# The Effect of β-Cyclodextrine on the Diastereoselective $NaBH_4$ Reduction of Cyclohexanone Derivatives

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β-Cyclodextrine (β-CD)[1] is a cyclic oligosaccharide constituted of seven D-(+)-glucose units (Fig. 1). β-CD contains a hydrophobic cavity, which can form an inclusion complex with organic molecules of the appropriate size in water.[2] Many examples of regioselective[3] and asymmetric[4] reactions *via* the β-CD-substrate complex have been reported. However reletively fewer studies have been reported on the influence of β-CD on the diastereoselective reactions.[5] This study examined the effect of β-CD and its derivatives on the diastereoselective $NaBH_4$ reduction of cyclohexanone derivatives.

## Results and Discussion

Cyclohexanone derivatives were reduced to the corresponding alcohols using $NaBH_4$. The *trans/cis* ratio of the product is summarized in Table 1. In the absence of β-CD, the ratio of isomers agreed well with the reference data in Table 1. According to the literature,[6] reducing reagents that are small, such as $NaBH_4$ and $LiAlH_4$, mainly give an axial attack product. The axial attack has been explained using the Felkin-Ahn model.[7] Large reducing reagents, such as Li(sec-Bu)$_3$BH, selectively give an equatorial attack product, owing to steric hindrance between the reducing reagent and 1,3-axial protons.[8]

β-CD increased the *trans*/*cis* ratio from 4.7 and 1.3 to 14.4 and 2.5 in the reduction of 2- or 4- substituted cyclohexanones (entries 1 and 2) respectively. For 3-substituted cyclohexanones, however, β-CD decreased the *trans*/*cis* ratio (entries 3 and 4). All of the results show the same trend,

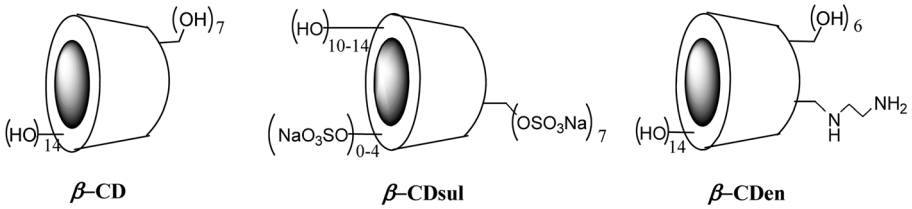
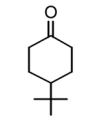
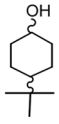
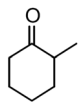
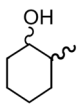
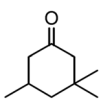
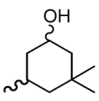
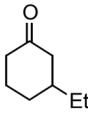
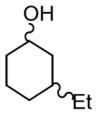



**Figure 1**. The structure of β-CD and its derivatives

**Table 1**. The effect of β-CD and its derivatives on the $NaBH_4$ reduction[a]

| Entry | Ketone | Alcohol | *trans* : *cis*[b] | | | | | References[e] |
|---|---|---|---|---|---|---|---|---|
| | | | without β-CD | β-CD[c] | β-CD$_{en}$[c] | β-CD$_{sul}$[c] | β-CD[c], $Et_3N$[d] | |
| 1 |  |  | 4.7 : 1 | 14.4 : 1 | 26.6 : 1 | 30.1 : 1 | 13.3 : 1 | 4a |
| 2 |  |  | 1.3 : 1 | 3.4 : 1 | 3.2 : 1 | 2.2 : 1 | 2.5 : 1 | 12 |
| 3 |  |  | 4.4 : 1 | 1 : 1.5 | 1 : 1.7 | 1 : 2.3 | 1 : 1.2 | 4a |
| 4 |  |  | 1 : 3.3 | 1 : 13 | 1 : 17 | 1 : 20 | 1 : 12 | 13 |

[a]All reactions were performed at rt. [b]The *cis*/*trans* ratio was determined by GC. [c]two equiv. of β-CD was used. [d]Two equiv. of $Et_3N$ was used. [e]Each isomer was assigned based on previously reported results in which $NaBH_4$ reduction was performed without β-CD.

