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PRIORITY COMMUNICATION

On the Implications of Hemiketal Formation during Ethyl Pyruvate Hydrogenation in Alcohol Solvents

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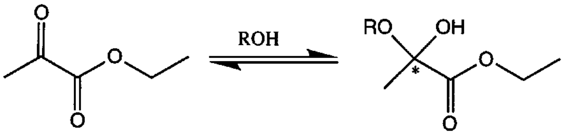
Hemiketal formation between alcohol solvents and α-keto esters is shown to be catalyzed not only by the basic cinchonidine modifier but also by the acidic Pt/Al_2O_3 catalyst. Theoretical considerations and experimental results demonstrate that reaction calorimetry is a valid and accurate measure of the hydrogenation reaction, provided that the substrate and its hemiketal remain in equilibrium over the course of the reaction. The rate of hemiketal formation and, thus, the probability that the preequilibrium step will remain unperturbed during the hydrogenation reaction, is sensitive to the acidic properties of the support. © 1998 Academic Press

INTRODUCTION

Relationships between catalytic behavior and solvent parameters in the asymmetric hydrogenation of α-keto esters (1) have been studied extensively (2,3). The formation of a hemiketal species between alcohol solvents and the substrate (Eq. [1]) has been noted (4), although it is generally agreed that this reaction does not contribute to the asymmetric reaction pathway:



[1]

We have previously demonstrated excellent agreement between two independent methods of measuring reaction rate, one of which detects hemiketal formation as well as hydrogenation, and one which accounts only for the actual hydrogenation reaction. More recently, however, questions have been raised about the potential for hemiketal formation to complicate measurement of the hydrogenation reaction (5). The results presented here show that hemiketal formation in *n*-propanol is catalyzed not only by the basic cinchonidine modifier but also by the acidic Pt/Al_2O_3 catalyst. Theoretical considerations and experimental results demonstrate that reaction calorimetry is a valid and accurate measure of reaction progress in the hydrogenation of α-keto esters in alcohol solvents, provided that the substrate and its hemiketal remain in equilibrium over the course of the reaction.

EXPERIMENTAL

Materials

The two Pt/Al_2O_3 catalysts employed in these studies were used as received. A 1 wt% Pt (Precious Metals Corporation, PMC) catalyst was the same lot number as that used in much of our previous work on this reaction (6). A 5 wt% Pt catalyst (Engelhard E4759) which has been used extensively by other workers in this field was also used. Ethyl pyruvate was distilled immediately prior to use to afford 99.9% purity. The solvent *n*-propanol was distilled prior to use.

Reaction Conditions

The instantaneous heat of formation of the *n*-propyl hemiketal of ethyl pyruvate was monitored by reaction calorimetry (Mettler RC1) as a function of time at 283 K under 1 bar Ar in the presence and absence of the Pt/Al_2O_3 catalysts and the chiral modifier cinchonidine. This system affords accurate measurement of the reaction heat flow to ± 0.1 W, corresponding to a reaction rate of approximately 1 μmol/s for a reaction with ΔH_{rxn} of 20 kcal/mol.

RESULTS AND DISCUSSION

Reaction Calorimetry as a Kinetic Tool

As shown in Eq. [2], reaction calorimetry measures the total rate of all concurrent reactions (in the general case,

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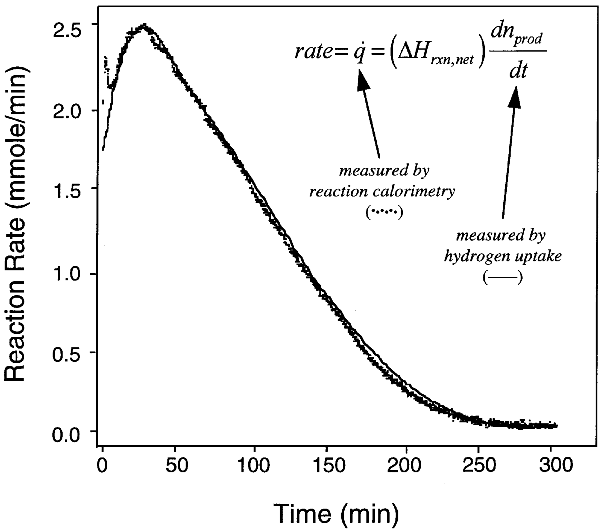


FIG. 1. Reaction rate as a function of reaction time in the cinchonidine-modified Pt/Al_2O_3 catalyzed hydrogenation of ethyl pyruvate in *n*-propanol at 283 K and 585 kPa hydrogen, as described in Ref. (6). The solid line is the rate of hydrogen uptake (Eq. [3]). The discrete data points give the heat flow $\dot{q}$ (Eq. [4]) measured by reaction calorimetry. The figure is redrawn from Ref. (6b).

