ASYMMETRIC HALOGENATION AND HYDROHALOGENATION OF *trans*-CINNAMIC ACID IN CRYSTALLINE CYCLODEXTRIN COMPLEXES

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ABSTRACT. Asymmetric halogenation and hydrohalogenation of *trans*-cinnamic acid have been achieved in the microcrystals of cyclodextrin complexes. The bromination of the organic acid in the cavity of β-cyclodextrin gave the *erythro*-dibromide in 40 % optical yield which was much larger than that from the resolution treatment of the racemic dibromide with β-cyclodextrin and the absolute configuration was opposite in sign. The asymmetric induction in the gas-solid reaction was not due to optical resolution but to the reaction itself which was influenced by the chiral frame of cyclodextrin. The reaction shows the molecular size effect that the acid in the cavity of α-cyclodextrin reacted with smaller hydrogen bromide but did not with larger bromine and chlorine. In contrast, the guest molecule in the wider cavity of β-cyclodextrin reacted with bromine and chlorine as well as hydrogen bromide. The stereospecificities of the gas-solid halogenations of the acid in β-cyclodextrin were similar to those of the both reactions in the solid state and in carbon tetrachloride solution without β-cyclodextrin: bromination of the acid yielded *erythro*-2,3-dibromo-3-phenylpropionic acid stereospecifically in 100 % in three different conditions, but chlorination gave an excess of *threo*-2,3-dichloro-3-phenylpropionic acid to the *erythro*-isomer in 72~87 % yields.

1. INTRODUCTION

A major problem in enzymology is to explain the specificities observed in enzymic reactions. A number of hypotheses have been proposed to account for specificity,[1] and various experimental evidence were given in support or rejection of these proposals. These data are very useful for discussing mechsnisms of enzymic reactions, though they seldom contribute to an understanding of specificity. Enzymes achieve much of their catalytic efficiency by molecular complexing which brings the substrate in good proximity. Effect, however, has been one of the stumbling blocks in accounting for enzymic catalysis.[2] Cyclodextrins are well known to form inclusion complexes with a variety of substrates, and recently have been proposed as simple models to account for this catalytic effect of enzymes.

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As one of the enzymic reactions, asymmetric synthesis catalyzed by cyclodextrins has been studied in the past,[3] but gave all the products in a low optical yield. We have already found a strong chiral induction for the chlorination of methacrylic acid in the crystalline cyclodextrin complexes.[4] 100 % enantiomeric excess (e.e.) of (-)-2,3-dichloro-2-methylpropionic acid and 88 % e.e. of its enantiomer were isolated in α- and β-cyclodextrins, respectively. This paper describes asymmetric addition of gaseous halogens and hydrogen halides in the crystalline complexes comprising *trans*-cinnamic acid as a reactant and α- or β-cyclodextrin as chiral matrix. Asymmetric bromination of menthyl cinnamate[5] and of salts from the acid and several chiral amines[6] have been reported, but gave low chiral inductions up to 2~16 % e.e..

2. MATERIALS AND METHODS

2.1. Materials

α- And β-cyclodextrins were obtained from Sanraku Ocean Co. and used directly. *trans*-Cinnamic acid and bromine were purchased from Wako Pure Chemical Co. and used without further purification. Chlorine and hydrogen chloride were purchased from Komatsugawa Sanso and Tsurumi Soda Co., respectively, and passed through a sulfuric acid trap prior to use. Hydrogen bromide was prepared by the procedure given in the literature.[7] All other chemicals were purified in the standerd ways.[8]

2.2. Preparation of Cyclodextrin Complexes

To 100 ml of aqueous solution of α-cyclodextrin (1.7×10^{-1} mol/l) or β-cyclodextrin (3.0×10^{-2} mol/l), equimolar amounts of *trans*-cinnamic acid in acetone (9 wt % the acid solution) were added at 40 °C. After stirring for 2 h at room temperature, the resultant white precipitates were filtered and dried *in vacuo*. Then the dried powders were washed with carbon tetrachloride to eliminate the guest molecule not included and dried again. X-ray powder diffraction and TG-DSC techniques were used to prove complex formation in the solid state.