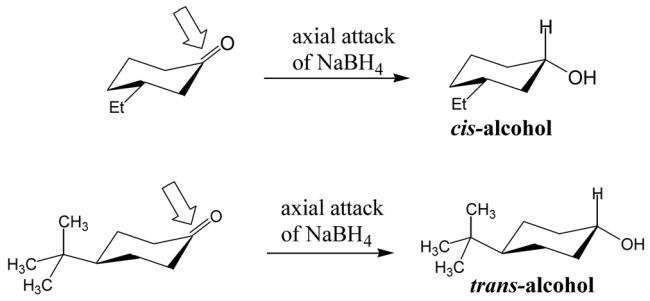



**Figure 2**. Axial attack products of cyclohexanone derivatives.

that is, β-CD induced axial attack. The axial attack of 2- or 4-substituted cyclohexanones produce the *trans* alcohols, while the axial attack of 3-substituted cyclohexanones give the *cis* alcohols as shown in Figure 2. When 4 equivalent instead of 2 equivalent of β-CD was used, the selectivity was slightly higher than data of Table 1.

These consistent results can be explained based on the transition state of the reduction reaction occurring in the β-CD cavity. According to a previous study,[6a] the structure of the transition state is near that of the product in the reduction of cyclohexanone in a protic solvent. As shown in Figure 3, due to the steric strain and the hydrophobic interior of the cavity, transition state **B**, in which the oxy-anion is positioned toward the outer water molecules, is more stable than transition state **A**.

Since the long reaction time (16 h) was thought to result from the low solubility of the β-CD-substrate complex, more soluble β-CD derivatives were used instead of β-CD. β-$CD_{en}$ and β-$CD_{sul}$, which contain one ethylenediamine group and several $SO_3Na$ groups, respectively, are much more water -soluble (Fig. 1). Using β-$CD_{en}$ and β-$CD_{sul}$, the reaction was completed within 3 h, and generally the selectivity was slightly better than with β-CD.

It has been reported that $Et_3N$ increases the enantioselectivity in the reduction of ketones using β-CD and $NaBH_4$.[11] The author postulated that this increase occurs because $Et_3N$ reduces the freedom of the substrate in the β-CD cavity *via* a three-component complex. In this study, however, no positive effect of $Et_3N$ was observed.

With the expectation of enantioselective reduction in the chiral cavity of β-CD, the enantiomeric excess (ee) was measured using a chiral GC column. The *cis*-product of 3-ethylcyclohexanone had the highest ee (26.5%), while the others had an ee of less than 15%.

In conclusion, β-CD induced axial attack in the $NaBH_4$ reduction of cyclohexanone derivatives. This axial attack can be explained by the stability of the transition state. The solubility problem can be solved by using more water -soluble β-CD derivatives, such as β-$CD_{en}$ and β-$CD_{sul}$.

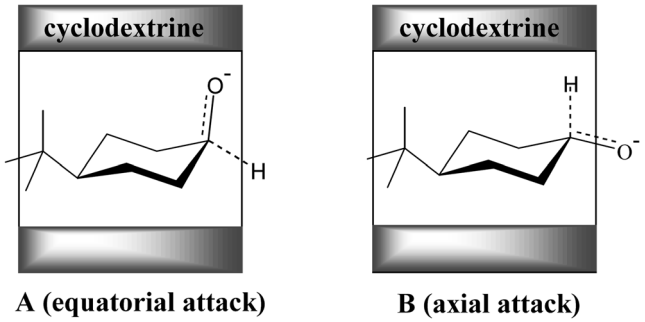



**Figure 3**. Expected transition state of hydride attack in the β-CD cavity.

## Experimental Section

**General.** β-Cyclodextrine, its sulfonated derivative (β-$CD_{sul}$) and cyclohexanone derivatives except 3-ethylcyclohexanone were purchased from Aldrich Co. Merck Silica Gel l60 (230-400 mesh) was used for flash column chromatography. Diastereoselectivity was determined using a Hewlett Packard 5890 Series (II) Gas Chromatograph.

