

## LETTER TO THE EDITOR

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

In the preceding Letter, Margitfalvi and Hegedüs (M & H) make interesting observations on the template model which we advanced in 1990 to interpret the observed sense of the enantioselectivity in  $\alpha$ -keto ester hydrogenation over cinchona-modified supported Pt catalysts. Furthermore, they comment critically on aspects of our experimental procedures and technique.

The template model was advanced as a first attempt to interpret the sense of the observed enantioselectivity in the hydrogenation of methyl pyruvate to methyl lactate catalysed by cinchonidine-modified and cinchonine-modified Pt (1). It was a geometrical model in concept and was built on certain assumptions that we went on to test experimentally. It was successful in that it fulfilled the role of a model by providing a framework for understanding and it guided further experiments. Its inadequacies soon became clear when we moved on to interpret the enhanced reaction rates that accompany enantioselectivity in this system (2, 3). Accordingly, the template model was challenged from within the Hull group in 1991 (4) and in work presented to the Tenth International Congress on Catalysis (5). These and later studies led us to conclude that enantiofacial selection occurs on reactant adsorption in a region adjacent to adsorbed alkaloid, and that H-bonding between the quinuclidine-N of the adsorbed alkaloid and the half-hydrogenated state derived from pyruvate is responsible for rate enhancement (3). In 1994 we published results of surface science studies, catalysis studies, and molecular modelling to show that this 1:1-interaction model is much more satisfactory than the template model in interpreting the larger body of experimental information now available to us (6). The template model has thus been superseded.

We now address M & H's seven numbered criticisms which contain a much larger number of separate matters.

(i) *Catalyst modification procedure.* It is the practice of the Hull group normally to modify Pt catalysts in a separate step and then to transfer freshly modified catalyst to the high pressure reactor followed by solvent, ester, and dihydrogen. This conforms to the original published procedure (7) and has the merit that the chemistry of catalyst modification can be separately studied. Our cata-

lyst modification is conducted using 200 mg alkaloid (see the published isotherm (1)). After decantation and addition of solvent and reactant, the alkaloid remaining is greatly in excess of the amount reported as necessary to achieve full modification, i.e., about 1 mg (8, 9). The presence of excess alkaloid does not impair enantioselectivity (8, 9). Thus, provided excess alkaloid is present, the extent of the excess is unimportant.

Next, M & H make reference to "erratic variations in rate" that we report in Ref. (5), and they ascribe this to variable amounts of modifier present in the reactor. This criticism is misguided. Under normal conditions rates of reaction show highly satisfactory reproducibility (which is remarkable in view of the complex competitive adsorption that occurs at the catalyst surface, the fact that dihydrogen is the most weakly adsorbed of the competing adsorbates, and that the rate is a function of the surface coverage of hydrogen). The only time we observed erratic rates over cinchona-modified Pt was in the unique situation where we had used mixtures of dextro- and laevo-rotatory modifiers (5). The general method is not to be condemned by reference to one exceptional circumstance.

The second paragraph of M & H's section (i) contains five fairly unrelated points which we answer in order. First, the role of oxygen in catalyst modification is certainly important. Under strictly anaerobic conditions no reaction occurs (6, 10, 11). Our XPS studies reveal that some products form when dioxygen is adsorbed from ethanolic solution onto Pt(111) in both the presence and the absence of dihydrocinchonidine (12). Furthermore, a paper on the role of reactive gases in catalyst modification is currently in preparation (11). Second, on occasions when alkaloid-N-oxides have been added to reaction mixtures over Pt (13) or Ir (14), such additions have not influenced enantioselectivities (Pt, Ir) or rates (Ir). Blaser *et al.* have proposed that such N-oxides are probably reduced very rapidly to the parent alkaloid under hydrogenation conditions (13). Third, we agree that 10,11-dihydrocinchonidine may be formed under normal reaction conditions, and to preclude this side reaction we frequently use dihydroalkaloids as modifiers. Fourth, our proposal that ethanol undergoes

dissociative adsorption to adsorbed  $-\text{OEt}$  and adsorbed  $-\text{H}$ , with subsequent desorption of dihydrogen (1) is *not* “very naive”; the process was supported by D-tracer evidence at the time and has since been confirmed by XPS (12). Fifth, we agree that, under certain conditions, acetic acid may be formed from ethanol and oxygen at the EUROPT-1 surface; such oxidation is evident from our XPS study (12).

