Molecular Orbital Studies on Pericyclic Reactions of Cinnamyl Xanthates in β-Cyclodextrin Cavities

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The solid β-cyclodextrin (β-CyD) complex of *O*-cinnamyl *S*-methyl dithiocarbonates (xanthate, 1a), upon heating at 45 °C, underwent asymmetric [3,3]-sigmatropic rearrangement to give the optically *S*-(1-phenylallyl) *S*-methyl dithiocarbonate (2a) with 60% ee. Heating the β-CyD complex of 2a at 120 °C caused extrusion of COS to give cinnamyl methyl sulfide (3a) in high yield. The reaction behavior and role of β-CyD are discussed based on molecular orbital calculation data.

Key words *O*-cinnamyl *S*-methyl dithiocarbonate; β-cyclodextrin; pericyclic reaction; *S*-(1-phenylallyl) *S*-methyl dithiocarbonate; PM3; asymmetric induction

Cyclodextrins (CyDs) consist of six or more α-1,4-linked D-glucose units forming truncated cone-shaped compounds. The inner cavity has a hydrophobic character, forming inclusion complexes with a wide variety of guest molecules. Therefore, CyDs have attracted much attention as host molecules in complexation and catalysis studies.[1] In particular, reaction controls using the hydrophobic interior as a reaction field have been studied in recent years.[2] However, although some asymmetric reactions in solution have been attempted in the presence of CyDs, satisfactory optical yields have not yet been obtained.[1]

Allylic xanthates (**1**) underwent [3,3]-sigmatropic rearrangement to give the dithiolcarbonates (**2**)[3] which, on heating, extruded COS to give the allylically rearranged sulfides (**3**).[4a] In this connection, we have communicated a preliminary result of the asymmetric [3,3]-sigmatropic rearrangement of *O*-cinnamyl *S*-methyl xanthate (**1a**) in crystalline β-CyD complex as a chiral environment.[5]

In this paper, we wish to report details of the asymmetric induction in the [3,3]-sigmatropic rearrangement of **1a** and rate enhancement of COS extrusion of the rearrangement product (**2a**) in β-CyD based on PM3[6a] calculation data.

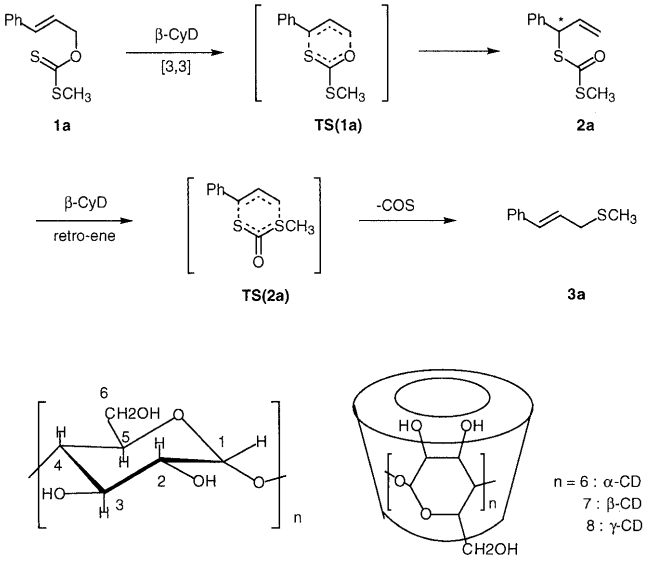

Chart 1

Results

Asymmetric Rearrangement of Cinnamyl Xanthates (1a—c) The complex of **1a** was prepared by the crystallization method from an aqueous saturated solution of β-CyD and was shown to be a 1 : 1 host guest complex by ^{1}H-NMR integration. The solid β-CyD complex of **1a** was heated at 80 °C for 6 h. The complex was dissolved in dimethyl sulfoxide (DMSO) and the guest was extracted with benzene to afford **2a** in 81% chemical yield. The product **2a** was enantiomerically enriched (46% ee). The extract from the complex of racemic **2a** did not show any optical activity, indicating that the observed enantioselectivity is not due to optical resolution. When the reaction was performed at 45 °C, an improvement in both yield (90%) and enantioselectivity (60% ee) was observed. The corresponding α or γ complex did not show sufficient enantioselectivity and *S*-alkyl groups bulkier than *S*-methyl showed low optical yields (see Table 1).

COS Extrusion Reaction of Dithiolcarbonates (2a—d) Next, the effect of CyD on the rate enhancement of the COS extrusion reaction was studied. Previously, we reported that the reaction was effectively accelerated by phenols which form hydrogen bonds between the dithiocarbonyl group and the hydroxy group of the phenols.[4b] When the 1 : 1 solid β-CyD complex of **2a** was heated at 120 °C for 6 h, cinnamyl methyl sulfide (**3a**) was formed as a single product in 81% yield (Table 2). In the case of the acetyl methyl derivative (**2d**), the extrusion of COS occurred smoothly to give the corresponding sulfide (**3d**) in 95% yield. The extrusion rate of **2a** based on the half-life of the complex was 2.0×10^{-4} s^{-1}

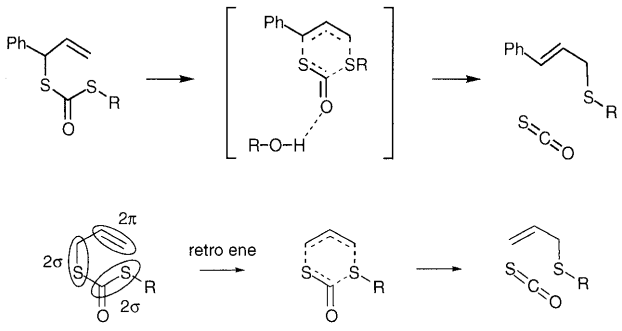

Chart 2

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while, in the absence of CyD, the rate was $1.18\times10^{-5}\,s^{-1}$. The rate enhancement is comparable with that of *p*-nitrophenol catalyst ($1.23\times10^{-4}\,s^{-1}$).[4b]

Molecular Orbital (MO) Calculations Semi-empirical MO calculations were run through the ANCHOR II interface using MOPAC6.0[6a] on a Fujitsu S-4/2 workstation or through the CS Chem3D Pro interface using MOPAC93 on a Power Macintosh G3 computer. Density functional theory (DFT) and Hartree–Fock (HF) computations[7] were carried out on a Scientists' Paradise Dragon AXP5A/433 computer or an HP Exemplar Technical Server V2250KS in the Kumamoto University Information Processing Center. The PM3-optimized structures were used as starting geometries for the HF and DFT calculations. The PM3 calculations of β-CyD and its inclusion compounds were carried out using a locally modified version of the MOPAC package[6a] on a Dragon AXP433 computer.

