly important when analyzing the hydrogenation of EP, the most widely applied test reaction, in which side reactions play important roles. Minimization of side reactions and the resulting catalyst deactivation can be best achieved by applying a weakly acidic solvent [9,10] and ensuring the appropriate order of addition of the reaction components into the reactor. Studies in nonacidic media [8,11], particularly in dichloromethane [7], cannot give reliable information on the intrinsic rate acceleration induced by the chiral modifier. A recent illustration of the role of acids was provided by the hydrogenation of EP on Pt/zeolite, for which a continuous loss of activity was observed in cyclohexane but improved long-term performance could be achieved by increasing the acidity of the zeolite or changing the solvent to acetic acid [12].

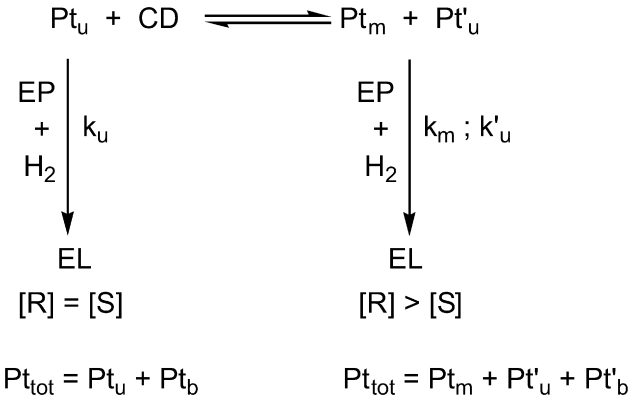
In their letter to the editor, Toukoniitty and Murzin [13] criticized our interpretation of the role of catalyst deactivation in determining the rate acceleration [1]. They proposed that the mechanistic concept of assuming a strong relationship between enantioselectivity and rate acceleration is erroneous. However, in their argument, they confused the changes in the intrinsic rates and the measured (overall) rates and used the latter for mechanistic conclusions. To support their view, they cited only papers reporting on pyruvate hydrogenation in nonacidic medium [7,8,11,14,15] and did not address our critical point [1] concerning the role of solvent in catalyst deactivation. They ignored the extensive work carried out in acidic medium, the data from which support the debated link between rate acceleration and enantioselectivity in α-ketoester hydrogenation [16–18]. They proposed that "ligand acceleration" would be associated mainly with EP hydrogenation over cinchonidine (CD)-modified Pt, whereas this phenomenon would be absent in other cases. This view is not objective; it neglects the significant (overall) rate acceleration observed in the hydrogenation of other α-ketoesters [19–22] and various other activated ketones, including ketopantolactone [23,24], α-keto acids [25], trifluoromethyl ketones [26,27], and α-keto acetals [28,29].

Before discussing the origin of the contradictory mechanistic interpretations, we must mention that the rate acceleration in the presence of modifier is frequently termed "ligand acceleration" [2], based on the analogy to homogeneous catalysis [30]. This term is misleading, however, because in homogeneous catalysis, the number of active metal sites remains unchanged by addition of the ligand, whereas in the case of chirally modified metals, a considerable fraction of the surface sites is covered by the modifier. A critical point, which we illustrate below, is that the number of free surface sites available for conversion of the substrate cannot be determined under reaction conditions, and this situation leaves ample space for speculation.

Chiral modification (i.e., the strong adsorption of CD) covers an unknown fraction of surface Pt atoms (Pt_{tot}) and generates modified sites (Pt_m) in the neighborhood (Scheme 1). On the modified sites, EP is converted preferentially to (*R*)-ethyl lactate, while racemic product is formed on the unmodified surface (Pt_u, Pt'_u). Some of the Pt sites (Pt_b, Pt'_b) are blocked by CD and strongly adsorbing species originating from side reactions and from impurities in the system. A major side reaction is the (poly)condensation of EP on Pt [31], the transformation of which is suppressed by adsorbed CD and hydrogen. Another degradation reaction that is retarded by preadsorbed hydrogen and CD is the Pt-catalyzed decarbonylation of EP, leading to adsorbed CO and an organic residue [32]. Aldol condensation of EP to dimers and oligomers also is catalyzed by the basic modifier [33] and the basic alumina sites [34], and these side reactions are suppressed by acetic acid. An additional source of strongly adsorbing species is the impurities in the reaction components, mainly in EP, and these impurities alone may have a dramatic influence on the reaction rate [35].

