Selective Ring-Opening Reaction of Epoxides with Sodium Borohydride in the Presence of Cyclodextrins in Aqueous Media[1)]

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In the presence of cyclodextrins (CDs), the ring-opening reaction of styrene oxide with $NaBH_4$ in aqueous media proceeded smoothly to give 1-phenylethanol with high selectivity of up to 94%, and kinetic resolution of the racemic epoxide was observed. Kinetic studies suggest the resolution based on the different reaction rates between two enantiomers included in the CD's cavity. The reaction of epoxides such as 1,2-epoxyindan and 1,2-epoxy-3-phenylpropane are also affected by the addition of CDs to proceed smoothly with high regioselectivities.

Inclusion phenomenon or "host and guest chemistry" has attracted growing attention and many efforts have been done to control chemical reactions by means of inclusion phenomenon. Cyclodextrins (CDs), macrocyclic compounds consisting of α-1,4-linked D-glucopyranose, are well-known naturally-occurring host molecules characterized by definite shape and size, chirarity, and solubility in water.[2)]

We have been interested in effects of CDs on organic reactions, and attempted to utilize CDs in organic synthesis. In previous studies, we have applied CDs as inverse phase-transfer catalysts to the oxidation reactions of olefins[3)] and benzylic alcohols,[4)] and as asymmetric reaction vessels to epoxidation of olefins.[5)]

As molecular reaction vessels, CDs are expected to exert microenvironmental effects leading to acceleration of reactions, and conformational effects resulting in selectivities of reactions. Such effects of CDs have been observed in many reaction systems. Breslow reported that CDs greatly accelerated the chlorination of anisole by hypochlorous acid, and that the reaction exhibited remarkable para-selectivity in the presence of CD.[6)] Komiyama used CDs and their derivatives in the formylation, carbonylation, dihalomethylation, and allylation of phenols for rate and regioselectivity enhancement.[7)] Moreover, the effects of CDs in some photoreactions and pyrolysis have been studied in detail by Eaton and Ramamurthy,[8)] and Abelt.[9)] Recently, some efforts have been done for using CDs in asymmetric synthesis. Asymmetric epoxidation of olefins,[5,10)] asymmetric halogenation and hydrohalogenation of styrene,[11)] and asymmetric reduction of ketones[12)] have been reported. Here, we wish to report the effects of CDs on the ring-opening reaction of epoxides with $NaBH_4$ in aqueous medium.

Many methods are known about the ring opening of epoxides, including the reaction with hydrides.[13)] Although $NaBH_4$ is a readily available and mild hydride source, it has long been considered inapplicable to the ring-opening reaction of epoxides to corresponding alcohols due to slow reaction rate. It was recently reported that the reaction of epoxides with $NaBH_4$ can be carried out in alcoholic solvents, but the method seems to be inconvenient for separating products.[14)] In the present study, we have found that in the presence of cyclodextrins, the ring-opening reaction of epoxides with $NaBH_4$ in aqueous media proceeds smoothly with high regioselectivity, and racemic epoxides are kinetically resolved during the reaction.

Results and Discussion

Ring-Opening Reaction of Styrene Oxide. Styrene oxide reacted with $NaBH_4$ in aqueous solution at room temperature very slowly, and gave 1- and 2-phenylethanol with predominance of 2-phenylethanol. When CDs were applied to the reaction, the effects of CDs were found in three respects (Table 1).

Firstly, the reaction was significantly accelerated by the addition of CDs. When the reaction was carried out in the presence of 20 mol% of α-, β-, or γ-CD without changes in other conditions, the conversion of styrene oxide increased from 17% to 54, 83, and 77%, respectively.

Secondly, the regioselectivity of ring opening was changed, i.e. the product ratio of 1-phenylethanol **2a** to 2-phenyl isomer **2b** was reversed as compared with that in the absence of CDs, and the main product of the reaction involving CDs was 1-phenylethanol. When the molar ratio between β-CD and styrene oxide was 2 : 1, 1-phenylethanol reached 94% selectivity.

Thirdly, when β- or γ-CD was used, 1-phenylethanol was obtained with a majority of (*S*)-(−)-1-phenylethanol, and recovered styrene oxide was rich in (*S*)-(−)-styrene oxide. Enantiomer excesses of produced 1-phenylethanol and of recovered styrene oxide were 46 and 31%, respectively, when styrene oxide racemate and β-CD were used in the molar ratio of 1 : 2.