Table 1. [3,3]-Sigmatropic Rearrangement of *O*-Cinnamyl *S*-Alkyl Xanthates (**1a—c**) in the Crystalline CyD Complexes

R	CyD	Temp. (°C)	Time (h)	**2**, Yield (%)	ee (%)[a]
Me (**1a**)	β	80	6	81	46
	β	70	12	70	56
	β	60	48	60	58
	β	45	48	90	60
	β	35	120	82	51
	α	60	48	40	3[b]
	γ	60	48	87	12[b]
Et (**1b**)	β	45	48	41	14
$PhCH_2$ (**1c**)	β	45	48	70	11

a) Determined by HPLC using a DAICEL CHILALCEL OJ column. *b*) See ref. 5*a*).

Table 2. COS Extrusion Reaction[a] of *S*-(1-Phenylallyl) *S*-Alkyl Dithiocarbonates (**2a—d**) in the Crystalline β-CyD Complexes

R	Product, Yield (%)
Me (**2a**)	**3a**, 81
Et (**2b**)	**3b**, 88
CH_2Ph (**2c**)	**3c**, 73
CH_2COMe (**2d**)	**3d**, 95

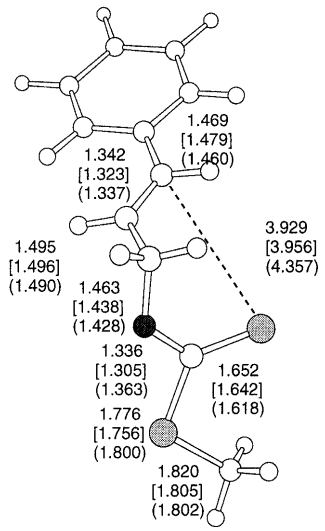
a) at 120 °C, 6 h.

Ground-State (GS) Structures of the Guests of Xanthate (1a) and Dithiolcarbonate (2a) First of all, conformational studies were undertaken on all the free guests. The PM3 calculation on **1a** showed the existence of two local minimum conformations. The methyl and methylene groups lie within the plane of the –O(C=S)S– moiety with *syn*/*anti* dispositions with respect to the C=S bond.[6b] The *anti* conformation was calculated to be *ca.* 1.4 kcal mol^{-1} more stable than the *syn* conformation. However, HF/6-31G* and DFT (B3LYP/6-31G*) calculations of **1a** gave an opposite prediction, the structural feature (*syn*) of which is in accordance with that observed in the crystal structures of analogous compounds.[8a]

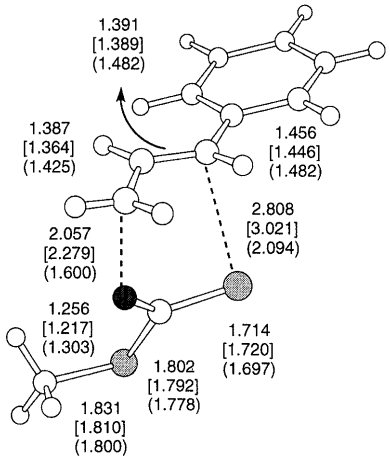
The minimum-energy geometry of the allylically rearranged product (**2a**) was also determined in a similar manner to that described above. The most stable conformation of **2a** is *syn*, in contrast to the PM3 optimized structure of **1a**. The structures calculated at 3-21G* and 6-31G* levels also have a *syn* conformation.[8b]

Transition Structure of [3,3]-Sigmatropic Rearrangement of Xanthate (1a) The transition structure strongly depends on the calculation levels. In the B3LYP/6-31G* transition-state (TS) structure, the bond distances to be created (S··C) and broken (C··O) were 2.808 and 2.057 Å, respectively, and those are very long in comparison with those of the PM3-calculated TS (C··O: 2.094 Å; S··C: 1.600 Å).

The energies calculated at the HF/3-21G* level are questionable. The rearranged product (**2a**) is estimated to be less stable (1.53 kcal mol^{-1} endothermic) than **1a** (Table 3). The HF/3-21G* calculations seem to overestimate the contribution of the resonance energy of the styrene moiety.[9] In contrast, the calculation at the B3LYP/6-31G* level is reasonable, indicating 3.67 kcal mol^{-1} exothermic. The reaction barrier calculated by the B3LYP/6-31G* is 25.1 kcal mol^{-1}, which is close to the experimental value (26.2 kcal mol^{-1}) in *n*-hexadecane. The PM3 reaction barrier (25.0 kcal mol^{-1}) is also close to the observed value (see Table 3).



1a



TS(1a)

Fig. 1. B3LYP/6-31G*, HF/6-31G* and PM3 Optimized Structures of **1a** and TS(**1a**)
HF/6-31G* and PM3 calculated values in parentheses [ ] amd ( ), respectively.