Obviously, in the presence of surface impurities, we do not know the number of surface sites involved in the racemic (Pt_u, Pt'_u) and enantioselective (Pt_m) hydrogenation of EP. Thus,

0021-9517/$ – see front matter
doi:10.1016/j.jcat.2007.06.027



Scheme 1. Hydrogenation of ethyl pyruvate (EP) to lactate (EL) on unmodified Pt (Pt_u) or cinchonidine (CD)-modified Pt ($Pt_m + Pt'_u$), leading to racemic lactate or dominantly (*R*)-lactate, respectively. The total number of surface Pt sites (Pt_{tot}) includes also the sites blocked by impurities on the achiral surface (Pt_b) and that blocked by the bulky modifier and surface impurities on the modified surface (Pt'_b). Note that only Pt_{tot} can be determined experimentally.

the *overall* reaction rate on the unmodified and modified Pt catalysts cannot give any reliable information on the relation between the *intrinsic* hydrogenation rates on unmodified and modified Pt in the presence of significant catalyst deactivation. In contrast, when the blocking of surface sites by byproducts and impurities is negligible, an equal or higher *overall* reaction rate on chirally modified Pt, related to unmodified Pt, clearly indicates *intrinsic* rate acceleration ("ligand acceleration"). Considering the likely high partial coverage of Pt by CD, even a lower overall reaction rate on chirally modified Pt is compatible with a small intrinsic rate acceleration. Clearly, a general interpretation of an equal or lower *overall* reaction rate on modified Pt as evidence against the existence of *intrinsic* rate acceleration [13] is false.

A special case is the use of a "reactive" solvent, such as dichloromethane. Dehalogenation of this solvent on Pt, particularly at high hydrogen pressure, affords HCl, which induces a new set of acid-catalyzed side reactions. We found a rapid loss of activity of Pt/alumina in this solvent, and determined that steady-state conditions could not be reached in the continuous-flow reactor at 10 bar [1]. In the hydrogenation of EP in dichloromethane at 30 bar in a batch reactor, Jenkins et al. [7] also observed a strong catalyst deactivation that could be reversed by the addition of CD. Inhibition of EP polymerization by CD is understandable, because the alkaloid neutralizes the HCl formed from the solvent, but generalization of this special case to a new mechanistic concept is astonishing. A thorough analysis of the intrinsic rate of the enantioselective pathway can hardly be made under conditions where the complex chemistry of catalyst deactivation is poorly understood [7,8].

Instead of analyzing the role of various reaction parameters on the deactivation of EP, it is more reasonable to choose a substrate for kinetic studies that does not undergo extensive side reactions. Hydrogenation of the cyclic α-ketoester ketopantolactone is not complicated by the aldol reaction, due to the missing α-H atom, and decarbonylation was barely detectable on Pt by ATR-IR spectroscopy [36]. The rate acceleration induced in this reaction by various chiral modifiers on Pt [23,24] and Rh [37] clearly contradicts the concept that "ligand acceleration" is linked to catalyst deactivation and not to the enantiodifferentiation step.

In the light of our general comment on the phenomenon of ligand acceleration given above, we wish to comment on some specific points raised by Toukoniitty and Murzin in their letter to the editor [13]. They stated that we were erroneous and misinterpreted two of their publications [8,11]. The fact is that in the abstract of Ref. [11], they wrote that the "presence of cinchonidine always led to a rate deceleration and appearance of enantioselectivity," which contradicts the behavior reported later [8] (see Fig. 1 in Ref. [8]). Unfortunately, the former results [11] were not even mentioned in this context in [8], where the authors reported that rate acceleration can be observed at high but not at low EP concentration (Fig. 1 in Refs. [13] and [8]).

