ASYMMETRIC HALOGENATION AND HYDROHALOGENATION OF ETHYL *trans*-CINNAMATE IN CRYSTALLINE CYCLODEXTRIN COMPLEXES

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ABSTRACT: The gas-solid halogenation and hydrohalogenation using microcrystalline cyclodextrin complexes are found to be efficient for production of the optical active halides of ethyl *trans*-cinnamate in moderate optical yields: On exposure to HBr at 20°C for 15-20 hr, the cinnamate in solid α- and β-cyclodextrin complexes yields ethyl R-(+)-3-bromo-3-phenylpropanoate in 46% e.e., and S-(-)-enantiomer in 31% e.e., respectively. No addition nor substitution products are obtained with HCl vapor at 0-50°C for 15-65 hr. Bromination of the β-cyclodextrin complex results in the formation of optical active ethyl *erythro*-2,3-dibromo-3-phenylpropanoate, while chlorination gives the optical active mixture of *trans* and *cis* addition products, ethyl *erythro*- and *threo*-2,3-dichloro-3-phenylpropanoates in 60-80% yields. Mechanism of chiral induction in the present gas-solid reaction has been proposed on the basis of the crystal structure of the complex.

I. INTRODUCTION

Asymmetric synthesis through reactions in the solid state demands the formation of chiral crystalline structures having certain inter- or intramolecular features. In 1969, Penzien and Schmidt [1] reported the first example of absolute asymmetric synthesis through topochemically controlled, solid state reaction in a chiral crystal of 4,4-dimethylchalcone with gaseous bromine. Since then, a number of examples of absolute asymmetric synthesis have been studied in chiral crystals [2]. These approaches, however, have to use compounds which form giant crystals in chiral space group, and a number of molecules available for such reactions are quite limited. In order to resolve this limitation, an approach has been investigated [3] for utilizing the chiral matrix of stable host molecules such as cyclodextrins in the form of microcrystals.

Cyclodextrins or cycloamyloses are cyclic oligomers composed of 6-8 glucose units, and are known [4] to catalyze many organic reactions in solutions. One of the characteristics of the catalysis of cyclodextrins is the specificity, which is attributable to their complex formation

Journal of Inclusion Phenomena **2**, 841–850. 0167-7861/84.15.

with the substrates prior to chemical transformation. Any reaction of cyclodextrin complexes in the solid state have not been found, and asymmetric synthesis catalyzed by cyclodextrins has been studied [4] in solutions, giving all the products in low optical yields.

Previously [3], a strong chiral induction has been found for the chlorination of methacrylic acid in the crystalline cyclodextrin complexes. This paper describes asymmetric additions of gaseous halogens and hydrogen halides to ethyl *trans*-cinnamate in the crystalline complexes of α- and β-cyclodextrins. Asymmetric bromination of 5-methyl-2-(1-methylethyl)cyclohexyl cinnamate [5] and salts of *trans*-cinnamic acid with several chiral amines [6] has been reported, but gives low chiral transformations up to 2-16% e.e.

2. EXPERIMENTAL

2.1. Materials

α- And β-cyclodextrins were purchased from Sanraku-Ocean Co., Ltd. and further purified by recrystllization once from 1-propanol and twice from water. Ethyl *trans*-cinnamate and other solid and liquid reagents were all reagent grades and used after purification by ordinary methods [7]. 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 obtained by the procedure given in the literature [8].

2.2. Preparation of Inclusion Complexes

To 100 ml of an aqueous solution containing α-cyclodextrin (1.2-1.7 x 10^{-1} mol/l) or β-cyclodextrin (2.8-3.0 x 10^{-2} mol/l), equimolar amounts of ethyl *trans*-cinnamate were added at 40°C and dissolved by stirring for 40 min. After stirring for 2 hr at room temperature, the resultant white precipitates were filtered and dried in vacuo. Then the dried powders were washed with n-pentane to eliminate the ester not included and dried again. X-ray diffraction technique was used to prove the complex formation. Thus, the white crystalline powders were obtained with α- and β-cyclodextrins in 80 and 95% yields, and composed of 0.5 or 1.0 mole of the guest molecule and of 1 mole of the corresponding host molecule, respectively. The contents of the ester in the complexes were determined by NMR in deuterated dimethyl sulfoxide and by elemental anaysis.

