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Asymmetric Halogenation and Hydrohalogenation of Styrene in Crystalline Cyclodextrin Complexes

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Abstract. Asymmetric halogenation and hydrohalogenation of styrene in microcrystalline cyclodextrin complexes were studied in the gas-solid state, and compared with the homogeneous reactions in aqueous or dimethyl sulfoxide solutions. The gas-solid brominations in the α- and β-cyclodextrin complexes produced predominantly (−)-1,2-dibromo-1-phenylethane. The chiral induction for the reaction of the α-cyclodextrin complex rose to 9 times that of the β-cyclodextrin complex. Brominations in the homogeneous solutions containing the α- or β-cyclodextrin complexes gave no dibromide but racemic bromohydrin. In the gas-solid chlorination, the α-cyclodextrin complex gave (−)-dichloride, *S*-(+)-2-chloro-1-phenylethanol (14% ee) and (+)-1,2,2-trichloro-1-phenylethane, and the β-cyclodextrin complex produced (+)-dichloride, *S*-(+)-chlorohydrin (8% ee) and (+)-trichloride. The chiral induction of the gas-solid halogenation using the solid cyclodextrin complexes is attributed to the ability to hold rigidly a chiral conformation of the crystalline state. However, the gas-solid hydrohalogenation all gave racemic products.

Key words: Asymmetric halogenation, hydrohalogenation, styrene, cyclodextrin complex.

1. Introduction

Asymmetric synthesis through reaction in the solid state demands the formation of chiral crystalline structures having certain intramolecular or intermolecular features [1]. Penzien and Schmidt [2] reported the first example of absolute asymmetric synthesis where a single crystal of 4,4′-dimethylchalcone reacts with gaseous bromine. Since this approach, however, has to use compounds which form giant single crystals in a chiral space group, the number of molecules available for such reactions are quite limited. Chiral host species such as cyclodextrins (CDs) form chiral crystalline inclusion complexes with prochiral guest molecules by incorporating them within the relatively nonpolar cavity of the host molecules [3]. Therefore, these materials may produce asymmetric reactions in the solid state, which are topochemically controlled by the crystalline lattice of the inclusion complexes. Such reactions of CD complexes in the solid state, however, have not been accomplished, but asymmetric syntheses such as reduction [4], epoxidation [5] and sulfoxidation [6, 7] catalyzed by native CDs have been studied in solution.

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All the products gave low optical yields with 0–34% ee. Furthermore, asymmetric halogenation of olefins with CD as a chiral matrix has not been investigated in the past apart from our reports [8–10].

Previously [8], the authors succeeded in achieving a strong chiral induction (88–100% ee) for the chlorination of methacrylic acid in the crystalline CD complexes. Here, we report on the asymmetric addition of gaseous bromine, chlorine, hydrogen bromide and hydrogen chloride to styrene in the crystalline complexes of α-CD (cyclohexa-amylose) or β-CD (cyclohepta-amylose).

2. Materials and Methods

2.1. MATERIALS

α- and β-CDs were purchased from Sanraku-Ocean Co., Ltd., and recrystallized from water. Styrene was distilled immediately before use. Chlorine and hydrogen chloride were purchased from Komatsugawa Sanso and Tsurumi Soda Co., Ltd., respectively, and passed through a sulfuric acid trap prior to use. Hydrogen bromide was prepared by the procedure given in the literature [11]. All other chemicals were purified using standard methods [12].

2.2. PREPARATION OF INCLUSION COMPLEXES

To 500 ml of aqueous solutions of α-CD (1.7×10^{-1} mol/l) or β-CD (3.0×10^{-2} mol/l), equimolar amounts of styrene were added at 40 °C and dissolved by stirring. After stirring for 2 h at room temperature, the microcrystalline precipitates were filtered and dried in vacuo at room temperature for 1 day. Then the dried powders were washed with n-pentane to eliminate the guest molecule not included and dried again. The complex formation was confirmed by X-ray powder diffraction and TG-DSC techniques. Thus, the crystalline 2:1 and 1:1 complexes were obtained for α- and β-CDs with styrene in 90 and 80% yields, respectively. The contents of styrene in the complexes were estimated by ^{1}H NMR spectra in dimethyl-d_6 sulfoxide (DMSO-d_6).