Most of the literature data were obtained in batch reactors, and rigorous comparison of these data with corresponding continuous fixed-bed reactor data is not straightforward, due to the different Pt/substrate and Pt/modifier ratios. In the fixed-bed reactor, these ratios are much higher at similar substrate concentrations. At very low pyruvate concentrations, the unusually high Pt/substrate ratio may lead to extensive Pt-catalyzed side reactions (Fig. 1 in Refs. [13] and [8]). We showed earlier that in the hydrogenation of 4-methoxy-6-methyl-2-pyrone, the high yield and enantioselectivity typical for batch operation [39] could not be reproduced in a fixed-bed reactor [40], due to the much higher Pd/substrate and Pd/CD ratios, leading to extensive side reactions.

Regarding our comment on page 73 in [1] on the role of solvent in the hydrogenation of ethyl benzoylformate, we indeed misunderstood a sentence in [38] on the role of solvent in the evolution of ee with time on stream. We apologize for this error.

To sum up, a change in the overall reaction rate in the hydrogenation of α-ketoesters due to the addition of a chiral modifier may hint at a change in the intrinsic rate only when the side reactions and the resulting catalyst deactivation are negligible. Even in this case, however, an equal or somewhat slower reaction rate on the modified surface does not prove the absence of intrinsic rate acceleration, because a considerable fraction of the Pt sites are covered by the modifier. We disagree with the interpretation of the rate acceleration phenomenon advocated by Toukoniitty and Murzin. The mechanistic concept assuming a fundamental relation between rate acceleration and enantioselection on chirally modified sites is strongly supported by studies demonstrating negligible catalyst deactivation.

References

[1] D.M. Meier, D. Ferri, T. Mallat, A. Baiker, J. Catal. 248 (2007) 68.
[2] M. Garland, H.U. Blaser, J. Am. Chem. Soc. 112 (1990) 7048.
[3] A. Baiker, H.U. Blaser, in: G. Ertl, H. Knözinger, J. Weitkamp (Eds.), Handbook of Heterogeneous Catalysis, VCH, Weinheim, 1997, p. 2422.
[4] H.U. Blaser, H.P. Jalett, M. Müller, M. Studer, Catal. Today 37 (1997) 441.
[5] P.B. Wells, R.P.K. Wells, in: D.E. De Vos, I.F.J. Vankelecom, P.A. Jacobs (Eds.), Chiral Catalyst Immobilization and Recycling, Wiley–VCH, Weinheim, 2000, p. 123.