2.3. Halogenation and Hydrohalogenation of the Crystalline Inclusion Complexes

A typical experimental procedure is as follows: The inclusion complex (ca. 2 g or 1 mmol) or ethyl *trans*-cinnamate with α-cyclodextrin was exposed to gaseous hydrogen bromide (ca. 2 molar ratio) in a desiccator (ca. 600 ml) in the dark under air at 20°C. After exposure of 20 hr, the excess of the gas was removed by evacuation and the complex was dis-

solved in water. The product was extracted with diethyl ether from the aqueous layer by stirring vigorously at room temperature. After 3 hr, the organic layer was separated, dried over anhydrous magnesium sulfate, and concentrated to give a light yellow oil. The extract was recovered in 90-98% yield and chromatographed with dichloromethane over Wako C-300 silica gel to give ethyl 3-bromo-3-phenylpropanoate in 17% yield, which was identified by NMR and IR spectra. Hydrochlorination, bromination, and chlorination of the inclusion complexes of the ester with the cyclodextrins were done by the similar procedure to this hydrobromination.

2.4. Test Methods

Optical rotations were measured in ethanol on a Parkin-Elmer 241 photoelectric spectropolarimeter or Union Giken PM-101 polarimeter using 1 dm cell. The infrared (IR) absorption spectra in the region of 650 to 4000 cm^{-1} were measured for a sample on a Hitachi Model 285 spectrometer. The sample was prepared by the neat technique on KBr plate or by the KBr pellet technique. The proton nuclear magnetic resonance (NMR) spectra were obtained at 60 MHz with a JEOL-PMX 60 spectrometer. Deuterochloroform and carbon tetrachloride were used as solvents with tetramethylsilane (TMS) as the internal reference standard. The X-ray diffraction patterns of the powdered samples were taken in the region of 5 to 37° by a Rigakudenki Model DC-8 X-ray diffractometer, using Ni-filtered Cu-Kα radiation.

3. RESULTS AND DISCUSSION

3.1. Inclusion Complexes

The solid inclusion complexes were obtained as precipitates from aqueous solutions of ethyl *trans*-cinnamate and α- and β-cyclodextrins in 80 and 95% yields, respectively. The ester in the complexes was determined by NMR in deuterodimethyl sulfoxide, and the molar ratios of the ester to the cyclodextrins were observed as 0.5 for the α-cyclodextrin complex and 1.0 for the β-cyclodextrin complex. The X-ray diffraction patterns of these complexes showed that they were highly crystalline as shown in Figure 1, and could not be described with those of the ester and the cyclodextrin; the precipitates should have different crystal structures from those of the guest and the hosts. These inclusion complexes have been prepared, and their dissolution and thermal behavior were examined by Uekama, et al. [9]. Hursthouse, et al. determined [10] the crystal structure of β-cyclodextrin complex with ethyl *trans*-cinnamate and showed that the complex was composed of 1 mole of the guest and 1 mole of the host.

3.2. Gas-Solid Bromination

The microcrystalline inclusion complexes, mentioned above, were brominated with gaseous bromine under air in the dark at several temperatures. The changes of the X-ray diffraction patterns of the samples

were followed during the course of bromination at 25°C, and a typical result is shown in Figure 1. In the initial state, the reacting phase was highly crystalline, but many peaks in the diagrams disappeared gradually as reaction proceeded. Therefore, the stacking structure of the inclusion complex of the ester with α-cyclodextrin could be assumed to be collapsed largely during the course of reaction. α-Cyclodextrin itself kept highly crystalline, except a little change in intensities of the diffraction peaks, under the same condition. In the case of the β-cyclodextrin complex, a few peaks in the lower angle region (2θ = 5-10 degree) disappeared gradually, but the collapse of the crystallinity should not be large, judging from the changes of the diffraction patterns.

CPK structural model shows that the dibromide and even smaller dichloride molecules can not enter nor be fitted fully into α-cyclodextrin cavity, but the cavity of β-cyclodextrin is able to include these dihalides of the ester. In fact, no α- but β-cyclodextrin was found to form the inclusion complex with the dibromide. Thus, the guest molecule reacted with bromine seems to escape gradually from the cavity of the α-cyclodextrin and the stacking structure of the inclusion complex may collapse, becoming less crystalline.

