Induced Circular Dichroism of β-Cyclodextrin Complexes with Substituted Benzenes

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The induced circular dichroism (ICD) of β-Cyclodextrin(β-CDx)-substituted benzene complexes was investigated. We observed the ICD on the absorption bands of achiral substituted benzene molecules, which is considered to be induced by the dissymmetric field of the chiral β-CDx host molecule. The electronic transitions which are polarized along the long axis of the substituted benzenes showed positive ICD, while the sings of the ICD of short-axis polarized transitions are negative. The rotational strengths of these inclusion complexes were calculated by the Kirkwood-Tinoco expression. From the comparison between the experimental and calculated results, it is concluded that these β-CDx complexes favor the axial inclusion in which the long axis of the substituted benzenes is parallel to the axis of the β-CDx cavity.

The cyclodextrins (CDxs) are a series of oligosaccharides produced by the action of *Bacillus macerans* amylase on starch.[1] CDxs are cyclic oligosaccharides composed of D(+)-glucopyranose units which are connected with each other by the α-(1,4)-glucoside bond. The number of glucose units of CDx is designated by a Greek letter: α- for 6, β- for 7, γ- for 8, and so on.

CDx has a hydrophobic cavity in the center of a CDx molecule. And it is known that CDx includes aromatic compounds, alkyl halides, gases, *etc.* as guest molecules in the CDx cavity, resulting in the formation of inclusion complexes.[2] These inclusion phenomena of CDx have been employed as one approach to the enzyme model, since CDx exhibited the steric specificity in a way similar to the formation of enzyme–substrate complexes.[3]

Inclusion complex formation is associated with a favorable enthalpy change and an unfavorable or slightly favorable entropy change. Several proposals[4] for the driving force of the complex formation have been made to interpret this favorable enthalpy change:

a) van der Waals interactions between the guest and host molecules

b) hydrogen bonding between the guest molecule and the hydroxyl groups of CDx

c) release of high energy water molecules in complex formation

d) decrease in strain energy in the ring frame of CDx.

From the results of the X-ray crystallography of the α-cyclodextrin–potassium acetate complex, Hybl *et al.*[5] revealed that α-CDx has a doughnut-shape with all the glucose units in substantially undistorted chair conformations. In addition, many investigations on the structure of inclusion complexes have been made by means of various physicochemical methods, *e.g.*, X-ray analysis,[6] NMR,[7] ESR,[8] UV,[9] CD,[10–12] *etc.*

Since CDxs are composed of chiral glucose units, the circular dichroism (CD) is expected to be induced on the absorption bands of the achiral guest molecules which are included in the cavity of chiral β-CDx. We thus investigated ICD spectra of β-CDx inclusion complexes with substituted benzenes in aqueous solution, and calculated the rotational strength on the basis of the Kirkwood-Tinoco equation,[13] with the goal of predicting the orientation of the guest molecules in these inclusion complexes,

Experimental

β-CDx and substituted benzenes were commercial products. β-CDx, benzoic acid, and *p*-nitrophenol were recrystallized from aqueous solutions. Aniline, phenol, and nitrobenzene were distilled under reduced pressure. *p*-Nitroaniline and *p*-hydroxybenzoic acid were recrystallized from methanol and ether, respectively. An inclusion complex was prepared by mixing β-CDx and the corresponding substituted benzene in an aqueous solution or in 0.1 M aqueous HCl.

The circular dichroism and absorption spectra were measured at room temperature using a JASCO J-20A spectropolarimeter and a Hitachi EPS-3T spectrophotometer, respectively.