2.3. Asymmetric Reactions in Crystalline Cyclodextrin Complexes

A typical experimental procedure is as follows. The β-cyclodextrin complex of *trans*-cinnamic acid (2 g, 1.6 mmol) sieved to 200~250 mesh size was introduced into a 600 cm^3 desiccator containing liquid bromine (0.1 ml, 2 mmol) under air in the dark at 25 °C. Bromine was admitted as vapour after 10 min. After exposure of 20 h, the excess of bromine was removed by evacuation and the complex powder was dissolved in water. The product was extracted with diethyl ether from the aqueous layer while stirring vigorously at room temperature. After 3 h, the organic layer was separated, dried over anhydrous magnesium sulfate, and concentrated to give a white solid. The extract was recovered in 90~98 % yield and was chromatographed with dichloromethane containing 1 % methanol over Wako C-300 silica gel to give *erythro*-2,3-dibromo-3-phenylpropionic acid in 49 % yield which was identified by NMR and IR spectra. Chlorination and hydro-

halogenations of the acid in cyclodextrin complexes were carried out by introducing the gases into a desiccator for 30 min and then maintaining the closed systems, and the following procedures were also done similar to bromination manner.

2.4. Asymmetric Reactions in Solution

The solution reactions were carried out with or without cyclodextrins in $(CH_3)_2SO$, $(CH_3)_2SO$-d_6 or carbon tetrachloride. The typical experimental procedure was as follows. *trans*-Cinnamic acid (11 mg, 0.08 mmol), powdered α-cyclodextrin complex (162 mg, contained 0.08 mmol of the acid), and β-cyclodextrin complex (100 mg, contained 0.08 mmol of the acid) were dissolved in 0.4 ml of $(CH_3)_2SO$-d_6, to which 0.1 ml of the same solvent containing bromine (0.08 mmol) was added at 25 °C. At 2 h intervals, the conversion of the acid was determined by NMR spectra. Then the reaction mixtures were poured into 20 ml of 15 wt % aqueous sodium chloride solution, followed by extraction with diethyl ether. The products were obtained as white solid by evaporation of the ether layer and their optical rotations were measured in ethanol on a polarimeter.

2.5. Test Methods

Optical rotation of the purified compound was measured in ethanol on Parkin-Elmer 241 or Union Giken PM-101 polarimeters using 1 dm cell. The other spectroscopic measurements were carried out by a JEOL-PMX 60 for NMR and Hitachi IR-285 spectrometers for IR spectra of the solid (KBr disk). The X-ray diffraction patterns of the powdered samples were taken in the region of 5 to 35° by a Rigakudenki Model DC-8 X-ray diffractometer using Ni-filtered Cu-K_α radiation. The thermal behavior of the specimens was observed with a Rigakudenki TG-DSC analyzer, which has been previously calibrated with a standard substances.

3. RESULTS AND DISCUSSION

3.1. Gas-Solid Reactions

The inclusion complexes were obtained in the form of precipitates from aqueous solutions of *trans*-cinnamic acid and α- or β-cyclodextrin, in 74 and 89 % yields, respectively. The acid in the complexes was determined by NMR in $(CH_3)_2SO$-d_6 and the observed acid/cyclodextrin ratios were 0.5 (α-cyclodextrin) and 1.0 (β-cyclodextrin). The X-ray powder diffraction patterns of these complexes showed that they were highly crystalline as depicted in Figure 1 and did not corresponded to those of the pure components, so should exist as inclusion complexes.[9] The thermal stability of *trans*-cinnamic acid in the complexes was found to be higher than those of the acid itself and in its mixture with cyclodextrins, as well as reported by Uekama, *et al.*[10] Therefore, the guest molecule should be included within the cavity of the host molecule but not located outside the cavity. However, since no X-ray structure analysis of the cyclodextrin complex is determined at present stage, it is difficult to know the precise location of carbon-carbon double bond of the acid in the cav-

ity of the crystalline complexes.

We have utilized directly these microcrystalline cyclodextrin complexes in the solid state reactions, which were carried out with gaseous halogens and hydrogen halides under air in the dark. The reaction products extracted from the matrices were isolated by liquid chromatography.