Buckeles, et al. reported [11] that the gas-solid bromination of cinnamic acid and other aryl olefins proceeds in either an absorbed phase or in a film of solution on the surface of the solid. At the end of the reaction with large excess (100 times molar)

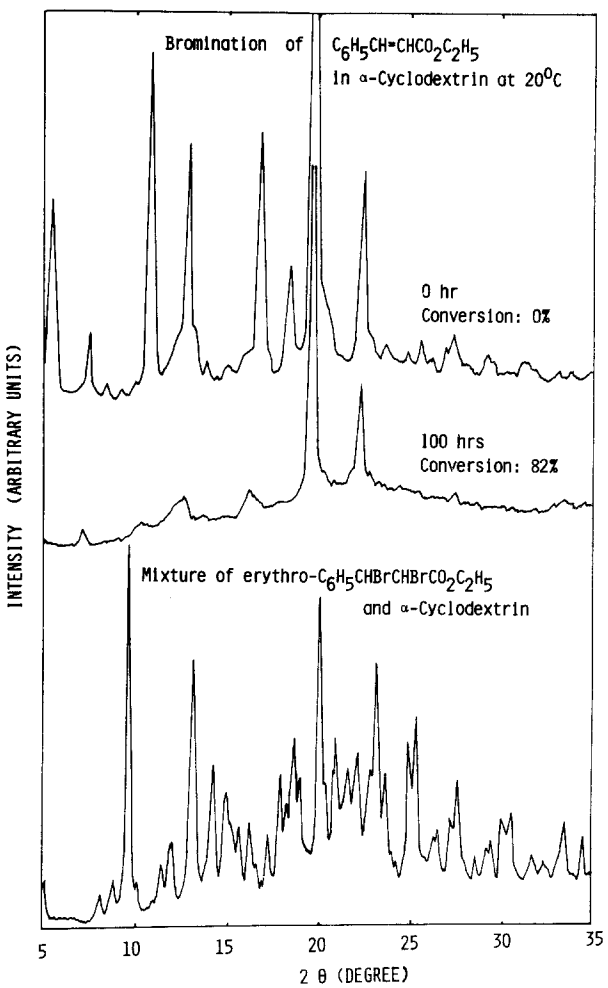

Fig. 1. A change of X-ray diffraction diagrams of the inclusion complex of ethyl *trans*-cinnamate with α-cyclodextrin on the gas-solid bromination at 25°C, and a diagram of a mixture of α-cyclodextrin and *erythro*-dibromide of the ester

Table I. Gas-solid bromination of ethyl *trans*-cinnamate in crystalline cyclodextrin complexes at various temperatures and times

Reaction condition			Product			
Cyclo-dextrin[a]	Temperature °C	Time hr	Yield[b] %	*erythro*[c] %	$[\alpha]_D^{25}$[d]	e.e.[e] %
α-CD	-5	20	40	67	+0.8	-
"	20	20-100	10-80	78-80	+0.6- + 1.6	-
β-CD	-5	0.5-80	5-88	100	+5.6- +13.8	9.5-23
"	0	0.5-60	8-85	100	+4.9- + 9.3	8.3-16
"	20	0.5-100	11-86	100	+3.9- + 7.1	6.6-12

a) α-CD and β-CD are α- and β-cyclodextrins, respectively.
b) Isolated chemical yield by chromatography.
c) Determined by NMR.
d) Determined in ethanol using 1 dm cell by a polarimeter at 589 nm.
e) Calculated from the reported $[\alpha]_D$(at 25°C) value given in Ref.[12].

of bromine under air, tacky solid reaction mixtures were obtained, but in the other cases, no visual evidence of liquid phase nor changes were observed on the crystals under microscope during the gas-solid bromination of the cyclodextrin inclusion complexes.

The bromination is also stereoselective: The δ-values of the ^{1}HNMR spectra of the bromination products in the β-cyclodextrin complex were 4.77 and 5.33 (1H, d, J=12.0 Hz, CHBr), 7.39 (5H, s, C_6H_5) in CCl_4. This shows the dibromide is a *trans*-adduct. The δ-values for the bromides in the α-cyclodextrin complex were 4.28, 5.00, 4.77, and 5.33 (1H, d, J= 9.0 and 12.0 Hz, CHBr), and 7.39 (5H, s, C_6H_5). Thus the bromination of the latter complex gives the mixture of *erythro*- and *threo*-dibromides, as shown in Table I. The *trans*-adducts have been also obtained [13] by the gas-solid bromination of some olefins without the cyclodextrins. Such unique product distribution could be evoked as proof that the crystal matrix controls this gas-solid reaction.