Formation constants, *K*, and the difference in the molar extinction coefficients for right and left circularly polarized light in liter $\mathrm{mol}^{-1}\,\mathrm{cm}^{-1}$, $\Delta\varepsilon$, of inclusion complexes were determined by means of Benesi-Hildebrand method.[14]

On the other hand, the composition ratio of inclusion complexes was defined by Job's continuous variation method.[15]

The dipole strengths, *D*, of substituted benzenes were estimated from the absorption spectra as accurately as possible by use of the following approximate expression:

$$D = 0.92 \times 10^{-38}\sqrt{\pi}\cdot\varepsilon_{\max}\cdot\frac{\Delta}{\lambda_{\max}} \tag{1}$$

where $\varepsilon_{\max}$ is the maximum value for the molar extinction coefficient, $\lambda_{\max}$ is the wavelength at absorption maximum, and Δ is the half-band width at 1/e of maximum absorption. Similarly, the experimental rotational strengths, *R*, were obtained by the expression of Moscowitz:[16]

$$R = 0.696 \times 10^{-42}\sqrt{\pi}\cdot[\theta]_{\max}\cdot\frac{\Delta}{\lambda_{\max}} \tag{2}$$

where $[\theta]_{\max}$ is the maximum value for the molar ellipticity and Δ is the half-band width at 1/e of maximum ellipticity.

Theoretical

The theoretical rotational strength of the transition from the ground state, 0, to the excited state, a, in benzene derivative, $R_{i0\mathrm{a}}$, was calculated by the following expression developed by Kirkwood and Tinoco:

$$R_{i0\mathrm{a}} = \pi\tilde{\nu}_{\mathrm{a}i}\mu_{i0\mathrm{a}}^2 \sum_j \frac{\tilde{\nu}_{\mathrm{b}j}^2(\alpha_{33}-\alpha_{11})_j(\mathrm{GF})_{ij}}{\tilde{\nu}_{\mathrm{b}j}^2-\tilde{\nu}_{\mathrm{a}i}^2} \tag{3}$$

$$(\mathrm{GF})_{ij} = \frac{1}{r_{ij}^3}\left[\hat{\boldsymbol{e}}_i\cdot\hat{\boldsymbol{e}}_j - \frac{3(\hat{\boldsymbol{e}}_i\cdot\vec{\boldsymbol{r}}_{ij})(\hat{\boldsymbol{e}}_j\cdot\vec{\boldsymbol{r}}_{ij})}{r_{ij}^2}\right]\hat{\boldsymbol{e}}_i\times\hat{\boldsymbol{e}}_j\cdot\vec{\boldsymbol{r}}_{ij} \tag{4}$$

Table 1. The averaged wave number of the electronic transitions ($\tilde{\nu}_{bj}$) and polarizability (α) of the bonds in a glucose residue

Bond	$(\alpha_{33}-\alpha_{11})\times10^{24}$ cm^3	$\tilde{\nu}_{bj}\times10^{-3}$ [a] cm^{-1}
C-C	0.71[b]	70.85[e,f]
C-OC	0.43[c]	67.53[g,h]
O-H	0.45[d]	80.78[g,h]

a) $\tilde{\nu}_{bj}$ is approximated by a wave number midway between the first absorption band and its ionization potential. b) C. G. LeFevre and J. W. LeFevre, *J. Chem. Soc.*, **1956**, 3549. c) R. J. W. LeFevre *et al.*, *J. Chem. Soc.*, **1963**, 479. d) C. G. LeFevre *et al.*, *J. Chem. Soc.*, **1960**, 123. e) L. W. Pickett *et al.*, *J. Chem. Soc.*, **73**, 4862 (1951). f) R. F. Pottie *et al.*, *J. Am. Chem. Soc.*, **83**, 3204 (1961). g) A. J. Harrison *et al.*, *J. Chem. Phys.*, **30**, 355 (1959). h) K. Watanabe, *J. Chem. Phys.*, **26**, 542 (1957).

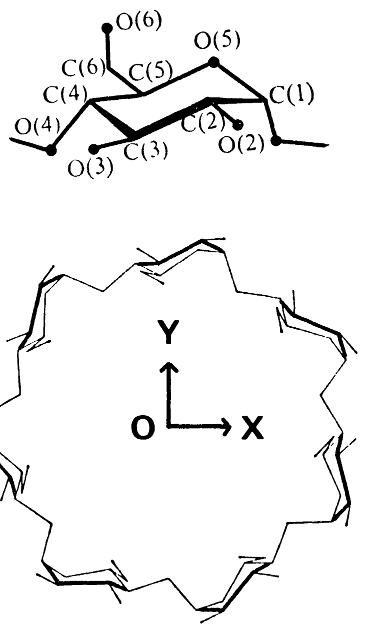


Fig. 1. A glucose residue and the assumed structure of β-CDx.

