

## LETTER TO THE EDITOR

## Cinchona-Modified Pt as a Catalyst for Enantioselective Hydrogenation: Criticism of the "Template Model"

In recent years interest in heterogeneous catalytic enantioselective hydrogenation reactions has greatly increased. In this field the hydrogenation of  $\alpha$ -keto esters over cinchona-modified supported Pt catalysts is one of the most widely studied model reactions. Two papers on hydrogenation of  $\alpha$ -keto esters over cinchona-modified supported Pt catalysts were published in the *Journal of Catalysis* (1, 2) and a template model was proposed to explain the induction of enantiodifferentiation (e.d.) (1). This model was slightly modified in Refs. (3-6), but has never been directly proved by experiments. The model has been cited in various publications (7-9) without criticism and is being accepted as sound (7). The aim of this Letter is to forestall further automatic acceptance of the template model. We also wish to demonstrate that its experimental basis is weak and to recall that it ignores one of the most important previous observations, namely that *no preadsorption of the modifier (or no premodification of the catalyst) is required to observe rate acceleration and induction of enantiodifferentiation* (9-19).

Our objections are as follows: (i) uncertainties and inaccuracies related to the catalyst premodification procedure, (ii) use of impure starting materials, (iii) negligence of side reactions, (iv) unsound experimental bases used for comparisons, (v) dubious approaches and concepts, (vi) overestimation of interactions taking place over the platinum sites, and (vii) neglect of chemical interactions induced by the alkaloid in the liquid phase. In light of the above objections and our recent and earlier experimental results (13-18) we consider the template model to be based on inaccurate and insufficient experimental data. The model is too idealistic and oversimplified. In the following paragraphs each of the objections given above will be separately elaborated.

(i) *Uncertainties and inaccuracies related to the catalyst premodification procedure.* The catalyst premodification procedure used in Refs. (1, 2) was not carried out precisely. *Our main objection is the fact that neither the correct amount nor the real form of the alkaloid introduced into the hydrogenation reactor is exactly known.* After the premodification procedure the separation of catalysts from the solution

containing excess alkaloid was carried out incorrectly in that "the modifier solution was decanted and the wet catalyst was transferred to the high-pressure reactor" (1). Based on the above description there is no doubt that a certain part of the alkaloid is in an adsorbed form, but a measurable amount of alkaloid is left in the liquid film adhering to the catalyst particles after decantation. *Using this method the total amount of alkaloid introduced into the reactor cannot be controlled.* We believe that the lack of control of the amount of alkaloid introduced into the hydrogenation reactor is responsible for the "erratic variations of the reaction rate" admitted in Ref. (6).

Unfortunately in Refs. (1, 2) there is no information about the processes or chemical interactions taking place during the premodification. We consider that more effort should be made to elucidate the role of oxygen in this procedure. We detected cinchonidine-N-oxide if cinchonidine (CD) and ethanol were contacted with air in the presence of Pt/Al<sub>2</sub>O<sub>3</sub> (20). The formation of dihydrocinchonidine (DHCD) was always observed if CD was left over Pt/Al<sub>2</sub>O<sub>3</sub> in ethanol in the absence of oxygen (20), the hydrogen being supplied by the ethanol. The scheme for the formation of hydrogen observed under similar conditions in Ref. (1) seems to us very naive. In the presence of air and Pt/Al<sub>2</sub>O<sub>3</sub> we observed formation of acetic acid from ethanol and this may also occur with EUROPT-1.

It was suggested in Ref. (2) that oxygen promoted the ordered adsorption of the alkaloid, again without any experimental evidence. We accept that over EUROPT-1 catalyst oxygen is required to obtain a high rate and high optical yield; however, *the need for oxygen has never been evidenced by any other research groups using different supported platinum catalysts.* Instantaneous rate acceleration can be obtained upon injection of CD into the reactor prior to or during the racemic hydrogenation (Fig. 1, expts. 1, 4, and 5), which clearly indicates that this reaction does not need oxygen even in trace amounts. Similar results were obtained in earlier publications (15, 16, 18). We believe that the need for oxygen is *a specific feature of the EUROPT-1 catalyst.*

