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Asymmetric Solid–Gas Hydrohalogenation of Unfunctionalized Olefins *via* Formation of Crystalline Cyclodextrin Complexes

HIDETAKE SAKURABA,* HIROKAZU ISHIZAKI,
TOSHIMORI NAKAI and YOSHIO TANAKA
Department of Industrial Chemistry, Faculty of Engineering, Kanto Gakuin University, 4834, Kanazawa-Mutsuura, Yokohama, Kanagawa 236, Japan.

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Abstract. Asymmetric solid–gas hydrohalogenation of styrene, β-methylstyrene, allylbenzene, and 2-norbornene as unfunctionalized olefins was carried out by using their chiral crystalline α- and β-cyclodextrin complexes by exposing them to gaseous HCl and HBr in the dark at room temperature. The optical purities of the Markovnikov products obtained from the ionic addition of HCl to the included olefins appear considerably higher than those from the reaction with HBr. The highest enantioselectivities of 58% and 62% enantiomeric excess (ee) were obtained for the hydrochlorination of 3-phenyl-1-propene (allylbenzene) in the crystalline α- and β-cyclodextrin complexes, respectively, and both reactions, which had little danger of racemization, gave (*S*)-(+)-2-chloro-1-phenylpropane as the same predominant product in moderate chemical yields. A much lower enantioselectivity ($<$10% ee) was observed in the hydrobromination of the same olefin in the solid α- and β-cyclodextrin complexes involving a racemization reaction. The enantiofacial selection provided the (*S*)-enantiomer similarly during hydrochlorination.

Key words: Asymmetric hydrohalogenation, solid–gas reaction, unfunctionalized olefin, cyclodextrin complex.

1. Introduction

As molecular reaction vessels, cyclodextrins (CDs) have been expected to induce asymmetry in molecules interacting with their chiral micromatrices in some useful reactions, but so far almost all the reactions in solution in the presence of CDs have shown low chiral inductions [1–4].

Previously, we achieved high enantioselectivities in the solid–gas chlorination, hydrochlorination, and hydrobromination of aliphatic α, β-unsaturated carboxylic acids *via* the formation of their crystalline CD complexes (60–100% ee) [5,6], but no chiral induction was found for the solid–gas hydrohalogenation of styrene as an unfunctionalized aromatic olefin in both the α- and β-CD complexes [7].

We report here a further examination of the solid–gas asymmetric hydrohalogenation of unfunctionalized olefins utilizing their crystalline inclusion complexes

* Author for correspondence.

with α- and β-CDs as a chiral template to establish the necessary and sufficient conditions for the achievement of the required high enantioselectivity.

2. Experimental

α- and β-CDs were purchased from Sanraku-Ocean Co., and purified by recrystallization from water. Olefins such as 1-phenylethene (styrene), (E)- or (Z)-1-phenyl-1-propene (β-methylstyrene), 3-phenyl-1-propene (allylbenzene), and bicyclo[2.2.1]hept-2-ene (2-norbornene) were distilled *in vacuo* before use. The solid CD complexes of the olefins were prepared by cocrystallization as described previously [7]. To 100 mL of an aqueous solution containing α-CD (1.7×10^{-1} M, (M = mol L^{-1})) and β-CD (3.0×10^{-2} M) were added equimolar amounts of the olefins at 40 °C. After remaining at room temperature for 2 h, the mixtures were then cooled to 0 °C for 1 day. The resulting white precipitates were filtered and dried *in vacuo* at room temperature for 1 day. The dried powders were then washed with n-pentane to remove any unincluded guest molecules, and dried again. The formation of a complex was confirmed by X-ray powder diffraction (XRD) measurements [7]. Gaseous HCl was obtained from Tsurumi Soda Co. and passed through a sulfuric acid trap prior to use. Gaseous HBr was prepared by the procedure given in the literature [8].