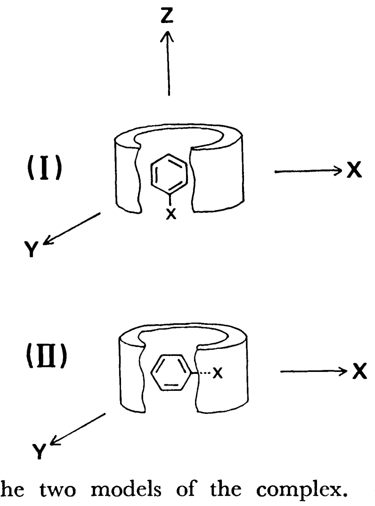


Fig. 2. The two models of the complex. (I); Axial inclusion, (II); equatorial inclusion.

Here $\hat{e}_j$ is the unit vector in the direction of the symmetry axis of the bond in β-CDx; $\hat{e}_i$ is the unit vector in the direction of the electric dipole moment, $\vec{\mu}_{i0a}$, of the transition from the ground state, 0, to the excited state, a, in the benzene derivative, and $\tilde{\nu}_{ai}$ is its wave number; α_{33} and α_{11} are bond polarizabilities at zero frequency parallel and perpendicular, respectively, to the symmetry axis of the bond in β-CDx; $\vec{r}_{ij}$ is the vector pointing from the center of benzene derivatives to each bond in β-CDx; and $\tilde{\nu}_{bj}$ is the averaged wave

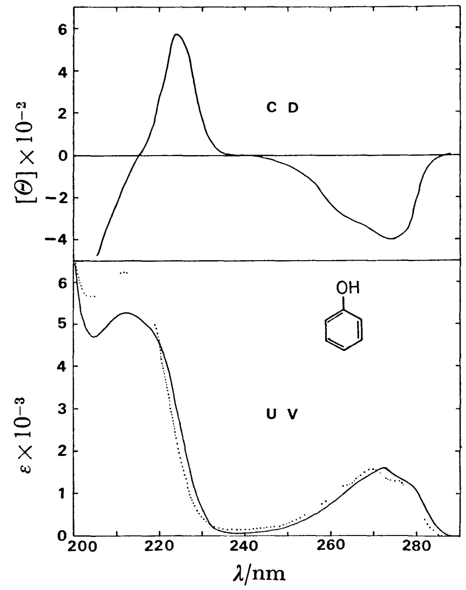


Fig. 3. CD (upper) and UV absorption (lower) spectra of β-CDx complex with phenol in aqueous solution at room temperature. Dotted line; in the absence of β-CDx, solid line; β-CDx (1.35×10^{-2} M)+phenol (2.09×10^{-4} M).

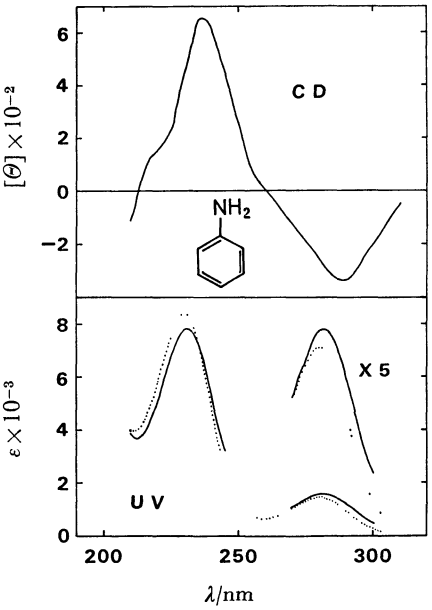
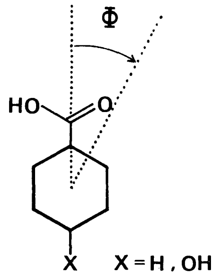


Fig. 4. CD (upper) and UV absorption (lower) spectra of β-CDx complex with aniline in aqueous solution at room temperature. Dotted line; in the absence of β-CDx, solid line; β-CDx (1.46×10^{-2} M)+aniline (1.56×10^{-4} M).