z reactions involving y different reactants, where $\Delta H_{rxn,i,j}$ and $dn_{i,j}/dt$ are respectively the heat and the rate of the ith reaction of component j):

$$rate = \dot{q} = \sum_{i=1}^{i=z}\sum_{j=1}^{j=y} \Delta H_{rxn,i,j}\frac{dn_{i,j}}{dt}. \qquad [2]$$

Therefore, it is important to establish by independent means that the measured heat flow in fact reflects the rate of the reaction under study. This is done in Fig. 1 for the constant pressure hydrogenation of ethyl pyruvate in *n*-propanol using cinchonidine-modified Pt (6b), where the reaction rate was measured by two methods, hydrogen uptake and reaction calorimetry, which monitor independent properties of the reacting system. The excellent agreement, even for the intitial transient period during which the reaction rate rises, establishes the validity of the calorimetric measurement of the hydrogenation reaction rate in this case. This is confirmed below by a mathematical description of the two methods of reaction rate measurement.

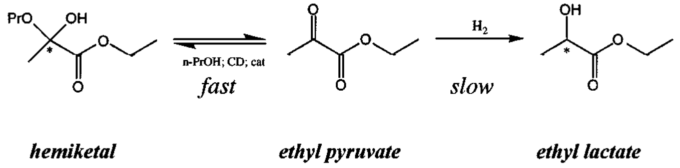
Measurement of the uptake of hydrogen accounts for any and all reactions which consume hydrogen. If substrate hydrogenation is the only reaction consuming hydrogen, then the 1 : 1 reaction stoichiometry means that hydrogen uptake, $dn_{\mathrm{H_2}}/dt$, may be taken as a direct measure of the total rate of appearance of the product, dn_{prod}/dt, where n_{prod} and $n_{\mathrm{H_2}}$ refer to the moles of the hydrogenation product formed and the hydrogen consumed, respectively:

$$rate = \frac{dn_{\mathrm{prod}}}{dt} = \frac{dn_{\mathrm{H_2}}}{dt}. \qquad [3]$$

The heat flow curve of Fig. 1 represents contributions from the hydrogenation reaction, consuming hydrogen and ethyl pyruvate with a heat of reaction $\Delta H_{\mathrm{rxn,H_2}}$ (7), and the reversible reaction between *n*-propanol and ethyl pyruvate (Eq. [1]), which involves ethyl pyruvate, but not hydrogen with a heat of reaction $\Delta H_{\mathrm{rxn,HK}}$. Under the conditions of the experiment shown in Fig. 1, an equilibrium mixture of ethyl pyruvate and hemiketal was formed before the hydrogenation reaction began. This reversible reaction is driven toward ethyl pyruvate as conversion increases. Thus, the total rate measured by heat flow calorimetry will be given by:

$$rate = \dot{q} = (\Delta H_{\mathrm{rxn,H_2}})\frac{dn_{\mathrm{H_2}}}{dt} - (\Delta H_{\mathrm{rxn,HK}})\frac{dn_{\mathrm{HK}}}{dt}. \qquad [4]$$

It is clear from examination of the two curves in Fig. 1 that the ratio of rates measured by the two methods is constant over the course of the reaction, which means that the ratio of Eq. [4] to Eq. [3] equals a constant. This constraint can be satisfied only if the hydrogenation rate and the net hemiketal formation rate are equal. This may be rationalized by assuming that the hemiketal formation is a fast preequilibrium step (Curtin-Hammett limit (8)). If the hydrogen addition step proceeds slowly by comparison, then the equilibrium is not perturbed. The rate at which the hemiketal reacts to form ethyl pyruvate is thus dictated by the rate at which ethyl pyruvate is consumed in the hydrogenation reaction:



[5]

These equations taken together provide the relationship between the global heat flow and the hydrogen uptake rate:

$$\dot{q} = (\Delta H_{\mathrm{rxn,H_2}} - \Delta H_{\mathrm{rxn,HK}})\frac{dn_{\mathrm{H_2}}}{dt}. \qquad [6]$$

Equation [6] gives the mathematical confirmation of what Fig. 1 demonstrated experimentally, which is that in this case *both* hydrogen uptake and reaction calorimetry methods accurately reflect the rate of ethyl pyruvate hydrogenation. The overall measured heat of reaction (determined by measuring the total area under the heat flow curve) will be lower than the thermodynamic value for ethyl pyruvate hydrogenation by the amount of heat initially required to establish this equilibrium and appears as the proportionality constant between the heat flow and the hydrogen uptake rate. In cases where such an equilibrium is not established, a discrepancy between heat flow and hydrogen uptake could be observed.