As seen from Table I, molecular size of attacking reagent affected this gas-solid reaction. *trans*-Cinnamic acid in the cavity of α-cyclodextrin reacted with smaller hydrogen bromide molecule but did not with bromine and chlorine with larger molecular sizes. In contrast, the guest molecule in the wider cavity of β-cyclodextrin reacted even with bromine and chlorine as well as hydrogen bromide. Hydrochlorination of the organic acid did not proceed at all with or without cyclodextrins. In fact, it has not been reported that the addition of hydrogen chloride to the organic acid gives 3-chloro-3-phenylpropionic acid, which is prepared by the substitution of 3-hydroxy-3-phenylpropionic acid with chlorinating agent as thionyl chloride.[11]

The reactions of the organic acid in the cavity of the complex with these reagents proceeded when the opening size of cavity of the complex was larger than the molecular size of the attacking reagents. In addition, bromination of the organic acid with or without cyclodextrins was carried out in $(CH_3)_2SO$-d_6 solution at 25 °C for 65 h. The acid with or without β-cyclodextrin reacted with bromine to give *erythro*-dibromide in 14 % ($[\alpha]_D^{25}$ -2.7°, 4 % e.e.) and 15 % yields, respectively, but did not react in the presence of α-cyclodextrin.

Molecular model study using CPK structural model predicts that

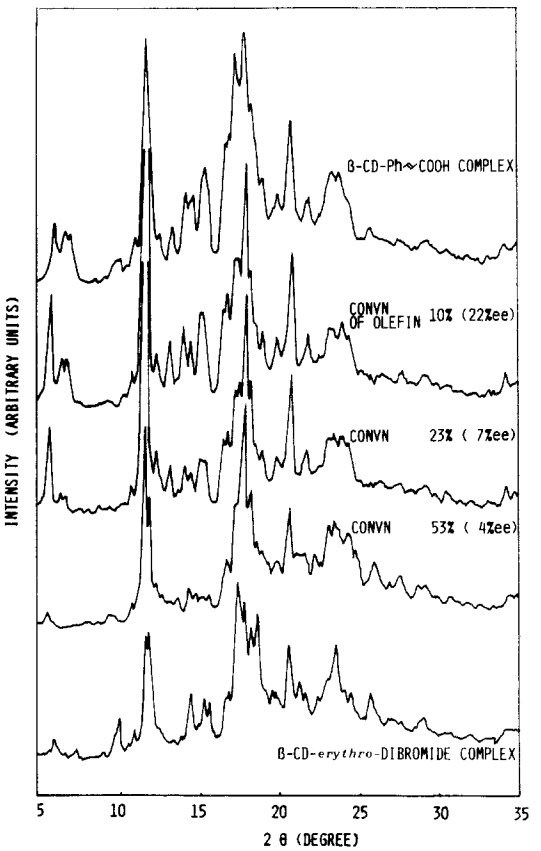

Figure 1. Changes of X-ray diffraction diagrams on the gas-solid bromination of β-cyclodextrin (β-CD)·*trans*-cinnamic acid inclusion complex at 25 °C, and the diagram of inclusion complex of β-CD with racemic *erythro*-2,3-dibromo-3-phenylpropionic acid.

Table I. Gas-Solid Halogenation and Hydrohalogenation of *trans*-Cinnamic Acid in the Cavity of Cyclodextrin Complexes or without Cyclodextrins [a]

Reagent	Conversion,% [b] α-CD [c] complex	β-CD [c] complex	without CD [c]
Br_2	0 (40) [d]	50 (49)	10 (10)
Cl_2	0	100 (56)	100 (97)
HBr	37 (27)	41 (31)	0
HCl	0	0	0

a) Reactions were performed at 25 °C for 20 h, under air in the dark. b) Isolated yields (%) of dihalides and monobromide are shown in parentheses. c) CD = cyclodextrins; α-CD = α-cyclodextrin; β-CD = β-cyclodextrin. d) Value shown in parenthesis is the yield of *erythro*-dibromide obtained on bromination at 25 °C for 100 h.

erythro-dibromide and even smaller dichloride molecules cannot enter nor be fitted fully into α-cyclodextrin cavity. The cavity of β-cyclodextrin, however, can include these dihalides. In fact, β- not α-cyclodextrin was found to form the inclusion complex with the dibromide.

This result assumes that the olefinic π bond of the acid is located at the middle of the cavity of cyclodextrins, so that the larger molecules bromine and chlorine cannot probably enter to the olefinic site of the acid in the narrower cavity of α-cyclodextrin complex.

It is known that, in general, dark halogenations and hydrohalogenations of olefins in the presence of a radical inhibitor such as oxygen [12~14] or air proceed through ionic intermediates in both polar and non-polar media. Moreover, Buckeles, *et al.*[15] reported that the gas-solid bromination of *trans*-cinnamic acid and other aryl olefins also proceeds through the ionic mechanism in either an absorbed phase or in a film of solution on the solid.

