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PRIORITY COMMUNICATION

Enantioselective Hydrogenation of Ketopantolactone: Effect of Stereospecific Product Crystallization during Reaction

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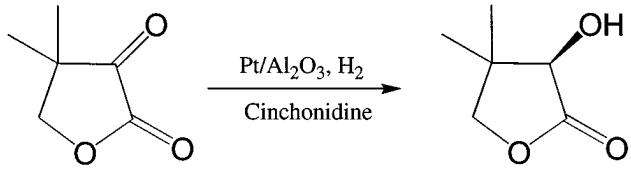
The hydrogenation of ketopantolactone over cinchonidine-modified Pt/alumina has been reinvestigated, focussing on the misleading effect of stereospecific product crystallization during reaction at medium to high conversions. The appropriate choice of reaction conditions afforded 91.6 ± 0.5% ee to *R*-(-)-pantolactone.

Key Words: **enantioselective; hydrogenation; Pt/alumina; ketopantolactone; cinchonidine.**



SCHEME 1

INTRODUCTION

(*R*)-pantolactone (*R*-PL) is an intermediate in the synthesis of pantothenic acid (1). Oxidation of PL to ketopantolactone (KPL) followed by the enantioselective hydrogenation of KPL to *R*-PL provides an alternative route to the presently applied three-step resolution process via the open chain hydroxy-acid form. In a previous paper (2) we reported the hydrogenation of KPL over a cinchonidine-modified Pt/Al_2O_3 catalyst (Scheme 1), affording up to 79% enantiomeric excess (ee), and we proposed a mechanistic model for the reaction. An interesting feature of the reaction was the rather poor reproducibility of the results noticed under certain reaction conditions (2) and no feasible explanation for the unusually high standard deviation could be found. In a continuation of our effort to get more insight into this industrially important reaction we have recognized that the low solubility of the product in apolar solvents resulting in stereospecific crystallization during reaction can severely distort the observed ee. This effect will be discussed briefly below.

METHODS

Ketopantolactone (KPL, Hoffmann-La Roche) was dried by azeotropic distillation with toluene. Cinchonidine (CD, >98%, Fluka) and toluene (>99.7%, Riedel-de Haën) were used without further purification. A sieve fraction of 50–100 μm of a 5 wt% Pt/Al_2O_3 catalyst (Engelhard 4759) was used for all experiments. The catalyst was pretreated before use in a fixed bed reactor by flushing with 12 ml min^{-1} nitrogen at 673 K for 30 min, followed by a reductive treatment in H_2 for 90 min at the same temperature. After cooling to room temperature in H_2, the catalyst was transferred to the reactor under argon. The metal dispersion after heat treatment was 0.27 as calculated from TEM images (2).

The hydrogenation of KPL was carried out in a 100-ml stainless steel autoclave (Parr) equipped with mechanical mixing at a frequency of 700 min^{-1}. It was shown that the rate of hydrogen uptake was independent of the mixing frequency above 500 min^{-1}. The reaction temperature was monitored by a temperature sensor in the solution. The pressure was held at 70 bar by a computerized constant volume-constant pressure equipment (Büchi bpc 9901). Conversion and ee were determined by an HP 5890A gas chromatograph (GC) with a chiral WCOT cyclodextrin-β-2,3,6-M-19 (Chrompack) capillary column. The estimated standard deviation of the GC method was ±0.5%. Before analysis the reaction mixture was diluted with ethanol in order to redissolve the product.

The reference experiment shown in Fig. 2 has been carried out in a magnetically mixed 100-ml autoclave (Baskerville) equipped with a 50-ml glass liner and PTFE cover (2). The reaction was followed by taking samples, filtering off the catalyst and analyzing the liquid with GC.

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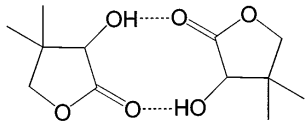
RESULTS AND DISCUSSION

We have shown (2) that the enantiodifferentiation in the hydrogenation of KPL over the Pt-CD system is favored by applying an apolar solvent (toluene) and low temperature around 280 K. Recently we have realized that under these conditions the solubility of the product is rather low and a fraction of the product can deposit on the catalyst. Unfortunately, this uncontrolled crystallization of PL was not observed when taking small samples from the reaction mixture, filtering off the catalyst on a micro filter and analyzing the solution with GC (2). Except at low conversions, the stereospecific crystallization of PL can falsify the ee. This effect is illustrated in Fig. 1. Under the conditions applied the ee increased considerably with ascending conversion, but this correlation could be observed unequivocally only when the reaction mixture was diluted with a polar solvent (e.g., ethanol) and the product crystals were redissolved before analysis. In case of direct analysis of the liquid phase the ee did not exceed 80% and its value was poorly reproducible. On the other hand, the ee in the crystals, which dropped out during reaction, was 92–98% to (*R*)-PL, depending on the extent of crystallization.

It has been shown by IR and NMR spectroscopy (3) that PL forms dimers in CCl_4. The dimer was the dominant form at concentrations above 0.03 *M* and at ambient temperature



PL dimer

SCHEME 2

or below. The structure of the cyclic dimer, stabilized by two hydrogen bonds, is illustrated in Scheme 2. It has also been proved that no selective association exists between the enantiomers.

Accordingly, the stereospecific crystallization during the enantioselective hydrogenation in toluene seems to be due to the different solubilities of the *(R-R)*, *(R-S)*, and *(S-S)* diastereomers (dimers). In general, significant product crystallization and change of *R/S* ratio in solution can be expected (i) in apolar solvents (in polar solvent the association with the solvent molecules can compete with the dimerization, and the solubility of PL is higher), (ii) at low temperature (due to low PL solubility and high dimerization constant), and (iii) at high conversions in concentrated solutions.