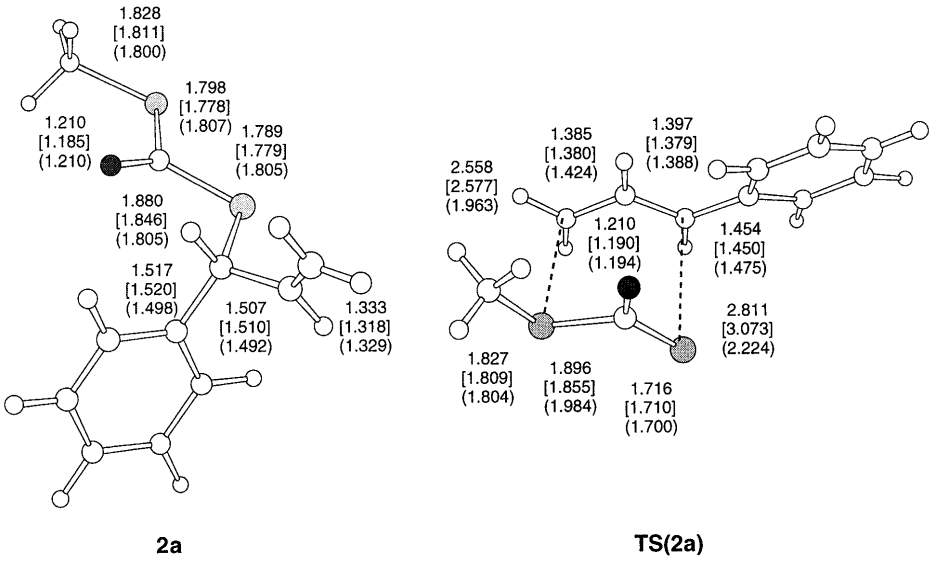


Fig. 2. B3LYP/6-31G*, HF/6-31G* and PM3 Optimized Structures of **2a** and TS(**2a**)
HF/6-31G* and PM3 calculated values in parentheses [ ] and ( ), respectively.

Table 3. Reaction Barriers and Heats of Formation for the [3,3]-Sigmatropic Rearrrangement of **1a** and COS Extrusion of **2a**

Reaction calculated	PM3[a]	HF/3-21G*[b]	HF/6-31G*[b]	MP2//HF/6-31G*[b]	B3LYP/6-31G*[b]
Sigmatropy of **1a**					
1a	41.9[c]	−1286.9366	−1293.3967	−1295.2128	−1297.9770[d]
TS	66.9[c]	−1286.8731	−1293.3386	−1295.1504	−1297.9370
2a	17.3	−1286.9318	−1293.4031	−1295.2287	−1297.9829
Reaction barrier	25.0	39.9[a]	36.5[a]	39.1[a]	25.1[a]
Heat of reaction	−24.6	1.53[a]	−3.97[a]	−9.97[a]	−3.67[a]
COS Extrusion of **2a**					
TS	46.1		−1293.3290	−1295.1564	−1297.9383
3a+COS	7.8		−1293.4278	−1295.2441	−1298.0030
Reaction barrier	28.8		46.5[a]	45.4[a]	27.9[a]

a) kcal mol^{-1}, *b*) Hartree, 1Hartree=627.5 kcal mol^{-1}, *c*) *syn*, *d*) *anti*, $E=-1297.9747$.

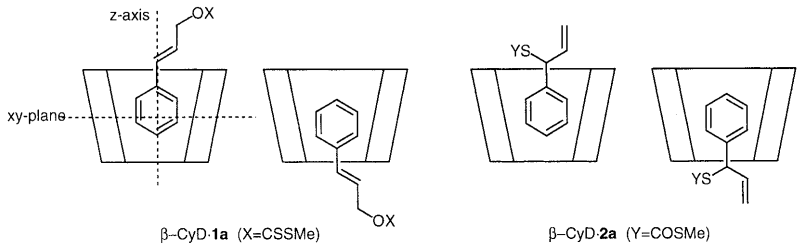


Fig. 3. Different Modes for the Entry of **1a** and **2a** into the Cavity of β-CyD

Transition Structure of COS Extrusion of Dithiolcarbonate (2a) The TS structures of the extrusion reaction show that the reaction proceeds through a six-membered nonionic cyclic $[2\pi+2\sigma+2\sigma]$ transition state.[4a] The B3LYP/6-31G* distances to be created and broken were 2.558 and 2.811 Å, respectively. The B3LYP/6-31G* reaction barrier is 27.9 kcal mol^{-1}.

PM3-Calculated Ground-State Structure of the Complexes To study the inclusion behavior, the energies and structures of the complexes were calculated. Theoretical treatments of the complexation process using molecular mechanics (MM) calculations have been reported.[10] However, there are few MM parameters involving sulfur functional groups in which electrostatic interactions have been estimated. In this study, the PM3 MO method was used to investigate the complexation.[6b] As the number of doubly occupied levels is very large (261), a workstation equipped with a high-performance DEC α CPU was used.

The initial structure of β-CyD was constructed by connecting seven units of α-D-glucopyranose by α-1,4-bonding and this was fully minimized. For the starting structure of the guest (**1a**), the PM3 optimized *syn* conformation was used. The entry of the phenyl ring of the guests may occur through either the larger or smaller rim of the truncated cone of β-CyD, giving rise to two different orientations (Fig. 3).

Initial geometries of the complexes for different inclusion modes were located by docking the guests with the host. The β-CyD molecule was oriented so as to have almost seven

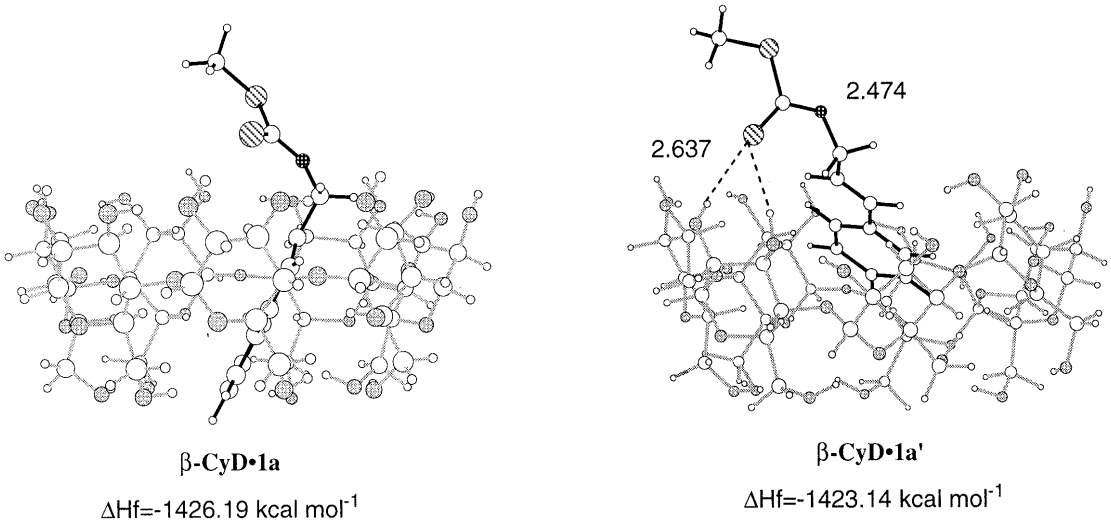


Fig. 4. GS Structures for the Nonhydrogen-Bonded and Hydrogen-Bonded Complexes of **1a** and β-CyD