In fact, at the end of the reaction of *trans*-cinnamic acid with chlorine under air, the sticky solid product was obtained, but with bromine no change of the solid was observed. However, when the addition of these reagents to the acid proceeded in the microcrystalline cyclodextrin matrix, there was no visual evidence of liquid phase on the crystal even in chlorination of it under microscope.

In this reaction in cyclodextrin, the transition state should involve the ternary molecular complex composed of microcrystalline cyclodextrin complex and a fixed gaseous reagent in it. Hadjoudis, *et al.*[16] also suggested that the solid α,β-unsaturated acids in polymorphic forms differ in their rate of bromine uptake and addition due to different packing arrangements.

trans-Cinnamic acid in β-cyclodextrin complex exposed to bromine vapour gave *erythro*-2,3-dibromo-3-phenylpropionic acid; to chlorine gas a

Table II. Stereospecificity on Halogenation of *trans*-Cinnamic Acid

Reagent	Reaction state [a]	Temp. /°C	Time /h	Convn. followed, %	Yield of dihalide,[b] %	Dihalide compn. *erythro*, %	*threo*, %
Br_2	I	25	20	50	98	100	0
	II	25	20	10	100	100	0
	III	30	20	100	100	100	0
Cl_2	I	-25	5-25	28-100	52 [c]	28 [d]	72 [d]
	I	-15	5-20	41-69	52 [c]	27 [d]	73 [d]
	I	25	3-5	81-100	53 [c]	24 [d]	76 [d]
	I	50	2	74	46	22	78
	II	-25	25	100	94	16	84
	II	25	20	100	97	13	87
	II	50	5	100	96	19	81
	III	30	0.5-6.5	10-100	96 [e]	22 [e]	78 [e]

a) I, gas-solid with β-cyclodextrin matrix; II and III, gas-solid and solution in carbon tetrachloride without β-cyclodextrin.
b) Based on *trans*-cinnamic acid consumed. Dihalides obtained from II and III conditions had zero optical rotations. c) ±3%. d) ±2%. e) ±0.5%.

mixture of *erythro*-, *threo*- 2,3-dichloro-3-phenylpropionic acid, and 1,2,2-trichloro-1-phenylethane; to hydrogen bromide gas 3-bromo-3-phenylpropionic acid, respectively. No halo-substitution products could be detected on the gas-solid reactions of cyclodextrin complexes.

The stereospecificity of halogen addition to the acid was studied for the gas-solid state with or without cyclodextrin and in carbon tetrachloride solution without cyclodextrin, and the typical result was shown in Table II. Bromination yielded *erythro*-dibromide stereospecifically in 100 % in three different conditions, but chlorination gave an excess of *threo*-dichloride in 72~87 % yields to the *erythro*-isomer. The composition of the reaction mixture showed no variation with extent of conversion in three reaction states at various temperatures and the remaining acid had retained nearly 100 % isomeric purity. Since chlorinated products were found to be stable under the conditions, these lower stereospecificities in the chlorination might be caused by the different addition mechanism from that of bromination which proceeded stereospecifically. Similar result was observed[17] for chlorine addition to methyl-*trans*-cinnamate. Therefore, similar mechanism could be considered for this gas-solid halogenation to those in solution reactions which proceed through the ionic rather than the radical mechanism. Bromination of the acid should proceed through a briged bromonium ion intermediate[18], while an open carbonium ion intermediate[19] could be involved in the chlorination. Since chlorine is a poorer neighbouring group atom in comparison with bromine,[20] electrophilic addition to the acid, proceeded *via* open carbonium ion, results in nonstereospecificity of the product. In the ionic addition of hydrogen bromide to the organic acid, bromide anion may attack the electron-poor carbon atom of the acid at the 3-position and give 3-bromo-3-phenylpropionic acid.[7,21]

3.2. Asymmetric Bromination in Crystalline β-Cyclodextrin Complex

trans-Cinnamic acid included in the cavities of cyclodextrin matrices were found to react with bromine, chlorine, and hydrogen bromide to produce the chiral halides in moderate optical yields.

The best data of this reactions are shown in Table III. The optical yields of the *erythro*-dibromide obtained from the gas-solid bromination of β-cyclodextrin complex were high in the early stage, decreased remarkably with an increase up to 10 % of the yield of dibromide, and reached a constant value as depicted in Figure 2.