Reaction Calorimetric Monitoring of Hemiketal Formation

Observations of hemiketal formation using reaction calorimetry help to shed light on the reasons for differences between our work and the suggestion of Baiker and coworkers (5b) that the hemiketal equilibration in *n*-propanol is slow. Specifically, we show below that the presence of the Pt/Al_2O_3 catalyst is important in achieving rapid formation of the hemiketal in *n*-propanol, while their work did not address the role of the catalyst itself in the hemiketal reaction in this solvent.

The heat flow was monitored for experiments in which *either* cinchonidine *or* the Pt/Al_2O_3 catalyst was added to an ethyl pyruvate–*n*-propanol mixture. When similiar experiments are carried out in toluene (which cannot form a hemiketal), no heat flow is observed, suggesting that the heat release cannot be due to adsorption of the substrate on the catalyst or its solution interaction with cinchonidine. Different alcohol solvents give results similar to *n*-propanol, with the total area under the heat flow curve increasing in the order *i*-propanol < *n*-propanol < ethanol, consistent with their increasing propensity for hemiketal formation. For experiments carried out in the absence of the catalyst, the heat flow curve is consistent in each case with hemiketal formation as measured by UV spectroscopy (4,5b,9). When ethyl pyruvate hydrogenation is carried out following these mixing experiments, the total area under the heat flow curve gives overall heats of reaction which are 3–5 kcal/mol lower in alcohol solvents than those measured in toluene, as is expected from Eq. [6]. These observations confirm that the heat release observed in Figs. 2 and 3 may be attributed to the formation of the hemiketal.

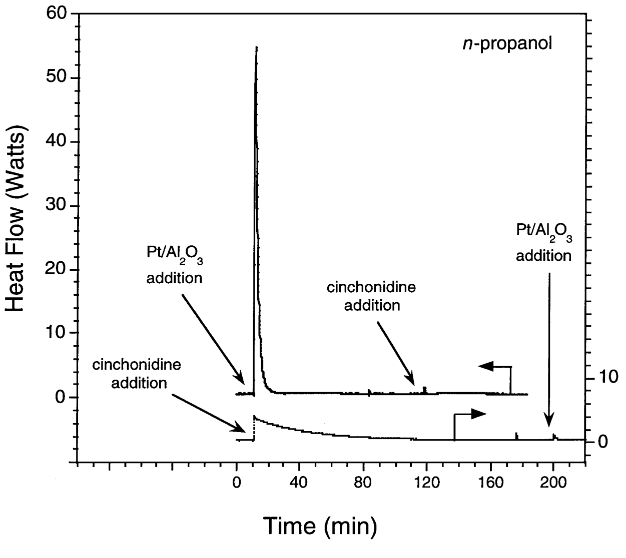


FIG. 2. Heat flow curves of ethyl pyruvate hemiketal formation in *n*-propanol at 283 K catalyzed by the addition of 2.5 g Pt/Al_2O_3 (1 wt% PMC) catalyst followed by 50 mg cinchonidine (top) or by 50 mg cinchonidine followed by 2.5 g Pt/Al_2O_3 (bottom).

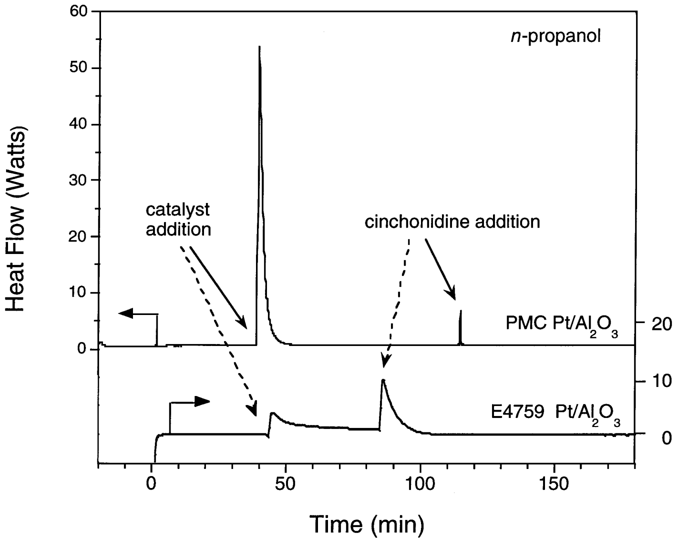


FIG. 3. Heat flow curves for the formation of hemiketal from ethyl pyruvate in *n*-propanol at 283 K catalyzed by the addition of Pt/Al_2O_3 followed by cinchonidine. Top curve: 2.5 g of 1 wt% Pt (PMC) addition followed by addition of 350 mg cinchonidine. Bottom curve: 0.5 g of 5 wt% Pt (E4759) followed by addition of 350 mg cinchonidine.