Figure 2 illustrates the real and the originally published (distorted) ee in toluene as a function of reaction temperature. When the analysis was performed appropriately, the ee increased with decreasing temperature without attaining a maximum till 265 K; lower temperature could not be used in this reactor.

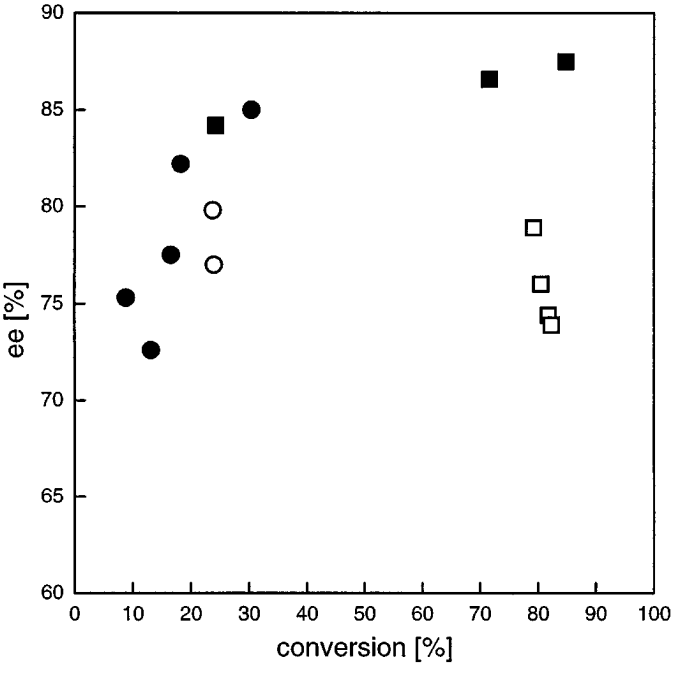


FIG. 1. Influence of stereospecific product crystallization on the ee as a function of KPL conversion. Filled symbols represent the composition of the total reaction mixture (PL crystals redissolved with ethanol), open symbols indicate the composition of the liquid. Conditions: ○, ●: 21 mmol KPL, 63 mg catalyst, 0.14 μmol CD, 50 ml toluene, 70 bar, 264 K; □, ■ 40 mmol KPL, 107 mg catalyst, 0.66 μmol CD, 50 ml toluene, 70 bar, 268 K.

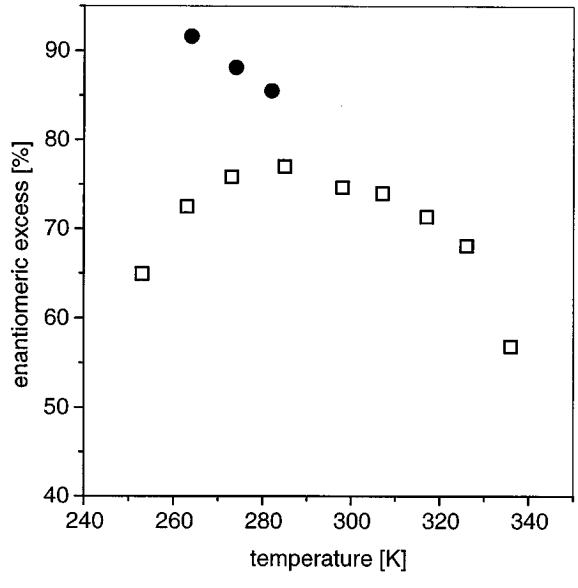


FIG. 2. Influence of temperature and stereospecific product crystallization on the ee. Filled symbols represent the composition of the total reaction mixture, open symbols indicate the composition of the liquid. Conditions: ● 60 mg catalyst, 0.054 μmol CD, 16 mmol KPL, 70 bar, toluene, mechanically mixed reactor; □: 150 mg catalyst, 0.067 mmol CD, 3.9 mmol KPL, 70 bar, toluene, magnetically mixed reactor (2).

Similarly, the formerly observed maximum in ee (less than 80%) as a function of CD concentration (Fig. 5 in (2)) was falsified by PL crystallization. After appropriate analysis of the reaction mixture a maximum of 90% ee was obtained at an unusually low CD concentration of 2.7×10^{-6} *M* at 268 K in toluene. Note the corresponding very low modifier/surface Pt atoms ratio of 0.019 and the high substrate/modifier molar ratio of 237'000.

Re-optimization of the crucial reaction parameters (pressure, temperature, concentrations) afforded $91.6 \pm 0.5\%$ ee at 60% conversion (16 mmol KPL, 60 mg catalyst, 0.14 μmol CD, 50 ml toluene, 70 bar, 264 K, 0.5 h). For comparison, the best ee achieved in this reaction with a homogeneous rhodium-complex catalyst is 99% (4).

CONCLUSIONS

More than 90% ee could be achieved in the Pt-catalyzed enantioselective hydrogenation of KPL to *(R)*-PL, using only a few ppm CD as chiral modifier. The excellent ee and the very low modifier/reactant ratio offer a synthetic potential for the procedure. As yet only the hydrogenation of ethyl pyruvate provided slightly better ee over a chirally modified Pt (5). It seems that the key to further improvement in enantioselectivity is to find a good compromise in solvent polarity and reaction temperature for the contradictory requirements of enantiodifferentiation and PL solubility.

ACKNOWLEDGMENT

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