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Conversion Dependence of Enantioselective Hydrogenation of Methyl Acetoacetate with Modified Ni–SiO_2 Catalyst

Gross and Rys (*1*) reported that the optical activity of methyl 3-hydroxybutyrate(MHB) varied with the extent of conversion in the enantioselective hydrogenation of methyl acetoacetate (MAA) on modified Raney nickel catalysts. On the other hand, Klabunovskii (*2*) has proposed a reaction mechanism which suggests that the optical activity is independent of conversion. Investigations of the relation between conversion and optical activity of product are important in order to obtain meaningful comparison of the enantioselectivity of various catalysts under different reaction conditions, for analysis of the mechanism and also for a search for conditions which will increase the optical activity.

In a previous paper (*3*), we described the preparation conditions for a Ni–silica(1 : 1) catalyst which has high and reproducible enantioselectivity and also high hydrogenation activity and which is a convenient material for investigation of the mechanism of the enantioselective hydrogenation on modified nickel catalysts. Prior to the kinetic analysis of the hydrogenation under mild reaction conditions, we studied the conversion dependence of optical activity using the Ni-silica catalyst.

A mixture of $Ni(NO_3)_2 \cdot 6H_2O$ (10 g) and a silica (Silica gel No. 1, Nakarai Chemicals, 60–200 mesh, 600 m^2/g) in 50 ml of distilled water was degassed for 1 min under vacuum, and then gently stirred for 15 min at 75°C. A solution of Na_2CO_3 (3.7 g) in 25 ml of distilled water at 75°C was added to the mixture using a syringe over a period of 1 min, with vigorous stirring. After 1 min, the precipitate was aged for 15 min at the same temperature with gentle stirring. The precipitate was then filtered, washed three times with portions of 50 ml of warm distilled water, and dried at 110°C for 24 h. Samples for replicated preparation were mixed, ground into a powder, and stored. For each of the subsequent experiments, a fresh catalyst was prepared by reducing 2 g of the stored sample in a hydrogen stream at a flow rate of 8 liters/h and at a temperature of 500°C, for 1 h.

Modification of the catalyst was carried out at 83°C by soaking freshly reduced catalyst in a 1.6% aqueous solution of (*R*,*R*)-tartaric acid (pH 5.1) for 1 h with occasional shaking, according to the method described by Izumi *et al.* (*4*). After modification, the catalyst was rinsed once with distilled water, twice with methanol, and then once with the solvent used for the reaction (10-ml portion of each). When benzene was used as a solvent, the catalyst was not rinsed with benzene but with methanol.

Hydrogenations were carried out at 60°C under a hydrogen pressure of 10 kg/cm^2 in a 50-ml glass autoclave (TEM-U-50, Taiatsu Glass Industry Co.) equipped with a vigorous stirring system. Twenty milliliters of MAA or, for smaller concentrations, a mixture of MAA and various solvents are used for the experiments. The MAA and solvents were dried and distilled before use.

Samples taken from the reaction mixture at various times were filtered and distilled under reduced pressure. Conversion during the reaction and purity of the distilled product were determined using GLC (Shimadzu model 4APT) with a 2-m column of 20% PEG 20M on Celite 545. The optical rotation (α_D) of the distilled product was determined with a Union PM-101 automatic digital polarimeter at 20°C in a 0.1-dm cell. Values of α_D for the products obtained from

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the reactions with lower conversions were corrected on the basis of separately determined dependence of α_D on the concentration of MHB in MAA. The optical yield (OY) of (−)-MHB was calculated from the observed α_D value according to the equation OY = (α_D/22.95) × 100 (*5*).

Figure 1 shows that OY of (−)-MHB is dependent on conversion as in the case of Raney-Ni catalysts under 90 atm H_2 (*1*). Maximum OY was attained at around 50% conversion. In the early stages of the reaction without solvent, or in ethyl acetate, OY increases with conversion, whereas, in the presence of a small amount of benzene or methanol, it is almost constant. The initial increase in OY diminishes when catalyst is left for 30 min under reaction conditions immediately before starting the reaction. On the other hand, OY in the final stages of the reaction decreases with increase in conversion for all the reactions examined.

The increase in OY with conversion in the early stages of the reaction can be explained by the difference in induction periods between the reactions on selective and nonselective sites of the catalyst. In fact, we observed a longer induction period for hydrogenation on modified than on unmodified catalysts. The use of benzene as a solvent instead of ethyl acetate resulted in a considerable decrease in initial hydrogenation rate and an increase in OY. This means that an unmodified site is deactivated by strong competitive adsorption of benzene, which decreases the difference between the reaction rates on selective and on nonselective sites, and so suppresses the initial increase in OY with conversion.

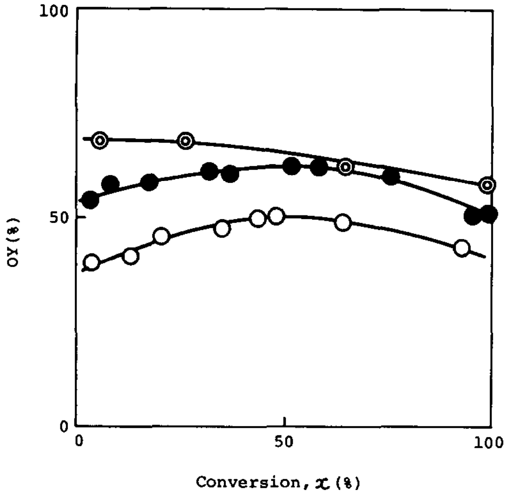

FIG. 1. Optical yield of (−)-MHB vs conversion of the reaction on modified Ni–SiO_2 catalyst. ○, 50% MAA in ethyl acetate; ●, 100% MAA; ◎, 80% MAA in benzene.

