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Kenjiro Hattori<sup>a</sup>; Keiko Takahashi<sup>a</sup>

<sup>a</sup> Department of Industrial Chemistry, Faculty of Engineering, Tokyo Institute of Polytechnics, Kanagawa, Japan

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# Asymmetric reduction of prochiral inclusion complex in aqueous media

KENJIRO HATTORI\* and KEIKO TAKAHASHI

*Department of Industrial Chemistry, Faculty of Engineering, Tokyo Institute of Polytechnics, Atsugi, Kanagawa 243-02, Japan*

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In the formation of an inclusion compound, the interaction of both ionic and hydrogen bonds were shown to be involved in the asymmetric reduction of a keto acid in the presence of 6-deoxy-6-amino- $\beta$ -cyclodextrin with  $\text{NaBH}_4$  in an aqueous buffer solution. Furthermore, multiple interactions were elucidated and the enantioface differentiating reduction was induced in the concerted interactions. Asymmetric reduction of a keto acid in the presence of newly prepared alkylamino-substituted  $\beta$ -cyclodextrin (CD) gave a higher optical yield. There should be a steric effect by a substituent group on the CD to form the conformation favoured by the multi-interaction between host and guest. A mechanistic scheme for the enantioface differentiating attack of a reducing reagent on the included substrate is suggested.

## INTRODUCTION

For an example using cyclodextrin (CD),<sup>1</sup> an asymmetric reaction in a solid crystalline complex by Sakuraba *et al.*<sup>2</sup> gave 91% e.e. (enantiomer excess) in one case. Further, a system with an aromatic ketone used by Fornasier *et al.*<sup>3</sup> gave 36% e.e. at maximum. Both short reports showed good potential for use of a crystalline complex as a reaction medium for asymmetric reduction using the cavity of CD. The design of an asymmetric field to carry out asymmetric reactions with inclusion using the modified CD was the key target of the present research.<sup>4</sup> Thereupon in this research, a host-guest inclusion phenomenon was emphasized for the molecular recognition capability for asymmetric differentiation with multiple interactions between host and guest in aqueous media. An experiment was first carried out for the purpose of controlling the asymmetric reaction, as well as simulating an enzyme reaction and evaluating the function of the modified CD to realize a 'Microreactor' at the molecular level, even in aqueous media (Scheme 1). By using benzoylformic acid BFA, an aromatic keto acid, in the cavity of 6-deoxy-6-amino- $\beta$ -CD (ACD), one amino group was expected to increase the

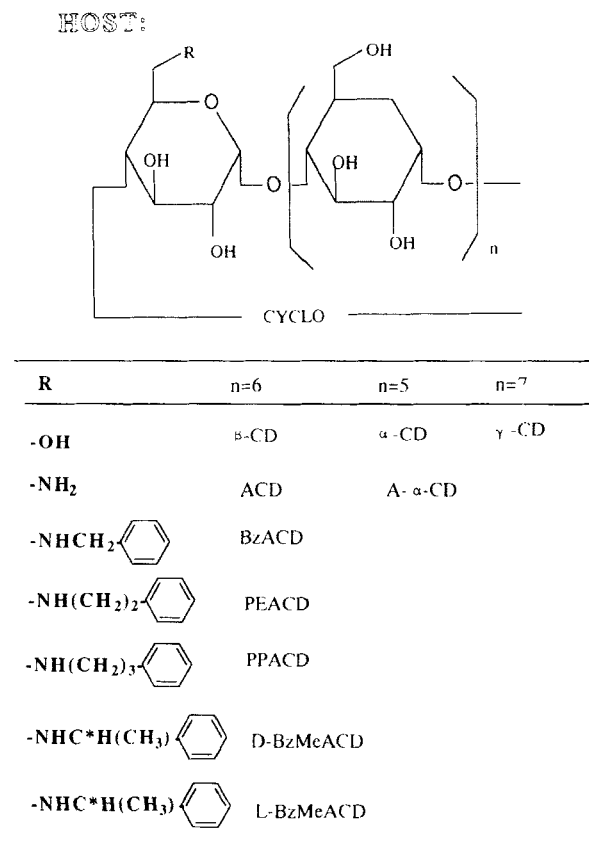
interaction due to electrostatic forces. Moreover, the molecular design to attach the arylalkylamine at the primary side of  $\beta$ -CD was expected to give more than the ionic interaction on including the substrate into the CD cavity. Newly prepared host compounds, which have dimethylamino, benzylamino (BzACD), phenylethylamino (PEACD), phenylpropylamino (PPACD), D-benzylmethylamino (D-BzMeACD), L-benzylmethylamino (L-BzMeACD), R-naphthylethylamino and S-naphthylethylamino substituents on the 6-position of the  $\beta$ -CD gave better results and suggested a system where some steric effects may promote the favoured geometry between the host and guest complex. With other guest compounds, indole-3-pyruvic acid (IPA) and *p*-hydroxyphenylpyruvic acid (pHPPA), instead of BFA, a specific steric effect was examined in the  $\beta$ -CD cavity.