[6] M. Bartók, Curr. Org. Chem. 10 (2006) 1533.
[7] D.J. Jenkins, A.M.S. Alabdulrahman, G.A. Attard, K.G. Griffin, P. Johnston, P.B. Wells, J. Catal. 234 (2005) 230.
[8] E. Toukonitty, D.Y. Murzin, J. Catal. 241 (2006) 96.
[9] M. von Arx, T. Mallat, A. Baiker, Top. Catal. 19 (2002) 75.
[10] A. Kraynov, R. Richards, Appl. Catal. A Gen. 314 (2006) 1.
[11] E. Toukoniitty, D.Y. Murzin, Catal. Lett. 93 (2004) 171.
[12] U. Böhmer, F. Franke, K. Morgenschweis, T. Bieber, W. Reschetilowski, Catal. Today 60 (2000) 167.
[13] E. Toukoniitty, D.Y. Murzin, J. Catal. Comment (2007).
[14] M. von Arx, N. Dummer, D.J. Willock, S.H. Taylor, R.P.K. Wells, P.B. Wells, G.J. Hutchings, Chem. Commun. (2003) 1926.
[15] J.L. Margitfalvi, E. Talas, Appl. Catal. A Gen. 301 (2006) 187.
[16] M. Schürch, T. Heinz, R. Aeschimann, T. Mallat, A. Pfaltz, A. Baiker, J. Catal. 173 (1998) 187.
[17] M. Bartók, K. Felföldi, G. Szöllösi, T. Bartók, React. Kinet. Catal. Lett. 68 (1999) 371.
[18] S. Cserényi, I. Bucsi, K. Felföldi, React. Kinet. Catal. Lett. 87 (2006) 395.
[19] K. Felföldi, K. Balázsik, M. Bartók, J. Mol. Catal. A Chem. 202 (2003) 163.
[20] M. Sutyinszki, K. Szöri, K. Felföldi, M. Bartók, Catal. Lett. 81 (2002) 281.
[21] K. Szöri, G. Szöllösi, M. Bartók, Adv. Synth. Catal. 348 (2006) 515.
[22] K. Balázsik, K. Szöri, K. Felföldi, B. Török, M. Bartók, Chem. Commun. (2000) 555.
[23] M. Schürch, O. Schwalm, T. Mallat, J. Weber, A. Baiker, J. Catal. 169 (1997) 275.
[24] E. Orglmeister, T. Mallat, A. Baiker, Adv. Synth. Catal. 347 (2005) 78.
[25] H.U. Blaser, H.P. Jalett, Stud. Surf. Sci. Catal. 78 (1993) 139.
[26] T. Varga, K. Felföldi, P. Forgó, M. Bartók, J. Mol. Catal. A Chem. 216 (2004) 181.
[27] S. Diezi, D. Ferri, A. Vargas, T. Mallat, A. Baiker, J. Am. Chem. Soc. 128 (2006) 4048.
[28] B. Török, K. Felföldi, K. Balázsik, M. Bartók, Chem. Commun. (1999) 1725.
[29] M. Studer, S. Burkhardt, H.U. Blaser, Chem. Commun. (1999) 1727.
[30] E.N. Jacobsen, I. Marko, W.S. Mungall, G. Schroder, K.B. Sharpless, J. Am. Chem. Soc. 110 (1988) 1968.
[31] J.M. Bonello, R.M. Lambert, N. Künzle, A. Baiker, J. Am. Chem. Soc. 122 (2000) 9864.
[32] D. Ferri, T. Bürgi, A. Baiker, J. Phys. Chem. B 108 (2004) 14384.
[33] D. Ferri, T. Bürgi, K. Borszeky, T. Mallat, A. Baiker, J. Catal. 193 (2000) 139.
[34] D. Ferri, S. Diezi, M. Maciejewski, A. Baiker, Appl. Catal. A Gen. 297 (2006) 165.
[35] H.U. Blaser, H.P. Jalett, F. Spindler, J. Mol. Catal. A Chem. 107 (1996) 85.
[36] N. Bonalumi, T. Bürgi, A. Baiker, J. Am. Chem. Soc. 125 (2003) 13342.
[37] M. Maris, T. Mallat, A. Baiker, J. Mol. Catal. A Chem. 242 (2005) 151.
[38] E. Toukoniitty, P. Maki-Arvela, N. Kumar, T. Salmi, D.Y. Murzin, Catal. Lett. 95 (2004) 179.
[39] W.R. Huck, T. Mallat, A. Baiker, Catal. Lett. 80 (2002) 87.
[40] N. Künzle, J.W. Soler, T. Mallat, A. Baiker, J. Catal. 210 (2002) 466.

Tamas Mallat
Alfons Baiker
Institute for Chemical and Bioengineering
Department of Chemistry and Applied Biosciences
ETH Zurich
Hönggerberg, HCI
CH-8093 Zurich
Switzerland
E-mail address: baiker@chem.ethz.ch (A. Baiker)

Available online 13 August 2007