2.3. HALOGENATION AND HYDROHALOGENATION OF THE CRYSTALLINE INCLUSION COMPLEXES

A typical experimental procedure was as follows. The solid α-CD inclusion complex of styrene (ca. 2 g, 1 mmol) was exposed to bromine vapour (10 mole % excess) in a desiccator (ca. 600 ml) in the dark under air at 0 °C. After an exposure of 2 h, the powder obtained was dissolved in water containing sodium thiosulfate as a reducing agent for the excess of bromine. The reacted and the unreacted guests were extracted repeatedly with diethyl ether from the aqueous solution until no aromatic compounds were detected in the aqueous layer by UV spectroscopy in the region of 230 to 350 nm. Thus, 95–98% of the extract was recovered from the water layer, and chromatographed with dichloromethane on silica gel (Wakogel C-300). The products were identified as 1,2-dibromo-1-phenylethane and 2-bromo-1-phenylethanol by ^{1}H NMR and IR spectra. Chlorination, hydrobromination and hydrochlorination of the CD complexes of styrene were carried out by a similar procedure to this bromination.

The homogeneous bromination was carried out by dissolving the α- and β-CD complexes (containing 1 mmol of styrene) in water (200 ml) or dry dimethyl sulfoxide (DMSO, 5 ml), to which an equimolar amount of bromine was added, at 25 °C for 10 min. Then the reaction mixture was poured into 100–200 ml of 15% aqueous sodium chloride containing sodium thiosulfate (1 mmol), followed by extraction with diethyl ether. The extract was recovered in 98% yield and chomatographed as described above.

2.4. ANALYTICAL METHODS

Optical rotations were measured in various organic solvents on a Union Giken PM-101 polarimeter using 1 dm cells. The other spectroscopic measurements were carried out by a JEOL-PMX 60 for ^{1}H NMR at 60 MHz and Hitachi IR-285 spectrometers for IR spectra. The X-ray powder diffraction patterns of the solid samples were taken in the region of 5 to 35° by a Rigakudenki Model 2037 X-ray diffractometer using Ni-filtered Cu-K_α radiation. The thermal behavior of the specimens was observed with a Rigakudenki TG-DSC standard analyzer at a fixed heating rate of 10 °C/min.

3. Results and Discussion

3.1. INCLUSION COMPLEXES

The inclusion complexes between styrene and α- or β-CDs were obtained as microcrystalline precipitates from the aqueous solutions in good yields. The molar ratios of styrene to CDs were found to be 0.5 for the α-CD complex and 1.0 for the