## RESULTS AND DISCUSSION

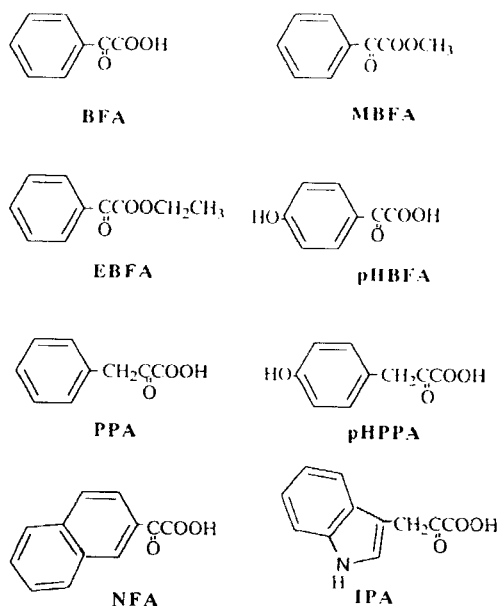
### Effects of various added cyclodextrins on asymmetric selectivity

The results are summarized in Tables 1 and 2. An examination using a CPK model to explain the results in Table 1 suggests that the size of the  $\alpha$ -CD and amino- $\alpha$ -CD cavity are big enough to include BFA.  $\alpha$ -CD is better suited to the included BFA. However, the results concerning asymmetric selectivity with the larger  $\beta$ -CD, ACD and  $\gamma$ -CD were better than those for  $\alpha$ -CD. This fact suggests that the size of the CD recognizes some degree of 'affordness' in order to show asymmetric selectivity. Namely, in  $\alpha$ -CD, BFA was included vertically in the cavity, and the plane including the carbonyl carbon of BFA may not be differentiated by the attack of a  $\text{BH}_4^-$  ion. The asymmetric selectivity should appear when the BFA molecule is included in the 'declined' mode in the afforded CD cavity space. The ionic interaction of the amino group further guides the BFA molecule

\* To whom correspondence should be addressed.



## GUEST:



Scheme 1 Various host cyclodextrins and guest keto acids.

advantageously. This conjecture does not contradict the later results on examination of the ionic interaction. According to the results in Table 2, the molecular design to attach the arylalkylamine at the primary side

**Table 1** Asymmetric reduction of BFA in the presence of various CDs

Run no.	CD	$[\alpha]_D^{25}$ (deg) <sup>a</sup>	Optical yield	Configuration
1	None	0	0	
2	$\alpha$ -CD	0	0	
3	A- $\alpha$ -CD	0	0	
4	$\beta$ -CD	-6	4	R
5	ACD	-20	13	R
6	$\gamma$ -CD	+3	2	S

Reaction conditions: [ACD] = [keto acid] = 5.0 mM, [NaBH<sub>4</sub>] = 50 mM, in 70 mM phosphate buffer (pH 7.0, *l* = 0.20) at 0 ± 2°C for 1 h.

<sup>a</sup> Maximum rotation value of  $[\alpha]_D^{25}$  for the R-mandelic acid was -174.3 (*c* = 0.75, methanol).

**Table 2** Asymmetric reduction of BFA, IPA and pHPPA (% e.e.) in the presence of arylalkylamino-CDs<sup>a</sup>

Guest	BFA	IPA	pHPPA
Host			
None	0	0	0
$\beta$ -CD	4	4	
ACD	18	36	29
BzACD	24	35	29
PEACD	33	39	32
PPACD	8	25	39
D-BzMeACD	8	20	28
L-BzMeACD	6	18	20
Configuration	R	R	S

<sup>a</sup> Reaction condition: [CD] = [keto acid] = 1.0 mM in 0.01 M Tris buffer solution (pH 7.2) at 0°C for 1 h. Optical yield is given in % e.e.

of  $\beta$ -CD suggested where some steric effects may promote the favoured geometry between the host and guest complex. It is presumed that the steric effect of a substituent phenylalkyl group on CD acts as the factor that controls the direction of the reducing reagent to increase the asymmetric selectivity of the reaction, in addition to the hydrogen bonding, hydrophobic interactions and ionic interactions that were previously estimated.

