The Enantioface-differentiating (Asymmetric) Hydrogenation of the C=O Double Bond with Modified Raney Nickel. XXX. The Temperature Dependency of the Optical Yield

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The effect of the reaction temperature upon the optical yield was studied in the liquid-phase enantioface-differentiating hydrogenation of methyl acetoacetate with various modified Raney nickel catalysts (MRNi) under an atmospheric pressure of hydrogen. The results obtained are as follows: 1) the enantiomer produced in excess in the reactions with (*S*)-alanine-, (*S*)-2-aminobutyric acid-, and (*S*)-valine-MRNi, changed from (*S*)-(+) to (*R*)-(−) with the elevation in the reaction temperature (The temperature, T_0, at which the direction of the differentiation changed decreased in the order of alanine-, 2-aminobutyric acid-, and valine-MRNi. The origin of T_0 is expected to be steric and polar effects that act in opposite directions for the differentiation of the enantioface.), and 2) the temperature dependence of the optical yield with (*R*,*R*)-tartaric acid- and (*S*)-lactic acid-MRNi differed from that with other catalysts. The OH group of the modifying reagent is expected to play an important role in enantioface-differentiation by making a hydrogen bond with the substrate.

The Raney nickel catalyst modified with an optically active substance (MRNi) is an intensively studied catalyst for the enantioface-differentiating hydrogenation of the β-keto ester. In a preceeding communication, it has been reported that the interaction of a substrate with a modifying reagent on the catalyst surface was the essential step in the enantioface-differentiation.[1]

To gain an insight into the origin of the inter-molecular forces participating the enantioface-differentiating process, the effect of reaction temperatures on the optical yield was investigated.

Results and Discussion

The enantioface-differentiating hydrogenation of methyl acetoacetate (MAA) to methyl 3-hydroxybutyrate (MHB) over various MRNi was carried out. As is shown in Fig. 1, each modifying reagent had a characteristic temperature, T_0, at which an optical yield of zero was observed.

The temperature dependence of the ratio of enantiomers produced (C_R/C_S) has generally been discussed based on the following relation:

$$\ln(C_R/C_S) = \Delta\Delta S^*/R - \Delta\Delta H^*/RT.$$

The existence of T_0 may be explained by the contribution of the $\Delta\Delta S^*$ term. If the enantioface-differentiation of MRNi were expressed by the above equation, the linear relationship of $\ln(C_R/C_S)$ toward $1/T$ should be expected. However, none of our results gave a linear relationship between $\ln(C_R/C_S)$ and $1/T$, as is shown in Fig. 2. This fact indicates that it is difficult to explain the result by a simple energetic correlation.

As for the (*S*)-monoamino monocarboxylic acid-MRNi in Fig. 1, the optical yields increase in the direction of an excess of (*R*)-(−)-enantiomer as the reaction temperatures increase. The temperatures, T_0, for valine-, 2-aminobutyric acid-, and alanine-MRNi were at 30—40 °C, 40—50 °C, and 50—60 °C respectively.

Figure 3 shows the temperature dependence of the optical yield in the enantioface-differentiating hydrogenation of methyl acetoacetate and butyl acetoacetate with (*S*)-valine-MRNi. T_0 also varies in accordance with the ester moiety of the substrate, and T_0 for methyl acetoacetate is higher than that for butyl acetoacetate. These results show that the temperature, T_0, becomes higher as the chain length of both the alkyl substituent of the modifying reagent and the ester moiety of the substrate decrease.

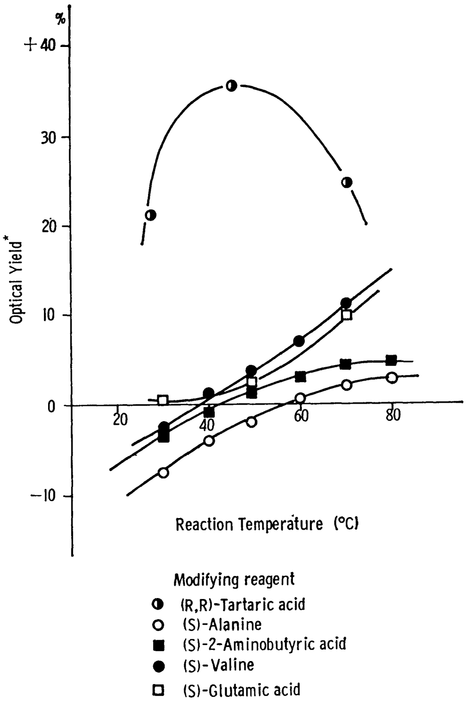

Fig. 1. Effect of modifying reagent on the temperature dependence of optical yield.
*The sign of optical yield is taken as + in the case of an excess of (*R*)-(−)-enantiomer.