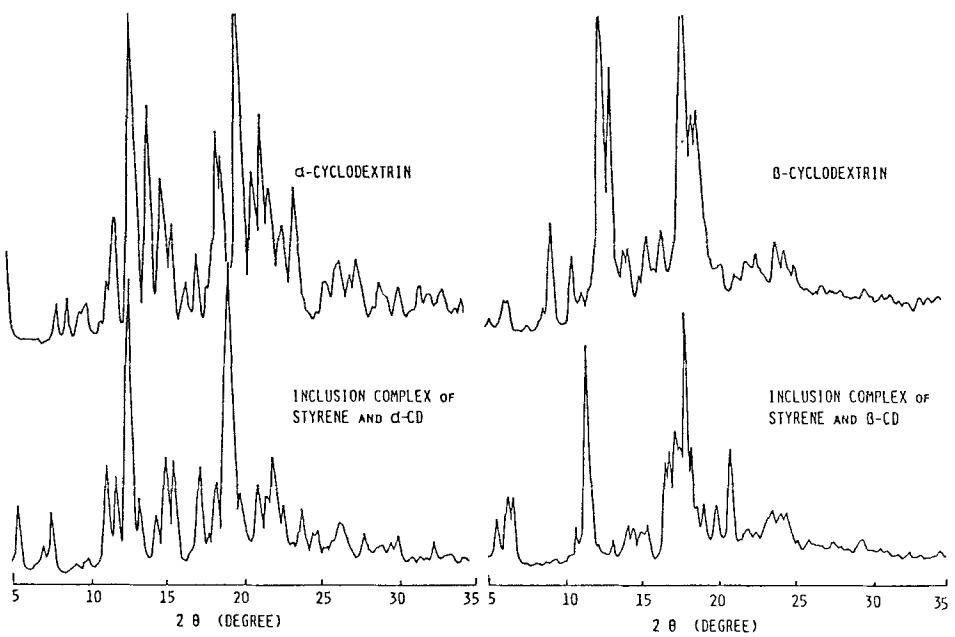

Fig. 1. X-ray diffraction patterns of α- and β-CDs, and their inclusion complexes with styrene.

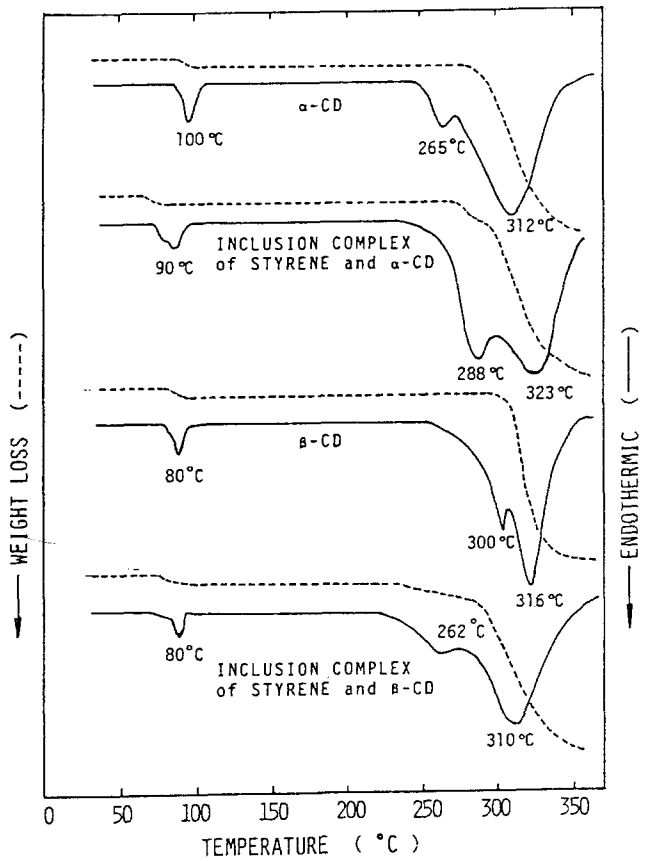

Fig. 2. TG-DSC curves of α- and β-CDs, and their inclusion complexes with styrene.

β-CD complex, respectively, by ^{1}H NMR in DMSO-d_6. The water content of the CD complexes, measured from ^{1}H NMR spectra ($\delta = 3.4$ ppm, *s*, H_2O, in DMSO-d_6), was about 7 in the molar ratio of the water molecules to CDs. The powder X-ray diffraction patterns of these complexes showed that they were highly crystalline, and did not correspond to those of CDs, as shown in Figure 1. The diffraction diagram of the physical mixtures of CDs and oily styrene (mp −31 °C), however, could not be obtained at room temperature. Attempts to prepare single crystals of the CD complexes for X-ray structure analysis were unsuccessful. Figure 2 shows the thermal behavior (TG-DSC curves) for CDs and their complexes with styrene. α- and β-CDs seem to dehydrate at 80–100 °C and decompose at 290–300 °C. The α-CD complex does not lose styrene (bp 146 °C) even at 250 °C and the β-CD complex also does not until reaching 230 °C, as a result of the formation of a complex. Although the decomposition temperature of α-CD was slightly lower than that of β-CD, the thermal stability of the α-CD complex was found to be higher than that of the β-CD complex.