**Temperature dependency of asymmetric selectivity**

As the temperature increased, the optical yield decreased. At a temperature of greater than 20°C, the optical yield was 0% e.e. Generally, in an asymmetrically selective reaction the difference of the free energy of the reactions between enantiomers increases at lower temperatures.<sup>5</sup> Lower temperatures favour high asymmetric selectivity for two reasons: the formation of inclusion is favoured and there is a larger difference in the free energy of the enantioface differentiating reaction. Furthermore, the attempt to improve the asymmetric selectivity at a temperature lower than 0°C failed. In either case, in spite of chemical yields of 100%, no asymmetric selectivity was observed. However it did not show any selectivity at temperatures

lower than 0°C in non-aqueous solutions such as DMSO and ethylene glycol. It is proposed that the selectivity did not appear without inclusion of BFA into ACD in these media.

### Structural effects of various substrates

The results are summarized in Table 3. The configuration of the reduced products is usually the *R* form except for pHPPA and pHBFA which showed the *S* form. It is thought that these substrates should interact with hydroxy groups at the hem of the CD cavity; this might cause a reversed configuration of the product. This would be especially true for pHPPA, which has greater motional freedom through part of the methylene group. This should reflect an improvement in the optical yield. Methyl or ethyl esters of BFA showed no asymmetric selectivity of the reduced products. Esters of BFA have no ionic site for an ionic interaction with host ACD, and vast changes of orientation between host and guest are expected.

### Formation of the inclusion complex

The optical yield in the presence of cyclohexanol decreased with increasing addition of cyclohexanol, and 5% e.e. was produced at 40 mM cyclohexanol in the ACD and BFA systems. Cyclohexanol is a well-known compound that forms inclusion compounds and inhibits cyclodextrin catalysis. ACD and various guests were examined using both fluorescence and circular dichroism spectra. The association constant  $K_a$  for the inclusion equilibrium with BFA was  $995 \text{ M}^{-1}$  and  $445 \text{ M}^{-1}$  for ACD and  $\beta$ -CD, respectively. The calculation showed that 70% of the added BFA was included in ACD and 55% in  $\beta$ -CD. By a circular dichroism spectrum the molecular

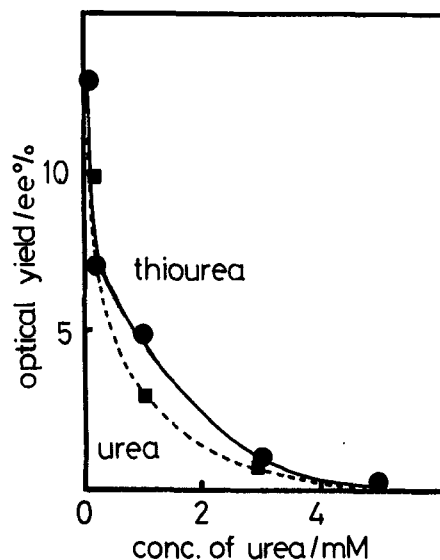


Figure 1 Dependence of optical yield on urea. Reaction condition  $[\text{ACD}] = 5.0 \text{ mM}$ ,  $[\text{BFA}] = 5.0 \text{ mM}$ ,  $[\text{NaBH}_4] = 50 \text{ mM}$  in 70 mM phosphate buffer (pH 7.0,  $I = 0.20$ ) at  $0 \pm 2^\circ\text{C}$  for 1 h.

ellipticities at 250 nm of the included form  $[\theta]$  complex became  $+7.20 \times 10^3 \text{ deg}$  for ACD and  $+4.34 \times 10^3 \text{ deg}$  for  $\beta$ -CD. This suggested the conformation of the complex was different for ACD and  $\beta$ -CD.

### Hydrogen bonding interactions

Figure 1 shows the change in the optical yield in the presence of added urea and thiourea (from 0.1 to 5 M). The optical yield decreased with an increase in concentration in both cases and selectivity became 0% e.e. with addition of 5 M urea. Urea and thiourea are known to form inclusion compounds and act as inhibitors against hydrogen bonding.<sup>6</sup> Also, it was reported that the urea did not inhibit inclusion in the CD cavity. Accordingly, the effect of urea in this reaction system is to inhibit hydrogen bonding between the hydroxy group and the substrate BFA. As  $\beta$ -CD also showed asymmetrically selective results, this should mean that the hydrogen bond forms the essential interaction to determine the 'reclined' position of substrate BFA; in other words, to allow the asymmetrically selective attack of  $\text{BH}_4^-$  on the BFA molecule in the inclusion compound.