With respect to the premodification procedure used in

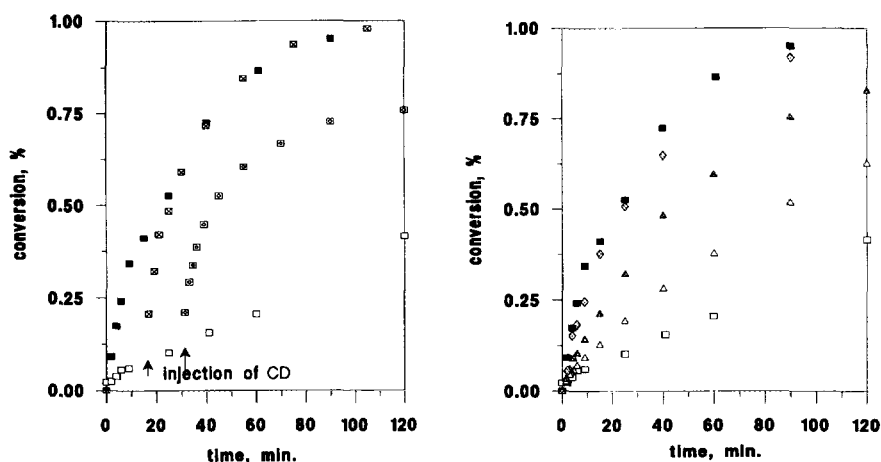


FIG. 1. Kinetic curves of the hydrogenation of ethyl pyruvate under different experimental conditions. Reaction temperature, 21°C; pressure, 50 bar;  $[\text{Etpy}]_0 = 1.0 M$  (Fluka, distilled);  $[\text{Modifier}]_0 = 0.85 \times 10^{-3} M$ ; solvent, ethanol; catalyst, 0.125 g Pt/ $\text{Al}_2\text{O}_3$  (with 5.0 wt.% Pt (E4759)). The optical yields (e.e.) measured at the end of the reaction are given in parentheses. ■, Exp. 1, injection of CD into the reactor at  $t = 0$  min (e.e. = 66.9%). ◇, Exp. 2, premixing the interacting components for 30 min before the hydrogenation (e.e. = 67.1%). □, Exp. 3, racemic hydrogenation. ☒, Exp. 4, injection of CD into the reactor during racemic hydrogenation at  $t = 15$  min (e.e. = 67.3%, corrected for the amount of racemate formed in the first 15 min). ◻, Exp. 5, injection of CD into the reactor during racemic hydrogenation at  $t = 30$  min (e.e. = 68.2%, corrected for the amount of racemate formed in the first 30 min). △, Exp. 6, racemic hydrogenation in the presence of triethylamine (TEA). ▲, Exp. 7, racemic hydrogenation in the presence of quinuclidine (Qn).

Refs. (1–16) there is still one more important question to be answered: why is this process still needed if both rate acceleration and induction of enantiodifferentiation can be observed without any premodification (9–19)?

(ii) *Use of impure starting materials.* Due to the use of impure starting materials, the reaction rates reported in Refs. (1, 2) are very questionable.  $\alpha$ -Keto esters are very reactive compounds, which upon storage can give products of dimerization, condensation, cyclization and oligomerization. Most of these impurities cannot be detected by GC, but can be detected by TLC (20, 21), HPLC (20), and NMR (22). Water, pyruvic acid, ethyl (or methyl) lactate, and high molecular weight products were found in unpurified methyl or ethyl pyruvate (Mepy or Etpy). The high molecular weight impurities can strongly poison the active sites of supported platinum catalyst, while free acid or water (23) results in an increase in the initial rate.