A typical experimental procedure for the solid-gas hydrohalogenation of olefins was as follows: the solid β-CD inclusion complex of 3-phenyl-1-propene (ca. 2.4 g, 2 mmol) was exposed to gaseous HCl (ca. 24 mmol) in a desiccator (ca. 600 mL) in the dark at 25 °C. After exposure for 50 h, excess gas was removed by evacuation and the complex was dissolved in water at neutral pH. The resulting aqueous solution was vigorously stirred with diethyl ether to extract the reacted and unreacted guest compounds. The organic layer was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. The extract was recovered in 95% yield and was chromatographed on Wako C-300 silica gel with CH_2Cl_2 as eluent to give optically active 2-chloro-1-phenylpropane in a chemical yield of 68%, as identified by comparing the ^{1}H-NMR and IR spectra with those of an authentic racemic sample. The optical rotation was measured in a suitable solvent on a Union Giken PM-101 spectropolarimeter equipped with a 1 dm cell at 25 °C. The absolute configuration and the % ee were determined from the known signs and values of the optical rotations given in the literature.

The solid–gas racemization reactions using the β-CD inclusion complexes of the optically active halide and alcohol were carried out using a procedure similar to the one already described. The solid inclusion compounds were prepared from an aqueous solution of β-CD (570 mg, 0.5 mmol) with (S)-1-chloro-1-phenylpropane of 44% ee (73 mg, 0.5 mmol) and (S)-2-chloro-1-phenylpropane of 62% ee (73 mg, 0.5 mmol), obtained from the present solid–gas hydrochlorination of the β-CD complexes of the corresponding olefins, and with (S)-1-phenylethanol of 98.2% ee (61 mg, 0.5 mmol) purchased from Tokyo Kasei Kogyo Co. and used without

further purification. The 1 : 1 inclusion complexes of β-CD with the chlorides and the alcohol were exposed to gaseous HCl at 25 °C and to HBr at −10 °C for 20 h, respectively. After the reaction, the isolation and identification of the guest compound was carried out using the same method as described previously.

3. Results and Discussion

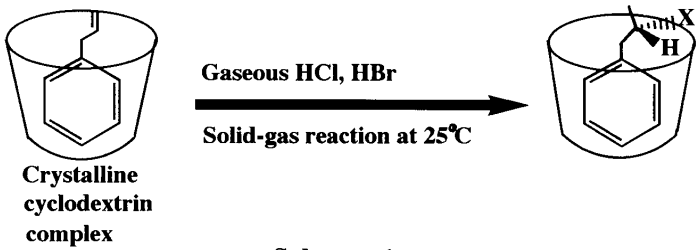
3.1. Inclusion Complexes

The solid inclusion complexes were obtained as microcrystalline precipitates from the aqueous solutions of olefins and α- or β-CDs in yields of over 85%. The XRD patterns of these powdered samples showed that they were highly crystalline and different from those of the physical mixtures of the CDs and olefins at the same molar ratio as that of the corresponding complex. β-CD formed a 1 : 1 (host : guest) crystalline complex with all the substrates used, whereas α-CD formed a 2 : 1 complex with the olefins, except for 2-norbornene, measured from the ^{1}H-NMR spectra in DMSO-d_6. Norbornene formed a 1 : 1 complex with α-CD like the complex with β-CD. No great change in the chiral induction was observed during the solid–gas hydrohalogenation using the 2 : 1 and 1 : 1 complexes with α-CD. The (*E*)-stilbene crystal, which is practically insoluble in water, did not form an inclusion complex with either the α- or β-CDs.

3.2. Solid–Gas Hydrohalogenation

The solid–gas hydrohalogenation was carried out on the crystalline CD complexes of the olefins, exposing them to gaseous HCl and HBr in the dark at 25 °C (Scheme 1). Table I shows the results of the reactivity and chiral induction in the asymmetric reaction utilizing the inclusion complexes. No hydrohalogenation of the solid CD complexes occurred at a temperature of 0 °C or below. The olefin fixed in the cavity of the solid CD reacted more rapidly with HBr than with HCl to give only the Markovnikov adducts as the ionic addition products, without the free-radical addition products in both cases. Since the polarizability of gaseous hydrogen halides increases in the order of HF<HCl<HBr<HI [9], the addition rates of the acid gases to olefins should increase in the same order. The differential reaction rates between HCl and HBr with olefins in the solid–gas state in the presence of CD were similar to those in a nonpolar or a weakly polar solvent in the absence of CD with stringent precautions, as reported by Dewar and Fahey [10–12]. These authors suggested that the intermediates in the homogeneous reactions are not the π-complex, but the classical carbonium ion. Cyclodextrins presumably promote the ionic addition through the hydrogen bonding interactions between their hydroxyl groups and the gaseous hydrogen halides, which both polarize the hydrogen–halogen bond of the gases and reduce entropy effects by bringing the two reactants together into the solid host, which is similar to the silica gel surface in hydrohalogenations reported by Kropp and co-workers [13]. Thus the ratio of heterolytic to homolytic