### Ionic interactions

That the esters of BFA showed 0% e.e. essentially suggests the existence of an ionic interaction. The optical yield, when the ion concentration of the buffer solution was changed from 0.1 to 1.5, was measured. As the ionic strength increased, the optical yield decreased from 13% e.e. to 5% e.e. It is conceivable that the change in the optical yield is due to an ionic

Table 3 Asymmetric reduction by  $\text{NaBH}_4$  of various keto acids in the presence of ACD

Run no.	Keto acid	$[\alpha]_D^{25}$ (deg) <sup>a</sup>	Optical yield	Configuration
1	BFA	-20	13	<i>R</i>
2	MBFA	0	0 <sup>b</sup>	
3	EBFA	0	0 <sup>c</sup>	
4	pHBFA	-4.1	3 <sup>d</sup>	<i>R</i>
5	PPA		- <sup>e</sup>	No reaction
6	pHPPA	+3.1	35 <sup>f</sup>	<i>S</i>
7	NFA	-44.9	30 <sup>g</sup>	<i>R</i>

Reaction conditions  $[\text{ACD}] = [\text{keto acid}] = 5.0 \text{ mM}$ ,  $[\text{NaBH}_4] = 50 \text{ mM}$ , in 70 mM phosphate buffer (pH 7.0,  $I = 0.20$ ) at  $0 \pm 2^\circ\text{C}$  for 1 h.

<sup>a</sup> Conditions for rotation measurement: run 1,  $c = 0.5$  in methanol; run 2 and 3,  $c = 1.8$  in methanol and water; run 4,  $c = 1.8$  methanol; run 6,  $c = 0.5$  in methanol; run 7,  $c = 1.1$  in ethanol.

<sup>b</sup> Reported<sup>8</sup>  $[\alpha]_D^{20} = +144$  ( $c = 1.0$ , methanol) for *R*.

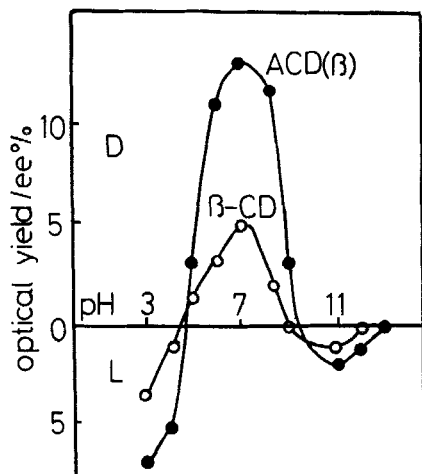
<sup>c</sup> Reported<sup>8</sup>  $[\alpha]_D^{20} = +134$  ( $c = 3.0$ ,  $\text{CHCl}_3$ ) for the *R*.

<sup>d</sup> Reported<sup>9</sup>  $[\alpha]_D^{20} = +144.4$  for *S*.

<sup>e</sup> Reported<sup>10</sup>  $[\alpha]_D^{25} = +20$  ( $\text{H}_2\text{O}$ ) for *R*.

<sup>f</sup> Reported<sup>11</sup>  $[\alpha] = +8.0$  ( $c = 0.5$ , methanol) for *S*.

<sup>g</sup> Reported<sup>12</sup> (95% e.e.)  $[\alpha]_D^{21} = +144.2$  ( $c = 0.98$ , ethanol) for *R*.



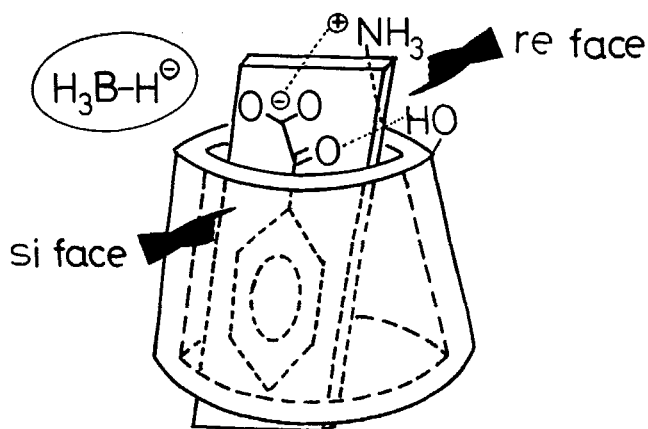
**Figure 2** Dependence of optical yield on pH. Reaction condition  $[ACD] = 17.0 \text{ mM}$ ,  $[BFA] = 5.0 \text{ mM}$ ,  $[NaBH_4] = 50 \text{ mM}$  in  $70 \text{ mM}$  in various buffer ( $I = 0.20$ ) at  $0 \pm 2^\circ\text{C}$  for 1 h.

