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Asymmetric Induction by β-Cyclodextrins in $NaBH_4$ Reduction of Ketones

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Abstract. Asymmetric reduction of various prochiral ketones was achieved with sodium borohydride utilizing β-CD or its derivative, mono-6-deoxy-6-[N-(2-aminoethyl)]amino-β-CD (β-CD-en) as a chiral template. It was found that pre-equilibrium between ketone and β-CD derivative and low reaction temperature increase asymmetric induction. The extent of asymmetric induction and the absolute configuration of the resulting secondary alcohols are highly dependent upon the nature of the ketones and also β-CD derivatives. A mechanistic scheme is suggested to explain the dependency.

Key words: reduction, β-cyclodextrin, asymmetric induction, sodium borohydride, enantioselectivity.

1. Introduction

β-Cyclodextrin (β-CD) is a cyclic oligosaccharide composed of seven α-(1,4)-linked D(+)-glucopyranose units. It has attracted widespread interest as a model for studies of enzyme–substrate interactions due to its ability to form inclusion complexes with a variety of substrates in its cavity [1]. The β-CD cavity has a chiral environment and induces stereoselective reactions for complexed substrates [1].

Sodium borohydride ($NaBH_4$) is one of the most popular reagents for the reduction of ketones. However, $NaBH_4$ does not have an asymmetric center and cannot induce asymmetric reduction of ketones. Thus, chirally modified borane derivatives have been widely used as asymmetric reducing agents for ketones. There have been several reports that asymmetric induction in sodium borohydride reduction of ketones could be achieved by using β-CD as a chiral template [2–6]. Baba et al. reported an asymmetric reduction of trifluoromethyl aryl ketones in 0–10% optical yields in the presence of β-CD [2]. Later, two groups reported that significant improvements on these inductions could be obtained by reducing preformed 1 : 1 β-CD–ketone complexes suspended in an aqueous alkaline solution

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of sodium borohydride [3, 4]. Enantioface differentiating reduction of keto acid was carried out in the presence of 6-deoxy-6-amino-β-CD [5].

Asymmetric reduction of ketones in the presence of β-CD or its derivatives was also carried out using 1-propyl-1,4-dihydronicotinamide (NAH) [2] or electrogenerated two-electron-reduced dimethyl viologen [7]. The configuration of the alcohols produced by these reductions was found to be the opposite of that of the alcohols obtained from $NaBH_4$ reduction. Sakuraba et al. reported effective asymmetric reduction of ketones utilizing crystalline cyclodextrin inclusion complexes of achiral amine-boranes [8]. They found that enantioselectivity in the reduction depends on the nature of the amines.

Our continuing interest in reactions in β-CD or its derivative media [7, 9, 10] and those studies mentioned above prompted this investigation. In this paper, we report the asymmetric reduction of various prochiral ketones with sodium borohydride utilizing β-CD or mono-6-deoxy-6-[N-(2-aminoethyl)]amino-β-CD (β-CD-en) as a chiral template: β-CD-en was used since the β-CD derivative is known to exhibit greater enantioselectivity in the deacylation reactions of chiral ester [10]. We found that the extent of asymmetric induction and the absolute configuration of the resulting secondary alcohols are highly dependent upon the structures of the prochiral ketones and the templates. A mechanistic scheme to explain the structural dependency is suggested.

2. Experimental

2.1. General

β-CD was purchased from Aldrich. β-CD-en was available from a previous study [9]. Ketones were obtained from Aldrich and used as received. ^{1}H-NMR spectra were obtained at 300 MHz and chemical shifts are reported in δ ppm relative to TMS as an internal standard. Optical rotation was measured with a JASCO DIP 140 polarimeter at 25 °C.

2.2. General procedure for $NaBH_4$ reduction of ketones

β-CD (6.8 g : 6.0 mmol) was suspended in 108 mL of 0.1 M aqueous potassium carbonate solution. To this, 0.6 mmol of ketone dissolved in 2 mL of acetonitrile was added and the mixture was stirred for a day at 35 °C. A solution of 0.15 g (4.0 mmol) of sodium borohydride and 0.14 g (1.0 mmol) of potassium carbonate in 10 mL of water was then added and allowed to react at 35 °C for 16 h. The reaction mixture was thoroughly extracted with ethyl ether: 100 mL of ethyl ether was added to the reaction mixture and stirred for 0.5 h. After the precipitated β-CD was removed, two layers were separated and the aqueous layer was extracted with ethyl ether (50 mL $\times$ 3). The filtered β-CD was suspended in 100 mL of warm water and extracted as above with ethyl ether. The combined ethyl ether layers

were dried with anhydrous sodium sulfate, concentrated and purified by column chromatography to afford the corresponding alcohol.