Table 4. PM3 Calculated Heats of Formation (ΔHf, kcal mol^{-1}) of the β-CyD Complexes of **1a**, TS(**1a**), **2a** and TS(**2a**)

Complex calculated	Orientation of the dithiocarbonyl group		[Guest+CyD]
	Larger rim side[a]	Smaller rim side[b]	
β-CyD **1a**	−1426.2 (−21.0)[d]	−1420.3 (−15.1)[d]	−1405.2 [41.9+(−1447.1)]
β-CyD·**1a**'[c]	−1423.1 (−17.9)[d]		
β-CyD·TS(**1a**)[c,e,f]	−1396.7 (−16.5)[d,g]		−1380.2 [66.9+(−1447.1)]
β-CyD·**2a**[c]	−1451.0 (−21.2)[d,h]	−1443.4 (−13.6)[d]	−1429.8 [17.3+(−1447.1)]
β-CyD·TS(**2a**)[c]	−1417.4 (−16.4)[d]		−1401.0 [46.1+(−1447.1)]

a) The dithiocarbonyl moiety orients to the secondary hydroxy groups. *b*) The dithiocarbonyl moiety orients to the primary hydroxy groups. *c*) Hydrogen-bonded complex. *d*) Stabilization energy due to complexation in parenthesis. *e*) The lowest two eigenvalues of Hessian are −445.56 and −1.56. *f*) The AM1 calculaion gave a similar TS structure. *g*) *R* form. The ΔHf for *S* isomer [β-CyD-*S*-TS(**1a**)] is −1392.2 kcal mol^{-1}. *h*) *R* form. The ΔHf for *S* isomer (β-CyD·*S*-**2a**) is −1446.7 kcal mol^{-1}.

glycoside oxygen atoms in the X–Y plane and the secondary hydroxy groups on the positive region of the Z axis. The guests were located by keeping the HC–Ph bond aligned with the C_7 symmetry axis (Z-axis) of β-CyD and several initial geometries were generated by moving the guest molecule along the Z axis from −4 to 4 Å distance to the XY plane. No restrictions were imposed on the optimization of the host and guest geometries. Energy minimization of the structures was performed until a gradient norm (GNORM) was less than about 0.1 kcal mol^{-1}. The structures[6c] and energies are shown in Fig. 4 and Table 4, respectively.

PM3-Calculated Transition Structures of the β-CyD Complex Next, the β-CyD complex (through the larger rim) of the cyclic TS [TS(**1a**)] of the [3,3]-sigmatropic rearrangement of **1a** was calculated by PM3. The crude TS geometry was obtained using the eigenvector following (EF) routine, keeping the C–O and C–S distances of the guest fixed (–CH_2··O 1.600 Å, =CHPh··S–CO 2.094 Å) (Table 4). Then, the obtained structure was fully optimized using the TS routine with the XYZ keyword. The TS geometry [β-CyD·TS(**1a**)] is shown in Fig. 5c.[6c] The vibrational frequency calculation indicated two imaginary frequencies for the stationary point (see Table 4 footnote e). However, the guest TS retains the authentic transition structure of TS(**1a**), in which the breaking C–O bond is slightly elongated (0.025 Å) compared with that of free TS(**1a**). Intrisic reaction coordinate (IRC) calculation starting from the transition state confirms the presence of the shallow inclusion complex of **1a** and β-CyD at the end of IRC. The rearrangement product has been obtained at the other end of IRC.

The β-CyD complex of the antipode (*S*) of TS(**1a**) is 4.5 kcal mol^{-1} less stable than the β-CyD·TS(**1a**) (*R* form). The phenyl moiety of the *R* isomer was found to be more deeply inserted into the cavity compared with that of the *S* isomer.[5b]

Similarly, the complex of β-CyD and the cyclic transition state [TS(**2a**)] of the COS extrusion reaction of **2a** was calculated. The transition structure [β-CyD·TS(**2a**)] is shown in Fig. 6 (see also Table 4).

Discussion

The stabilization energy due to the formation of the inclusion compound was estimated as the energy difference (ΔΔHf) between ΔHf(guest·β-CyD) and ΔHf(guest)+ΔHf(β-CyD). In the case of the β-CyD·**1a** complex, the values for the larger and smaller rim are 21.0 kcal mol^{-1} and 15.1 kcal mol^{-1}, respectively. The difference [ΔHf(larger)−ΔHf(smaller)] in heat of formation is 5.9 kcal mol^{-1}, suggesting that the entry of **1a** through the larger rim of β-CyD is favorable. Hereafter, we took no account of the complexation through the smaller rim.

The most stable GS structure of the complex [β-CyD·**1a**] has no hydrogen bonds between the thione sulfur and the secondary hydroxy groups of β-CyD, in which the phenyl ring is fixed by the H/H close contacts between the aromatic hydrogens and the inner >C–H protons of β-CyD. On the other

