Asymmetric Oxidation of Alkyl Aryl Sulfides in Crystalline Cyclodextrin Complexes

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Alkyl aryl sulfides were enantioselectively oxidized in the crystalline cyclodextrin (CD) complexes under various conditions. The oxidation of alkyl phenyl sulfoxides in the β-cyclodextrin (β-CD) complexes resulted in higher chiral induction than that in the α-CD complexes. Methyl 1- or 2-naphthyl sulfides were oxidized more enantioselectively in β-CD than in γ-CD. By changing the methyl substituent of 1-naphthyl sulfide to an isobutyl group, the reaction of the γ-CD complex increased the chiral induction reversely. The highest optical yield, 81%, was achieved in the combination of peracetic acid and methyl 1-naphthyl sulfide in the crystalline β-CD complex suspended in water at the oxidizing condition of 0 °C under nitrogen, which afforded the formation of the (*S*)-(−)-sulfoxide in high chemical yield without formation of sulfone. The binding constants, K (M^{-1}), were not reflected on the chiral induction for the oxidation with the crystalline CD complexes.

Introduction

Chiral sulfoxides have been widely used as a chiral auxiliary for the asymmetric synthesis involving chiral carbon–carbon bond formation.[1-3] Andersen synthesis is most commonly used for the preparation of chiral sulfoxides from menthyl sulfinates and Grignard reagents, but it requires several complicated steps.[4-6] Recently, simple methods for asymmetric oxidation of sulfides to chiral sulfoxides have been presented: the usage of Sharpless reagent, which is modified with water[7] or with excess diethyl tartrate[8] (up to 91% enantiomeric excess (ee)), oxidation in the chiral hydrophobic domain of bovine serum albumine with sodium metaperiodate (81% ee),[9] and oxygen-transfer reaction of chiral oxaziridines.[10]

Cyclodextrins (CDs) provide also a chiral binding site capable of including various kinds of hydrophobic compounds[11] and are known to resolve racemic sulfoxides optically in 1–15% ee.[12] They are found to induce asymmetric oxidation of aromatic sulfides dissolved in water[13] or in pyridine[14] or suspended in water[15,16] with various inorganic and organic oxidizing agents to give the corresponding sulfoxides in the moderate optical yields of 34,[13] 30,[14] 12,[15] 54%,[16] respectively. Recently, we achieved high enantioselectivity in the gas–solid halogenation and hydrohalogenation of olefins in crystalline CD complexes (40–100% ee).[17-21] In addition, highly enantioselective reduction of ketones has been achieved with the crystalline β-CD inclusion compounds of amine–borane complexes as chiral reducing agents suspended in water (91% ee).[22] Judging from these observations, we expected that effective discrimination of the enantiotopic electron pairs of sulfur atom in sulfide should be also achieved by fixing the sulfide in the chiral environment of CDs, especially in the crystalline state.

We report here a detailed study of the asymmetric oxidation of alkyl aryl sulfides utilizing the crystalline inclusion complexes with CDs as a chiral template to establish the optimum conditions for the achievement of required high stereoselectivity and discuss the structure of the guest molecules that are responsible for the chiral induction.

Results and Discussion

The solid complexes of alkyl aryl sulfides were obtained as crystalline precipitates from an aqueous solution of each sulfide with α-, β-, γ-, heptakis(2,6-di-*O*-methyl)-β-, and heptakis(2,3,6-tri-*O*-methyl)-β-CDs in the yields of 80–98%. The formation of complexes was confirmed by X-ray powder diffraction and by TG-DSC techniques. The X-ray diffraction patterns of these complexes show that they are highly crystalline and different from those of the physical mixtures of CDs and sulfides at the same molar ratio as that of the corresponding complexes. The thermal stability of methyl 1-naphthyl sulfide included in β-CD seems to be higher than that of the 2-naphthyl derivatives in the same host molecule. The 1- and 2-naphthyl sulfide molecules as guests release from the cavity of β-CD at 300 and 285 °C, respectively, just before the maximum decomposition of the complexes occurs. Both data are presented in the supplementary material.

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Table I. Effect of Solvent on Asymmetric Oxidation of *n*-Butyl Phenyl Sulfide in a Crystalline β-Cyclodextrin Complex[a]

solvent (ε)[c]	*n*-butyl phenyl sulfoxide $[\alpha]^{25}_D$, deg	ee,[d] % (config)	released guest,[b] mol %
H_2O (78.39)	+79.7	45 (*R*)	0.2
CCl_4 (2.24)	+70.8	40 (*R*)	3
pentane (1.84)	+53.1	30 (*R*)	9
CH_2Cl_2 (8.93)	+24.8	14 (*R*)	40
acetone (20.70)	+8.9	5 (*R*)	70
MeOH (32.70)	+1.8	1 (*R*)	100
$(CH_3)_2SO$ (46.68)	0	0	*e*

[a] The crystalline β-cyclodextrin complex of *n*-butyl phenyl sulfide (2 mmol) was oxidized with peracetic acid (2 mmol) in an aqueous or in an organic suspension system (solvent, 5 mL) at 0 °C for 20 h or at −20 °C for 120 h, respectively. The sulfoxide was obtained in the isolated yields of 80–94% without sulfone formation. [b] Total amount (mol %) of sulfoxide and sulfide released from the crystalline complex to the solvent after reaction was based on the amount of substrate included in the complex used. [c] Dielectric constant (ε) given in ref 23, pp 536–543. [d] Based on the maximum rotation value of $[\alpha]^{25}_D$ −177.1° (ethanol) for the *S* enantiomer, given in refs 12 and 14. [e] The solid complex was dissolved in DMSO. The reaction condition is shown in the Experimental Section.