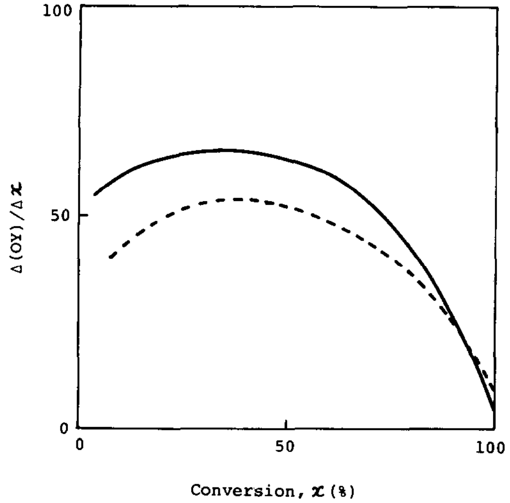

FIG. 2. Differential optical yield of (−)-MHB calculated from the data in Fig. 1. ——, 100% MAA; ---, 50% MAA in ethyl acetate.

A change in OY at an early stage of the reaction does not significantly affect the final value of OY. On the other hand, a 5% decrease in OY during an increase in conversion from 90 to 100% corresponds to the production of almost racemic MHB at the stage of the reaction, as shown in Fig. 2, where the ordinate represents the optical yield of (−)-MHB for the fresh product. No racemization occurs under the reaction conditions used in this work. The remarkable decrease in enantioselectivity in the last stage of the reaction may be due to (i) a decrease in the amount of selective sites with the progress of the reaction, or (ii) a decrease in reaction rate on selective relative to nonselective sites. In the case of (i), OY should decrease for repeated runs. However, OY does not change with reused catalyst; the values of OY obtained for a sequential series runs are 36.1, 37.1, 35.6, and 36.2%, respectively. Gross and Rys (*1*) and Tatsumi (*6*) have reported similar results for modified Raney-Ni catalysts. Therefore, it seems that the number of selective sites does not change as the reaction proceeds. Consequently, the decrease in OY in the later stages of reaction can be explained only by a decrease in the reaction rate on the selective relative to the nonselective sites.

Hubbell and Rys (*7*) suggested that competitive adsorption of reactants and products is one of the factors causing the decrease in specificity with conversion. Similarly Neupokoev *et al.* (*8*) suggested a modifying action of the product which accumulates during the reaction with a modified Raney-Co catalyst. However, these suggestions were not confirmed by an experimental study. Figure 3 shows the effect of the concentration of (−)-MHB which was previously added to the reaction mixture on the optical selectivity of the reaction.

Thus, when 5 ml of MAA was hydrogenated in 10 ml of ethyl acetate and 5 ml of MHB with varying percentage concentration of (−)-isomer, the increasing percentage of (−)-isomer resulted in MHB having a lower optical activity. This observation supports the idea that (−)-isomer in the product inhibits the reaction on selective sites and so causes a decrease in OY of the final (−)-MHB. Since the (−)-isomer is predominantly produced on selective sites, there is probably a strong interaction of (−)-isomer with the modifier on the selective sites, which inhibits adsorption of the reactant. It is possible to explain the result shown in Fig. 3 by assuming that both (+)- and (−)-isomers inhibit the reaction on nonselective sites, while only (−)-isomer inhibits the reaction on selective sites. However, this idea is in conflict with the result shown in Fig. 1; the reaction rate decreases with conversion to a greater extent on the selective rather than on the nonselective sites.

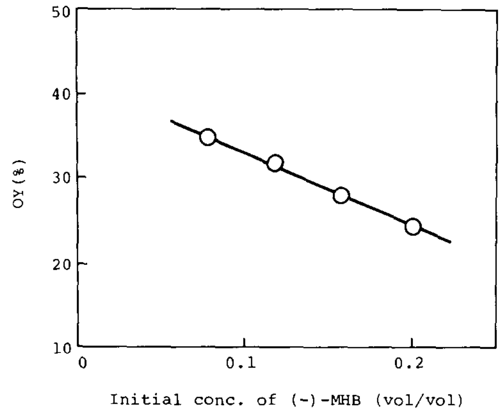

FIG. 3. Effect of the amount of previously added (−)-MHB on the optical purity of the product.

In the previous paper (*9*), we showed that OY for (−)-MHB at 100% conversion increases linearly with increasing initial concentration of MAA. A similar result was obtained for the initial value of OY for (−)-MHB at about 15% conversion, where the inhibitory effect of product can be neglected; the initial values of OY were 29.3, 37.5, 41.2, and 54.2% for 25, 50, 75, and 100% of the initial concentrations of MAA, respectively. This shows that the influence of reduction in concentration of MAA with increasing conversion is another factor causing the decrease in the optical activity of fresh product.

This result, showing that the concentration of MAA affects the optical activity of the product, suggests that the reaction rates on selective and on nonselective sites depend differently on the concentration of MAA. This point will be discussed in detail later.

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