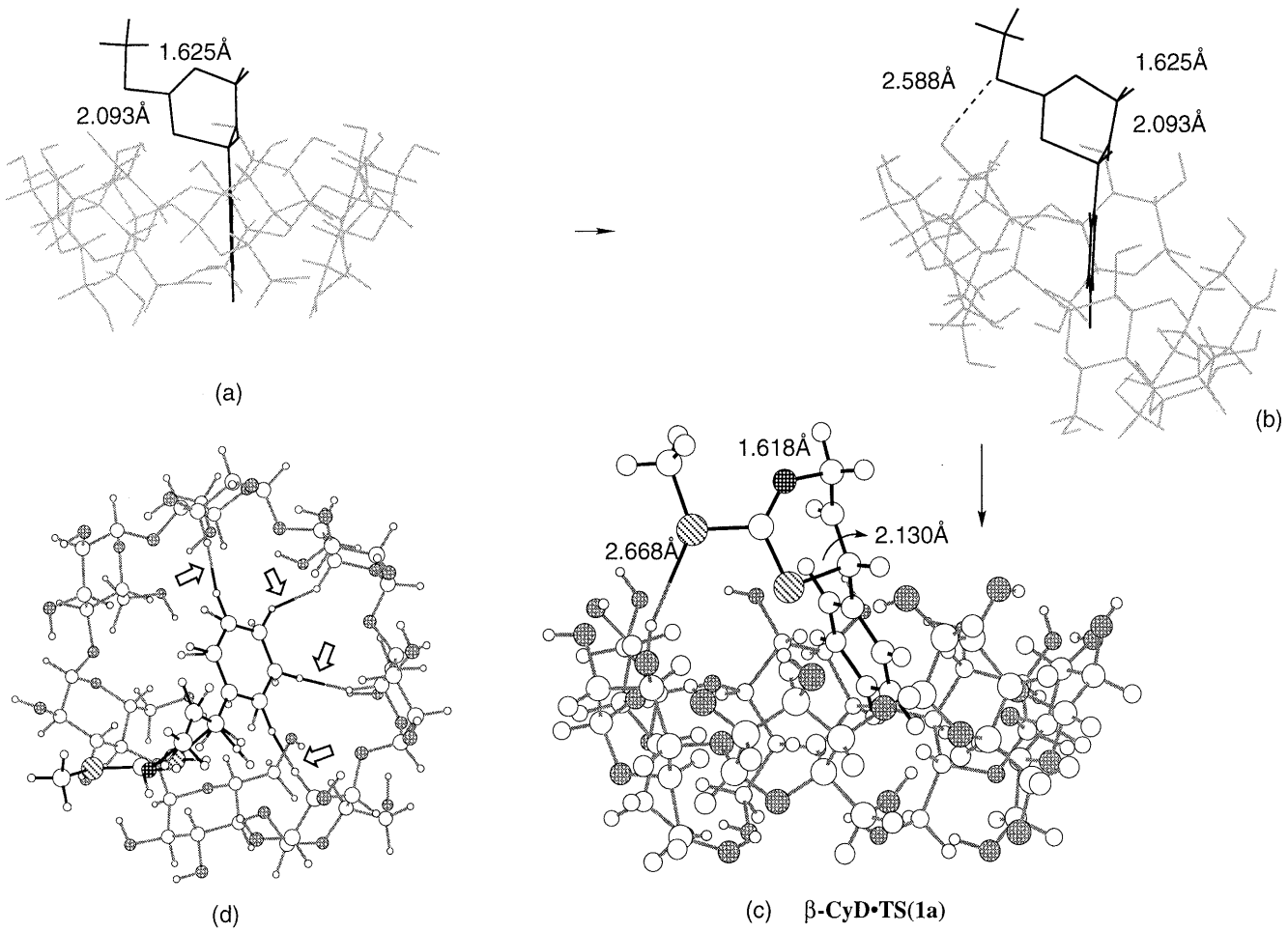


Fig. 5. Input GS Structure (a), Partially-Optimized TS (b) and Fully Optimized TS (c) Structures for β-CyD·TS(**1a**) Complex, (d) H/H Contacts in β-CyD·TS(**1a**) Complex

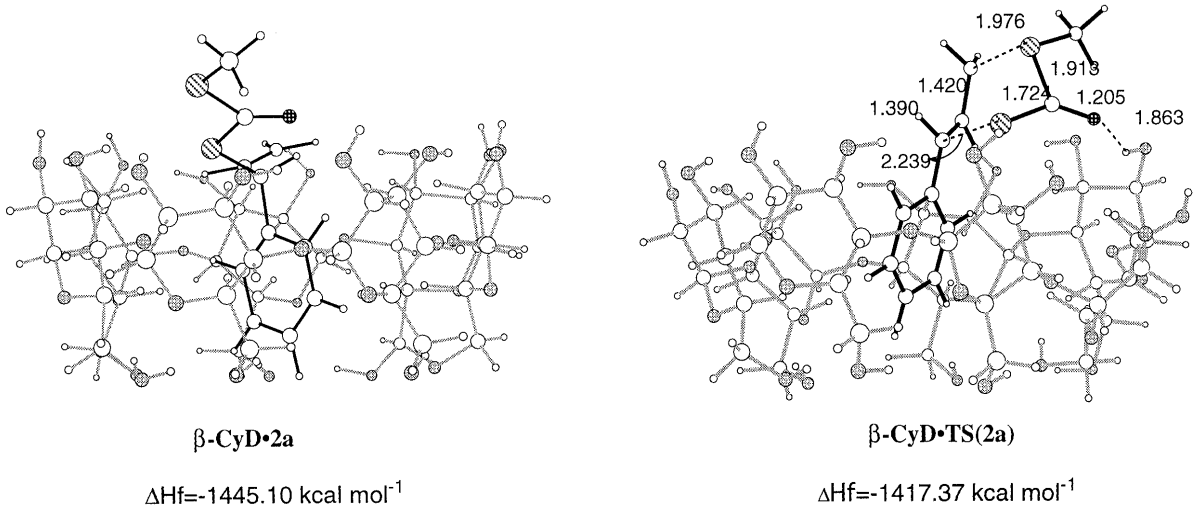


Fig. 6. GS Structure of **2a** and TS Structure for the Retro Ene Reaction of **2a**

hand, we obtained a hydrogen-bonded inclusion complex of **1a** and β-CyD at the end of IRC starting from the [3,3]-sigmatropic TS [β-CyD·TS(**1a**)]. The calculated structure of the complex [β-CyD·**1a**′] is depicted in Fig. 4. As can be seen in Fig. 4, the guest is shallowly inserted and the complex is about 3.0 kcal mol^{-1} less stable than the deeply-inserted nonhydrogen-bonded complex, in which the thione sulfur forms hydrogen bonds with two secondary hydroxy groups of β-CyD (2.463, 2.708 Å). The degree of stabilization[11] due to the hydrogen bonding is assumed to be *ca.* 6.3 kcal mol^{-1} on the basis of a model calculation of the hydrogen-bond formation between *O*-allyl *S*-methyl xanthate and isopropyl alcohol (see Table 5), in which the hydrogen bond distance was calculated to be 2.57—2.62 Å. The HF and DFT calculations predicted a similar result.

