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Transient behavior of the enantioselective hydrogenation of a hydroxymethylpyrone

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Various 2-pyrone derivatives are important intermediates in the synthesis of biologically active compounds. Pd chirally modified by cinchona alkaloids has a potential in the enantioselective hydrogenation of 4-hydroxy-6-methyl-2-pyrone to the corresponding 5,6-dihydropyrone. A study of various parameters (solvent, temperature, pressure, concentration) and catalyst systems (Pd/alumina and Pd/titania, modified by cinchonidine or cinchonine) revealed striking variations of the reaction rate and enantioselectivity with conversion. This transient behavior is interpreted by the effect of competitive adsorption and hydrogenation of the substrate and modifier.

Keywords: enantioselective, hydrogenation, cinchonidine, cinchonine, palladium, pyrone

1. Introduction

The asymmetric hydrogenation of substituted 2-pyrones has gained increasing interest in pharmaceutical chemistry, due to the importance of the structure of 2-pyrone and its partially hydrogenated derivatives in natural and synthetic biologically active compounds [1,2]. A homogeneous chiral Ru complex catalyst [3] affords up to 98% enantiomeric excess (ee) and good chemoselectivities to 5,6-dihydropyrones. A limitation of this catalyst is that the reaction does not stop at this stage and a mixture of *trans*- and *cis*-tetrahydropyrones forms when the substrate is not alkylated at the *C-3* position (e.g., 4-hydroxy-6-methyl-2-pyrone **1** in scheme 1). The heterogeneous enantioselective hydrogenation of **1** over the Raney Ni/tartaric acid/NaBr system yields the tetrahydro-derivative **3** with only 17% ee [2].

Pd is the only metal hydrogenation catalyst which can reduce, under mild conditions, **1** to the 5,6-dihydro-derivative **2** [4]. In the presence of cinchonidine (CD) the hydrogenation provides up to 85% ee to the (S)-enantiomer [5]. Unfortunately, the reaction is very slow and accompanied by the hydrogenation of the alkaloid modifier. Here we report an interesting feature of this new process, the transient behavior characterized by unusually strong changes in the reaction rate and enantioselectivity.

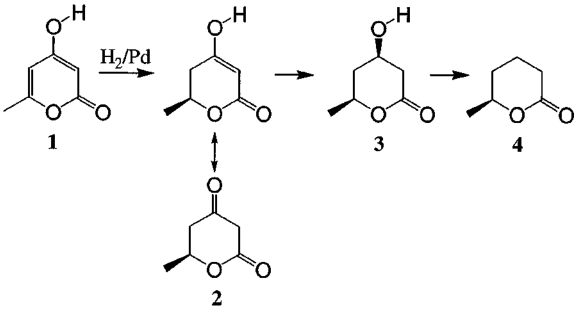
2. Methods

A 5 wt% Pd/alumina (Engelhard 40692, metal dispersion 0.21, determined by TEM) and a 5 wt% Pd/titania (metal dispersion 0.18, determined by hydrogen chemisorption) were used for the reactions. The latter was prepared by neutralizing an aqueous H_2PdCl_4 solution with Na_2CO_3 in the presence of TiO_2 (P 25, Degussa, 60 m^2/g).

4-hydroxy-6-methyl-2-pyrone (**1**, Fluka 98%) was purified before use by column chromatography (silica gel 60, 40–63 μm, hexane/ethyl acetate 1/1) and recrystallization. All solvents were distilled before use. Cinchonidine (CD) and cinchonine (CN) (both from Fluka) were used as received.

A magnetically stirred 100 ml glass reactor was used for the reactions at 1 bar. High-pressure experiments were carried out in a 100 ml stainless-steel autoclave equipped with a 50 ml glass liner and a Teflon cap and stirrer. The pressure was held at a constant value by a computerized constant volume–constant pressure control unit (Büchi BPC 6002). Under standard conditions, 40 mg catalyst in 20 ml solvent was pretreated with H_2 under reaction pressure for 5 min, at room temperature. Then the appropriate amount of modifier and 300 mg **1** were added and the reaction was started.

Conversion and selectivity were determined by an HP 6890 gas chromatograph using a fused silica capillary column (HP-5). For the separation of enantiomers a cyclosil



Scheme 1. Consecutive reaction steps in the hydrogenation of 4-hydroxy-6-methyl-2-pyrone (**1**).