In this respect the reproducibility problem observed in earlier work (11, 14, 16, 23, 24) should be mentioned. Both the rate of hydrogenation and the enantiomeric excess (e.e.) strongly depended on the origin of the substrate (organic reactant) and the mode of its purification. Our recent results on the influence of the purification of Etpy are summarized in Table 1. We observed an increase in the reaction rate in the presence of a small amount of water (exps. 1 and 2). Upon using Etpy from different suppliers (exps. 3 and 8) alterations both in the rate of hydrogenation and the e.e. values were observed. The difference in the rate of hydrogenation between purified and unpurified Etpy was more than 100% (see exps. 5 and

6 for racemic and exps. 7, 8, and 9 for enantioselective hydrogenation). Etpy, even after distillation, resulted in measurable changes both in rate and optical yield (exps. 3 and 4). Some batches of Etpy could not be used at all due to the presence of unknown impurities left after distillation (14, 16). Unpurified Etpy often gave higher e.e. values than the purified Etpy. The removal of acidic residues by neutralization with  $\text{NaHCO}_3$  strongly reduced the optical yield (exps. 9, 7, and 8). This issue will be the subject of a separate communication (20).

It is not excluded that contrary to our findings and literature data (11, 14, 16, 23, 24) the authors of Refs. (1) and (2) had found no difference in the initial rates. If so it would indicate that the Pt/ $\text{SiO}_2$  catalyst used in Refs. (1, 2) is so strongly poisoned that any additional poisoning by impurities has no further influence on the reaction rate. We cannot distinguish whether the reported slight S-character of the kinetic curves is due to the presence of impurities or whether it is related to the intrinsic reaction kinetics, but it seems to us very doubtful to attribute the observed S-character of the kinetic curves to the hydrogenation of the vinyl group of CD (2). For the reasons given above we cannot accept reaction kinetic data given in Refs. (1–6) without serious doubts. The use of unpurified substrate may be one of the reasons for the "erratic variation of the reaction rate" mentioned in Ref. (6).

(iii) *Negligence of side reactions.*  $\alpha$ -Keto esters readily react with alcohols both in the presence and absence of alkaloid with the formation of the corresponding half-ketal (15, 18, 22). We have observed the formation of high molec-

TABLE 1  
Influence of the Purification and Source of Ethyl Pyruvate (Etpy) on the Rate of Hydrogenation and the Optical Yield

Number	Hydrogenation	Ethyl pyruvate source and purification	Rate constant <sup>d</sup> $k_1$ (sec <sup>-1</sup> )	Optical <sup>b</sup> yield (%)
1	Racemic	Fluka, distilled	0.30	—
2	Racemic <sup>c</sup>	Fluka, distilled	0.72	—
3	Enantioselective	Fluka, distilled	2.76	66.9
4	Enantioselective	Fluka, <sup>d</sup> distilled	3.24	71.0
5	Racemic	Sigma, as received	0.12	—
6	Racemic	Sigma, distilled	0.30	—
7	Enantioselective	Sigma, as received	2.64	86.1
8	Enantioselective	Sigma, distilled	6.06	81.2
9	Enantioselective	Sigma, neutralized, <sup>e</sup> distilled 2×	5.34	67.9

Note. Catalyst, 5% Pt/Al<sub>2</sub>O<sub>3</sub> (Engelhard 4759) = 0.125 g; [Etpy]<sub>0</sub> = 1.0 M; [CD]<sub>0</sub> = 0.85 × 10<sup>-3</sup> M (injected separately before the hydrogenation); temperature, 21°C; pressure, 50 bar.

<sup>a</sup> Calculated first order rate constant.

<sup>b</sup> Measured at the end of hydrogenation.

<sup>c</sup> In the presence of 0.05 M H<sub>2</sub>O.

<sup>d</sup> New batch of Etpy.

<sup>e</sup> Neutralized by NaHCO<sub>3</sub>.

ular weight products from Etpy not only during the hydrogenation reaction but upon slurrying Etpy with Pt/Al<sub>2</sub>O<sub>3</sub> in ethanol (20). In CD<sub>3</sub>OD transesterification of Mepy and Etpy and deuterium exchange was observed (15, 18, 22). Recently, we have observed the formation of half-ketal from Etpy and D-ethyl lactate in the presence of CD (20). There is no doubt that all of these side reactions take place after mixing substrate, CD, catalyst, and solvent (ethanol) in the reactor prior to the introduction of hydrogen, and the resulting products can strongly alter the intrinsic kinetic data in the hydrogenation of  $\alpha$ -keto esters.