No attempt was made to attain reproducible rates by using thin film

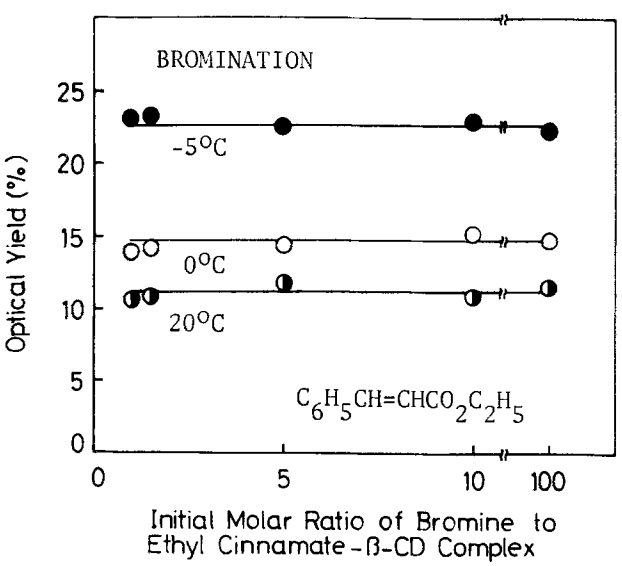

Fig. 2. Dependence of optical yields on the initial molar ratio of bromine to ethyl *trans*-cinnamate in the gas-solid bromination of the β-cyclodextrin inclusion complex at various temperatrues

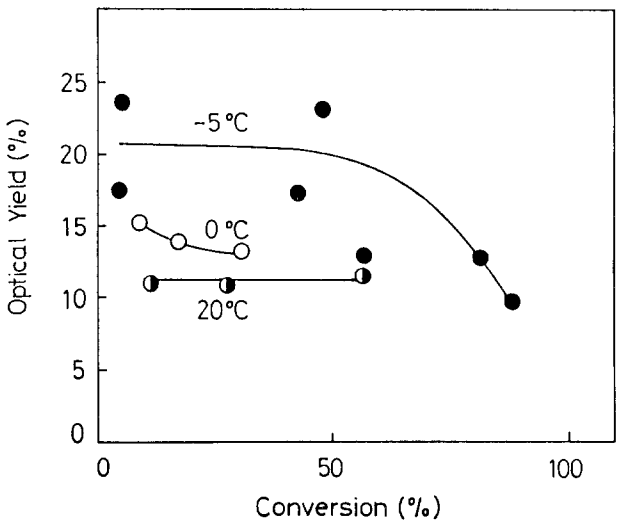

Fig. 3. Dependence of optical yields on conversion of the ester in the gas-solid bromination of the β-cyclodextrin inclusion complex at various temperatures.

samples, single crystals or powders whose particle size were controlled by sieving procedures. Addition rates of bromine gas to the crystalline cyclodextrin complexes were dependent on the concentration of the gas. With large amounts of the gas up to 100 molar times, the addition was rapid as (temperature in °C, time in hr, yield in %, and e.e. in % are given): -5, 0.5, 25, 22; 0, 0.5, 38, 15; 20, 0.5, 57, 12. Smaller amounts of bromine gave lower rates, but pure isomer, i.e., *erythro*-dibromide, with no trace of the other isomer. As shown in Figure 2, however, the best values of the optical yield for *erythro*-dibromide obtained did not depend on the initial amounts of the gas but the reaction temperature. Figure 3 shows the dependence of the optical yield of the dibromide on the conversion of the ester in the gas solid bromination of the β-cyclodextrin inclusion complex at various temperatures. The optical yields were high in the early stage at the lower temperature such as -5°C, decreased gradually with an increase of the conversion, and reached a constant value of 10 % or less. In the higher temperature reactions, the asymmetric bromination did not depend on the conversion and gave lower yields even at the initial stage. This could be due to the racemization of dibromide produced: The optical active *erythro*-dibromide of *trans*-cinnamic acid has been found [14] to racemize to 78 % for 3 hr and to 100 % for 10 hr at 25°C, and to decrease its e.e. from 40 % to 9 and 0 %, respectively, in the β-cyclodextrin inclusion complex. In contrast, this dibromide itself does not racemize at all even after exposure of bromine for 20 hr without the cyclodextrin.