decomposition of hydrogen halides is much greater around the highly polar rims of the CD in the absence of light than in a nonpolar solvent without special precautions, giving 10–20% of the free-radical addition product [12]. In addition, the solid-gas reaction shows a host molecular size effect such that the additions of HBr and HCl to guest molecules in the wider cavity of β-CD are slightly faster than those in the narrower cavity of α-CD.

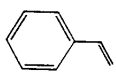
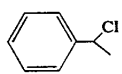
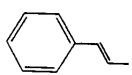
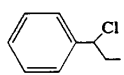
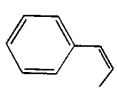
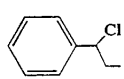
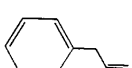
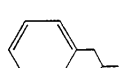
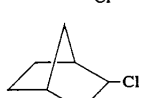
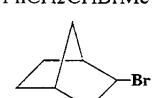


Scheme 1

The addition of HBr to conjugated olefins such as styrene and β-methylstyrene not only gave the 1-bromo-1-phenyl derivatives as main products, but also 1-phenyl alcohols; however, the reaction of HCl only produced the 1-chloro-1-phenyl derivatives, and no alcohols were detected in both additions of HBr and HCl to nonconjugated olefins such as allylbenzene and norbornene. During the hydrohalogenation of the conjugated olefins, the phenyl moiety substituted on the olefinic carbon atom exerts an effect of electron-releasing resonance stabilization on the positive charge of the carbonium intermediate. Considering the lifetime of the same carbonium ion intermediate paired with the different counterions during the course of the reactions of HBr and HCl, the lifetime of the cation would be shorter in an ion pair with the more nucleophilic bromide ion than in one with the less nucleophilic chloride ion and in water molecules [11]. The production of alcohols with the addition of HBr to the conjugated olefins is therefore less probable through the acid-catalyzed hydration between the olefins and water molecules under an excess of HBr. The 1-phenyl alcohol derivatives are presumably formed by the substitution of the 1-bromo-1-phenyl adducts by the water of crystallization in the solid CD complex.

During the chiral induction of the solid–gas hydrohalogenation of the olefins, it was observed that the optical yields with the addition of HCl appeared considerably higher than those with the HBr addition, 15–62% vs. 0–17% ee, as shown in Table I. However, no optically active products were formed by the hydrohalogenation of the α- and β-CD inclusion complexes of styrene [7]. The magnitude and orientation of the enantioselection process in this solid–gas reaction varied either due to a slight structural difference of the olefins or due to that of the α- and β-CDs in a manner which was difficult to rationalize, as observed in the solid–gas hydrobromination of (E)-cinnamic acid [14] and its ethyl ester [15], resulting in the induced chiralities of these α- and β-CD complexes having the same and opposite configurations in the two cases, respectively.

Table I. Solid–gas hydrohalogenation of unfunctionalized olefins in crystalline cyclodextrin complexes[a]