α-CD formed a 1:2 (guest–host) crystalline complex with alkyl phenyl or methyl 1-naphthyl sulfides, whereas β-CD formed a 1:1 crystalline complex. α-CD did not include isobutyl 1-naphthyl and methyl 2-naphthyl sulfides, which are more bulky aromatic compounds than alkyl phenyl sulfides. Methyl 9-phenanthryl sulfide did not form host–guest complexes with both α- and β-CDs. However, γ-CD formed a 1:1 complex with the naphthyl or phenanthryl sulfide derivatives. Heptakis(2,6-di-*O*-methyl)- and heptakis(2,3,6-tri-*O*-methyl)-β-CDs formed a 1:1 complex with methyl 1-naphthyl sulfide in 80% yield.

For the successful asymmetric oxidation of the CD complex, the selection of the suitable solvents on the heterogeneous reaction should be one of the key factors to maintain the crystalline state of the CD complexes and to keep the guest molecules inside the cavity of CD during the course of the reaction. Therefore, the effect of solvents on the chiral induction was studied for the asymmetric oxidation of *n*-butyl phenyl sulfide in the crystalline β-CD complex with peracetic acid as an oxidizing agent and is shown in Table I. The oxidation of the solid β-CD complex in water or in CCl_4 led to (*R*)-sulfoxide in the highest optical yields of 45 and 40%, respectively, whereas the reactions in the other organic solvents decrease the chiral induction. In the reactions resulting in the lower chiral induction, the reacted and unreacted guest molecules were released considerably from the solid complex to these organic media without dissolution of β-CD during the course of the reaction. The solid complex, however, was dissolved in dimethyl sulfoxide (DMSO). The amount (mol %) of the guest molecules released seems to be in proportion to a magnitude of the dielectric constants (ε)[23] of these organic media. However, the oxidation of the solid complex suspended in water having the highest dielectric constant (ε = 78.39)[23] in the solvents tried gave the sulfoxide in the maximum optical and chemical yields, and furthermore, the amount of guest molecules released from the solid complex to water was minimized during the oxidation. This inverse solvent effect of water seems to be correlated to the fact that the aromatic sulfide is not very soluble in water but in these organic media and, further, the hydrophobic substrate is more suitable in the interior of the CD cavity with low dielectric constant[24] than in the surrounding polar water.[25] These results show that the enantioselective oxidation of sulfide requires the guest molecule to be held rigidly in the chiral cavity of the CD complex in the solid state. In fact, no chiral induction was observed in the homogeneous oxidation of the CD complex dissolved in DMSO.

Table II. Effect of Oxidizing Agent on Asymmetric Oxidation of Methyl Phenyl and Methyl 1-Naphthyl Sulfides in Crystalline β-Cyclodextrin Complexes[a]

sulfide, Ar	ArSR, R	reaction condition: oxidizing agent	time, h	sulfoxide, Ar-S(O)-R: yield,[b] %	ee, % (config)	sulfone yield,[b] %
phenyl	Me	CH_3CO_3H	3	98	15 (*S*)[c]	0
		t-BuOOH	20	11	1 (*S*)[c]	0
		H_2O_2[d]	20	34	3 (*S*)[c]	0
		NaOCl	5	10	0	0
			20	54	3 (*R*)[c]	34
1-naphthyl	Me	CH_3CO_3H	20	50	81 (*S*)[e]	0
		NaOCl	5	7	0	0
			20	22	25 (*R*)[e]	31

[a] The crystalline β-cyclodextrin complexes of sulfides were dispersed in water and oxidized with an equimolar amount of an oxidizing agent at 0 °C under nitrogen. [b] Isolated yields. [c] Based on the maximum rotation value of $[\alpha]^{25}_D$ −149.0° (ethanol) for the *S* enantiomer, given in ref 32. [d] Reaction was carried out at room temperature. [e] Determined by ^1H NMR ($CDCl_3$, 270 MHz) with Eu(hfc)$_3$ or by HPLC analysis using Daicel Chiralcel OB column. Configuration and the sign of optical rotation were previously determined.[32]

When the oxidation of the same crystalline complex suspended in CCl_4, which solidifies at −21.95 °C,[23] was carried out at 25, 0, −10, and −20 °C, the heterogeneous reaction gave (*R*)-*n*-butyl phenyl sulfoixde in the optical yields of 10, 22, 33, and 40%, respectively. As the reaction temperature is lowered from 25 to −20 °C, the chiral induction expectedly increases. This effect is probably related to increased rigidity of the conformation of the guest included in the solid β-CD complex. In addition, lowering the temperature to −20 °C gave a lower amount of the guest that was released from the solid complex.