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CB (J&W) column was used after methylation of **2**. Derivatization with trimethylorthoformate in the presence of an acidic ion exchange resin (Diaion RCP1 60H) was carried out in methanol at 50 °C for 15 h. The products **2**, **3** and **4** (scheme 1) were identified by NMR and GC-MS analysis, and optical rotation. The reaction rate was calculated by differentiation of fitted experimental conversion–time curves. The incremental ee values (Δee) were calculated from two subsequent ee values.

3. Results

Hydrogenation of the hydroxymethylpyrone **1** with Pd/alumina in isopropanol is a facile reaction even at ambient conditions, affording the corresponding dihydroderivative **2** with higher than 98% chemoselectivity. In the presence of CD the chemoselectivity was still high (>97%), but the conversion rate diminished remarkably (figure 1(a)). The initial reaction rates without CD and with 3 mg CD were 190 and 3 mmol/h g_{cat}, respectively. A considerable deactivation of Pd (by a factor of 4–140) in the presence of a cinchona, vinca or ephedra alkaloid seems to be a general feature of chirally modified Pd [6–8]. However, the sudden rate enhancement at medium conversions is rather unusual. The unprecedented behavior becomes more evident when the reaction rate derived from the differentiated conversion–time curve is plotted for the reaction carried out with 3 mg CD, as shown in figure 1(b). Strikingly, the conversion rate of **1** showed a prominent maximum after about 8 h. A small but significant enhancement in the incremental ee (3%) in the first 5 h was followed by a continuous decrease to zero at less than 80% conversion (24 h). The results shown in figure 1(a) clearly indicate that the variations in rate and enantioselectivity strongly depend on the amount of alkaloid modifier. With increasing CD concentration the range of unusual rate acceleration is shifted to longer reaction times (figure 1(a)).

The unusual transient behavior was observed irrespective of the solvent, catalyst or reaction conditions. Some other examples using Pd/titania and CN in water are shown in figure 2(a). Under these conditions ee increased initially

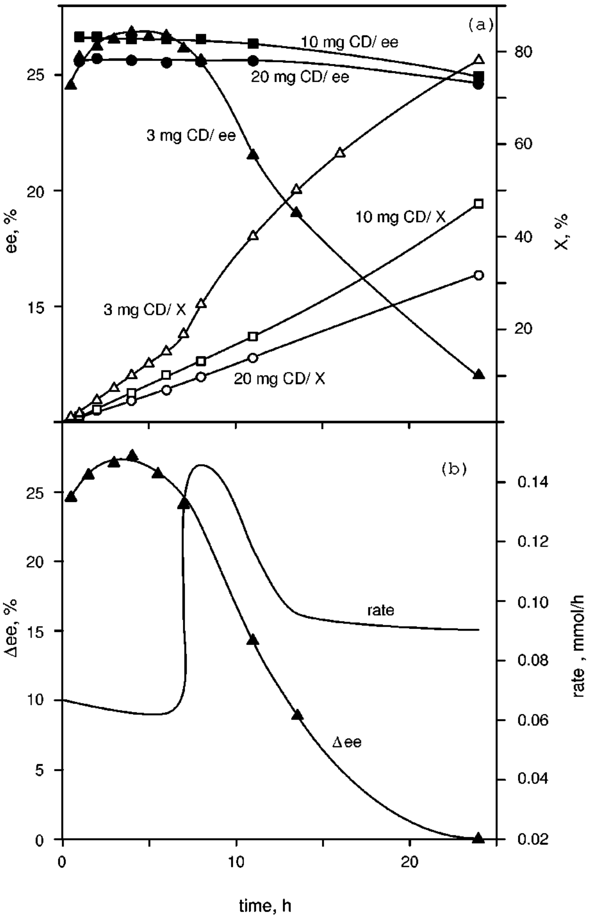


Figure 1. (a) Influence of the amount of CD on the conversion (X) of **1** and enantiomeric excess (ee) in isopropanol. (b) Reaction rate and incremental ee for the hydrogenation with 3 mg CD. Conditions: 300 mg **1**, 40 mg 5 wt% Pd/alumina, 20 ml isopropanol, 1 bar, 24 °C, chemoselectivity >97%.