3.2. REACTION PRODUCTS

The gas-solid halogenation of styrene **1** in the crystalline CD complexes produced

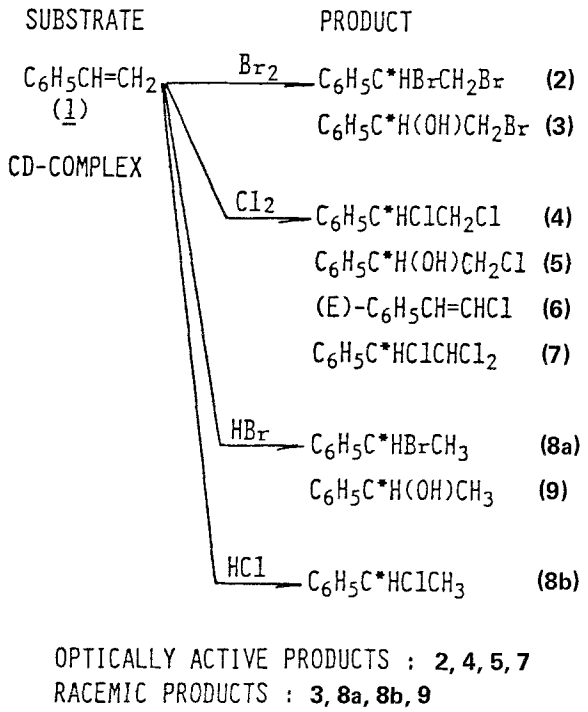

Fig. 3. Products from the gas-solid halogenation and hydrohalogenation of styrene in the crystalline cyclodextrin complexes.

optically active products, but the hydrohalogenation gave racemic products. As shown in Figure 3, the bromination of the CD complexes produced (−)-1,2-dibromo-1-phenylethane (**2**) and racemic 2-bromo-1-phenylethanol (**3**). In the chlorination, the CD complexes gave (+)-1,2-dichloro-1-phenylethane (**4**), (+)-2-chloro-1-phenylethanol (**5**) and (+)-1,2,2-trichloro-1-phenylethane (**7**), and accompanied with (*E*)-1-chloro-2-phenylethane (**6**). The CD complexes produced racemic 1-bromo-1-phenylethane (**8a**) and 1-phenylethanol (**9**) in hydrobromination and racemic 1-chloro-1-phenylethane (**8b**) in hydrochlorination. The ^{1}H NMR and IR spectra of all products were virtually identical with those of the authentic samples given in the literature, e.g., **6** and **7** [13]. **6**: NMR (CCl_4) δ 6.62 (1H, *d*, $J = 14.2$ Hz, β-CH), 6.92 (1H, *d*, $J = 14.2$ Hz, α-CH), 7.28–7.75 (5H, *m*, aromatic H); IR (neat) 1620 cm^{-1}, (Found: C, 69.5; H, 5.2%. C_8H_7Cl requires C, 69.3; H, 5.1%). **7**: NMR (CCl_4) δ 5.20 (1H, *d*, $J = 6.0$ Hz, α-CH), 6.00 (1H, *d*, $J = 6.0$ Hz, β-CH), 7.45 (5H, *s*, aromatic H), (Found: C, 46.0; H, 3.4%. $C_8H_7Cl_3$ requires C, 45.9; H, 3.4%).

3.3. GAS-SOLID HALOGENATION

Table I shows the results for the gas-solid bromination and chlorination of styrene in the crystalline CD complexes. However, the maximum values of the specific optical rotation cannot be found in the literature for the optically pure halides apart from halohydrin derivatives of styrene. The optical yield of chlorohydrin (**5**) was calculated from the maximum value $[\alpha]_D^{25}$ −48.1° (*c*, 1.73, cyclohexane)

