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INDUCED CIRCULAR DICHROISM OF RACEMIC METHYLCYCLOHEXANONES INCLUDED IN β-CYCLODEXTRIN

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When cyclohexanone and its methyl derivatives were included in the cavities of cyclodextrins, the induced circular dichroism (CD) bands were observed in the absorption region of n-π^* transition of the carbonyl chromophore. The sign of induced CD band of 2-methylcyclohexanone included in β-cyclodextrin was same as that of resolved R-isomer. From these observations the mode of inclusion and structure of β-cyclodextrin complex with methylcyclohexanone were discussed.

Since cyclodextrin has a large asymmetric cavity, various compounds have been shown to induce the extrinsic Cotton effects upon binding to cyclodextrins.[1-4] It has been thought that the induced circular dichroism (CD) bands, which were observed when an optically inactive compound was disolved in optically active solvent, must arise from the tightly asymmetric solvent cage about chromophore and/or prefered dissymmetric configuration of solute.[5,6] We previously demonstrated that biphenyl derivatives were fixed into one prefered dissymmetric configurations (R-configuration) in a cavity of β-cyclodextrin.[7] In this paper we report that cyclohexanone and its methyl derivatives also show the CD bands by the formation of inclusion complexes with cyclodextrins in water. All CD spectra were measured at room temperature by a Jasco-20A recording spectropolarimeter. Methyl derivatives of cyclohexanone, which are insoluble in water, were solubilized by addition of α- or β-cyclodextrin. 2-Methyl- and 3-methylcyclohexanones used in this study were of racemic mixtures.

Although cyclodextrin has neither CD nor absorption band at longer wavelength than 220 nm, inclusion complexes with cyclohexanones showed new CD bands around the absorption region of carbonyl n-π* transition of cyclohexanones. Observed CD spectra following the binding of cyclohexanones to β-cyclodextrin were shown in Fig. 1, where their UV absorption spectra were also shown. The induced CD spectra of methylcyclohexanone systems showed single CD bands in the absorption region of carbonyl chromophore, while cyclohexanone system showed two peaks with opposite sign; weak positive band at 307 nm and large negative band at 285 nm which locate near absorption maximum of carbonyl n-π* transition.

In the case of racemate such as 2-methylcyclohexanone and 3-methylcyclohexanone, both of (R)-(+)- and (S)-(-)-isomers may be involved in the complexation with cyclodextrin. To clarify which configuration is preferable to form the inclusion complex, we attempted to resolve the optically active 2-methylcyclohexanone by β-cyclodextrin. When concentration of the inclusion complex in water was increased, colorless prism precipitated, from which included 2-methylcyclohexanone was extracted with ether. The CD spectrum of this extract showed a positive sign which is same as (R)-(+)-2-methylcyclohexanone.[8] This simply suggests that (R)-(+)-isomer was predominantly included in β-cyclodextrin. Although same amount of resolved (S)-(-)-isomer coexists as a free state with that of the included (R)-(+)-isomer in the aquous solution of racemic 2-methylcyclohexanone and β-cyclodextrin system, the positive sign of the CD band observed in this system may be arisen from significantly increased rotational strength by hydrophobic and/or hydrogen bonding interaction between asymmetric sites of β-cyclodextrin and included (R)-(+)-isomer. If the hydrophobic interaction between methyl group of methylcyclohexanone and cyclodextrin is predominant, the sign of the induced CD band may be determined by octant rule. On the other hand, if hydrogen bonding between carbonyl group of methylcyclohexanone and hydroxy group of cyclodextrin is predominant, the sign of the induced CD band may be subjected to back octant rule. The fact that the sign of resolved 2-methylcyclohexanone was same as that of the induced CD band indicates that the sign of the induced CD band may be subjected to the hydrophobic interaction. Indeed appreciable change of chemical shift in NMR spectrum assigned to inner hydroxy group of β-cyclodextrin could not be observed.

In the case of cyclohexanone and 4-methylcyclohexanone which have not asymmetric center, it is also assumed that they are fixed into asymmetric cavity of cyclodextrins by hydrophobic interaction, and eventually the CD bands are induced in the n-π* transition of these compounds. The fact that the magnitude of induced CD band observed for less water soluble 4-methylcyclohexanone was larger than that for water soluble cyclohexanone indicates that hydrophobic interaction may play an important role in the