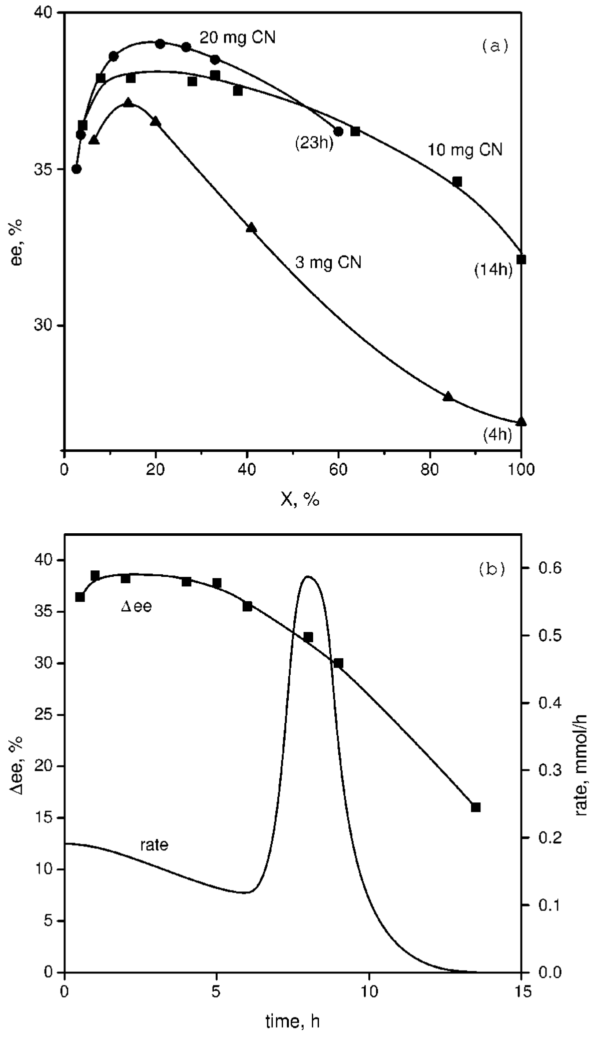


Figure 2. (a) Change of the enantiomeric excess (ee) with conversion (X) of **1** in water, as a function of the amount of CN. (b) Reaction rate and incremental ee for the hydrogenation with 10 mg CN. Conditions: 300 mg **1**, 40 mg 5 wt% Pd/titania, 20 ml water, 1 bar, 24 °C, chemoselectivity >92%.

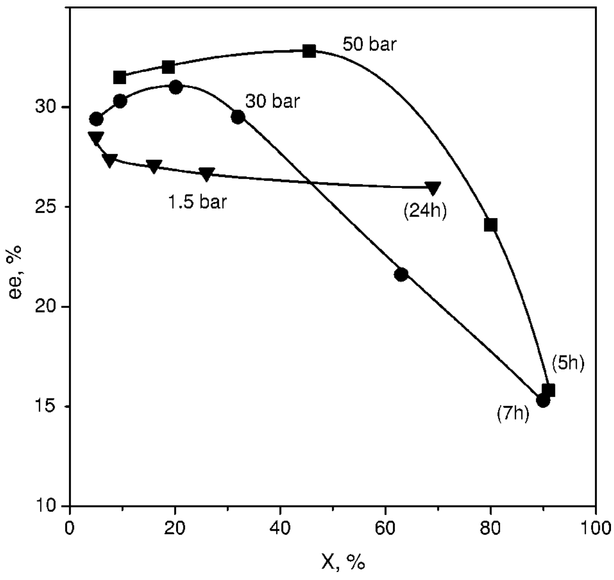


Figure 3. Change of the enantiomeric excess (ee) with conversion (X) of **1** as a function of pressure in acetic acid. Conditions: 300 mg **1**, 40 mg 5 wt% Pd/alumina, 10 mg CD, 20 ml acetic acid, 24 °C.

up to 10–20% conversion at all modifier concentrations. Besides, the incremental ee did not drop to zero even at full conversion of **1** (figure 2(b)). In the reaction carried out with 10 mg CN the rate decreased in the first 6 h parallel to the decrease in substrate concentration. At this point, corresponding to 28% conversion, the rate of substrate conversion suddenly increased about five times and then declined to zero at full conversion. Although changes in incremental ee were extensive in the range of the sudden rate acceleration, no clear correlation between rate and ee could be derived.