Table I. Asymmetric halogenation of styrene in crystalline CD complexes

Host	Gaseous reagent	Temp. °C	Time h	Yield[a] %	Product[b] compn./%	$[\alpha]_D^{25}$/° ($c = 0.5$, solvent)	ee %[c] (Config.)
α-CD	Br_2	0	2	90	96 (**2**)	−47.0 (CH_2Cl_2)	–
					4 (**3**)	0 ($CHCl_3$)	0
β-CD	Br_2	0	2	95	100 (**2**)	−5.5 (CH_2Cl_2)	–
α-CD	Cl_2	−20	48	0	–	–	–
α-CD	Cl_2	0	48	25	12 (**4**)	−4.1 (CH_2Cl_2)	–
					36 (**5**)	0 (C_6H_{12})	0
					52 (**6**)	–	–
α-CD	Cl_2	25	2	38	43 (**5**)	+6.6 (C_6H_{12})	14 (*S*)
					57 (**7**)	+6.5 (C_6H_{12})	–
β-CD	Cl_2	−20	48	47	43 (**4**)	+20.5 (CH_2Cl_2)	–
					15 (**5**)	0 (C_6H_{12})	0
					12 (**6**)	–	–
					30 (**7**)	+20.5 (C_6H_{12})	–
β-CD	Cl_2	25	2	22	68 (**4**)	+6.5 (CH_2Cl_2)	–
					14 (**5**)	+3.8 (C_6H_{12})	8 (*S*)
					18 (**7**)	+6.3 (C_6H_{12})	–

[a] Based on styrene consumed as estimated from ^1H NMR analysis.
[b] Based on the total amount of isolated products obtained by silica gel chromatography. Percentages are normalized to 100%.
[c] Enantiomeric excess (ee) values based on $[\alpha]_D^{25} - 48.1°$ (C_6H_{12}) for R-**5** from [14].

for R-**5** [14]. We tried to determine the enantiomeric excess (ee) of the other products by means of ^1H NMR analysis with chiral shift reagents such as Eu(hfc)$_3$ (tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III)) or Eu(fod)$_3$, or by other methods such as liquid chromatography with various chiral stationary phases, e.g., Daicel, Chiralcel, OB or OC, but could not succeed in the optical resolution of the products. Thus, it is not clear in the present experiment how much of the chiral induction on the gas-solid halogenation of styrene is due to the use of CDs.

3.3.1. *Gas-Solid Bromination*

As shown in Table I, when styrene in the α-CD complex was brominated at 0 °C for 2 h, the levorotatory dibromide (**2**) ($[\alpha]_D^{25}$ −47.0°) and racemic bromohydrin (**3**) were isolated in 90% yield (**2**:**3** = 96:4). Bromination of the olefin in the β-CD complex gave no **3** but **2** ($[\alpha]_D^{25}$ −5.5°) in 95% yield at the same reaction condition. The chiral induction for the reaction of the α-CD complex rose to 9 times that of the β-CD complex. The same sign of the specific rotations of **2** shows that styrene forms complexes with α- and β-CDs such that the access of bromine to the olefinic plane occurs into the same enantiotopic face in the two cases, and this face may be slightly less blocked by the inclined plane in both the asymmetric cavities of CDs. A detailed mechanism, however, cannot be described at the present time, because neither crystalline nor molecular structures were determined for the solid CD complexes. No bromination of styrene in the CD complexes occurred at a temperature of −10 °C or below because the vapor pressure of bromine is not enough to sustain the reaction: bromine solidifies at −7.3 °C.

Next, the chiral induction of the gas-solid bromination was compared with that of the homogeneous reactions in DMSO or aqueous solutions. The homogeneous reactions in the presence of CDs gave no **2** but **3** in 60–75% yields at 25 °C for 10 min. No chiral induction was observed in the homogeneous reactions. The racemic bromohydrin (**3**) is produced non-enantioselectively through the reaction of the bromonium cation with water contained in the CD complexes in dry DMSO solution, and not by the hydrolysis of **2** under the same condition. Thus, it is clear that the observed chiral induction in the gas-solid reaction is due to the ability to hold rigidly the chiral conformation of the CD complex in the crystalline state. This solid state of the inclusion complex is essential but complex formation occurs in solution.