Prior to the hydrogenation described in Refs. (1–6) the catalyst was left for several minutes in a solution containing substrate, modifier, and solvent. During this period, which could last at least 5–20 min, a variety of by-products could be formed. Mixing of interacting components in different ways strongly influences both the initial rate and the optical yield (15, 16, 18). Figure 1 shows kinetic curves of hydrogenation obtained under different modes of introduction of CD. If the modifier is introduced separately (at  $t = 0$ ) the initial rate of hydrogenation has the highest value (exp. 1). The rate acceleration is instantaneous if the modifier is introduced into the reactor after 15 or 30 min (exps. 4 and 5) of racemic hydrogenation. If all of the interacting components were left in a nitrogen atmosphere for 15 and 30 (exp. 2) min prior to the start of the hydrogenation the initial rate decreased by 50–60% compared to the experiment with separate injection of CD (exp. 1). The decrease of the reaction rate after 50% conversion was even more pronounced. These and earlier similar results (14) show that in the presence of CD the Pt catalyst is poisoned by

by-products formed from Etpy and ethanol prior to the enantioselective hydrogenation. We note that in all the studies in Refs. (1–6) the interacting components were mixed in a way similar to that in exp. 2. In such experiments the intrinsic kinetic data are masked by by-product poisoning.

After 60% conversion a strong decrease in the rate of hydrogenation was also observed in Refs. (1, 2). The kinetic curves (Fig. 4. in Ref. (1) and Fig. 2. in Ref. (2)) strongly resemble our results, discussed above. In this respect the authors declared that the observed decrease in the reaction rate is "due to inhibition by product" (2). *This statement was made without any experimental proof.*

(iv) *Unsound experimental basis used for comparisons.* We refer here briefly to two comparisons, normal vs anaerobic modification and racemic vs enantioselective hydrogenation. In Ref. (2) the normal and anaerobic modifications were compared, but not under the same conditions. The concentration of alkaloid during the anaerobic modification was 40% less than in the normal modification. The most striking difference is that after anaerobic modification the total amount of modifier was introduced into the reactor, resulting in several times higher alkaloid concentration than in other experiments.

The authors of Ref. (2) do not state how the Pt/SiO<sub>2</sub> catalyst used in racemic hydrogenation was pretreated prior to the hydrogenation reaction. If the catalyst was not stirred in ethanol in the presence of air, their comparison between results obtained in racemic and enantioselective hydrogenation is false.

We have carried out both racemic and enantioselective

hydrogenation with a Pt/Al<sub>2</sub>O<sub>3</sub> catalyst (E4759) treated with pure oxygen for 1 h in ethanol at room temperature prior to the hydrogenation. The oxygen treatment resulted in a twofold rate increase in the racemic and a more than 50% increase in enantioselective hydrogenation, but no noticeable change in the optical yield was observed. However, if the oxygen treatment was carried out in the presence of CD we observed a decrease in the rate of hydrogenation. Similar results were obtained earlier (16).

We suggest that in the absence of alkaloid the oxygen treatment probably creates a new type of site which is either more active both in racemic and enantioselective hydrogenation reactions or is less sensitive toward poisoning than the parent Pt sites. Contrary to this, if both oxygen and CD are present during the premodification procedure, different irreversible interactions, such as formation of alkaloid-N-oxide and Pt leaching, can take place. The above interactions might be responsible for the observed decrease in the rate of hydrogenation.

(v) *Dubious approaches and concepts.* In this respect experiments designed to confirm the rate acceleration effect induced by aminoalcohols (3) should be mentioned. The use of aminoalcohol ignores that published results (17) have demonstrated that there is no need for any aminoalcohol moiety in the modifier to induce e.d. The authors of Ref. (3) used different secondary amines (such as 3-hydroxypiperidine and diethanolamine) as modifiers; this is a faulty concept, as they react with  $\alpha$ -keto esters.

The study of the order of the reaction in methyl pyruvate was made at unusually high substrate concentrations (1.9–7.5 M) (1). In the low concentration range (0.1–1.0 M) we always observed first order in substrate. Similar results were observed in our earlier studies (15, 16).

