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Multiple Interactions between Host Cyclodextrin and Guest Compound Assisting Asymmetrically Selective Reduction with $NaBH_4$ in Aqueous Media

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In the presence of 6-mono-deoxy-amino-β-cyclodextrin, benzoylformic acid was enantioselectively reduced with sodium borohydride in aqueous solution. The dependence of the optical yield on pH, ionic strength, cyclohexanol and urea suggested that the concerted host-geust interaction arose from both hydrophobic and ionic interaction as well as hydrogen bonding.

Several compounds have been known as host-guest type catalyst that exerts an asymmetrically selective field during the reduction reaction of a keto-compound with inorganic reducing agent such as sodium borohydride. For example, cyclophane,[1] bovine serum albumin[2] and cyclodextrin(CD)[3] were reported to be chiral molecular recognizing catalysts that can be simulated as a sort of enzyme model. We wish to report the enantioselective reduction with $NaBH_4$ in aqueous media involving inclusion of host cyclodextrin and guest keto-acid. The interactions between host and guest were examined and the structural scheme is suggested.

6-Mono-deoxy-amino-β-cyclodextrin(ACD) was prepared by the reported procedure.[4] A typical reaction was carried out as follows. ACD was dissolved in phosphate buffer solution of pH 7.0 and benzoylformic acid (BFA) and $NaBH_4$ were added to the solution at 2 °C. After a few hours the intended reduced product, mandelic acid, was then separated as follows.

The product was extracted with ethyl acetate after adjusting the pH of the aqueous reaction mixture to 2 with 1 M(1 M= mol·dm^{-3}) hydrochloric acid. The ethyl acetate solution was dried over anhydrous sodium sulfate, and then evaporated to dryness under reduced pressure. The chemical yield of mandelic acid was determined by HPLC analysis. Under the reaction conditions ranging pH from 3.0 to 13.0, no by-product was observed and the chemical yield was 100% by weight measurement as well as HPLC analysis of the product. Optical rotation of the product was measured in ethanol at 25 °C (concentration: 6.0 g·dm^{-3}) to calculate the optical yield. The product D- and L-mandelic acids were not racemized in the course of the reaction at pHs from 3 to 13 in the presence or absence of ACD.

No asymmetric reduction was observed when α-CD was used as a host compound. However, mandelic acid was obtained with a 4% optical yield in the presence of β-CD and 12% in the presence of ACD. Cyclohexanol is known to instantly form a 1:1 inclusion complex with CD and to be a competitive inhibitor for the inclusion. The optical yield was decreased to 5% in accordance with an increase of cyclohexanol concentration to 40 mM (2.4 equiv. mole of added ACD). In other words, the hydrophobic cavity is an indispensable structure for the present asymmetric reduction.

The interaction between CD and BFA was examined by the spectrometric measurement of association constant K_a for inclusion equilibrium. K_a values with BFA were 995 M^{-1} and 445 M^{-1} for ACD and β-CD respectively. It is suggested that ACD included BFA more strongly than β-CD. In other words, this asymmetric reduction was caused by the tigther inclusion of BFA into ACD. The calculation showed that 70% of the added BFA(5 mM) was included in ACD(17 mM) and 55% in β-CD. By a circular dichroism spectrum the molecular ellipticities at 250 nm of included form $[\theta]_{complex}$ value became $+7.20\times10^3$ degree for ACD and $+4.34\times10^3$ degree for β-CD.([BFA]= 6×10^{-4} M, [CD]= 5×10^{-3} M) This suggested that the conformation of the complex was different between ACD and β-CD.

Next, the examination of the ionic strength was carried out in order

to clarify the intermolecular ionic interaction between host and guest. As the ionic strength of the buffer solution increased from 0.1 to 1.5, a decrease from 13% to 5% in the optical yield was observed. The ionic interaction should play an important role in this asymmetric reduction.

The examination of pH dependence of optical yield was done as shown in Fig. 1. Here, D-selectivity was observed in the pH range from 4 to

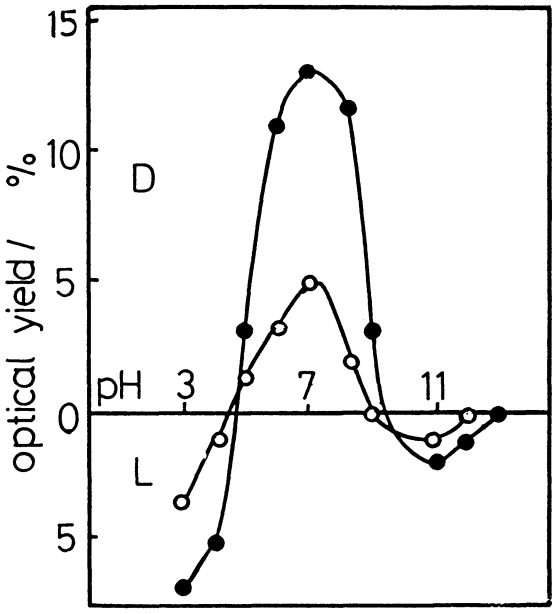

Fig. 1. Dependence of optical yield on pH.
Reaction condition: [CD]= 17 mM, [BFA]= 5.0 mM, [$NaBH_4$]= 50 mM, in succinic-borate buffer(pH 3.0-4.0), phosphate buffer(pH 4.0-9.0) and carbonate buffer (pH 9.0-13.0); ionic strength I= 0.20 at 0 ±2°C for 1 h.
(1 M= 1 mol·dm^{-3}= 10^3 mM)
o : β-CD, ● : ACD

10 in the reaction solution at the presence of either ACD or β-CD. On the other hand slight L-selectivity was obtained at pH over 10 and below 4. The similar pH dependence of optical yield in both cases for ACD and β-CD suggested that the hydrogen bonding essentially regulated the asymmetrical selectivity. The carboxyl group of BFA and the amino group of ACD are related to the effective ionic interaction in the neutral pH region, because of pK_a 4.2 for BFA and pK_a 8.1 for ACD. D-selectivity was obtained in this pH range. Without the ionic interaction, other interactions became dominant and regulating the asymmetrical selectivity.

It can be concluded that the role of the hydrogen bonding between some of primary hydroxyl group and carbonyl group of BFA was essentially important to cause the asymmetrically selective reduction, ascertained by the pH dependence of β-CD as in Fig. 1 and urea dependence. Presence of

1 M urea in the reaction system caused only 4% optical yield and 5 M urea resulted in no asymmetric selectivity. Also this asymmetric selectivity was amplified through the ionic interaction between the amino group and carboxylic acid, based on the results of the ionic strength and the pH dependence of the optical yield beside the hydrophobic interaction between the CD cavity and phenyl ring of the substrate as evidenced by the cyclohexanol inhibition effect.

A reaction mechanism could be involved in the hydrophobic inclusion of the CD cavity, ionic interaction between the amino group and carboxylic group and hydrogen bonding between the C-6 hydroxyl groups of CD and BFA. The substrate was asymmetrically included in ACD, facing one specific side of the carbonyl plane of BFA to the outside of the cavity. The balancing of these three kinds of interaction should determine the complex structure which caused the asymmetric reaction. Borohydride anion then attacks the carbon atom of the keto group of the included BFA in ACD cavity from the specific open side(Si face for D-product). BFA was reduced asymmetrically to D- or L-mandelic acid depending on the complex structure.

Further designs of each structure of host and guest molecules and a detailed mechanism are now currently under investigation.

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