Olefin	Cyclo-dextrin (CD)	Reaction with gaseous HCl: Time (h)	Product	Yield[b] (%)	$[\alpha]^{25}_D$[c] (°)	ee (%)(Config.)	Reaction with gaseous HBr: Time (h)	Product	Yield[b] (%)	$[\alpha]^{25}_D$[c] (°)	ee (%)(Config.)
	α-CD	20		29	0	0	3	PhCHBrMe	15	0	0
								PhCH(OH)Me	13	0	0
	β-CD	20		37	0	0	3	PhCHBrMe	27	0	0
								PhCH(OH)Me	25	0	0
	α-CD	50		15	+10.4	21 (R)[d]	5	PhCHBrEt	3	0	0
								PhCH(OH)Et	51	-5.9	15 (S)[e]
	β-CD	50		16	-22.0	44 (S)[d]	5	PhCHBrEt	45	0	0
								PhCH(OH)Et	40	+2.7	7 (R)[e]
	α-CD	50		5	+7.5	15 (R)[d]	5	PhCHBrEt	4	0	0
								PhCH(OH)Et	16	0	0
	β-CD	50		9	-9.5	19 (S)[d]	5	PhCHBrEt	16	0	0
								PhCH(OH)Et	62	0	0
	α-CD	50		53	+9.8[f]	58 (S)[g]	15	PhCH2CHBrMe	60	+1.1	5 (S)[h]
	β-CD	50		68	+10.5[f]	62 (S)[g]	15	PhCH2CHBrMe	72	+1.8	8 (S)[h]
	α-CD	50		trace	–	–	5		28	-2.5	12 (1R,2R,4S)[i]
	β-CD	50		trace	–	–	5		23	-3.7	17 (1R,2R,4S)[i]

[a] The solid CD complexes were exposed to gaseous reagents in the dark at 25 °C. [b] Isolated yield. [c] Measured in the same solvent given in the references [20–23]. [d] Based on the reported maximum rotation value of $[\alpha]_D^{20} = -50.3$ (Et_2O) for the S enantiomer [20]. [e] Based on the reported maximum rotation value of $[\alpha]_D^{20} = +40.0$ (benzene) for the R enantiomer [21]. [f] Measured at 436 nm. [g] Based on the reported maximum rotation value of $[\alpha]_{436}^{25} = +17.0$ (EtOH) for the S enantiomer [22]. [h] Based on the reported maximum rotation value of $[\alpha]_D^{14} = -23.0$ (EtOH) for the R enantiomer [22]. [i] Based on the reported maximum rotation value of $[\alpha]_D^{25} = -21.3$ ($CHCl_3$) for the $1R, 2R, 4S$ enantiomer [23].

The highest optical yields, 58% and 62% ee, were achieved with the HCl addition of 3-phenyl-1-propene (allylbenzene) in the respective α- and β-CD complexes, which gave predominantly (*S*)-(+)-2-chloro-1-phenylpropane in moderate chemical yields. On the other hand, the HBr addition of the same olefin in both the α- and β-CD complexes produced (*S*)-(+)-2-bromo-1-phenylpropane in the much lower optical yields of 5 and 8% ee, respectively. The enantioselective additions of both HCl and HBr to allylbenzene in both cavities of the α- and β-CDs preferentially induce the same *S*-chirality in the four cases, so it seems that these reactions occur in a similar chiral environment formed between the allylbenzene and the α- or β-CD. However, no detailed explanation of the stereochemistry of the solid–gas hydrohalogenation of the CD complexes can be proposed at present due to the absence of crystalline molecular structures of the α- and β-CD inclusion complexes of host–guest molar ratio 0.5 and 1, respectively. Attempts to prepare single crystals of the α- and β-CD complexes of the olefins for X-ray structure analysis have been unsuccessful.

The attacks of gaseous HCl on the (*E*)- and (*Z*)-1-phenyl-1-propenes as conjugated olefins gave (*R*)-(+)-1-chloro-1-phenylpropane in 21 and 15% ee from the α-CD, and the opposite (*S*)-enantiomer in 44 and 19% ee from the β-CD inclusion complexes, respectively. These results show that both isomers form complexes with α- and β-CDs such that the addition of HCl occurs with different enantioselections in the two host molecules to yield the monochloro derivatives with opposite chiralities. In contrast, the addition of HBr to the (*E*)- and the (*Z*)-isomer yielded 51 and 40% of the optically active 1-phenyl-1-propanol in the α- and β-CD matrices, respectively, with the reverse configurations to those of 1-chloro-1-phenylpropane as the hydrochlorination product of the same olefin in the respective α- and β-CD complexes, the (*S*)-alcohol in 15% ee from the α-CD, and the (*R*)-alcohol in 7% ee from the β-CD inclusion complex. These alcohol enantiomers are probably formed by the nucleophilic substitution of water in the solid CD complexes in the initially formed optically active monobromide, involving incomplete Walden inversion. However, no optically active monobromides were detected in the extracted mixture after the reaction of the conjugated olefins. On the other hand, the reaction of the (*Z*)-isomer did not afford the optically active products at all in either CD matrix. Concerning the orientation of the enantioselection process, the role of CDs as a chiral template causes us to note, interestingly, that the induction of (*R*)- or (*S*)-chirality is affected by the respective host–guest hydrophobic interactions between the CDs and substrates; the (*R*)-enantiomer is predominantly obtained from the HCl addition of the α-CD inclusion complexes of the (*E*)- and (*Z*)-β-methylstyrenes. The (*S*)-enantiomer is obtained from the HCl addition of the β-CD complexes of the (*E*)- and (*Z*)-isomers and from the reactions of HCl and HBr using both α- and β-CD complexes of allylbenzene, respectively.