When the reaction was carried out in the presence of β-CD-en, 0.15 mmol of ketone dissolved in 1 mL of acetonitrile was added to a solution of 0.9 g (0.75 mmol) of β-CD-en in 27 mL of 0.1 M aqueous potassium carbonate. After stirring for a day, a solution of 0.038 g (1.0 mmol) of sodium borohydride in 5 mL of 0.1 M aqueous potassium carbonate was added and reacted at 35 °C for 16 h. The reaction mixture was extracted with ethyl ether (30 mL $\times$ 5). The ether layers were dried, concentrated and purified as above.

The isolated products were identified by their NMR spectra. The absolute configuration and the enantiomeric excess (ee) were determined from optical rotation data using the reported values of specific rotation. When the maximum rotation value of the product alcohol is not known, the ee was determined by the use of Mosher's method [11] as described in the following paragraph.

2.3. Determination of ee by Mosher's reagent

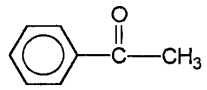
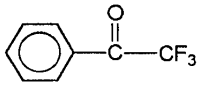
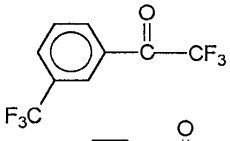
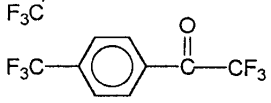
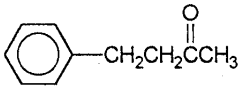
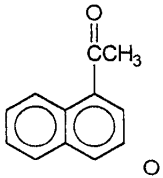
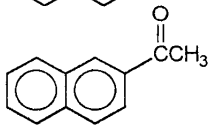
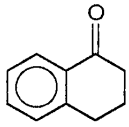
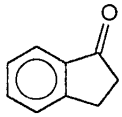
In the case of entries 3 and 4 (Table I), the product alcohol was reacted with an equimolar amount of Mosher's reagent, (R)-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (Aldrich) as described in the literature [11], The ratios of the resulting diastereomeric esters were analyzed by relative peak areas corresponding to methoxy groups in ^{1}H-NMR spectra in $CDCl_3$. The chemical shifts of the methoxy groups of the esters were δ 3.62 (q, J = 1.3 Hz) and 3.47 (q, J = 1.2 Hz) with the area ratio of 52.5 : 47.5 in entry 3, and δ 3.61 (q, J = 1.3 Hz) and 3.47 (q, J = 1.2 Hz) with the area ratio of 48 : 52 in entry 4.

3. Results and Discussion

Various prochiral ketones were reduced with sodium borohydride in aqueous alkaline solution in the presence of ten molar excess of β-CD (50 mM) or five molar excess of β-CD-en (23 mM). The ketones were pre-equilibrated with β-CDs for a day before adding a solution of sodium borohydride. The chemical and optical yields of the resulting alcohols and their absolute configurations are summarized in Table I. In the case of entry 2, both optical rotation measurement and Mosher's method were applied to determine the enantiomeric composition and the results agreed well with each other.

The present procedure gives significant enantioselectivity for reduction of trifluoromethyl phenyl ketone (entry 2), whereas reduction of the same substrate in 0.01 M borate buffer in the presence of β-CD showed no appreciable asymmetric induction [2]. Methyl phenyl ketone (entry 1), benzylacetone (entry 5), 1′-acetonaphthone (entry 6), and 2′-acetonaphthone (entry 7) were also reduced by suspending the preformed solid β-CD-ketone complexes in $NaBH_4$ aqueous alkaline solution by Fornasier et al. [3]. The configuration of the preferred enantiomer

Table I. Asymmetric reduction of ketones in the presence of cyclodextrins[a]

entry	ketone	cyclo-dextrin	alcohol: isolated yield (%)	alcohol: $[\alpha]_D$(solvent)	alcohol: optical yield (%)[b]	alcohol: configuration
1		β-CD	82	1.4(CH_2Cl_2)	3	*R*
		β-CDen	82	-1.9(CH_2Cl_2)	4	*S*
2		β-CD	89	3.5(C_6H_6)	24	*S*
		β-CDen	80	-3.0(C_6H_6)	20	*R*
3		β-CD	89		5[c]	
4		β-CD	71		4[c]	
5		β-CD	97	2.9(C_6H_6)	9	*S*
		β-CD	95	3.5(C_6H_6)[d]	11	*S*
		β-CDen	98	-2.3(C_6H_6)[d]	7	*R*
6		β-CD	95	7.9(EtOH)	11	*R*
		β-CD	90	14.9(EtOH)[d]	20	*R*
		β-CDen	93	6.0(EtOH)[d]	8	*R*
7		β-CD	94	-5.1(EtOH)	12	*S*
		β-CD	88	-9.8(EtOH)[d]	23	*S*
8		β-CD	82	5.8(C_6H_6)	22	*S*
9		β-CD	88	-0.8($CHCl_3$)	2	*R*