In order to examine the enantioselectivity in the attack of the oxidizing agents such as peracetic acid, *tert*-butyl hydroperoxide, hydrogen peroxide, and sodium hypochlorite (NaOCl) upon sulfides, the crystalline β-CD complexes of two methyl sulfides having phenyl or 1-naphthyl substituents were oxidized with these reagents, as shown in Table II. Peracetic acid was the best oxidizing agent for the asymmetric oxidation of methyl phenyl and methyl 1-naphthyl sulfides to give (*S*)-sulfoxides in the optical yields of 15 and 81%, respectively. In contrast, the oxidation of the same substrates with NaOCl showed no enantioselectivity in the earlier stage of 7–10% conversions, but the reaction beyond 50% conversion gave the optically active sulfoxides with the opposite configuration (*R*) in the lower optical yields, involving the sulfone formation.

To explain the predominant production of (*R*)-sulfoxides involving formation of sulfone on the asymmetric oxidation with NaOCl, the kinetic resolution of racemic methyl phenyl sulfoxide in the crystalline β-CD complex was examined by the oxidation with equimolar NaOCl. As shown in Figure 1, when the conversion of racemic sulfoxide to sulfone reached 90% for 60 h, the observed optical purity of the recovered sulfoxide with the *R* configuration increased up to 90% ee. Thus, the (*S*)-sulfoxide was oxidized

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Table III. Asymmetric Oxidation of Alkyl Aryl Sulfides in Crystalline Cyclodextrin Complexes[a]

sulfide, Ar	ArSR, R	cyclodextrin (CD)	time, h	sulfoxide, ArS(O)R yield,[b] %	$[\alpha]^{25}_D$, deg	(c, solvent)	ee,[c] %	config	ref
phenyl	Me	α-CD	3	96	−6.0	(0.7, EtOH)	4	S	32
		β-CD	3	98	−22.4	(1.0, EtOH)	15	S	32
phenyl	Et	α-CD	20	97	−17.7	(0.5, EtOH)	10	S	12, 14
		β-CD	20	95	−46.8	(0.6, EtOH)	26	S	12, 14
phenyl	Pr	α-CD	20	95	+28.0	(0.5, EtOH)	11[d]		
		β-CD	20	92	+80.2	(1.0, EtOH)	30[d]		
phenyl	*n*-Bu	α-CD	20	98	+11.5	(0.5, EtOH)	6	R	12, 14
		β-CD	20	94	+79.7	(1.0, EtOH)	45	R	12, 14
phenyl	*i*-Bu	α-CD	20	96	+6.1	(0.3, EtOH)	3	R	12, 14
		β-CD	20	90	+133.7	(1.0, EtOH)	57	R	12, 14
phenyl	*t*-Bu	α-CD	20	95	+12.0	(0.6, EtOH)	7	R	33
		β-CD	20	75	+68.6	(1.0, EtOH)	38	R	33
1-naphthyl	Me	α-CD	20	92	−4.6	(0.5, EtOH)	1[e]	S	32
		β-CD	65	95	−372.7	(0.1, EtOH)	81[e]	S	32
		γ-CD	20	97	−85.1	(1.0, EtOH)	19[e]	S	32
		DM-β-CD[f]	20	80	−35.1	(1.5, EtOH)	8[e]	S	32
		TM-β-CD[f]	20	65	−16.3	(1.5, EtOH)	4[e]	S	32
1-naphthyl	*i*-Bu	α-CD	no inclusion						
		β-CD	65	40	+118.2	(0.5, $CHCl_3$)	31[d]		
		γ-CD	20	42	+205.3	(1.0, $CHCl_3$)	53[d]		
2-naphthyl	Me	α-CD	no inclusion						
		β-CD	65	98	+69.1	(1.0, $CHCl_3$)	49	R	7, 32
		γ-CD	20	94	+48.3	(1.8, $CHCl_3$)	34	R	7, 32
9-phenanthryl	Me	α-CD	no inclusion						
		β-CD	no inclusion						
		γ-CD	20	87	+99.5	(0.5, $CHCl_3$)	37[g]		

[a] The crystalline cyclodextrin complexes of alkyl aryl sulfides (2 mmol) were dispersed in water (5 mL) and oxidized with peracetic acid (2 mmol) at 0 °C under nitrogen. [b] Isolated yields. [c] Calculated from the reported rotation values given in the references. [d] Determined by HPLC analysis using Daicel Chiralcel OB column. [e] Determined by ^1H NMR ($CDCl_3$, 270 MHz) with Eu(hfc)$_3$ or by HPLC analysis using Daicel Chiralcel OB column. Configuration was previously determined on the sign of optical rotation given in the reference. [f] DM- and TM-β-CD mean heptakis(2,6-di-*O*-methyl)- and heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrins. The reactions proceeded in aqueous solution (homogeneous oxidation). [g] Determined by ^1H NMR with Eu(hfc)$_3$ or by HPLC analysis using Daicel Chiralcel OC column.

faster than the *R* enantiomer in the crystalline β-CD complex. Similarly, in the case of the oxidation of sulfides with NaOCl, as shown in Table II, the (*S*)-sulfoxide in the racemic product that was produced in the earlier stage of the reaction is also preferentially oxidized in the kinetic reaction process, resulting in the *R* enantiomer being more recovered than the *S* enantiomer. In addition, no optical resolution of racemic methyl phenyl sulfoxide was observed by forming crystalline complex with β-CD using the equimolar guest molecule.