We proved independently that the hydrogenation rate of **1** was not affected by mass transport limitation. Although accuracy of the differential curves in figures 1(b) and 2(b) could be improved by taking more samples during reaction, the experimental results unambiguously indicate a striking rate acceleration after a relatively long initial “normal” behavior accompanied with a considerable loss of enantioselectivity. This change cannot be considered as a typical initial transient period [9,10].

The conversion rate of **1** increased with increasing pressure, as expected, but the enantioselectivity improved only in acetic acid, as shown in figure 3. At low pressure the ee decreased very slowly with conversion, while at higher pressure the ee increased until a maximum was reached at 20–40% conversion and then dropped to about one-half at 90% conversion. Application of higher amounts of CD (20–40 mg, instead of 10 mg) at 50 bar did not result in higher ee, but the decline of ee started at higher conversion (up to 70%). High pressure favoured the consecutive hydrogenation of **2** to **3** and **4** (scheme 1). For example, at 50 bar the chemoselectivity to **2** dropped to 65% at 90% conversion [5].

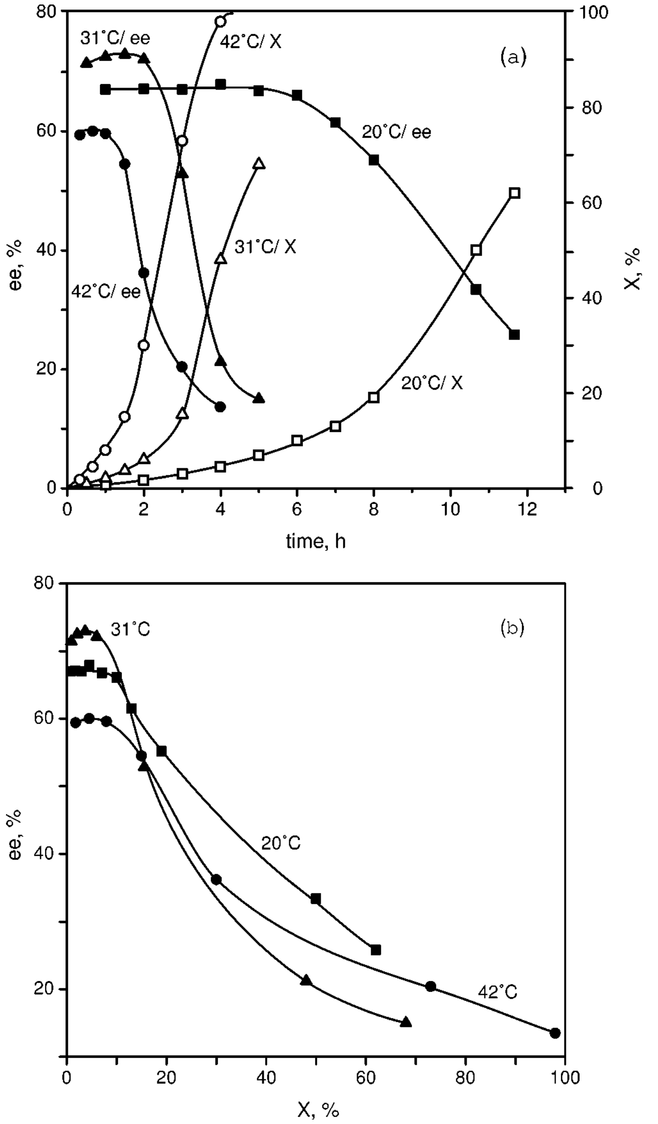
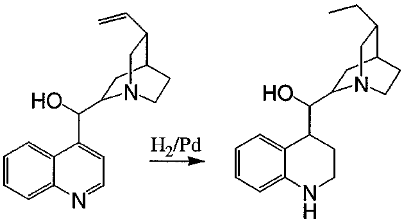


Figure 4. (a) Effect of temperature on the transient behavior of the hydrogenation of **1** in acetonitrile. (b) Dependence of enantiomeric excess (ee) on conversion (X) of **1**. Conditions: 150 mg **1**, 20 mg 5 wt% Pd/titania, 3 mg CD, 10 ml acetonitrile (0.25 vol% water), 1 bar.