The good effects of CDs on the reaction may be interpreted by formation of water-soluble inclusion complexes between styrene oxide and CDs. The low solubility of styrene oxide in water prevents it from ring-opening reaction with $NaBH_4$. When CD is absent, the molecules of styrene oxide aggregate together and are difficult to come into direct contact with a reagent

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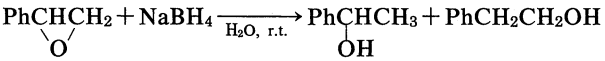
Table 1. Effects of CDs on the Ring-opening Reaction of Styrene Oxide



1 **2a** **2b**

5 mmol 10 mmol

CD	Time	Recovered **1**		Product			
		Recovery	e.e.	**2a**		**2b**	Selectivity
mmol	h	%	%	Yield/%	e.e./%	Yield/%	of **2a**/%
—	48	83	0	6	0	11	35
α-CD(1)	48	45	0	31	0	23	57
β-CD(1)	48	17	25(*S*)	66	15(*S*)	17	80
γ-CD(1)	48	23	0	53	2(*S*)	24	68
β-CD(10)	72	49	31(*S*)	48	46(*S*)	3	94

E.e. of styrene oxide and 1-phenylethanol were determined by HPLC and specific rotatory power.

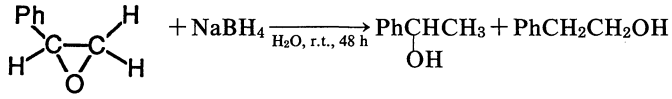
dissolved in water. In the presence of CD, a styrene oxide molecule will be included into CD's cavity and move into water. The resulting inclusion complex will encounter easily a reagent, BH_4^-, in water. Instead of CDs, we applied methyl α-D-glucoside and dextrin, which are a sub-unit of CD and open-chain oligomers of glucopyranose, to the ring-opening reaction of styrene oxide. No effects could be observed with these compounds. This fact indicates that the effects of CDs on the reaction are inseparable from the property of inclusion complex formation. In addition, among the three kinds of CDs, β-CD showed the best effects on the reaction, also indicating that inclusion complex formation was involved, and that the shape of styrene oxide molecule is fittest to the cavity of β-CD.

Kinetic Resolution of Styrene Oxide. We confirmed that (*R*)-(+)-styrene oxide gave only (*S*)-(−)-1-phenylethanol; and (*S*)-(−)-styrene oxide gave only (*R*)-(+)-1-phenylethanol. Because the conformation of the asymmetric center should be retained during the ring-opening reaction, it is clear that the origin of the formation of the optically active products is due to kinetic resolution.

By examining the reaction of the two enantiomers, it was found that in comparison with (*R*)-(+)-styrene oxide, the reaction of (*S*)-(−)-styrene oxide was accelerated in a smaller extent and gave a lower selectivity of 1-phenylethanol (Table 2).

In which step did the the kinetic resolution occur? Two possibilities can be considered: One is that CD includes one of the enantiomers selectively. Another is that in CD's cavity the reaction rates of the two enantiomers are different. In order to answer the question, we measured dissociation constants of two enantiomers with β-CD in aqueons solution. The dissociation constants obtained are 8.3×10^{-3} M (1 M=1 mol dm^{-3}) for the inclusion complex of β-CD with (*R*)-(+)-styrene oxide and 9.8×10^{-3} M for the inclusion complex of β-CD with (*S*)-(−)-styrene oxide. The difference between the dissociation constants of two enantiomers seems too small to result in kinetic resolution. Furthermore, we isolated an inclusion complex of β-CD with styrene oxide and proved that the kinetic resolution does not

Table 2. Ring-Opening Reaction of Each Isomer of Styrene Oxide



R or *S*-Isomer *R* or *S*-Isomer

5 mmol 10 mmol **2a** **2b**

Substrate	β-CD	Recovered styrene oxide		Product			
		Recovery	e.e.	**2a**		**2b**	Select. of **2a**
		%	%	Yield %	e.e. %	Yield %	%
1-*R*	—	72	~99(*R*)	11	~99(*S*)	16	41
1-*R*	1 mmol	13	~99(*R*)	73	~99(*S*)	14	84
1-*S*	—	67	~99(*S*)	14	~99(*R*)	19	41
1-*S*	1 mmol	35	~99(*S*)	48	~99(*R*)	18	72

occur in the step of inclusion complex formation. Thus, the inclusion complex was prepared by stirring an excessive amount of racemic styrene oxide with a saturated aqueous solution of β-CD at room temperature. The inclusion complex produced was collected by filtration from the mixture. By extraction with diethyl ether, the excessive styrene oxide was recovered. Styrene oxide included by β-CD was recovered by suspending the inclusion complex in water, and then extracting with diethyl ether. We found that both styrene oxide included by CD and excessive styrene oxide remained freely were racemates as measuring optical rotation of the recovered styrene oxide.