It was an assumption of the template model that cinchona alkaloid and oxygen underwent ordered coadsorption on Pt in a manner comparable to that observed for benzene and CO on Pt(111) (15). Accordingly, we undertook LEED studies to search for such ordered adsorbed states. Although some were found, quinoline and dihydrocinchonidine do not undergo ordered adsorption on Pt(111) (6, 12). This was one component of information that caused us to move away from the template model (6). The oxygen effect is not specific to EUROPT-1; we have studied Pt supported on oxides other than silica and find that they all have the same oxygen requirement in modification as EUROPT-1 (4). There is nothing unusual in the experimental results shown by M & H in their Fig. 1; in our view reaction is facilitated by oxygen (air) dissolved in the solution, and we respectfully suggest that they repeat their experiment with dioxygen-free materials and report their findings. As mentioned above, we are not the only group to report very poor or zero rates and enantioselectivities for strictly anaerobic reactions (10).

Finally, we normally prefer to modify catalysts in a separate process, rather than charge all components directly into the reactor for three reasons, (i) it gives control over the all-important process of alkaloid adsorption, (ii) it enables us to investigate that process in isolation, and (iii) it enables us to maximise both modification and reaction, e.g., by using the most effective solvent for each stage (16), and by using the most appropriate reactive gas, which need not necessarily be dioxygen (11).

(ii) *Quality of starting materials.* The methyl pyruvate (from Fluka) used in our investigations has been used “as received” and after purification; rates and enantioselectivities have always concurred (14). Methyl pyruvate obtained from Sigma is of lower nominal quality and we are not unduly surprised by results 5 to 9 in M & H’s Table 1. It is unfortunate that they do not record the performance of material from Fluka used “as received.” Enantioselective hydrogenation of pyruvate is certainly accompanied by side reactions, as witnessed by the viscous oily residue that remains when product is distilled off. However, we refute the suggestion that our Pt/silica (EUROPT-1) was strongly poisoned; strongly poisoned catalysts do not convert reactant at  $2 \text{ mol h}^{-1} \text{ g}_{\text{cat}}^{-1}$ . Finally, the initial acceleration in rate (which M & H call the S-curve) for reactions over catalysts modified by all cinchona alkaloids containing the vinyl group is intriguing. The experimental fact is that this

initial acceleration is almost (but not quite) removed by use of the equivalent 10,11-dihydro compounds as modifier (17). It is reasonable therefore to ascribe the acceleration to some process involving adsorption of the modifier by the vinyl group. Dihydrocinchonidine is formed during reaction over cinchonidine-modified Pt and geometric considerations indicate that this material must be formed from cinchonidine adsorbed only by the vinyl group. Alkaloid so adsorbed is not well situated to participate in the rate enhancement process. Thus, to associate the removal of this redundant adsorbed state of cinchonidine with the acceleratory region is entirely reasonable.

(iii) *Side reactions.* M & H are correct in saying that “a variety of by-products could be formed” if “catalyst was left for several minutes in a solution containing reactant, modifier, and solvent.” They assess that, in our work, “this period . . . could last at least 5 to 20 minutes.” We do not conduct our experiments in so leisurely a fashion! Typically, the time taken to charge our reactors, flush three times, admit dihydrogen, and commence reaction is *less than one minute*. We agree that performance is impaired by slow charging of the reactor, and we are not surprised by the poor performance of run 2 reported in M & H’s Fig. 1. We are, of course, aware of hemit-ketal formation and of the conclusion of Minder *et al.* that its involvement as an intermediate in pyruvate hydrogenation can be excluded (18).

In our first publications it was necessary to comment on the strong retardation in rate that occurred at about 60% conversion. Contrary to M & H’s assertion, we reported both that the reaction is poisoned upon intentional addition of product and that our published hydrogen uptake against time curves conformed to Hinshelwood’s equation for product-inhibited reaction (1).