A small increase in enantioselectivity could be achieved in all solvents by increasing the temperature to 30–40 °C. The temperature effect was the highest in acetonitrile (figure 4(a)), with a maximum in ee at around 30 °C. An interesting effect of temperature variation is that the first period of high and almost constant ee is shortened considerably with increasing temperature. Replotting the ee as a function of conversion (figure 4(b)) revealed that in fact the ee dropped always at about the same conversion of **1** (ca. 10%).

4. Discussion

The parameter study of the enantioselective hydrogenation of **1** to **2** over cinchona-modified Pd is characterized by remarkable variations of reaction rate and enantioselectivity with conversion. This unprecedented behavior is strongly influenced by the reaction conditions (solvent, temperature,



Scheme 2. Major product in the partial hydrogenation of cinchonidine (CD) over Pd.

pressure and modifier concentration) and the catalyst system applied. We propose that this behavior can be traced to the competitive adsorption and hydrogenation of the substrate and chiral modifier.

Applying 3 mg CD under standard conditions, the modifier : substrate molar ratio is 1 : 230. Even at this low modifier concentration the initial rate of the hydrogenation of **1** decreased by a factor of 63, compared to the rate over unmodified Pd. This relationship indicates that either the adsorption of CD on Pd under reaction conditions is considerably stronger than that of the substrate or the substrate–modifier interaction on the metal surface reduces the reactivity of the C=C double bond in **1**. Hydrogenations using either CD or 10,11-dihydrocinchonidine afforded very similar results, indicating that the influence of the vinyl group on the rate and ee is negligible. The missing effect is likely due to the rapid saturation of the C=C bond at the beginning of the reaction. NMR analysis revealed that during reaction CD is hydrogenated with a significant rate. Beside the saturation of the vinyl group, the quinoline ring system is also hydrogenated. At medium conversions of CD (ca. 60%) saturation of the heteroaromatic ring is more than 20 times faster than that of the unfunctionalized aromatic ring (scheme 2). The flat aromatic ring system of CD is considered as the "anchoring moiety" of the modifier on Pd [11,12] and Pt [13,14]. Saturation of the quinoline rings leads to a considerable weakening of the adsorption of the modifier and a complete loss of enantio-differentiation [5]. It has been shown [15] that Pd is the most active catalyst among the Pt metals in the hydrogenation of the quinoline ring system of CD.

On the basis of the above considerations we can explain the variation of rate and enantioselectivity during hydrogenation of **1**. The changes with time or conversion can be described by more or less clearly distinguishable periods. In the initial period the surface modifier concentration is high and the conversion of the substrate is slow. The ee may be constant or increases slightly, depending on the reaction conditions (figures 1–4). During this period also the modifier is hydrogenated slowly and replaced by CD from the solution as the unreduced alkaloid adsorbs more strongly. With decreasing CD concentration in solution the surface concentration of CD decreases. This period is indicated by a slow decrease of ee, in particular the incremental ee, with time or conversion. Decreasing CD concentration favors the adsorption and hydrogenation of **1**. At a certain CD concentration these changes result in a strong rate enhancement which may be accompanied by a rapid loss of enantioselectivity (figures 1(b) and 2(b)). In the final period the rate declines rapidly due to a decrease of the concentration of **1**. The relative rate of the hydrogenation of CD and **1** depends on the reaction conditions, which explains the substantial variations illustrated in figures 1–4.

It is interesting to compare the influence of pressure and temperature on the transient behavior of the reaction. With increasing pressure the relative rate of hydrogenation of CD and **1** changes. Accordingly, the length of the first period in conversion, characterized by high ee, varies in a broad range (figure 3). In contrast, the significant drop in ee and the accompanying rate enhancement occurred always at around 10% conversion, independent of the temperature (figure 4(b)). Apparently, the relative rate of the hydrogenation of substrate and modifier was independent of the temperature in the investigated range 20–42 °C.

5. Conclusions

The enantioselective hydrogenation of 4-hydroxy-6-methyl-2-pyrone (**1**) over cinchona-modified Pd catalysts is complicated by the weak adsorption and slow hydrogenation of the substrate, and the competing hydrogenation of the chiral modifier, leading to a successive loss of enantio-differentiation. These competing reactions render the interpretation of the effects of various reaction parameters difficult. It is hoped that optimization of the reaction conditions will afford high ee at high conversion, though a better solution may be to find a more stable modifier for Pd.

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