[a] The ketones were reacted with $NaBH_4$ in water at 35 °C unless specified.
[b] Based on the reported maximum rotation value of $[\alpha]_D$: −52.5(CH_2Cl_2) for *S*-1-phenylethanol;[12a] +14.76(C_6H_6) for *S*-1-phenyl-2,2,2-trifluoroethanol;[12b] −32(C_6H_6) for *R*-4-phenyl-2-butanol;[12c] +74.4(EtOH) for *R*-1-(1-naphthyl)ethanol;[12d] −41.9(EtOH) for *S*-1-(2-naththyl)-ethanonl;[12e] −26.5(C_6H_6) for *R*-1,2,3,4-tetrahydro-1-naphthol;[12f] −34($CHCl_3$) for *R*-1-indanol.[12g]
[c] The ee values were determined by the use of Mosher's reagent (see Experimental).
[d] The value of the reaction product at 0 °C.

of the product alcohols of this work and Fornasier's work is the same for entries 5–7, but reversed for entry 1. The optical yields of the alcohols are 3 (entry 1), 9 (entry 5), 11 (entry 6), and 12% (entry 7) in this work, whereas the corresponding preformed β-CD-ketone complexes were reduced with 3.5, 16, 26, and 20% optical yields, respectively [3]. However, when the present procedure was carried out at 0 °C instead of the usual 35 °C, the optical yields increased considerably, i.e 11% yield in entry 5, 20% in entry 6, and 23% in entry 7, and became close to the values obtained with the corresponding preformed β-CD-ketone complexes. This indicates that the pre-equilibrium between the substrate and β-CD, which has been attained in this work, might be helpful in increasing the enantioface selectivity and the enhanced effects of the pre-equilibrium on the asymmetric induction is almost tantamount to those of preformation of β-CD-ketone complexes.

Table I shows that the extent of asymmetric induction and the absolute configuration of the resulting secondary alcohols are highly dependent upon the structures of both the prochiral ketones and the β-CD derivatives. Introduction of fluorine atoms in place of hydrogens in the methyl group of acetophenone (compare entries 1 and 2) increases enantioface selectivity remarkably and gives alcohols with the opposite configuration. This is in contrast to the finding that the reduction with the crystalline β-CD complex of pyridine–borane yields the corresponding (S)-alcohols with 91 and 4% ee for entry 1 and 2, respectively [6]. The introduction of a trifluoromethyl group into the benzene ring of trifluoromethyl phenyl ketone decreases selectivity (compare entries 2, 3, and 4). A decrease of one methylene unit in a benzofused-carbocyclic ring results in a large difference in selectivity (compare entry 8 and 9). On the other hand, the use of ethylenediamine-appended β-CD derivative, β-CD-en, instead of β-CD inverts the configuration (see entries 1, 2, and 5) or decreases the selectivity (entry 6).

Various factors are needed to explain the dependency of the extent of asymmetric induction and the absolute configuration upon the structures of the prochiral ketones and β-CD derivatives. One is the binding affinity of the ketones to the β-CD cavity, which is expected to be greater than 70 M^{-1} [13]. This value indicates that more than 77% of substrates are bound to β-CD under our experimental conditions, [β-CD] = 50 mM. Since the complexed ketones react faster than the free ketones [3], the enantioselectivity of the reduction should be greater than 77% if the β-CD-substrate complexes exhibits 'perfect' enantioface differentiating ability as enzyme–substrate complexes in biological systems. The observed smaller enantioface selectivity suggests that the guest substrates maintain substantial degrees of freedom in the complexes, various configurations of the complexes being possible. The difference in energies among the different configurations, and thus the decrease of the degrees of freedom of the guest substrates, would be the deciding factor for the enantioselective reduction. This is well supported by the observation of a large increase in enantioselectivity upon lowering the reaction temperature for entries 5, 6, and 7, and for the reduction of keto acids [5]. The large difference in enantioselectivity between entries 8 and 9, though the binding constants of the substrates

with β-CD are expected to be similar, is another indication of the importance of the configuration of substrate-host complexes for asymmetric induction.