(iv) *Conditions used for experimental comparisons.* In our study of catalysts modified under normal and anaerobic conditions we did indeed compare reactions that contained different quantities of modifier. Our reply is covered by our comments under (i) above. In our comparison of racemic and enantioselective reactions we should indeed have stirred our catalysts in solvent under air for 1 h before transfer to the reactor to make their pretreatment identical to that for alkaloid-modified catalysts. Since that time, two workers at Hull have compared racemic hydrogenation rates for unmodified Pt catalysts prepared with and without this pretreatment in air. We now report that such pretreatments have resulted in no change in rate or in reductions of up to 25%; we do not observe the two-fold rate enhancement reported by M & H. In our analogous study of Ir catalysts, where racemic hydrogenation rates were fast (faster than the rates of enantioselective reaction) such pretreatment in air further enhanced the racemic hydrogenation rate. The origin of this effect is not clear. Without

more experimental evidence, we would not wish to concur with M & H's speculation that "oxygen treatment probably creates a new type of site."

(v) *Approaches and concepts.* Our paper of 1991 (2) was concerned with interpreting the remarkable enhanced rate that accompanies enantioselectivity over cinchonidine-modified Pt. We were (and still are) intrigued by the role of the HO-C-C-N unit in cinchonidine (and other families of alkaloids) and our choice of aminoalcohols for addition to the racemic reaction was based on their possessing this functionality. We were, of course, investigating their role as accelerators, *not* as modifiers. The conclusion that we drew from that work led to our interpretation of the origin of the enhanced rate (6), with which others concur (19).

M & H criticise us for measuring the order in pyruvate as "unusually high reactant concentrations (1.9 to 7.5 M)," where the order is zero. Many investigators have worked in this region (20–22) where the surface concentration of pyruvate is unlikely to be a variable. We considered this a sensible precaution. It is an elementary expectation that such a reaction will become first order in the limit of low concentration, as we too have reported (8). There was nothing dubious about our approach in this matter.

(vi) *Conditions at the Pt surface.* All five paragraphs of M & H's Section (vi) present various criticisms of the template model. Since we have departed from this model in favour of a 1:1-interaction model (6), this section requires no formal reply. Nevertheless, we must point out two errors in the criticisms themselves. First, the template model did *not* require "complete coverage of Pt by alkaloid," which M & H repeatedly state (paragraphs 2, 3, and 4 of their Section (vi)). Indeed, the central requirement of the template model was that the surface should contain a *nonclose-packed* ordered array of adsorbed alkaloid; otherwise the shaped Pt ensembles thought to be necessary for selective enantiofacial adsorption of the reactant would not have existed. It is still a live issue, in our view, as to how the surface coverage of alkaloid is prevented from becoming so high that reaction is completely poisoned. The coadsorption of solvent and reactive gas along with alkaloid during modification apparently regulates the surface coverage of modifier (11). Second, we never suggested that the template model required "an absolutely clean Pt surface." Supported metal catalysts seldom, if ever, contain "absolutely clean" active phases.

(vii) *Chemical interactions of cinchonidine in the liquid phase.* It is correct that the mechanisms published by the Hull group have not featured interactions between the modifier and reactant in the liquid phase before adsorption, although these were considered as long ago as 1989. It is a basic tenet of scientific philosophy that a proposed mechanism should contain only those features and elements that

are required in order to interpret the experimental results. An investigator will, from time to time, be aware that other chemical reactions are taking place in a system, but if they are not required for the interpretation of the results then they have no place in the discussion. For example, we suspect that solvent is adsorbed at the Pt surface during enantioselective reaction, but our mechanisms do not show it because the majority of our experimental results, as published so far, do not reveal it. If M & H wish to propose that [reactant-modifier] complexes adsorb from solution and are hydrogenated they should first describe experimental results that lead them to this conclusion. Our view of the importance of such complexes is rather different. The hydrogenation of methyl pyruvate over cinchona-modified Pt can be achieved not only in the liquid phase, but also in the gas phase where interaction of reactant and modifier before adsorption cannot possibly occur (23). Moreover, it is possible to conduct liquid-phase reactions in the presence of such minute quantities of alkaloid that the concentration of alkaloid in solution is extremely low, and yet the reactions can be highly enantioselective (8). Such reactant-modifier interactions before adsorption from the liquid phase are therefore not essential to the achievement of enantioselective hydrogenation in this system.

Finally, it should be clearly understood that the experimental evidence used to support the 1:1 interaction model has been interpreted on the assumption that molecules of cinchona alkaloid are adsorbed randomly on the Pt surface; if cooperative effects were shown to be present in alkaloid adsorption, the interpretation of certain key experiments would have to be reviewed.

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Received June 7, 1995