The reason of kinetic resolution therefore must rest on the different reaction rates of two enantiomers included in the cavity of CD. That is to say, both enantiomers can be included easily by CD to almost the same extent, but exhibit a different reaction rate in the cavity of CD. To confirm this, we attempted to do kinetic study on the reactions of two enantiomers. Unfortunately, the attempt has falled off success due to the complexity of the reaction.

Ring-Opening Reaction of Other Epoxides. Besides styrene oxide, the ring-opening reaction of other epoxides involving CDs was also investigated. As shown in Table 3, the accelerating effect of CDs on the ring-opening reaction of epoxides are remarkable, and the ring-opening reaction is regioselective in the presence of CDs. Especially, racemic 1,2-epoxyindan and 1,2-epoxy-3-phenylpropane were optically resolved to some extent during the reaction involving CD.

1,2-Epoxyindan reacted with $NaBH_4$ in aqueous solution and gave 2-indanol as the sole product. After the reaction involving CDs, recovered 1,2-epoxyindan showed optical rotation, indicating that 1,2-epoxyindan was kinetically resolved during the reaction. When the molar ratio of 1,2-epoxyindan to α-CD was 1 : 1, recovered 1,2-epoxyindan showed specific rotatory power of 12° corresponding to 20% enantiomer excess which was determined by ^1H NMR spectrum using $Eu(hfc)_3$ as a chiral shift reagent.

1,2-Epoxy-3-phenylpropane was another interesting substrate. In the absence of CD, 1,2-epoxy-3-phenylpropane almost did not react with $NaBH_4$ in aqueous solution. All CDs uniformly accelerated the reaction remarkablely. 1-Phenyl-2-propanol was the sole ring-opening product. Among the three kinds of CDs, the effect of α-CD was outstanding. The reaction of 1,2-epoxy-3-phenylpropane required only a catalytic amount of α-CD (Table 4). It was found that during the reaction involving α-CD, 1,2-epoxy-3-phenylpropane racemate was resolved. One thing worthy to be noted is that the effects of CDs were not modified simply by raising the amount of α-CD added. The best efficiency for optical resolution was observed when about 10 mol% of α-CD was used. Then both the reaction rate and the efficiency for optical resolution tended downwards as the increasing amount of α-CD.

By examining the inclusion mode with CPK molecular models, it seems that the decrease in the reaction rate and effeciency in optical resolution can be explained considering the formation of a 2 : 1 CD-epoxide inclusion complex (Figure 1), as the amount of α-CD is

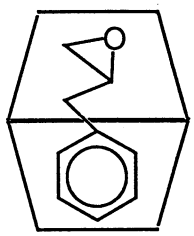


Fig. 1. 2 : 1 CD-1,2-epoxy-3-phenylpropane complexes.

Table 3. Ring-Opening of Some Epoxides

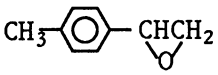
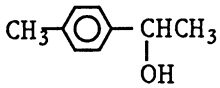
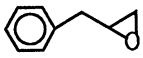
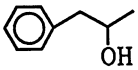
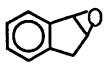
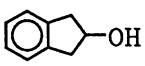
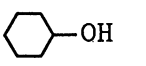
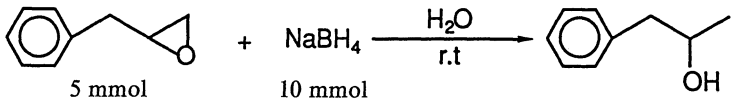
Epoxide	Product	CD	Time	Recovered epoxide		Product	
		mmol	h	Recovery/%	e.e./%	Selec./%	$[\alpha]_D$/deg.
		—	24	94	0	17	—
		β-CD(1)	30	63	0	68	—
		—	24	92	0	100	—
		α-CD(0.5)	5	41	26	100	−8.7
		—	5	52	0	93	
		α-CD(5)	15	38	20	95	
		—	5	73		100	
		β-CD(1)	5	5		100	
$CH_3(CH_2)_7CHCH_2$	$CH_3(CH_2)_7CHCH_3$	—	312	100			
O	OH	γ-CD(1)	312	26		100	

Table 4. Ring-Opening Reaction of 1,2-Epoxy-3-phenylpropane



5 mmol 10 mmol

CD mmol	Time h	Conv. %	e.e.[a] of Recovered epoxide/%	$[\alpha]_D^{23}$ [b] of alcohol deg.
—	24	6	0	0
α-CD(1)	24	98	—	—
β-CD(1)	24	46	0	0
γ-CD(1)	24	81	—	−0.8
α-CD(0.3)	6	41	11	—
α-CD(0.5)	5	59	26	−8.7
α-CD(1)	5	61	18	−9.9[c]
α-CD(3)	17	49	4	−1.4
α-CD(5)	72	24	<1	—

a) E.e. of 1,2-epoxy-3-phenylpropane was determined by HPLC. b) $[\alpha]_D^{23}$ was measured in $CHCl_3$. c) $[\alpha]_D^{23}=-9.9°$ corresponds to 24% e.e. as determined by ^1H NMR spectroscopy. According to the report of Bell, the sample was rich in (*R*)-(−)-1-phenyl-2-propanol.[16]

increased. It is clear that the inclusion mode shown in Fig. 1 would undoubtedly interrupt the reaction of the epoxide.