In order to know whether this decrease of the optical yield was due to a reduction of chiral induction or a racemization of the products, the change of X-ray powder diffraction patterns were followed during the course of bromination at 25°C, as depicted in Figure 1.

In the case of the β-cyclodextrin, these patterns showed the reacting phase was highly crystalline. However, a few peaks in the lower angle region (2θ = 5~10 degree) disappeared gradually and the diffraction pattern of the complex in 53 % conversion was similar to that of the β-cyclodextrin complex with racemic *erythro*-dibromide. Therefore, it is possible to assume that the stacking structure of β-cyclodextrin complex was not largely collapsed during the course of bromination.

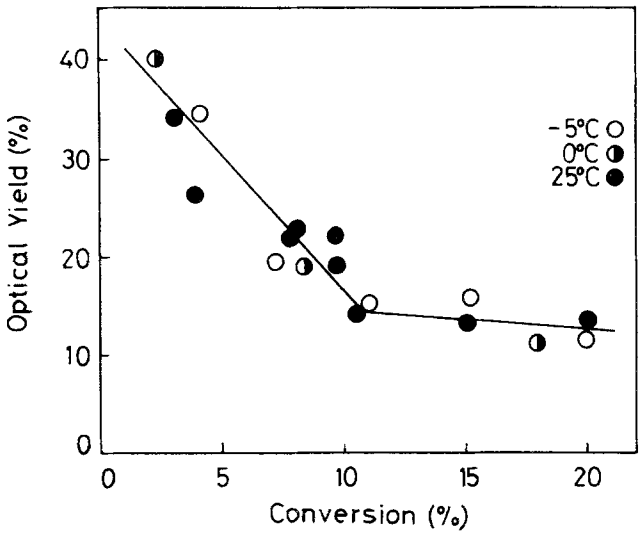

Figure 2. Optical yields on asymmetric addition of bromine to *trans*-cinnamic acid in β-cyclodextrin cavity at various temperatures.

Table III. Asymmetric Halogenation and Hydrohalogenation of *trans*-Cinnamic Acid in Crystalline Cyclodextrin Complexes

Cyclo-dextrin	Reagent	Reaction state [a]	Temp. /°C	Time /h	Convn., %	Yield,[b] %	$[\alpha]_D^{25}$,[c] °	ee.,[d] %
α-CD	Br_2	I	25	100	61	40 [e]	+1.3	2
β-CD	Br_2	I	0	5	3	3 [e]	-27.2	40
β-CD	Br_2	I	25	2	3	3 [e]	-23.1	34
β-CD	Br_2	II	25	2	4	4 [e]	-3.8	6
β-CD	-	III	-	-	-	-	+2.5	4
β-CD	Cl_2	I	-15	20	69	10 [f]	+25.0	37
						26 [g]	+23.8	-
						15 [h]	+24.5	-
α-CD	HBr	I	25	20	37	27 [i]	+13.5	14
β-CD	HBr	I	25	20	41	31 [i]	+10.3	11

a) I, gas-solid; II, in Me_2SO; III, optical resolution by the method of F. Cramer and W. Dietsche(ref.23). b) Isolated yields. c) Measured by a Perkin-Elmer 241 photopolarimeter using 1 dm cell in EtOH. d) Calculated from the reported $[\alpha]_D^{25}$ values given in the references. e) *erythro*-2,3-Dibromo-3-phenylpropionic acid. f) *erythro*-2,3-Dichloro-3-phenylpropionic acid. g) *threo*-2,3-Dichloro-3-phenylpropionic acid. h) 1,2,2-Trichloro-1-phenylethane. i) 3-Bromo-3-phenylpropionic acid.

The acid in the narrower cavity of α-cyclodextrin did not react with bromine at all after 24 h, but reacted after exposure for a long time (see Table I). After 100 h of bromination, it converted in 61 % and yielded 40 % of a 2 % e.e. of *erythro*-dibromide with the opposite configuration to that of product obtained from the reaction in β-cyclodextrin matrix, and many peaks in the X-ray diffraction pattern disappeared as depicted in Figure 3. α-Cyclodextrin alone kept highly crystalline in spite of exposure to bromine under the same condition except a little change in intensities of the diffraction peaks (Figure 4).

In the reaction at along time, the guest molecule reacted with bromine seems to escape gradually from the cavity of the complex and the stacking structure of the complex collapses becoming less crystalline.