Asymmetric oxidation of methyl 1-naphthyl sulfide in the β-CD complex suspended in water was carried out by varying the molar concentration of peracetic acid at 0 °C for 20 h under nitrogen. Interestingly, the results depicted graphically in Figure 2 showed that the chiral induction was almost constant with the optical yield of ca. 80% at molar ratios of 1:5 of peracetic acid to the substrate, and the chemical yields of the sulfoxide were not beyond 50% with varying quantities of the oxidizing agent for the limited reaction time of 20 h; that is, the rate of oxidation of the crystalline β-CD complex in an aqueous suspension system was almost constant, being independent upon the concentration of peracetic acid. The heterogeneous oxidation required a total of 65 h for completion apart from the concentration of the oxidizing agent to give preferentially the (*S*)-sulfoxide without a decrease of the optical purity in the chemical yield of 95%. The immutability of the reaction rate and optical yield over higher molar concentration of peracetic acid may be described by the observation that guest molecules react in turn on successive layers in the crystal exposed to the reagent. Thus, the attack of one molecule of peracetic acid proceeds via the formation of ternary molecular complex composed of β-CD–substrate complex and the reagent in the crystalline state. In the preferred diastereomeric transition state, peracetic acid may preferentially attack the *pro-S* electron pair on the sulfur atom located in the wider inside of the cavity of the β-CD complex. In fact, the crystallinity of the complex was not largely decreasing under such aqueous suspension even for 65 h.

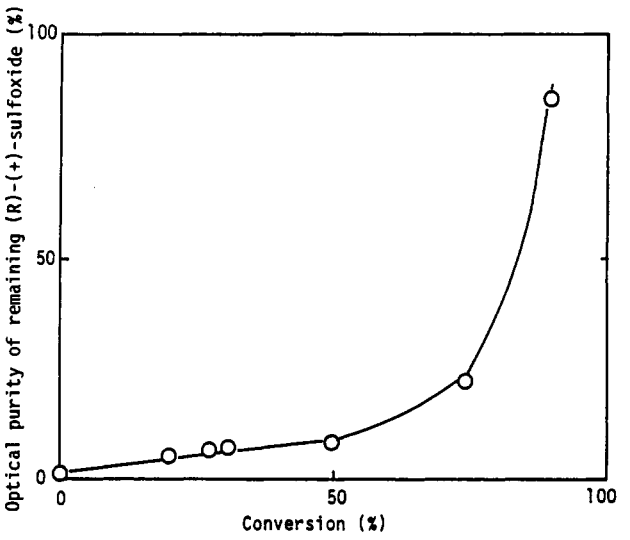

Figure 1. Kinetic resolution of racemic methyl phenyl sulfoxide in a crystalline β-cyclodextrin complex by oxidation with NaOCl.

A series of alkyl aryl sulfides were examined under the optimum conditions mentioned previously. The results summarized in Table III show that the stereoselectivity for the asymmetric oxidation of the β-CD–sulfide inclusion complexes is considerably higher than that for the α-CD complexes, i.e., 15–81% vs 1–11% ee. The lower chiral induction in the reaction of α-CD complexes may be due to a narrower internal diameter (4.5 Å)[11] of the host, which is too small to fit the sulfide moiety of alkyl aryl sulfides deeply in the internal cavity. The alkylthio group of the

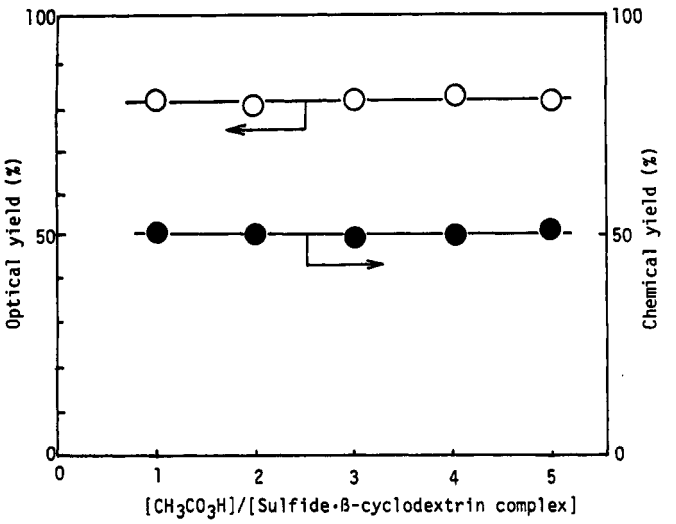

Figure 2. Dependence of the initial molar ratio of peracetic acid to methyl 1-naphthyl sulfide on the enantioselective oxidation of the sulfide in the crystalline β-cyclodextrin complex: ○, optical yield of methyl 1-naphthyl sulfoxide (ee, %); ●, isolated yield of sulfoxide (%). The details for the oxidation are described in the text.