3.3. Gas-Solid Chlorination

No chlorination was observed in the gas-solid chlorination of ethyl *trans*-cinnamate included in the cavity of α-cyclodextrin at temperatures from -5 to 50°C for 20-45 hr, as shown in Table II. The chlorination of the ester gave mixtures of *erythro*- and *threo*-dichlorides having optical activities, while (+)-*erythro*-dibromide was the only product on the bromination of the ester inclusion complex with β-cyclodextrin (Table I). The [α] value in D line or 589 nm at 25°C cannot be found for the pure

Table II. Gas-solid chlorination of ethyl *trans*-cinnamate in crystals of cyclodextrin complexes at various temperatures and times

Reaction condition			Product		
Cyclo-dextrin[a]	Temperature °C	Time hr	Yield[b] %	$[\alpha]_D^{25}$ [c] deg.	*erythro*[d] %
α-CD	-5- +50	20-45	0	-	-
β-CD	-15	20	64-77	-3.4- -4.1	65-66
"	20	20	63	+3.3	37
"	25	20-45	63-72	+1.2- +7.2	35-57

a) α-CD and β-CD are α- and β-cyclodextrins, respectively.
b) Isolated chemical yield by chromatography.
c) Determined in ethanol using 1 dm cell by a polarimeter at 589 nm.
d) Determined by NMR.

Table III. Gas-solid hydrohalogenation of ethyl *trans*-cinnamate in crystalline cyclodextrin complexes under various conditions

Reaction condition				Product			
Cyclo-dextrin[a]	Gas	Temperature °C	Time hr	Yield[b] %	$[\alpha]_D^{25}$ [c] deg.	e.e.[d] %	Configu-ration[e]
α-CD	HBr	20	20	17	+8.8	46	R
"	HCl	0-50	15-64	0	-	-	-
β-CD	HBr	20	15	21	-5.9	31	S
"	HCl	0-50	15-64	0	-	-	-

a) α-CD and β-CD are α- and β-cyclodextrins, respectively.
b) Isolated chemical yield by chromatography.
c) Determined in ethanol using 1 dm cell by a polarimeter at 589 nm.
d) Calculated from the reported $[\alpha]_D$(at 25°C) value given in Ref. [15].
e) Determined with the data in Ref. [15].

optical active *erythro*- or *threo*-dichlorides in the literature, and could not be determined in the present experiment; no optical yield could be obtained for the dichloride. The δ-values of the peaks in the ^{1}HNMR spectra of the chlorination products were found at 4.50 and 5.14 (1H, d, J=10.8 Hz, CHCl), and 7.41 (5H, s, C_6H_5) corresponding to *erythro*-dichloride, and 4.54 and 5.22 (1H, d, J=9.0 Hz, CHCl) and 7.41 (5H, s, C_6H_5) corresponding to *threo*-isomer in CCl_4 solution, respectively. Thus, the chlorination is not stereselctive.

In the chlorination of *trans*-cinnamic acid in the β-cyclodextrin inclusion complex, the optical yield of *erythro*-dichloride and the $[\alpha]_D$ at 25°C value and yield ratio of *threo*-dichloride were found [14] to be independent of the conversion of the guest. These optical active dichlorides should be stable, not racemize nor isomerize under the condition. The stability of the dichlorides of ethyl *trans*-cinnamate, however, was not examined at the present study. Moreover, no visual evidence of liquid phase on the crystalline inclusion complex was observed during the course of chlorination; the reaction can be classified as a

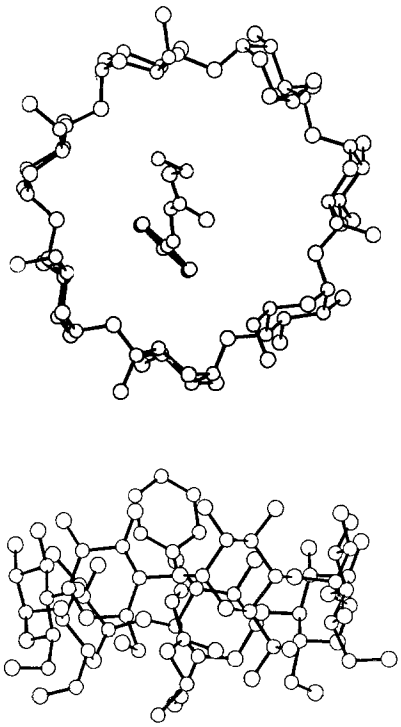

Fig. 4. Structure of the ethyl *trans*-cinnamate included in β-cyclodextrin (depicted with the data in Ref. [10])

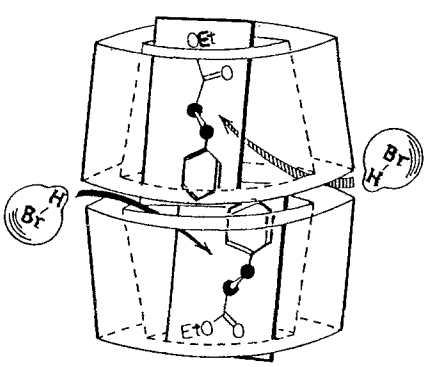

Fig. 5. A schematic drawing of the attacking feature of hydrogen bromide molecule to ethyl *trans*-cinnamate in β-cyclodextrin cavity

solid-state one.