The structures of the complex [β-CyD·TS(**1a**)] of β-CyD

and the TS of **1a** are shown in Fig. 5c. The reaction center of the six-membered cyclic transition state of the guest is located entirely outside of the cavity and the sulfur atom of the methylthio group forms a hydrogen bond with one of the secondary hydroxy groups of the β-CyD edge. The DFT calculation (B3LYP/6-31+G**) indicates that the hydrogen bond energy of >S··HOMe is half that of >C=S··HOMe.[12]

A molecular modeling study of the deeply-inserted TS complexes made by docking, such that the six-membered cyclic reaction center is inserted into the middle of the cavity, indicated that such complexes are energetically unfavorable due to the presence of serious close contacts. During the structural optimization of a deeply-inserted TS complex [Fig. 5a], the reaction center got out of the β-CyD cavity and was transformed into the shallowly-inserted hydrogen-bonded TS complex, in which the phenyl moiety is fixed by the H/H close contacts (1.7—1.75 Å) between the aromatic hydrogens of the guest and the >C–H hydrogens of β-CyD [see Fig. 5c, 5d].

The degree of stabilization due to the hydrogen bonding between the methylthio sulfur atom and a secondary hydroxy group of β-CyD is assumed to be *ca.* 1.1 kcal mol^{-1} on the basis of a model calculation of the hydrogen-bond formation of *O*-allyl *S*-methyl xanthate with isopropyl alcohol (see Table 5).

Table 5. Stabilization Energies due to Hydrogen Bonding between Alcohols and Xanthates

Method	Substrate	ΔHf[a] or E^{b}	ΔΔHf
PM3			
	Allyl xanthate	19.56[a]	
	IsoPrOH	−64.00[a]	
	Allyl xanthate+isoPrOH	−44.44[a]	
	Allyl xanthate−isoPrOH		
	Coordination to thioether	−45.56[a]	1.12
	Coordination to thione	−46.61[a]	2.17
	Two isoPrOH coordination	−114.55[a]	6.12
B3LYP/6-31G* (coordination to thione)			
	Dimethyl xanthate	−989.5243[b]	
	IsoPrOH	−194.3533[b]	
	Dimethyl xanthate+isoPrOH	−1183.8776[b]	
	Dimethyl xanthate−isoPrOH	−1183.8841[b]	4.1[c]
	Allyl xanthate	−1066.9158[b]	
	IsoPrOH	−194.3533[b]	
	Allyl xanthate−isoPrOH	−1261.2692[b]	
	Allyl xanthate−isoPrOH	−1261.2773[b]	5.1[c]

a) ΔHf: kcal mol^{-1}. *b*) *E*: Hartree. *c*) Δ*E*.

Inspection of the guest conformation of the complex [β-CyD·**1a**] indicates that the plane of the styrene moiety of the guest located at the center of the chiral environment is inclined against the pseudo-seven-fold axis of β-CyD (see Fig. 7A).[13] The two rooms devided by the plane involving the styrene moiety are not identical. This spatial discrepancy may affect enantioselectivity. As shown in Fig. 7, the thione sulfur would enantioselectively attack the inclined plane of the C=C bond from the side facing the wider opening site.

As described above, the hydrogen-bonded complex (β-CyD·**1a**′) is *ca.* 3 kcal mol^{-1} less stable than the deeply-inserted complex (β-CyD·**1a**). The intereacting =S···CH(Ph)= distance in β-CyD·**1a**′ is *ca.* 1 Å longer than that of the deeply-inserted complex (β-CyD·**1a**). The hydrogen-bonded complex is considered to be formed only during the transformation process from the deeply-inserted complex (β-CyD·**1a**) to the TS [β-CyD·TS(**1a**)].

Previously, we reported the [3,3]-sigmatropic rearrangement rate of **1a** was moderately sensitive to solvent ionizing power compared with *O*-allyl *S*-methyl xanthate. Plots of the rearrangement rates of **1a** *vs.* Grunwald–Winstein *Y*-values showed an excellent linear relationship for alcohols,[14] and analysis of the rearrangement rates of **1a** by the Kamlet–Taft equation implied that solvent polarity and solvent hydrogen-bond donation ability (acidity) are important factors in the allylic thione-to-thiol rearrangement reactions.[15]

Taking these facts into consideration, we can safely say that the TS of **1a** is anchored by the hydrogen bond between one of the secondary hydroxy groups of β-CyD and the methylthio sulfur atom.[12] However, the MO calculation of the complex of the TS of **1a** suggests that the [1,3]oxathiane ring is out of the cavity. This probably results in the reduced influence of the chiral environment upon the substrate, leading to moderate ee (*ca.* 60%) yields.

Next, the rate enhancement of the retro-ene type reaction[4a] of **2a** in β-CyD was investigated. In the complex (β-CyD·**2a**), the complexation through the larger rim is also favorable. The interacting distance between the sulfur atom of *S*-Me and the allyl γ carbon of **2a** (5.687 Å) is *ca.* 0.6 Å shorter than that of the relaxed GS structure (6.308 Å). Fig-