interaction in the reaction. The asymmetric selectivity, depending on the pH change with ACD compared with  $\beta$ -CD, is shown in Figure 2. The results shown here reflect the asymmetric selectivity, along with the reduction reaction, suggesting the ionic interaction depends on the pH. A small *S* selectivity appeared at pH 5 and higher *R* selectivity from pH 5 to 11. The optical yield decreased at pH > 11. The  $pK_a$  of BFA and ACD were determined to be 4.2 and 8.4, respectively, by a neutral titration method. The ionic interaction between ACD and BFA caused stronger inclusion in the reaction process. Therefore, regarding the ionic interaction, it can be said that it not only increased the amount of inclusion, but also enhanced the asymmetrically selective attack of the reagent. Also, the reaction showed *R* selectivity when ACD and BFA were dissociated, but *S* selectivity when the ionic group of ACD and BFA was not dissociating. With  $\beta$ -CD a similar trend was shown, although the extent of the change was small. As shown in the results regarding the pH dependence of the asymmetric reduction, the same tendency was also seen for the case of  $\beta$ -CD. Therefore, merely an ionic interaction cannot explain the asymmetric selectivity, though the presence of an ionic interaction significantly enhanced the asymmetric selectivity. Rather, the orientation and geometry of the guest molecule in the inclusion complex is determined primarily through hydrogen bonding, depending on the assistance of the ionic interaction between host and guest.

## CONCLUSIONS

It has been shown that the substrate is included into the CD cavity through the hydrophobic interaction

for an asymmetric reduction in this system. In a larger cavity some 'affordness' may be desirable to have asymmetric selectivity of the attacking reagent, since 'reclining' of the BFA molecule may cause the asymmetric results. As illustrated in Scheme 2, it is thought that some ionic interaction amplifies the inclusion ability of the complex. It is also shown that the hydrogen bonding of the hydroxy group at the hem of the CD cavity determines the orientation of the BFA molecule in the CD cavity. Furthermore, the total concerted effects of these three interactions control the complex conformation. The *R* configuration selectivity of the reduction product (*R*-mandelic acid) is brought about through an attack from the *si* face of the prochiral keto carbonyl carbon in BFA by the  $BH_4^-$  ion. However, as for *p*-hydroxyphenyl compounds,  $BH_4^-$  attack occurs through the *re* face on the opposite side of *si*, and the *S* selectivity of the product is preferential. A clear explanation is not yet available concerning these results together with the results at the extreme pH ranges. When ACD is added to the aqueous solution to control the attacking direction of the reducing reagent, asymmetric selectivity can be realized. It can be said that this is the first 'Microreactor' system which shows asymmetric reaction function in aqueous media using CD derivatives with molecular recognition. To improve the optical yield, the appropriate orientation of the substrate in the included form is suggested. The stereochemical characteristics of the inclusion complex, such as fitness for the interacting sites as a relative positional relationship of host-guest, the length of the arm between the phenyl group and the CD cavity and the bulkiness of the guest molecule, are all conceivably



**Scheme 2** Suggested scheme of asymmetric reduction with host and guest in aqueous solution at neutral pH.

sensitive to the higher asymmetric selectivity depending on a delicate structure change.

## EXPERIMENTAL SECTION

The synthetic procedures for various arylalkylamino-CD derivatives were carried out starting with 6-deoxy monotosyl- $\beta$ -CD.<sup>7</sup> The products were purified by chromatography and recrystallization from water. The chemical yield was in the range of 10–30%. The structural confirmation by NMR, MS and elemental analysis was satisfactory. An experiment for asymmetric reduction is as follows: a CD derivative ( $1 \times 10^{-4}$  mol) was dissolved in tris buffer (pH 7.2 of 50 ml), and the same mol quantity of guest was added and stirred for 10 min in an ice bath. The same mol quantity of NaBH<sub>4</sub> was then added to start the reduction reaction. The product was filtered using a membrane, and subjected to HPLC analysis using an Enantio L1 optical resolving column (TOSO) eluted with aqueous 1 mM CuSO<sub>4</sub> solution at 50°C and detected with UV (245 nm).

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