To give asymmetric selectivity in the reduction, the ketone should be included in the β-CD cavity in an inclined mode rather than in a vertical mode so that attack of borohydride ion occurs more easily on one face of the carbonyl group than the other face. The tilt causing asymmetric reduction would be possible when both carbonyl and methyl or trifluoromethyl groups interact with the CD's rim. NMR spectroscopic studies on the inclusion complexes with aromatic guests indicated that the aromatic groups are inserted into the β-CD cavity mainly from the secondary hydroxyl side and the polar substituent is positioned on the wider rim region of β-CD [16]. Therefore, the tilted structure of the substrates in the β-CD cavity would arise from hydrogen bonding between the carbonyl group of ketones and the secondary hydroxyl groups of β-CD [3, 4]. The pK_a of the secondary hydroxy groups of β-CD is about 12 [1]. The groups are partly deprotonated in the experimental condition of 0.1 M potassium carbonate solution, pH $\cong$ 11.5 [17]. The secondary alkoxide ion of β-CD cannot be involved in hydrogen bonding with the carbonyl group of the substrates, but may interact with methyl or trifluoromethyl groups. The combination of the hydrogen bonding and alkoxide – CH_3 (or CF_3) interaction seems to decrease the degrees of freedom of guest substrates and guides the direction of attack of the borohydride anion. The larger asymmetric induction in trifluoroacetophenone (entry 2) than in acetophenone (entry 1) can be attributed to the stronger interaction of the former compounds with the alkoxide anion of β-CD. CPK modeling indicated that introduction of the trifluoromethyl group into the benzene ring of trifluoromethyl phenyl ketone (entries 3 and 4) causes large steric hindrance for the inclined inclusion of the substrates. This agrees well with the observation of low asymmetric induction in the reduction of the substrates, compared to entry 2.

It is interesting to note that the use of ethylenediamine-appended β-CD, β-CD-en, instead of β-CD gives alcohols with the opposite configuration (entries 1, 2, and 5). Similar to this, Fornasier et al. reported that $NaBH_4$ reduction of the 1 : 1 complex of (E)-4-phenyl-3-butene-2-one with heptakis(2,6-di-O-methyl)-β-CD yields the corresponding (R)-alcohol, whereas reduction of the β-CD complex of the same substrate gives the (S)-alcohol [3]. Though the exact mechanism for the opposite asymmetric induction is not known at this point, it is clear that the acetyl and trifluoroacetyl groups of the substrates interact with the ethylenediamine moiety of β-CD-en. This seems quite relevant to our earlier finding that the ethylenediamine moiety substituted at the 6-hydroxyl position of β-CD participates in the cleavage reactions of aryl esters [10]. The interaction is possible when the aromatic moiety of the substrates is inserted into the β-CD cavity from the primary hydroxyl side. The enantioselectivity of the reduction of the complexes seems to be opposite to that from the prevailing complexes where the aromatic group is inserted from the secondary hydroxyl side and the carbonyl groups interact with the secondary hydroxyl groups.

So far, we have shown that enantioface selectivity in borohydride reduction of ketones to secondary alcohols is highly dependent on the structures of the ketones and hosts, and the reaction temperature. No general rule governing the extent of asymmetric induction and the absolute configurations of alcohols is derived at this point. However, it is clear that the absolute configuration of the products depends on the conformational structure of the host–guest complexes and the decrease of the degrees of freedom of the guest molecules in the complexes is a deciding factor for the enhancement of enantioselectivity. The latter could be achieved by strong specific interaction between guest and host via proper functional groups of guest and host molecules and optimization of reaction conditions. To elucidate the mechanism of the asymmetric induction and enantioselectivity in the reaction in cyclodextrin media, detailed information on the substrate-CD complexes and the reaction intermediates are necessary.

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13. The association constants (K) of benzoylformic acid and benzoylacetic acid with β-CD are reported to be 445 and 100 M^{-1}, respectively [5, 14]. The K value of diphenyl carbonate, which has two phenyl groups, was estimated to be 140 M^{-1} from kinetic data [15]. From these results, we assume that the lower boundary of K values for substrates of entries 1 and 2 is 70 M^{-1}. The association constants of other substrates would be greater than this value as they have greater hydrophobicity and fit better into the β-CD cavity [1].
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17. Dissociation of hydroxyl groups is supported by a large increase in solubility of β-CD in the reaction condition; solubility of β-CD in water is 1.85 g/100 ml [1], which gives 16.2 mM for saturated solution.