substrate is probably located protruding from the chiral cavity of α-CD in its crystalline complex, which includes the phenyl moiety of the sulfides in the cavity. However, the structure of the α-CD complex that was found to be 0.5 for the molar ratio of the guests to the host cannot be described at present because neither crystalline nor molecular structure was determined for the solid complex. Nevertheless the higher enantioselectivity in the oxidation reaction with the β-CD–sulfide complexes than that in the reaction with the α-CD complexes may be explained by the complexation model such that the thio group is located to fit tightly in the wider cavity of β-CD (7.0 Å),[11] speculated from CPK space-filling models. Whereas γ-CD has an internal diameter (8.5 Å)[11] that is too large to fit tightly even the naphthyl moieties of the substrates, the enantioselectivity is lower than that of β-CD. In the reaction of isobutyl 1-naphthyl sulfide, however, the γ-CD complex induced higher stereoselectivity than the β-CD complex (53 vs 31% ee). Methyl 9-phenanthryl sulfide, having a more bulky aromatic moiety that can complexate only in the widest cavity of γ-CD, was oxidized to the corresponding sulfoxide with 37% ee in the yield of 87%. On the other hand, when the oxidation of methyl 1-naphthyl sulfide was carried out by using both the solid complexes with heptakis(2,6-di-*O*-methyl)- or heptakis(2,3,6-tri-*O*-methyl)-β-CDs as chiral host molecules, these complexes immediately dissolved homogeneously in water containing peracetic acid even at 0 °C. These reactions also afford the low chiral inductions of 4–8% ee because of a perfect collapse of crystalline chiral structure and a decrease or a disappearance of hydrogen bond between the nucleophilic lone-pair electrons on the sulfur atom of the substrate and the remaining hydroxyl groups of the modified β-CDs.

In the reaction of the β-CD complexes with alkyl phenyl sulfides, there is a trend of increasing stereoselectivity with increasing size of the alkyl substituents attached to the phenylthio group in the series. The stereoselectivity was enhanced from 15 to 57% ee on going from Me to *i*-Bu substituents in the phenyl sulfides. However, the oxidation of the sulfides having a *t*-Bu group, which is the most sterically bulky group, gave the (*R*)-sulfoxide in the moderate optical yield of 38%, contradictorily. Furthermore, on changing the aromatic substituents of methyl sulfide from the phenyl to 1- and 2-naphthyl groups, the chiral inductions increased from 15 to 81 and 49% ee, respectively. The best optical yield obtained, 81%, is explicable in terms of the tight inclusion of the 1-naphthyl moiety into the cavity of β-CD. This value is much higher than those reported previously by other workers.[13-16] The bulky naphthyl residue cannot fit into the cavity of β-CD along its short axis, but fits along its long axis nicely, similar to the complexation of CDs with α-1-naphthylethylamine having the molecular dimensions of 6.8 × 12 Å, reported by Trans et al.[26] The structure, assumed from CPK space-filling models, indicates that the methylthio residue of methyl 1-naphthyl sulfide fits into the chiral cavity of β-CD, whereas the methylthio group of the 2-naphthyl sulfide somewhat protrudes from the rim of secondary hydroxyl groups of β-CD, with the result that the latter methylthio residue is located somewhat loosely even in its crystalline structure. The (*S*)-sulfoxide (81% ee) obtained was recrystallized from a pentane–diethyl ether solution to yield the sulfoxide, which had a purity of 100% ee.

The configuration of the sulfoxide preferentially obtained from the oxidation of each sulfide in the α-, β-, and γ-CD complexes was in agreement with each other, but it changed unexpectedly when examined on alkyl or aryl substituents in the sulfides. These results show that CDs form the crystalline complexes with each sulfide in the peculiar chiral conformation reflecting in a slight difference of the structure of guest molecules. Interestingly, the homogeneous oxidation of the same substrates included in β-CD in a pyridine solution containing hydrogen peroxide[14] gave the sulfoxide with the opposite configuration: the heterogeneous reactions produced (*S*)-ethyl, (*R*)-*n*-butyl, and (*R*)-isobutyl phenyl sulfoxides in the optical yields of 26, 42, and 57%, respectively, whereas the homogeneous reactions gave the corresponding sulfoxides with the opposite configurations in the lower optical yields: *R* 9.8, *S* 30.0, and *S* 1.7% ee,[14], respectively.

Alkyl aryl sulfides are not very soluble in water. Their solubility increases in the presence of β-CD. Determination of the binding constants, K (M^{-1}), between aqueous β-CD solutions and methyl or isobutyl phenyl sulfides and methyl 1- or 2-naphthyl sulfides led to moderately strong binding constants (4200, 2200, 1200, and 1600 M^{-1}); these K values are comparable to the binding constants[11] obtained in the interaction of other hydrophobic compounds with CDs, and the stereoselectivities for the heterogeneous oxidation of the preformed solid complexes were *S* 7, *R* 57, *S* 81, and *R* 49% ee, respectively. Interestingly, these binding forces between aromatic sulfides and aqueous β-CD solutions are not related to the chiral induction in the oxidation with the crystalline β-CD complexes that were preformed from the supersaturated aqueous solutions of guest and host molecules; that is, the complexation of methyl 1-naphthyl sulfide with β-CD indicates the lowest binding constant in aqueous media, but the oxidation of this combination in crystalline state induced the highest stereoselectivity. These results reveal that the rigidity of guest molecules in the crystalline CD complex should be not reflected to the binding equilibrium constant between host and guest molecules in aqueous solution.