Figure 4 shows the changes of the specific rotations of **2** during the course of the gas-solid bromination with the α-CD complex. The values were constantly up to 90% conversion of styrene, but decreased with an increase of reaction time after 2 h. Furthermore, after exposure for 40 h the value decreased to 44% of that for a 2 h exposure. When the optically active **2** ($[\alpha]_D^{25}$ −47.0°) included in the crystalline β-CD complex, not done in α-CD, was exposed to bromine vapour at 0 °C for 20 h, the optical purity of recovered **2** ($[\alpha]_D^{25}$ −33.2°) also decreased to 29.4%. In contrast, the optically active **2** crystal (mp 72 °C) did not racemize under bromine vapour. These results show that the racemization was catalyzed by CDs through exposure of bromine vapour for a long time.

In an additional result, the optical resolution of racemic **2** by the method of Cramer [15] did not recover the optically active **2** from the β-CD inclusion complex, and the racemic **2** did not form the inclusion complex with α-CD having at narrower cavity. Therefore, the formation of the β-CD complex with the racemic **2** was completely non-stereospecific.

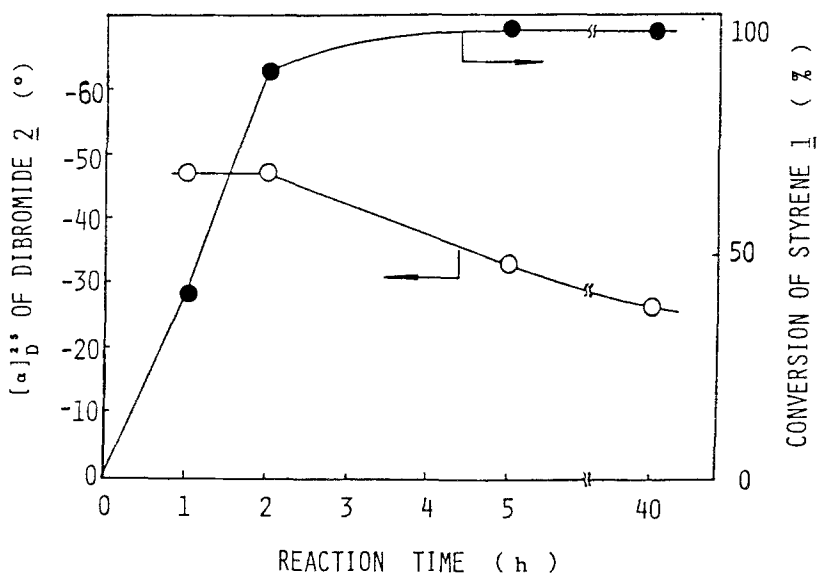

Fig. 4. Changes of specific rotations of dibromide during the course of the gas-solid bromination of styrene in the α-CD complex at 0 °C. ○, Change of specific rotations of dibromide **2**, measured in dichloromethane; ●, change of conversions (%) of styrene **1**.

3.3.2. *Gas-Solid Chlorination*

The gas-solid chlorination of the α-CD complex did not proceed at -20 °C. Dichloride **4** ($[\alpha]_D^{25}$ $-4.1°$) was obtained at 0 °C, but repeating the experiments two more times lacked reproducibility for the yields (0 ~ 3%) and the specific rotations ($[\alpha]_D^{25}$ 0 ~ $-2°$) of **4** under the same condition. Chlorination at a higher temperature such as 25 °C gave no dichloride **4** but *S*-chlorohydrin **5** (14% ee) and trichloride **7** ($[\alpha]_D^{25}$ $+6.5°$), as shown in Table I. Chlorination of the β-CD complex, however, proceeded at -20 °C for 48 h, gave the optically active products, **4** and **7** (the same specific rotation of $[\alpha]_D^{25}$ $+20.5°$), racemic **5** and (*E*)-1-chloro-2-phenylethene **6** in 47% yield (**4**:**5**:**6**:**7** = 43:15:12:30). The reaction at 25 °C gave no chloroolefin **6** but three optically active products, **4**, **5** and **7** ($[\alpha]_D^{25}$ $+4 \sim +7°$). The chlorination afforded different product species from those obtained in the bromination. The formation of **7** as a typical different product may proceed through the addition of chlorine to **6**, which is formed by dehydrochlorination between a free chloride anion and an open carbonium intermediate (**A** in Figure 5) involving the C_α–C_β rotation of the latter [16]. In the case of the bromination, the reaction proceeds through a strong bridged ion intermediate, so that the C_α–C_β rotation of the intermediate is difficult to occur, thus showing no dehydrobromination. Furthermore, since the trichloride **7** was the optically active product, both the dehydrochlorination and the subsequent chlorination of **6** should proceed in the chiral cavities of CDs without an escape of the guest molecule from the cavities. The chlorohydrin **5** was also produced by nucleophilic attack of water to a carbonium cation intermediate (C in Figure 5) similar to the formation of **3** on bromination, but was the optically active product (8 ~ 14% ee) different from the racemic **3** formed by bromination. In the chlorination of anisole in aqueous solution, Breslow *et al.* [17] suggested the covalent participation by the CD: the chloronium cation transferred first to a