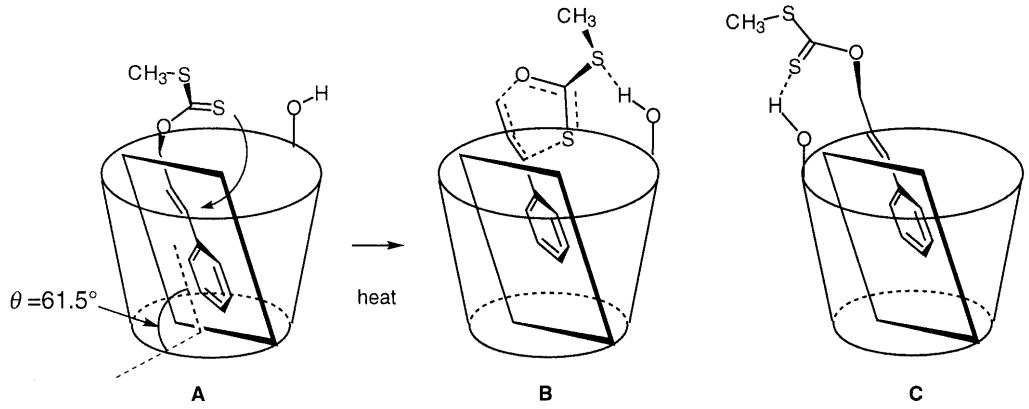


Fig. 7. Schematic Representation of the Asymmetric Induction

A: Deep inclusion complex of **1a** and β-CyD (nonhydrogen bonded). The angle [θ(Plane 1/Plane 2), deg.] between the best planes 1 and 2 is 61.5°, where Plane 1 is the best plane through the ether oxygen atoms connecting the sugar moieties, Plane 2 is that of the phenyl ring.
B: Inclusion complex of the TS of **2a** and β-CyD.
C: Shallow Inclusion complex of **1a** and β-CyD (IRC calculation product).

ure 6 shows that in the TS structure in β-CyD the interacting bond distances are essentially the same as those of the free TS. The carbonyl oxygen atom of the TS structure forms a hydrogen bond with one of the secondary hydroxy groups of β-CyD, very favorable for the extrusion of COS.[4a)]

In summary, the [3,3]-sigmatropic rearrangement of **1** and the retro-ene type reaction of **2** in the solid β-CyD complex were investigated. Lowering the reaction temperature improved the enantioselectivity to 60% ee[16)] The PM3 calculations suggested that the phenyl rings of the guests (**1**, **2**) are included from the larger rim of the β-CyD host molecule and the TS structure are stabilized by a hydrogen bond with one of the hydroxy groups of β-CyD.

Experimental

IR Spectra were recorded with a Hitachi 270-30 spectrophotometer. ^{1}H-NMR Spectra were recorded with JEOL JNM-EX 270 (270 MHz) and GX-400 (400 MHz) spectrometers using tetramethylsilane (TMS) as an internal standard and chemical shifts are expressed in δ values. The coupling constants (*J*) are presented in Hz. High resolution mass spectra (HR-MS) were recorded with a JEOL JMS-DX303HF spectrometer. HPLC analyses were performed on a JASCO 880-PU chromatograph equipped with a JASCO 875-UV detector.

Materials β-CyD was supplied from Nippon Shokuhin Co. Ltd., and further purified by recrystallization from water. *O*-Cinnamyl *S*-alkyl xanthates (**1a**—**d**) were prepared by the procedure given in the previous paper.[3)]

Preparation of Crystalline β-CyD Inclusion Complexes Xanthate (**1a**, 135 mg, 0.6 mmol) was added to 100 ml saturated aqueous solution containing β-CyD (2.0 g). After stirring for 72 h at room temperature, the resulting white precipitates were collected by centrifugation, washed with Et_2O to remove **1a**, then dried under vacuum. The white crystalline powder was obtained as a 1 : 1 molar complex of **1a** with β-CyD. The amount of **1a** in the complex was determined by ^{1}H-NMR spectroscopy in DMSO-d_6. The ^{1}H-NMR spectra of the complexes prepared using an excess of β-CyD (>2 mol) indicated the presence of a 1 : 2 molar complex of **1a** with β-CyD.

The inclusion complexes of dithiolcarbonates (**2a**—**d**) with β-CyD were prepared in a similar manner.

Rearrangement of the Crystalline Inclusion Complex The solid 1 : 1 complex (100 mg) of **1a** with β-CyD was heated at 45 °C. After 48 h, the residue was dissolved in DMSO (4 ml), then stirred vigorously with benzene (30 ml) to extract the guests. The organic layer was separated, washed with water, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by chromatography on silica-gel to afford the dithiolcarbonate (**2a**) as a colorless oil. The rearrangement product (**2a**) was identified by comparison of the spectral data with those of an authentic sample.[3)]

The enantiomeric excess of the dithiolcarbonate was determined by chiral HPLC analysis (eluent; n-hexane/ethanol, 8 : 2, flow rate; 1.0 ml min^{-1}; detection; UV 250 nm). **2a** t1 = 11 min, t2 = 27 min. **2b** t1 = 9 min, t2 = 17 min, **2c** t1 = 16 min, t2 = 26 min.

2d: IR (KBr) cm^{-1}: 1720 (>C=O), 1646 (ester SCOS); ^{1}H-NMR (270 MHz, $CDCl_3$): 2.26 (3H, s, CH_3), 3.81 (2H, s, SCH_2–CO), 5.23 (1H, ddd, *J* = 10.2, 1.0, 1.0 Hz, CH=C$\underline{H}_2$), 5.26 (1H, ddd, *J* = 17.2, 1.0, 1.0, CH=C$\underline{H}_2$), 5.41 (1H, d, *J* = 6.9, >CHS–), 6.10 (1H, ddd, *J* = 17.2, 10.2, 6.9, –C$\underline{H}$=CH_2), 7.23—7.36 (5H, m, aromatic H); HR-MS/FAB Calcd for $C_{13}H_{14}O_2S_2Na$ (M+Na$^+$) 289.0278, Found 289.0333.

Sulfide Formation Reaction of the Crystalline Inclusion Complex The solid 1 : 1 complex (100 mg) of **2a** and β-CyD was heated at 120 °C. After 6 h, the residue was dissolved in DMSO (4 ml), then stirred vigorously with benzene (30 ml) to extract the reacted guests. The organic layer was separated, washed with water, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel to give the sulfide (**3a**) as a colorless oil (81%). A similar procedure was followed for **2b**, **2c** and **2d**. The sulfides (**3a**—**d**) were identified by comparison of the spectral data with those of authentic samples.[4b)]

3d: IR (KBr) cm^{-1}: 1708 (>C=O); ^{1}H-NMR (400 MHz, $CDCl_3$): 2.27 (3H, s, CH_3), 3.22 (2H, s, –S$\underline{CH}_2$–CO), 3.29 (2H, dd, *J* = 7.6, 1.3, =CHC$\underline{H}_2$–S–), 6.12 (1H, dt, *J* = 15.5, 7.6, PhCH=C$\underline{H}$–), 6.47 (1H, d, *J* = 16, PhC$\underline{H}$=), 7.20—7.39 (5H, m, aromatic H); MS (*m*/*z*) 206 (M$^+$). HR-MS/EI Calcd for $C_{12}H_{14}OS$ (M$^+$) 206.0765, Found 206.0737.