**Synthesis of mono-(6-β-aminoethylamino-6-deoxy)-β-cyclodextrine (β-$CD_{en}$).** β-Cyclodextrine was tosylated to mono-6-*p*-toluensulfonyl-β-cyclodextrine (β-CD-OTs)[9] and then treated with 1,2-diaminoethane to give β-$CD_{en}$.[10] β-CD (12 g, 10.6 mmol) was dissolved in water (100 mL) and then NaOH (13 g, 32.8 mmol) in water (10 mL) was added. *p*-Toluenesulfonyl chloride (2 g, 10.6 mmol) in $CH_3CN$ (10 ml) was added dropwise and stirred for 16 h at rt. The resulting precipitate was filtered off and the filtrate was stored at 4 °C for 16 h. The resulting white solid was filtered and then dried under vacuum to get β-CD-OTs (1.4 g) as a white solid. β-CD-OTs (1 g,) was dissolved in 1,2-diaminoethane (1 mL) and stirred for 1 h at 70 °C. The reaction mixture was chromatographed (cellulose, 0.05 M ammonium bicarbonate) to give β-$CD_{en}$ (0.4 g). $^1$H NMR ($D_2O$) 2.7-2.9 (m, 3H), 3.0 (dd, 1H), 3.21(t, 2H), 3.45 (t,1H), 3.5-4.1 (m, 39H), 5.1 (m, 7H). $^{13}$C NMR ($D_2O$) 27.6, 41.1, 52.6, 61.2, 71.4, 72.9, 73.0, 74.3, 82.2, 85.5, 103.0. FABMS m/z 1177.2 $(+H)^+$.

**Synthesis of 3-ethylcyclohexanone.** Diethyl zinc (70 mL, 1 M in hexane) was added to a solution of 2-cyclohexen-1-one (5 g, 52 mmol), CuI (0. 5 g, 2.5 mmol), and dimethylsulfide (1 mL, 13.6 mmol) in dry toluene (30 mL) and stirred for 2 h at rt. After quenching with 1 N HCl, extracting with diethyl ether, drying with $Na_2SO_4$, concentrating, and chromatography (pentane/diethyl ether = 5/1) 4.2 g of 3-ethylcyclohexanone was obtained. $^1$H NMR ($CDCl_3$): $\delta$ 0.92 (t, 3H), 1.36 (m, 3H), 1.67 (m, 2H), 1.83-2.10 (m, 3H), 2.22-2.47 (m, 3H).

**$NaBH_4$ reduction of cyclohexanones without β-CD and its derivatives.** $NaBH_4$ (320 mg, 6.5 mmol) was added to cyclohexanone derivatives (6.5 mmol) in MeOH (10 mL), and stirred for 30 min at rt. The reaction mixture was diluted with water (30 mL) and then extracted twice with diethyl ether (10 mL). The diethyl ether layer was dried with $Na_2SO_4$ and concentrated to give the corresponding alcohols.

**$NaBH_4$ reduction in the presence of β-CD and its derivatives.** β-Cyclodextrine or its derivatives (1.3 mmol) were dissolved in 0.2 M aqueous $Na_2CO_3$ (10 mL). Cyclohexanone derivatives (0.65 mmol) were added to this solution, and the resulting suspension was stirred for 16 h at rt. After

adding $NaBH_4$ (32 mg, 0.65 mmol), the reaction mixture was stirred at rt until the starting ketone disappeared on TLC. The reaction mixture was extracted with diethyl ether and organic solution was subjected to GC determination.

**Determination of the stereoselectivity of alcohols.** Diastereoselectivity was determined using gas chromatography (Hewlett Packard 5890 Series II) and an $\alpha$-DEX-120 column (Supelco, 30 m, 0.25 mm ID). Configuration of each isomer was determined by comparison with literature data (Table 1) in which $NaBH_4$ reduction was performed without $\beta$-cyclodextrine.

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