(vi) *Overestimation of interactions taking place over the platinum sites.* Our analysis of Refs. (1, 2) strongly indicates that both in the original template model (1, 2) and its modified versions (3–6) the role of interactions taking place over the platinum sites is overestimated.

Formation of preadsorbed CD on Pt is not required to observe rate acceleration and enantiodifferentiation (Fig. 1. and Refs. (15, 16, 18)). We believe that the ordered layer of alkaloid proposed in Refs. (1, 2) is simply an artificial creature. In recent work (6) it is admitted that "ordered adsorption, though desirable, appears not to be a necessary pre-requisite for enantioselective reaction provided the total coverage (of platinum) by the alkaloid is maintained." However, we believe that neither the ordered layer of alkaloid nor the complete coverage of Pt by alkaloid can be achieved over any working catalyst containing organic moieties, such as adsorbed  $\alpha$ -keto esters or their derivatives (i.e., by-products formed).

In the absence of substrate the time required for the equilibrated adsorption of the modifier into the catalyst

was 20 h or more (1). Our experiments support this observation (20). These results indicate that after the introduction of CD during the racemic hydrogenation of Etpy the instantaneous formation of an ordered overlayer of CD over platinum (1, 2) or the total coverage of Pt by alkaloid (6) can hardly be assumed, yet the rate acceleration is always instantaneous.

If the adsorbed form of alkaloid were involved in the rate acceleration, then after the formation of an ordered overlayer (or after achieving the complete coverage of Pt by alkaloid) the rate of hydrogenation should increase. Contrary to that, in ethanol we always observe a decrease in the rate after 6–12 min of enantioselective hydrogenation.

One of the most serious disadvantages of the template model is that both in its original (1, 2) and its revised forms (3–6) the model requires an absolutely clean Pt surface, which cannot exist under either racemic or enantioselective hydrogenation. Based on the discussion in (i)–(v) we argue that the template model cannot be applied to the platinum surface precovered with an organic overlayer formed either after mixing all of the interacting components or under racemic hydrogenation.

(vii) *Neglect of chemical interactions induced by cinchonidine in the liquid phase.* Cinchona alkaloids can be used as modifiers inducing e.d. in different organic reactions (25), the e.d. being attributed to the modifier–substrate interactions taking place in the liquid phase. These interactions are completely ignored in the hydrogenation of  $\alpha$ -keto esters in the presence of cinchona-modified Pt/SiO<sub>2</sub> catalysts (1–6).

We suggest that the formation of by-products from  $\alpha$ -keto esters observed in the presence of CD is due to the overall increase of the reactivity of the substrate. The increase of the reactivity is attributed to the perturbation of the molecule of  $\alpha$ -keto ester *vis substrate–modifier interaction taking place in the liquid phase*. In this interaction both conjugated carbonyl groups of the substrate (26) and the tertiary nitrogen atom of the modifier are involved. The formation of half-ketal requires the perturbation of the keto carbonyl group, while in the formation of transesterification products the perturbation of the ester carbonyl group is involved. We suggest that the interaction leads to the formation of a weak [substrate–modifier] complex in which the  $\alpha$ -keto ester is hydrogenated with preferential formation of (R)-ethyl lactate. We believe that role of the metal is to (i) provide adsorbed hydrogen for the hydrogenation, (ii) be inactive in the hydrogenation of the quinoline ring of the alkaloid, and (iii) be relatively insensitive to by-product poisoning.

We consider that the quinoline part of the modifier has a key role in the e.d., providing a specific "shielding effect" via  $\pi$ – $\pi$  overlapping between the aromatic ring and the conjugated  $\pi$ -bonds of the  $\alpha$ -keto esters. Similar shielding

effects have been invoked elsewhere (27, 28). By using molecular graphics and quantum chemical calculations the nature of the substrate–modifier interaction was modelled (29). This model strongly supports the “shielding effect” induced by the quinoline ring. Further work is in progress in our laboratory to elucidate the exact nature of the enantiodifferentiation step in the hydrogenation of  $\alpha$ -keto esters in the presence of cinchona-modified supported platinum catalysts.

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