As the main difference in alkyl substituents is their bulkiness, the above facts may indicate that the steric interaction between a modifying reagent and a substrate is one of the factors in enantioface-differentiation.

As is shown in Fig. 1, the dependence of the optical yield on the reaction temperature for (*R*,*R*)-tartaric acid-MRNi is different from that for amino acid-MRNi.

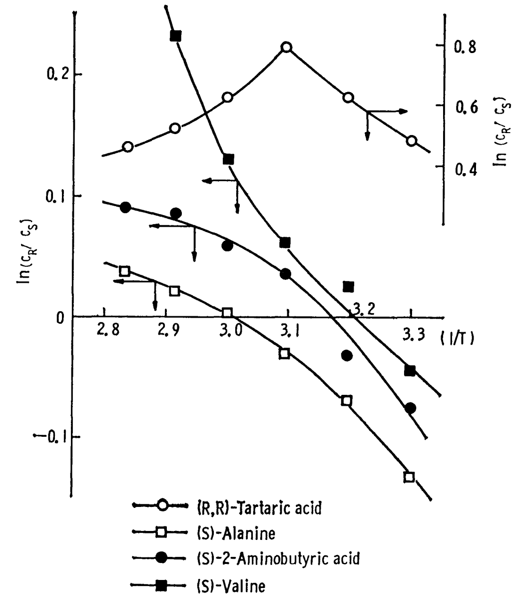

Fig. 2. Plots of $\ln(C_R/C_S)$ against $1/T$.

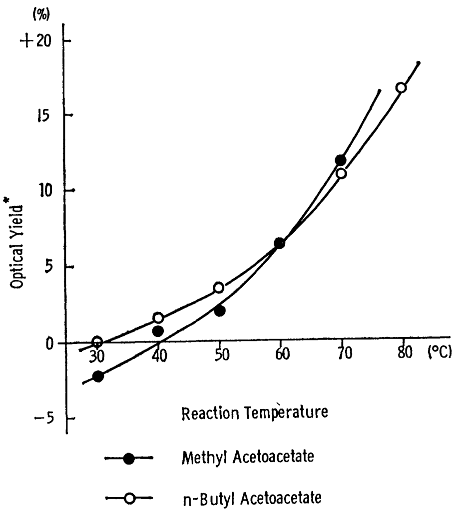

Fig. 3. Effect of ester group in substrate on the temperature dependence of optical yield.
*The sign of optical yield is taken as + in the case of an excess of (*R*)-(−)-enantiomer.

The maximum optical yield is observed at around 50 °C, and the optical yield decreases both above and below this temperature.

Taking into consideration the fact that this temperatue of 50 °C corresponds to the initial temperature of the dissociation of the hydrogen bond, the convex shape of the temperature dependence of the optical yield for (*R*,*R*)-tartaric acid-MRNi can be interpreted by the idea that the OH groups in the modifying reagent participate predominantly in enantioface-differentiation by making a hydrogen bond with the substrate up to the temperature at which the hydrogen bond disappears.

In order to investigate the role of the hydroxy group in α-hydroxy acid-MRNi in enantioface-differentiation, hydrogenations with catalysts modified with α-hydroxy carboxylic acids and their *O*-methyl derivatives were carried out. The results are listed in Table 1. (*S*)-Lactic acid-MRNi tends to afford (*S*)-(+)-enantiomer in excess as the reaction temperature rises.

TABLE 1. EFFECT OF THE MODIFYING REAGENT ON THE TEMPERATURE DEPENDENCE OF THE OPTICAL YIELD

Modifying reagent	Reation temperature (°C)	Optical yield[a] (%)
(*S*)-lactic acid	30	0.00
	60	−0.65
	80	−1.08
(*S*)-2-methoxy-propionic acid	60	−0.07
	80	0.33
(*S*)-2-methoxy-3-methylbutyric acid	40	0.00
	60	0.24
	80	1.06

a) The sign of the optical yield is taken as + in the case of an excess of the (*R*)-(−)-enantiomer.