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References and Notes

1) Bender M. L., Komiyama M., "Cyclodextrin Chemistry," Springer-Verlag, Berlin, 1978.
2) *a*) Breslow R., Guo T., *J. Am. Chem. Soc.*, **110**, 5613—5617 (1988); *b*) Tanaka Y., Sakuraba H., Nakanishi H., *J. Org. Chem.*, **55**, 564—567 (1990); *c*) Schneider H.-J., Sangwan N. K., *Angew. Chem. Int. Ed. Engl.*, **26**, 896–897 (1987); *d*) Pitchumani K., Velusamy P., Banu H. S., Srinivasan C., *Tetrahedron Lett.*, **36**, 1149—1152 (1995).
3) Harano K., Taguchi T., *Chem. Pharm. Bull.*, **20**, 2348—2356, 2357—2365 (1972); *Idem, ibid.*, **23**, 467—472 (1975).
4) *a*) Eto M., Nishimoto M., Kubota S., Matsuoka T., Harano K., *Tetrahedron Lett.*, **37**, 2445—2448 (1996); *b*) Harano K., Yamashiro S., Misaka K., Hisano T., *Chem. Pharm. Bull.*, **38**, 2956—2959 (1990). The reaction mechanism belongs to the category of a retro ene reaction and the rate enhancement due to the hydrogen bond is attributable to lowering of the LUMO energy level of the C–SR bond in the three-system interaction ($2\pi+2\sigma+2\sigma$), in which the C=C, MeS–CO and CH–S bonds are π-HOMO, σ-LUMO and σ-LUMO, respectively.
5) *a*) Harano K., Kiyonaga H., Hisano T., *Tetrahedron Lett.*, **32**, 7557—7558 (1991); *b*) The absolute configuration of the rearrangement product has not yet been determined. The NMR spectral information about the host-guest interaction has not yet been obtained because of the insolubility in D_2O.
6) *a*) Stewart J. J. P., A Semi-Empirical Molecular Orbital Program, QCPE 455 (1983): *idem*, *J. Comp. Chem.*, **10**, 209—220, 221—264 (1989). The program source written for the main frame computer systems was ported to the engineering workstation (Fujitsu S4/2, S4/10 and Scientists' Paradise Dragon AXP5A/433 computer). The main modifications are the time routine, input/output file system and enlargement of the array sizes. *b*) The AM1 calculation cannot reproduce the C=S distance of xanthates which is *ca.* 0.1 Å shorter than the crystallographic values. *c*) The coordinates of the calculated structures are available on request by E-mail.
7) Gaussian 94, Revision D.4, Frisch M. J., Trucks G. W., Schlegel H. B., Gill P. M. W., Johnson B. G., Robb M. A., Cheeseman J. R., Keith T., Petersson G. A., Montgomery J. A., Raghavachari K., Al-Laham M. A., Zakrzewski V. G., Ortiz J. V., Foresman J. B., Cioslowski J., Stefanov B. B., Nanayakkara A., Challacombe M., Peng C. Y., Ayala P. Y., Chen W., Wong M. W., Andres J. L., Replogle E. S., Gomperts R., Martin R. L., Fox D. J., Binkley J. S., Defrees D. J., Baker J., Stewart J. P., Head-Gordon M., Gonzalez C., Pople J. A., Gaussian, Inc., Pittsburgh PA, 1995.
8) *a*) Abrahamsson S., Innes M., *Acta Crystallogr. Sec. B*, **30**, 721—725 (1974); Dahlen B., *Acta Chem. Scand. Ser. A*, **31**, 407—411 (1977); *b*) X-Ray analysis of the [4+2]-cycloadduct of phencyclone and *S*-allyl *S*-methyl dithiocarbonate showed that the dithiol ester adopts the syn conformation, *Tetrahedron lett.*, **41**, 4395—4400 (2000).
9) In the HF/3-21G* calculation, *S*-allyl *S*-methyl dithiocarbonate is 4.34 kcal mol^{-1} more stable than *O*-allyl *S*-methyl xanthate (exothermic).
10) Jaime C., Redondo J., Sanches F. Virgili A., *J. Org. Chem.*, **55**, 4772—4776 (1990); Lipkowitz K. B., *ibid.*, **56**, 6357—6367 (1991); Fathallah M., Fotiadu F., Jaime C., *ibid.*, **59**, 1288—1293 (1994).
11) The value is of similar magnitude to the hydrogen-bond energy for the cytosine–thymine (C–T) base pair.
12) The calculated hydrogen-bond energies between dimethyl xanthate and methanol are as follows.

Method	>C=S··HOMe	>S··HOMe
PM3	2.62 kcal mol^{-1}	1.21 kcal mol^{-1}
B3LYP/6-31+G**	3.71 kcal mol^{-1}	2.16 kcal mol^{-1}

13) The angles (θ, deg.) between the best planes A and B are as follows: θ(Plane 1/Plane 2), 61.5; θ(Plane 1/Plane 3), 64.0; θ(Plane 2/Plane 3), 11.7, where Plane 1 is the best plane through the ether oxygen atoms connecting the sugar moieties, Plane 2 is that of the phenyl ring and Plane 3 is that of the double bond.
14) *a*) Harano K., Kiyonaga H., Yokote C., Hisano T., *Chem. Pharm. Bull.*, **39**, 1952—1957 (1991); *b*) The hydrogen-bonding stabilization of the GS of xanthates seems to be small. In the visible absorption spectra of

xanthates in alcohols, the blue shift of the C=S group of xanthates due to solvation of alcohols is very sensitive to the xanthate conformation (manuscript in preparation).
15) Eto M., Tajiri O., Nakagawa H., Harano K., *Tetrahedron*, **54**, 8009—8014 (1998).
16) The enhancement of ee at a lower temperature may be due to the suppression of mobility and thermal dissociation of the guest molecule.