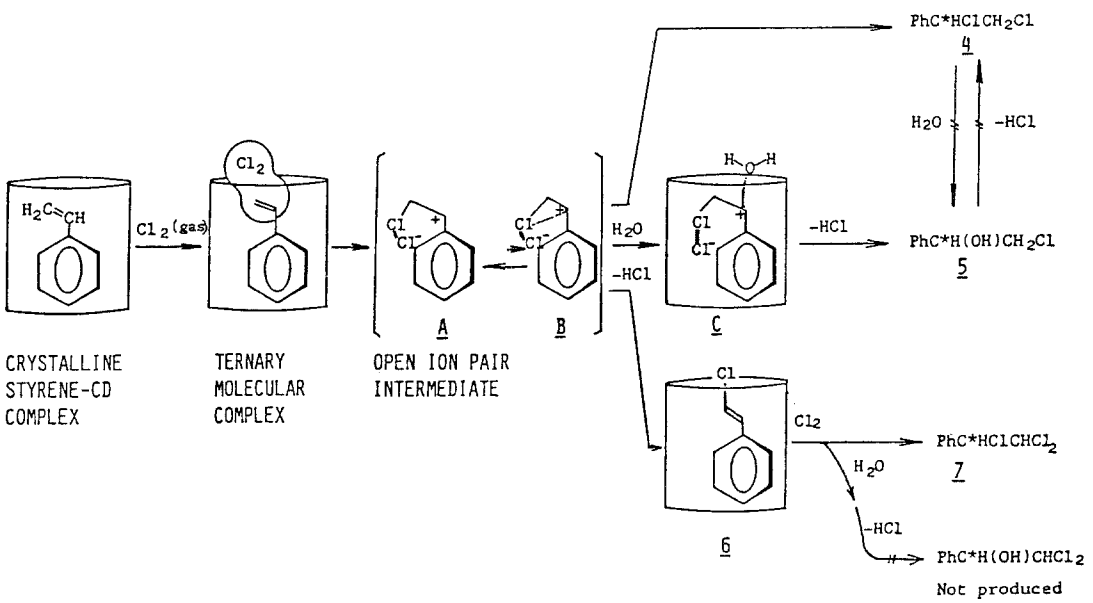

Fig. 5. Reaction mechanism of the gas-solid chlorination of styrene in the CD complexes.

hydroxyl group of the CD, then to the guest. Such a scheme also seems to occur in this reaction. However, no chloride-substituted products (e.g., *p*-chlorostyrene derivatives) and chlorinated CD were detected by ^{1}H NMR analysis of the recovered extract and CD in 95~98% yields after reaction. Thus, in the solid state, the hydroxyl groups of the CD should be less reactive than those in solution [17].

In the chlorination of the β-CD complex, the optical yields of **4** and **7** increase about three times on lowering the temperature from 25 to −20 °C. Judging from the result that the chiral induction and reactivity for the gas-solid chlorination of styrene included in β-CD depends on the temperature, the motion of the guest molecule within the host molecule should be restricted by decreasing temperature. This result, however, is different from that of the gas-solid chlorination of (*E*)-cinnamic acid in the β-CD cavity, where the optical yields of products were nearly constant over the temperature range −25 to 50 °C as reported previously [9].