In this paper, we reported the efficient and simple method to oxidize alkyl aryl sulfides to chiral sulfoxides in a high enantioselectivity via preformed, crystalline CD complexes of substrate.

The result in which the optically pure methyl 1-naphthyl sulfoxide was prepared by this method led us to a study,

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published recently, on the utilization of the sulfoxide as a chiral auxiliary in the nucleophilic addition to alkyl phenyl ketones, resulting in the reaction with a perfect stereoselectivity.[27]

We are currently investigating the precise mechanism of the stereoselective oxidation in the crystalline CD complex and the extension of this simple method to the other asymmetric synthesis.

Experimental Section

Materials. α-, β-, and γ-CDs were purchased from Sanraku-Ocean Co. and purified by recrystallization from water. Heptakis(2,6-di-*O*-methyl)- and heptakis(2,3,6-tri-*O*-methyl)-β-CDs were obtained from Toshin Chemical Co. and used without further purification. Alkyl phenyl sulfides having Me, Et, Pr, *n*-Bu, and *i*-Bu groups as alkyl substituents and methyl 2-naphthyl sulfide were prepared by reaction of the sodium thiolates with the corresponding alkyl bromides according to the literature.[28] *tert*-Butyl phenyl sulfide was synthesied from benzenethiol and 2-methylpropene in 75% sulfuric acid.[28] Methyl or isobutyl 1-naphthyl sulfides and methyl 9-phenanthryl sulfide were prepared by alkylation of the lithium thiolates, synthesized from the corresponding aryl Grignard reagents and sulfur with $LiAlH_4$, and the alkyl bromides according to a reported procedure.[13] Peracetic acid as a 40% aqueous solution was purchased from Mitsubishi Kagaku Co. Other oxidizing agents were obtained from Kanto Chemical Co. and used as received. Tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) ($Eu(hfc)_3$) as a chiral shift reagent in NMR analysis was obtained from Aldrich Chemical Co. All other chemicals were purified in the usual ways.[28]

Analytical Method. UV spectra were measured in an aqueous solution containing 0.2% methanol using a thermostated cell (1 cm) at 25 ± 0.1 °C. Optical rotations were measured in a 1-dm cell at 25 °C. Analytical and preparative HPLC separations were run using a UV detector (254 nm). Analytical HPLC for optical separation was performed by a column (4.6 × 250 mm) packed with Daicel Chiralcel OB or OC, purchased from Daicel Chemical Co., at a flow rate of 2 mL/min using *n*-hexane-2-propanol (98:2) as eluent. The X-ray diffraction diagrams and TG-DSC curves of the β-CD complexes are illustrated in the supplementary material.

Preparation of Inclusion Complexes. To 100 mL of an aqeous solution containing α-CD (8×10^{-1} M), β-CD (1×10^{-1} M), or γ-CD (8×10^{-1} M) were added equimolar amounts of the alkyl aryl sulfides at 70 °C and further dissolved by mixing at 80 °C for 30 min. After being stirred for 2 h at room temperature, the mixtures were then cooled at 0 °C for 1 day. In preparation of the methylated β-CD complexes, an equimolar amount of methyl 1-naphthyl sulfide was added to an aqueous solution (10 mL) of heptakis(2,6-di-*O*-methyl)-β-CD (5×10^{-1} M) or heptakis(2,3,6-tri-*O*-methyl)-β-CD (2×10^{-1} M) and dissolved by mixing at 25 °C. The solution was then cooled at 0 °C for 3 days. The CD complexes were collected by filtration and used without drying in vacuo; the order of their crystallinity was found to decrease upon dehydration.[29] White microcrystalline complexes were obtained in the yields of 80–98%. The stoichiometry of the complexes was determined by ^1H NMR spectra of the precipitates in DMSO-d_6.

Determination of Binding Constants. The binding constants, K (M^{-1}), for the β-CD complexes with methyl or isobutyl phenyl sulfides and methyl 1- or 2-naphthyl sulfides were determined spectrophotometrically in an aqueous solution containing 0.2% methanol by the method of Cramer et al.[30] The UV absorption changes of given sulfides (1.0×10^{-4} M) in the presence of β-CD (varied from 1.0×10^{-4} to 5.0×10^{-3} M) were measured in the region of 220–360 nm. A linear relationship was observed between the spectral change and the added concentration of β-CD, treating by the Benesi–Hildebrand equation.[31] The K value was calculated from the slope and the intercept of a straight line observed on the equation plots.