3.4. Gas-Solid Hydrohalogenation

Table III shows the results of hydrobromination and hydrochlorination of the ethyl *trans*-cinnamate inclusion complexes. No hydrochlorination was observed at various temperatures after long exposure of hydrogen chloride gas similar to the reaction of *trans*-cinnamic acid [14]. Addition of hydrogen bromide to the ester gave an optically active and regioselective product, ethyl R-(+)-3-bromo-3-phenylpropanoate in 46 % e.e. from the α-cyclodextrin, or ethyl S-(-)-3-bromo-3-phenylpropanoate in 31 % e.e. from the β-cyclodextrin inclusion complex.

A detailed description of a mechanism for the observed asymmetric induction in these gas-solid reactions of the cyclodextrin inclusion complexes requires knowledge about the crystalline and molecular structures of the complexes. Hursthouse et al. [10] determined the crystal structure of ethyl *trans*-cinnamate included in β-cyclodextrin, and found the ester molecule is entirely within the cavity, the ester group being located at the narrower opening side with the primary hydroxyl-groups of the cyclodextrin. The enantiomeric plane of the carbon-carbon double bond of the ester is shown to be somewhat inclined in the center of the cavity of the host, and the apolar side is expected to have a largely asymmetric environment. Thus, a gaseous reagent molecule, such as hydrogen bromide and bromine, seems to attack enantioselectively on the inclined plane of the C=C bond from the side facing the wider opening site, as Figures 4 and 5 show. The side of the sinister-face of olefinic plane in the complex of β-cyclodextrin is found to be wider than the other side, and the hydrogen bromide molecule should attack predominantly to the former, leading to

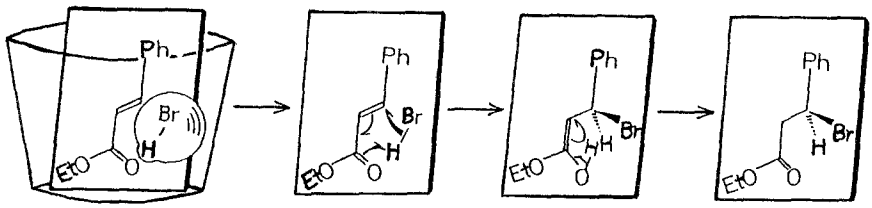

Fig. 6. Reaction mechanism of asymmetric addition of hydrogen bromide to ethyl *trans*-cinnamate in the cavity of β-cyclodextrin

the observed chiral induction, to form (S)-isomer, as shown in Table III.

Hydrobromination of the same substrate in the α-cyclodextrin complex gave the monobromide with the opposite configuration at 46 % e.e.. This clearly shows that ethyl *trans*-cinnamate forms complexes with α- and β-cyclodextrins such that the anti-addition of hydrogen bromide occurs with high but different enantioselectivities in the two cases to yield monobromide derivatives of opposite chiralities. A detailed mechanism, however, could not be described at the present time for the observed asymmetric induction in the hydrobromination and bromination of the α-cyclodextrin complex, because no crystalline or molecular structures were determined for the ester included in α-cyclodextrin.

Dark halogenation and hydrohalogenation of olefins in the presence of the radical inhibitor such as oxygen or air are well known [16-19] to proceed through ionic intermediates in both polar and nonpolar media. However, the true nature of the hydrobromination process still remains in doubt. Gould [20] suggests ¶-complex formation at the olefinic bond to acount for the predominantly *trans*-hydrohalogenation, whereas Dewar [21] has suggested that 1,4-addition to the conjugated system of the unsaturated acids is more reasonable. Vaughan [22] proposes a multistep mechanism in which carbon-bromine bond formation is rate determining and subsequent "ketonization" of the resultant "acid-enol" is structure determining. The hydrobromination of ethyl *trans*-cinnamate in the cavity of the cyclodextrin may proceed through a similar course of the addition reaction to that in solution, as shown in Fig. 6. At the present study, however, we cannot estimate whether the gas-solid hydrobromination involves *trans*- or *cis*-addition predominantly. A detailed study on this problem is now in progress and will be published elsewhere.

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