Conclusion

It has been demonstrated by the results presented here that CDs affect the ring-opening reaction of epoxides dramatically. In comparison with the known processes for the ring-opening reaction of epoxides using organic solvents and sensitive hydrides such as lithium aluminum hydride and diborane, the present method has the advantages of easy procedure, high regioselectivity, and high yield of ring-opening product, and provides a practical method applicable for organic synthesis. In addition, although the efficiency of kinetic resolution by CDs is not satisfied at present, it has been suggested that CDs may be used to asymmetric syntheses based on the formation of inclusion complexes.

Experimental

Instruments. GLC analyses were performed on a Shimadzu GC-12A chromatograph equipped with a 3-m Thermon-1000 column. HPLC analyses of asymmetric compounds were carried out on a Shimadzu LC-6A chromatograph equipped with a 25-cm Chiralcel OF column. Optical rotations were measured on a Jasco DIP 370 polarimeter. ^1H NMR spectra were recorded on a Bruker AM 360 instrument. UV spectra were recorded with a Hitachi U-3400 spectrophotometer.

Materials. CDs, $NaBH_4$, (±)-styrene oxide, (*R*)-(+)-styrene oxide, (*S*)-(−)-styrene oxide, cyclohexene oxide, and 1,2-epoxydecane were commercially available. 1,2-Epoxyindan, 1,2-epoxy-3-phenylpropane and *p*-tolyloxirane were prepareded by KOH treatment of corresponding bromohydrins[16] which were obtained from corresponding olefins by the Guss method.[17] The chemical purities of all epoxides were checked by gas chromatography and confirmed to be higher than 98%. The optical purities of (*R*)-(+)-styrene oxide and (*S*)-(−)-styrene oxide were higher than 99% according to HPLC analysis.

Ring-Opening Reaction of Epoxides. The ring-opening reaction of all epoxides was carried out by stirring a mixture of epoxide, $NaBH_4$ and CD in water at room temperature. In the reactions involving CD, 2 ml of water per 1 mmol of CD was used, and 2 ml for all reactions in the absence of CD. The reaction mixture was extracted with ether, and crude products were analyzed by GLC and HPLC. The crude products were purified by silica gel column chromatography with hexane–ethyl acetate. All products of the reactions were identified by ^1H NMR and IR spectroscopy.

Optical purities of styrene oxide, 1-phenylethanol, 1,2-epoxy-3-phenylpropane, and *p*-tolyloxirane were determined by HPLC analysis.

Optical purities of recovered 1,2-epoxyindan and 1-phenyl-2-propanol were determined by ^1H NMR spectroscopy using $Eu(hfc)_3$ as a chiral shift reagent.

Dissociation Constants of β-CD-Styrene Oxide Inclusion Complex. Since the ultraviolet spectrum of styrene oxide is modified by binding into CD's cavity, a UV spectroscopic method was used to determine the dissociation constant K_d.[17]

To each of several 50 ml volumetric flasks containing accurately measured quantity of β-CD, 5 ml of 5.3×10^{-3} M solution of (*R*)- or (*S*)-styrene oxide in water was added. The solutions were diluted to the marks with water. The absorption at 257 nm of each of these solutions was measured at 25 °C. The reference compartment contained a solution of β-CD of identical concentration.

For the calculation of dissociation constants, following equation was used:

$$C_0S_0/\Delta\mathrm{Abs} = K_d/\Delta\varepsilon + (C_0+S_0)/\Delta\varepsilon$$

where C_0 is the initial concentration of β-CD, S_0 is the initial concentration of styrene oxide, ΔAbs is the change in absorbance at a particular wavelength from the absorbance of styrene oxide alone at this concentration, and $\Delta\varepsilon$ is the difference in molar extinction coefficient for the complex and the pure styrene oxide. Thus, a plot of C_0S_0/ΔAbs vs. C_0+S_0 yields a straight line with intercept/slope$=K_d$.

Caution. (*R*)-(+)-Styrene oxide and (*S*)-(−)-styrene oxide showed plus and minus optical rotation in neat state, respectively. However, the signs of optical rotation of these two isomers reversed when the optical rotation was measured in $CHCl_3$ or CH_2Cl_2 solution at low concentrations, and the specific rotatory power significantly varied with the concentration of the solution. Calibration curves of specific rotatory power must be made for analysis.

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