Figure 2 shows that the formation of the hemiketal proceeded much more rapidly in the presence of the PMC catalyst (with *no* cinchonidine) than it did in the presence of cinchonidine in the *absence* of the catalyst. The half-life for hemiketal equilibration was less than 2 min in the presence of the catalyst, and the process was 95% complete in less than 10 min. Addition of the modifier after this equilibration gave no further heat flow. When cinchonidine was added in the *absence* of the catalyst, the equilibration half-life increased by an order of magnitude and the total equilibration required more than 2 h.

Baiker and coworkers (4) noted that hemiketal formation is base-catalyzed and that N-bases such as cinchonidine are effective for this transformation. Grunwald(10) has shown, however, that hemiketal formation may be catalyzed by bases and also by acids. In the case shown in Fig. 2, the alumina support may serve as the acid catalyst for hemiketal formation. This accelerating role of the catalyst would not be noted in solvents such as ethanol where the cinchonidine-catalyzed process is inherently faster.

If alumina serves as an acid catalyst in the formation of hemiketal, it may be important to consider the properties of the particular alumina employed. In Fig. 3, we compare the heat flow trace of hemiketal formation rate of the 1 wt% Pt/Al_2O_3 PMC catalyst to that (on an equal Pt basis) of the 5 wt% Engelhard 4759 Pt/Al_2O_3 catalyst which was used in the hemiketal studies of Refs. (4) and (5b). Figure 3 shows that the rate was much slower in the presence of E4759; a greater than 10-fold difference in rate, compared to the PMC catalyst, is larger than could be accounted for simply by the difference in total amount of alumina in the two cases.

Addition of cinchonidine (seven times more than used in the experiment shown in Fig. 2) afforded completion of the process of hemiketal formation for the E4759 sample. Thus, it may be concluded that under some conditions the hemiketal equilibrium may indeed be perturbed by the ensuing hydrogenation step when the E4759 catalyst is used.

Combined Kinetic Measurements

This work shows that the use of multiple kinetic tools provides a powerful mechanistic approach to understanding complex reactions. Because they rely on different physical measurements to assess the same reaction parameter (reaction rate), the combination of hydrogen uptake and reaction calorimetry teaches us more about the hydrogenation reaction than either can alone. The agreement between the two methods during the initial transient period suggests that hemiketal formation plays no special role in the rising initial rate which was observed. This agreement also supports the suggestion that hydrogen is consumed principally in the main reaction and not in side reactions of impurities, unless such side reactions coincidentally exhibit rates and thermodynamic heats of reaction identical to the rate and heat of reaction of ethyl pyruvate and are not detectable in the product analysis.

The excellent reproducibility of the reaction calorimetric method (within 5% agreement) is also demonstrated in the hemiketal reactions shown in Figs. 2 and 3 (top curve, both figures). That the technique provides accurate data concerning reaction kinetics and energetics is well known in the pharmaceutical industry, where it was originally developed at Ciba-Geigy(11) for carrying out safety calculations in the design and scale-up of organic reactions such as catalytic hydrogenation (12). For example, reaction calorimetry is used to calculate the rate and extent of reactor temperature rise which may be expected under adiabatic reaction conditions designed to simulate the "worst-case scenario" of the unlikely event that a reactor loses all external cooling capability. The requirement for accuracy in such a measurement is evident, as are the potential consequences of error. More recently, the technique has been exploited for accurate kinetic measurement of intrinsic reaction properties under well-controlled conditions (6,13). Within this focus, reaction calorimetry can provide both fundamental mechanistic information as well as practical aid in efficient process research and development.

CONCLUSIONS

It is demonstrated both theoretically and experimentally that reaction calorimetry provides a valid and accurate measure of the rate of hydrogenation of α-keto esters in alcohol solvents, provided that a preequilibrium step between the substrate and its hemiketal is rapid on the time scale of the hydrogenation reaction. In this case, the sum of the rates of (hemiketal formation + hydrogenation) is proportional to the hydrogenation rate. The equilibrium is established by both acid and base catalysis. This work points out the advantages of using multiple independent measures of instantaneous reaction rate as a means of deriving mechanistic information about reaction processes.

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