Enantioselectivity for the chlorination with both the α- and β-CD complexes provided the products, **5** and **7** but no **4**, with the same configuration similar to that of the bromination.

3.4. GAS-SOLID HYDROHALOGENATION

Table II shows the results for the gas-solid hydrohalogenation of the α-and β-CD complexes with styrene at 25 °C. Both the CD complexes produced racemic **8a** and **9** in 30~50% yields (**8a**:**9** = 1:1) under hydrobromination for 3 h, and no **9** but racemic **8b** in 30~40% yields under hydrochlorination for 20 h.

Table II. Gas-solid hydrohalogenation of styrene in crystalline CD complexes at 25 °C

Host	Gaseous reagent	Time h	Yield[a] %	Product[b] compn./%	ee %
α-CD	HBr	3	28	52 (**8a**)	0
				48 (**9**)	0
β-CD	HBr	3	52	51 (**8a**)	0
				49 (**9**)	0
α-CD	HCl	20	29	100 (**8b**)	0
β-CD	HCl	20	37	100 (**8b**)	0

[a] Based on styrene consumed estimated from ^{1}H NMR analysis.
[b] Based on the total amount of isolated products obtained by silica gel chromatography. Percentages are normalized to 100%.

The hydrohalogenation shows a remarkable decrease in the enantioselectivity of halide anions attacking the carbonium cation intermediate, formed by first addition of the acids to the olefin [18]. This nonchiral induction suggests that the rotation of the groups on C_α of the intermediate occurs even in the crystalline CD complexes.

4. Conclusion

Asymmetric bromination and chlorination of styrene are achieved in microcrystalline

cyclodextrin complexes. It is attributed to the ability to hold rigidly a chiral conformation of the crystalline state. The homogeneous reaction shows no chiral induction. The gas-solid hydrohalogenation, however, gave racemic products.

References

1. B. S. Green, M. Lahav, and D. Rabinovich: *Acc. Chem. Res.* **6**, 191 (1979).
2. K. Penzien and G. M. Schmidt: *Angew. Chem., Int. Ed. Engl.* **8**, 608 (1969).
3. M. L. Bender and M. Komiyama: *Cyclodextrin Chemistry*, Springer-Verlag, Berlin (1978).
4. N. Baba, Y. Matsumura, and T. Sugimoto: *Tetrahedron Lett.* 4281 (1978).
5. S. Banfi, S. Colonna, and S. Julia: *Synth. Commun.* **13**, 1049 (1983).
6. A. W. Czarnik: *J. Org. Chem.* **49**, 924 (1984).
7. J. Drabowicz and M. Mikolajczyk: *Phosphorus and Sulfur* **21**, 245 (1984).
8. Y. Tanaka, H. Sakuraba, and H. Nakanishi: *J. Chem. Soc., Chem. Commun.* 947 (1983).
9. H. Sakuraba, T. Nakai, and Y. Tanaka: *J. Incl. Phenom.* **2**, 829 (1984).
10. Y. Tanaka, H. Sakuraba, Y. Oka, and H. Nakanishi: *J. Incl. Phenom.* **2**, 841 (1984).
11. O. Shimamura and M. Takahashi: *Bull. Chem. Soc. Jpn.* **22**, 60 (1949).
12. J. A. Riddick and W. B. Bunger: *Organic Solvents*, Wiley-Interscience, New York (1970).
13. M. C. Cabaleiro, M. D. Johnson, B. E. Swedlund, and J. E. Williams: *J. Chem. Soc. B*, 1022 (1968).
14. L. C. J. van der Laan, J. B. N. Engberts, and T. J. de Boer: *Tetrahedron* **27**, 4323 (1971).
15. F. Cramer and W. Dietsche: *Chem. Ber.* **92**, 378 (1959).
16. R. C. Fahey and C. Schubert: *J. Am. Chem. Soc.* **87**, 5172 (1965).
17. R. Breslow and P. Campbell: *J. Am. Chem. Soc.* **91**, 3085 (1969).
18. F. Freeman: *Chem. Rev.* **75**, 439 (1975).