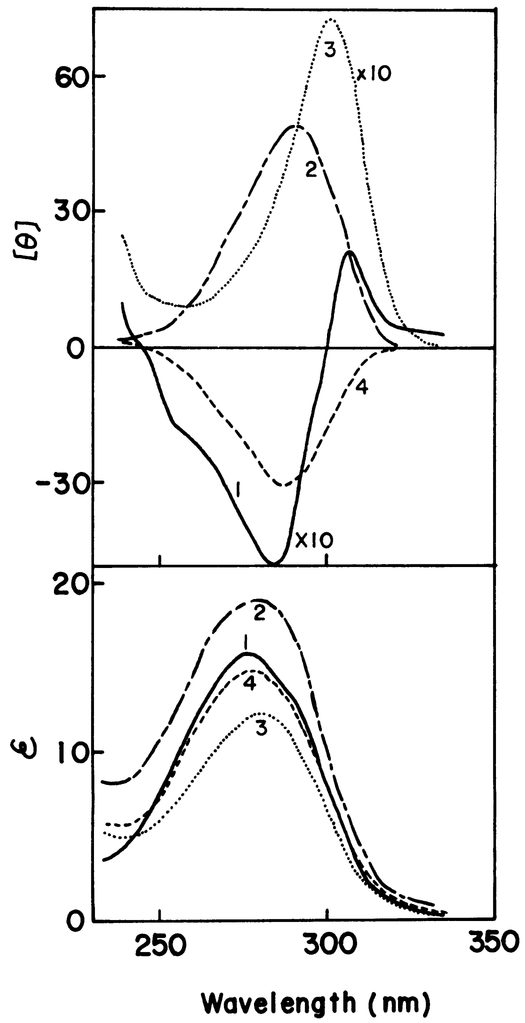

Fig. 1. Circular dichroism (upper) and absorption (lower) spectra of cyclohexanone and its methyl derivatives (1 x 10^{-2} M) in the presence of β-cyclodextrin (1 x 10^{-2} M) in water.

(1) ———, cyclohexanone
(2) — — —, 2-methylcyclohexanone
(3) ··········, 3-methylcyclohexanone
(4) - - - - -, 4-methylcyclohexanone

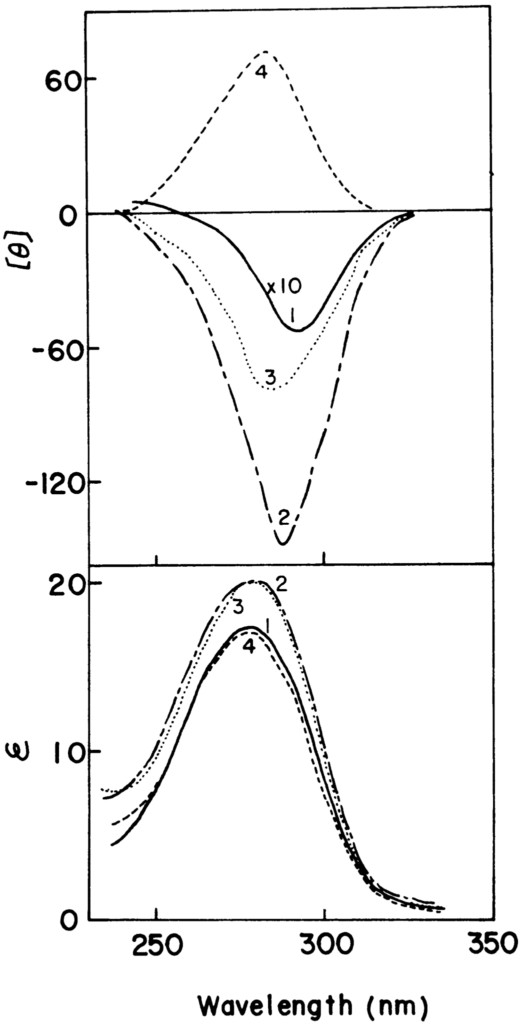

Fig. 2. Circular dichroism (upper) and absorption (lower) spectra of cyclohexanone and its methyl derivatives (1 x 10^{-2} M) in the presence of α-cyclodextrin (1 x 10^{-2} M) in water.

(1) ———, cyclohexanone
(2) — — —, 2-methylcyclohexanone
(3) ··········, 3-methylcyclohexanone
(4) - - - - -, 4-methylcyclohexanone

formation of inclusion complex. Since the electric transition dipole moment of carbonyl n-π^* is small, the electric dipole-dipole interaction between cyclohexanones and cyclodextrins seems to be less important factor for the generation of induced CD band.

From these evidences the structure of inclusion complex was proposed as shown in Fig. 3, in which methylcyclohexanone moiety was included in the cavity of cyclodextrin and carbonyl group was outside the ring.

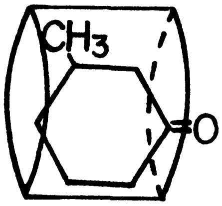

Fig. 3. Schematic representation of 3-methylcyclohexanone in the cavity of β-cyclodextrin.

Cyclohexanone and its methyl derivatives also showed induced CD bands by the formation of inclusion complexes with α-cyclodextrin, as is shown in Fig. 2. It is noted that the magnitude of the induced CD bands (CD/absorbance) of α-cyclodextrin systems was larger than that of β-cyclodextrin systems, indicating that the inclusion complex with α-cyclodextrin is more stable than that with β-cyclodextrin. In contrast to β-cyclodextrin systems, however, the sign of the induced CD bands observed for methylcyclohexanone—α-cyclodextrin systems was opposite to that for methylcyclohexanone—β-cyclodextrin systems. Further study on this problem is in progress and details will be reported elsewhere.

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