Asymmetric Oxidation of Alkyl Aryl Sulfides. The general procedure for the oxidation of sulfides in the CD inclusion complexes was as follows. The crystalline inclusion compounds (2.5–3 g wet weight, 2 mmol) prepared from an aqueous solution of CDs with sulfides were suspended and stirred in water (5 mL) containing peracetic acid (380 μL of 40% aqueous solution, 2 mmol) at 0 °C for 3–65 h under N_2. All the reaction mixtures were heterogeneous under such conditions, but the methylated β-CD complexes were dissolved in water containing peracetic acid. After the reaction, the 0.1 M aqueous $Na_2S_2O_3$ (10 mL, 1 mmol) was added to decompose the unreacted peracetic acid, and then water was added to dissolve the complex. The aqueous solution was extracted with CH_2Cl_2 (3×), and the resulting precipitate CD–solvent complex was separated. The combined organic layers were washed with aqueous NaCl, dried over $MgSO_4$, and evaporated in vacuo. The extract was recovered in 95–98% yields and was chromatographed on Wako C-300 silica gel with CH_2Cl_2 containing 0.5% methanol as eluent to give optically active sulfoxides in the chemical yields of 40–98%, as identified by comparison of their ^1H NMR and IR spectra with those of authentically racemic samples. A similar procedure was followed for the reaction of isobutyl phenyl sulfide in the crystalline β-CD complex with peracetic acid in organic media instead of water as a dispersion medium for 120 h at −20 to 25 °C. After the reaction at −20 °C, an amount (mol %) of the reacted and unreacted guest molecules, released from the inclusion complex to organic media during the course of the oxidation, was measured by UV spectroscopy of the organic solutions in the region of 240–430 nm. The homogeneous oxidation was carried out by dissolving the solid β-CD complexes (ca. 2 mmol) in DMSO (5 mL) containing an equimolar peracetic acid at 25 °C for 20 h. Then the reaction mixture was poured into water (200 mL), followed by extraction with diethyl ether. The extract was recovered in 98% yield and chromatographed as described previously.

Kinetic Resolution. The crystalline inclusion compound prepared from an aqueous solution of β-CD (2.3 g, 2 mmol) with racemic methyl phenyl sulfoxide (280 mg, 2 mmol) was suspended in water containing NaOCl (3 mL of 5% aqueous solution, 2 mmol) as an oxidizing agent at 0 °C for 10–60 h in a procedure similar to the asymmetric oxidation of the sulfide of the β-CD complex. At every tenth hour, the unreacted sulfoxide extracted with CH_2Cl_2 was isolated by column chromatography on silica gel and its absolute configuration and optical yield were determined from the sign and the specific rotation of the isolated sample. Before the kinetic resolution experiments by oxidation, the solid complex (ca. 1.5 g, 1 mmol) was dissolved in water and followed by extraction with CH_2Cl_2 to recover the sulfoxide as the guest molecule with 0% ee in 99% yield.

(*S*)-(−)-Methyl 1-Naphthyl Sulfoxide. Oxidation of methyl 1-naphthyl sulfide in β-CD with peracetic acid at 0 °C for 65 h under N_2 gave methyl 1-naphthyl sulfoxide: yield 180 mg (95%); mp 55–58 °C (lit.[32] mp 58–65 °C); IR (KBr) 1049 (S=O) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.84 (s, 3 H, CH_3), 7.56–7.70 (m, 3 H, aromatic), 7.91–7.99 (m, 3 H, aromatic), 8.18 (dd, 1 H, J = 7.25, 1.32 Hz, aromatic); $[\alpha]^{25}_D$ −372.7° (*c* 0.1, ethanol), 81 and 80% ee (*S* predominates[32]), as confirmed by HPLC analysis on a Daicel Chiralcel OB column and by ^1H NMR ($CDCl_3$, 270 MHz) with $Eu(hfc)_3$ (0.4 equiv to sulfoxide), respectively. Recrystallization of the (*S*)-sulfoxide from diethyl ether–pentane mixture (3:1) gave the sulfoxide, which had a purity of 100% ee in the yield of 70%, as confirmed by HPLC and ^1H NMR methods as described previously: $[\alpha]^{25}_D$ −459.8° (*c* 0.1, ethanol); ^1H NMR ($CDCl_3$, 270 MHz, $[Eu(hfc)_3]/[(S)$-(−)-sulfoxide] = 0.4) δ 6.12 (s, 3 H, CH_3), 9.76 (d, 1 H, J = 8.30 Hz, aromatic); HPLC (Daicel Chiralcel OB) retention volume of 86.5 mL. For the racemic sulfoxide: mp 62–63 °C; ^1H NMR ($CDCl_3$, 270 MHz, $[Eu(hfc)_3]/[(\pm)$-sulfoxide] = 0.4) δ 6.11 (s, 3 H, CH_3, (*S*)-(−)), 6.20 (s, 3 H, CH_3, (*R*)-(+)), 9.75 (d, 1 H, J = 8.30 Hz, aromatic, (*S*)-(−)),

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9.93 (d, 1 H, J = 8.30 Hz, aromatic, (*R*)-(+))($\Delta\Delta\delta$ 0.18 ppm); HPLC (Daicel Chiralcel OB) retention volumes of 86.9 ((*S*)-(−)) and 125.5 ((*R*)-(+)) mL, respectively.