On the other hand, the catalysts modified with (*S*)-α-methoxy carboxylic acids showed the same temperature dependence as (*S*)-α-amino acid-MRNi, in which the amino group has much less capacity of making a hydrogen bond and T_0 decreased with the change in the α-alkyl group from methyl to isopropyl.

These phenomena indicate that the OH group plays an important role in the enantioface-differentiation by its ability of hydrogen bonding and that the function of the OH group in the enantio-differentiation differ from that of the NH_2 or OCH_3 group.

As has been reported, the comparative study of the rate and the optical yield indicates that the role of a modifying reagent can be divided into two independent functions. One is to regulate the rate by occupying a part of the active area of the catalyst, and the other is to differentiate the enantiofaces of the substrate as a reference chiral system.[1)]

It is also known that at least two polar groups must attach to a chiral center of a modifying reagent for the stereo-differentiating reaction to take place.[2)] When these facts are taken into account, the formation of dipolar interaction or a hydrogen bond between the substrate and modifying reagent could be the essential step in the enantio-differentiating hydrogenation.

Since the mode of the interaction is expected to be determined by the balance of an associative dipolar interaction or hydrogen bond and repulsive steric effect, the origin of T_0 can be explained by the change in the balance of the two effects because of their different temperature dependences.

Thus, T_0 and the feature of the temperature dependence of the optical yield may give a clue to the nature of the stereo-differentiating reaction. In order to understand the origin of T_0 and the temperature dependence of the optical yield in detail, there are still several problems to be solved, such as the temperature effect on the interaction between the modifying reagent and the catalyst and the effect of the minor contaminants of the catalyst, such as the aluminum ion, water, and methanol, on the mode of interaction between the substrate and the modifying reagent.

Further investigation on the origin of T_0 is in progress.

Experimental

The GLC analysis was carried out with a Shimadzu GC-3AH apparatus with a TC detector, using a 300×0.5 cm stainless-steel column packed with PEG 20-M (10%) on Chromosorb W. The optical rotations were measured at the Na-D line with a Perkin-Elmer 241 Polarimeter with a quartz cell (length of light path, 1 dm). All the materials except those listed below were obtained from commercial sources and were used without further purification. Butyl acetoacetate,[3] (*S*)-lactic acid (as Zn salt), $[\alpha]_D$ −7.9 (*c* 2, H_2O),[4] (*S*)-2-methoxy-3-methylbutyric acid,[5] $[\alpha]_D$ −77.6 (neat), and (*S*)-2-methoxypropionic acid,[5] $[\alpha]_D$ +69.1 (neat), were prepared by published procedures.

Preparation of the Catalyst. Into an alkaline solution (52 g of sodium hydroxide in 260 ml of deionized water), which had been cooled to 20 °C on an ice bath, 19.5 g of a well-pulverized Raney alloy (Ni 42%, Al 58%, Kawaken Fine Chemical Co.) was added in portions at such a rate that the temperature of the mixture was maintained at 20±2 °C with occasional shaking. The resulting suspension of Raney nickel was kept at 75—78 °C for 45 min and then allowed to stand at room temperature for 2 h. After the removal of the alkaline solution by decantation, the Raney nickel was washed four times with 650 ml portions of deionized water. The modification of the catalyst was carried out at 0 °C by a published method.[6] The pH of the modifying solution was adjusted to an isoelectric point for each monoamino monocarboxylic acid and to 5.1 for each hydroxy acid.

Hydrogenation. Into an atmospheric-pressure hydrogenation vessel filled with hydrogen, 0.6 g of a catalyst suspended in 17.5 ml (0.15 mol) of a substrate was introduced. The mixture was then heated at the stated temperature for 3 h under shaking. After the subsequent removal of the catalyst from the reaction mixture by filtration, the filtrate was flash-distilled under reduced pressure. The optical rotation and the concentration of product in the distillate were determined by means of polarimetry at 25 °C and by GLC (90 °C) respectively. The optical purity of the product was determined by means of a calibration chart.

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