It is well known that the optically active secondary haloalkanes bearing a phenyl substituent at their α-carbon are prone to racemization [16–19]; for example, during the methanolysis of the halides in the absence of a base [16] or simply during the

distillation of the reaction mixture [19]. It is therefore possible that the much lower optical yields for the asymmetric additions of HCl and HBr to both conjugated and nonconjugated olefins are due to racemization of the products in the CD matrices during the course of the hydrohalogenation. This was checked using the crystalline β-CD inclusion complexes of the optically active monohalides and alcohols, exposing them to gaseous HCl and HBr. When the solid β-CD complex of the (*S*)-1-chloro-1-phenylpropane of 44% ee obtained from the solid–gas reaction (see Table I) was exposed to HCl gas at 25 °C for 20 h, the optical purity of the recovered guest molecule decreased to 25% ee. In contrast, the isolated (*S*)-2-chloro-1-phenylpropane of 62% ee (see Table I) barely racemized under the same conditions using the β-CD complex, resulting in the recovery of the chloride in 60.5% ee and 95% yield. The stability of the optically active bromides, however, was not examined in the present study, because of the much lower optical purity of the bromide products. According to the higher polarizability of C—Br over C—Cl bonds [9], the optically active monobromide should be racemized more easily through the heterolysis of the C—Br bond than the corresponding chloride. Using the same method, when the nearly optically pure (*S*)-(−)-1-phenylethanol (98.2% ee) in the β-CD complex was exposed to HBr gas at −10 °C for 20 h, the optical purity of the alcohol recovered in 70% yield decreased to 30% ee, and the remaining alcohol was transformed into the racemic 1-bromo-1-phenylethane in 30% yield. These results show that the optically active products having a phenyl group on their asymmetric carbons are in danger of racemization during the course of hydrohalogenation, but that the 2-chloro derivative bearing a benzyl group (instead of a phenyl group) is fairly stable under the solid–gas conditions examined. The acid-catalyzed racemization of the secondary alkyl aryl halides and alcohols could be accounted for in terms of a reaction mechanism involving a carbonium intermediate ion, formed during the rate-determining step as an ion pair with a halide ion or a hydroxide ion [17]. Therefore, the rate of racemization is presumably affected by the lifetime of the intermediate ion. The more the carbonium cation is stabilized by the resonance effect of a phenyl moiety, the easier the optically active adduct is racemized [17]. Non-chiral induction for all the hydrohalogenations of styrene *via* a more stabilized carbonium intermediate ion suggests that the rotation of the groups on Cα about the bond between Cα and a phenyl moiety fixed in the cavity of CD occurs before the second attack of the halide ion, and a rapid racemization of the products occurs also simultaneously during the course of the reaction. In contrast, the magnitude of the enantioselection (up to 62% ee in the hydrochlorination of allylbenzene using the crystalline α- and β-CD complexes) should be generally true, except for only a slight danger of racemization.

Although further study is needed to clarify the enantioselection mechanism, our studies suggest that this loss in optical activity is primarily due to racemization of the products and not to the inherent chiral induction of the crystalline CD complex [5–7,14,15]. The optimization of olefinic properties in the substrate, then, may

bring about substantial improvement, thus preventing the danger of racemization in the asymmetric solid–gas hydrohalogenation, especially hydrochlorination.

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