(*R*)-(+)-Methyl 2-Naphthyl Sulfoxide. Oxidation of methyl 2-naphthyl sulfide in β-CD with peracetic acid at 0 °C for 65 h under N_2 gave methyl 2-naphthyl sulfoxide: yield 186 mg (98%); mp 105–107 °C (lit.[32] mp 103–108 °C); IR (KBr) 1040 (S=O) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.79 (s, 3 H, CH_3), 7.56–7.62 (m, 3 H, aromatic), 7.89–8.00 (m, 3 H, aromatic) 8.22 (s, 1 H, aromatic); $[\alpha]^{25}_D$ +69.1° (*c* 1.0, $CHCl_3$), 49% ee (*R* predominates) based on $[\alpha]^{25}_D$ +127° (*c* 2, $CHCl_3$), 90% ee,[7] (*R*)-(+).[32]

(+)-Methyl 9-Phenanthryl Sulfoxide. Oxidation of methyl 9-phenanthryl sulfide in γ-CD with peracetic acid at 0 °C for 20 h under N_2 gave methyl 9-naphthyl sulfoxide: yield 209 mg (87%); mp 113–115 °C; IR (KBr) 1060 (S=O) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.89 (s, 3 H, CH_3), 7.62–7.78 (m, 4 H, aromatic), 7.89–8.06 (m, 2 H, aromatic), 8.46 (s, 1 H, aromatic), 8.66–8.78 (m, 2 H, aromatic); $[\alpha]^{25}_D$ +99.4° (*c* 0.5, $CHCl_3$), 37% ee, as confirmed by HPLC analysis on a Daicel Chiralcel OC column or by ^1H NMR method as mentioned previously; ^1H NMR ($CDCl_3$, 270 MHz, [Eu(hfc)$_3$]/[(+)-sulfoxide] = 0.4) δ 6.09 (s, 3 H, CH_3 (−)-sulfoxide), 6.16 (s, 3 H, CH_3, (+)-sulfoxide), 9.61 (m, 1 H, aromatic, (−)-sulfoxide), 9.87 (m, 1 H, aromatic, (+)-sulfoxide); HPLC (Daicel Chiralcel OC) retention volumes of 179.0 ((+)-sulfoxide) and 213.4 ((−)-sulfoxide) mL, respectively. No optical separation of the sulfoxide, however, was observed by HPLC analysis using a Daicel Chiralcel OB column.

Supplementary Material Available: X-ray diffraction diagrams and TG-DSC data for β-CD complexes of methyl 1- and 2-naphthyl sulfides (3 pages). Ordering information is given on any current masthead page.

1-Chloroalkyl *p*-Tolyl Sulfoxides as Useful Agents for Homologation of Carbonyl Compounds: Conversion of Carbonyl Compounds to α-Hydroxy Acids, Esters, and Amides and α,α′-Dihydroxy Ketones

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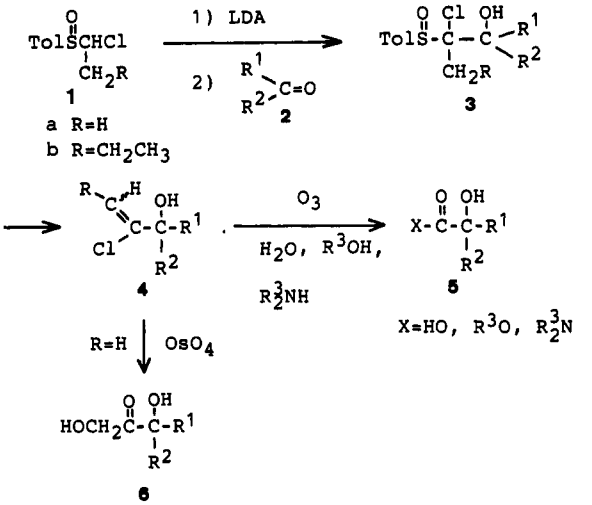
One-carbon homologation of carbonyl compounds to α-hydroxy acids, esters, and amides by the use of 1-chloroalkyl *p*-tolyl sulfoxide as a hydroxycarbonyl anion equivalent is reported. Oxidation of the vinyl chlorides, the intermediates of the above-mentioned method, with osmium tetraoxide gives α,α′-dihydroxy ketones which are found in biologically active natural products such as cortisone and adriamycin.

One-carbon homologation of carbonyl compounds is an important and extensively used method in organic synthesis.[1] Various kinds of homologating agents have been reported;[1] however, in view of the usefulness of the method, new homologating agents are eagerly sought.

We recently reported some novel synthetic methodologies using 1-chloroalkyl aryl sulfoxides via α,β-epoxy sulfoxides.[2] In continuation of our studies on the use of 1-chloroalkyl *p*-tolyl sulfoxides **1**, including optically active ones, in organic synthesis, we describe herein a novel method for homologation of carbonyl compounds **2** into α-hydroxy acids (**5**, X = OH), esters (**5**, X = R^3O), and amides (**5**, X = R^3_2N) and α,α′-dihydroxy ketones **6** (Scheme I).

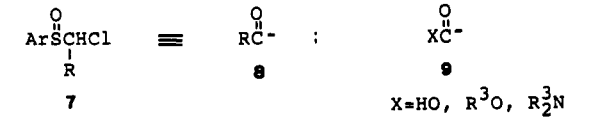
Scheme I



Results and Discussion

Homologation of Carbonyl Compounds to α-Hydroxy Acids, Esters, and Amides with 1-Chloroethyl *p*-Tolyl Sulfoxide as One-Carbon Homologating Agent. Innumerable methods for the synthesis of aldehydes and ketones from lower carbonyl compounds by homologation have been reported;[1] however, relatively few methods for the synthesis of carboxylic acids, esters, or amides by one-carbon homologation have appeared.

Scheme II



Classically, α-hydroxy acid derivatives are synthesized from carbonyl compounds with hydrogen cyanide via cyanohydrins.[3] This reaction requires a toxic reagent, and

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