The effect of racemization on this reaction was examined by using the optical active *erythro*-dibromide ($[\alpha]_D^{25}$ -27.2° , 40 % e.e.; calculated from the value $[\alpha]_D^{25}$ -68.3° in literature[22]), as shown in Table IV. When the optical active dibromide included in β-cyclodextrin was exposed to bromine at 25 °C for 3 h, the e.e. of recovered *erythro*-dibromide, identified by NMR, decreased remarkably, its decrease corresponding to 78 % of racemization, and then the dibromide racemized perfectly after 10 h. In contrast, the optically active dibromide alone did not racemize even after 20 h of exposure to bromine. This result shows that the racemization was catalyzed by β-cyclodextrin.

It is well known[3] that cyclodextrins bring about the optical resolution of some racemic compounds by means of complex formation. Therefore, it was possible that the

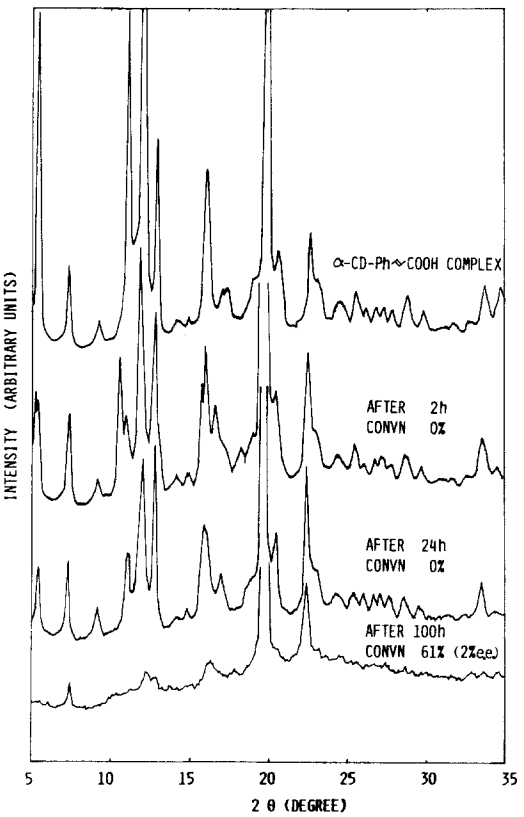

Figure 3. changes of X-ray diffraction diagrams on the gas-solid bromination of α-cyclodextrin(α-CD)·*trans*-cinnamic acid inclusion complex at 25 °C.

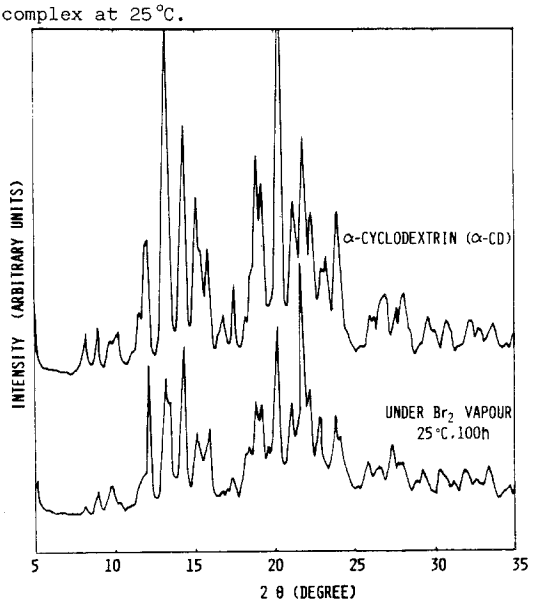

Figure 4. X-ray diffraction diagrams of α-cyclodextrin before and after exposure of bromine vapour at 25 °C for 100 h.

Table IV. Racemization of *erythro*-2,3-Dibromo-3-phenylpropionic Acid with Bromine Gas

CD used	Temp. /°C	Time /h	$[\alpha]_D^{25}$	ee, %	Racemization, %
β-CD	25	3	-6.0	8.8	78
β-CD	25	10	0	0	100
none	25	20	-27.0	39.5	⩽1

$[\alpha]_D^{25}$ of used dibromide is -27.2° (39.8%ee).

nresent results were simply due to optical resolution of racemic products formed in the reaction. The optical resolution of the racemic dibromide was carried out according to the procedure described by Cramer and Dietsche.[23]

As shown in Table III, the optical yield of the dibromide from the resolution treatment was much smaller than that from the gas-solid reaction; moreover, the absolute configuration was opposite in sign. Thus, it is clear that the observed asymmetric induction in the gas-solid reaction was not due to optical resolution but to the reaction itself which was influenced by the chiral frame of cyclodextrin.

Next, the asymmetric bromination of the cyclodextrin complex in the solid state was compared with the homogeneous reaction in $(CH_3)_2SO$ solution (see Table III). The optical yield from the homogeneous reaction was much smaller than that from the gas-solid reaction, although the absolute configurations were the same. This result shows that the gas-solid reaction is topochemically controlled by the crystalline lattice of the cyclodextrin complex.

3.3. Asymmetric Chlorination in Crystalline β-Cyclodextrin Complex

Though only (-)-*erythro*-dibromide was obtained on the bromination of *trans*-cinnamic acid, the chlorination gave (+)-*erythro*- and *threo*-dichlorides; the e.e. of the *trans*-adduct reached 37 % (calculated from the value $[\alpha]_D^{25}$ +67.3°in literature[24]) and the specific rotation of the *cis*-adduct was +23.8°.

The other reaction product, optically active 1,2,2-trichloro-1-phenylethane ($[\alpha]_D^{25}$ +24.5°) was obtained in 15 % yield on chlorination within β-cyclodextrin but not given without the matrix.

As seen from Figure 5, the composition ratios and the optical yields of the products were kept nealy constant over the temperature

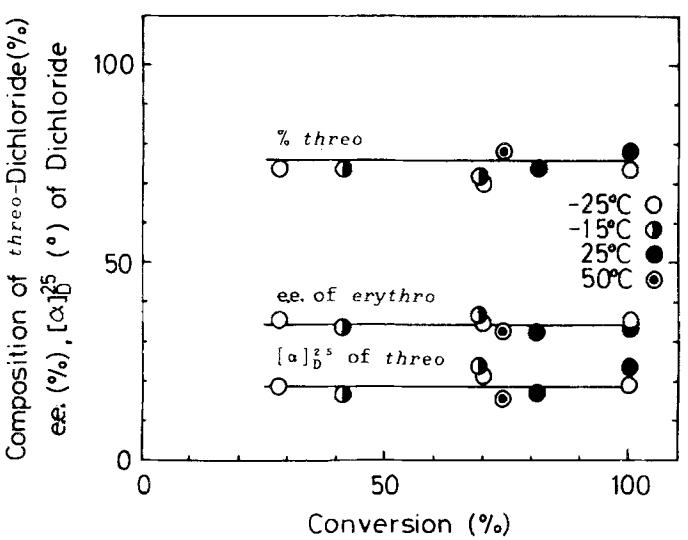

Figure 5. Optical yields and stereospecificity on asymmetric addition of chlorine to *trans*-cinnamic acid in β-cyclodextrin cavity.

range -25 to 50 °C. This result shows that these optically active products were extremely stable during the course of chlorination, that is, they were not racemized and not isomerized under exposure to chlorine. The products included in β-cyclodextrin, as it stands, kept longer in excess chlorine at 25 °C and the following data were observed: reaction time, recovered yield, and $[\alpha]_D^{25}$ are given; 5 h, 13 %, +21.6° and 15 h, 13 %, +21.2° as to *erythro*-dichloride, 5 h, 40 %, +23.7° and 15 h, 39 %, +23.5° as to *threo*-dichloride, 5 h, 22 %, +21.5° and 15 h, 21 %, +22.0° as to 1,2,2-trichloro-1-phenylethane. Therefore, the trichloride may be not produced *via* addition of chlorine to the products from decarboxylative elimination of the dichlorides.

In the case of the addition of hydrogen bromide to the organic acid, the optically active and regioselective product, 3-bromo-3-phenylpropionic acid ($[\alpha]_D^{25}$ +13.5 , 14 % e.e. from α-cyclodextrin, $[\alpha]_D^{25}$ +10.3° , 11 % e.e. from β-cyclodextrin; calculated from the value $[\alpha]_D^{25}$ +96° in literature[25]) was isolated. The e.e. for the reaction in narrower cavity of α-cyclodextrin was barely higher than that for the reaction in the wider cavity of β-cyclodextrin (see Table III).

As seen from Table III, the e.e. values of all products were higher as the molecular size of gaseous reagents were greater.

Thus, we concluded that the observed asymmetric induction in the gas-solid reaction should be due to molecular size effect of reagents.

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