Table 2. Observed and calculated energy and dipole strength (D) of the electronic transitions of benzene derivatives

Benzene derivative	Experiment		Calculation		Assignment and Φ
	$\tilde{\nu}\times 10^{-3}$ cm^{-1}	D Debye^2	$\tilde{\nu}\times 10^{-3}$ cm^{-1}	D Debye^2	
Phenol[c]	37.0[a]	1.37	37.0	0.98	B_2
	47.4	6.26	46.3	4.5	A_1
			54.2	14.1	B_2
			54.8	19.0	A_1
Aniline[c]	35.6[a]	1.15	35.1	1.3	B_2
	43.5	8.00	43.2	9.6	A_1
			52.0	8.1	B_2
			53.8	15.7	A_1
Nitrobenzene[c]	—[a]	—	35.8	0.48	B_2
			39.7	10.7	A_1(CT)
			47.9	1.2	B_2
			50.2	1.9	B_2
			52.2	7.1	A_1
p-Nitrophenol	31.6[b]	20.23	26.7	15.3	A_1(CT)
			29.4	0.06	B_2(CT)
			39.9	0.13	B_2
			43.9	0.38	A_1(CT)
	44.1	8.15	44.7	3.8	B_2
			48.0	3.0	A_1
p-Nitroaniline[d]	26.3[a]	27.51	32.6	18.9	A_1(CT)
			34.7	0.24	B_2
	44.1	14.52	43.1	4.1	B_2(CT)
			48.7	0.15	A_1
Benzoic acid[c]	36.5[b]	0.70	37.7	0.23	A′(131.3°)
	43.4	10.27	44.1	11.8	A′(9.8°)
			50.8	1.1	A′(−32.4°)
			52.9	10.4	A′(82.8°)
			53.4	13.4	A′(5.5°)
p-Hydroxy-benzoic acid			36.5	0.21	A′(−12.6°)
	39.1[b]	19.34	39.4	19.6	A′(3.3°)
			45.7	2.0	A′(86.7°)
	48.5	14.44	48.6	9.4	A′(97.8°)



a) In aqueous solution. b) In 0.1 M aqueous HCl. c) A. Kaito, A. Tajiri, and M. Hatano, *J. Am. Chem. Soc.*, **98**, 384 (1976). d) A. Kaito, A. Tajiri, and M. Hatano, *Bull. Chem. Soc. Jpn.*, **49**, 2207 (1976).

number of the electronic transitions of the bond in β-CDx.

In this paper, $\tilde{\nu}_{bj}$ is approximated by a wavenumber midway between the first absorption band in the bond of β-CDx and its ionization potential. The values of $(\alpha_{33}-\alpha_{11})$ and $\tilde{\nu}_{bj}$ for each bond are listed in Table 1.

Table 2 shows the observed and calculated wave number, $\tilde{\nu}$, and dipole strength, D, of the electronic transitions of benzene derivatives, along with the assignment of each electronic transition.[17] The calculated values in this table were obtained by the Pariser-Parr-Pople (PPP) method. The experimental values in Table 2 were used for the calculation except in the case of nitrobenzene. The experimental value of nitrobenzene could not be estimated because of its insolubility in water.

As shown in Fig. 1, the origin of the coordinates was chosen in the center of a ring of β-CDx which was assumed to have a seven-fold symmetry axis. The coordinates of a glucose residue were determined so as to fit the distance of O(4)–O(4′) with X-ray data (4.23 Å).[18] In the determination of the coordinates of β-CDx, hydroxyl groups of O(2)–H and O(3)–H were assumed to form hydrogen bonding with the hydroxyl group of the neighboring glucose unit. The effect of all the C–H bonds was neglected, since these bonds may have isotropic polarizability.

In the present calculation, we considered two models for the inclusion complexes, as shown in Fig. 2: *i.e.*, the axial inclusion (I) in which the long axis of benzene derivatives is parallel to the axis of β-CDx cavity (z-axis) and the equatorial inclusion (II) in which the short axis is parallel to the z-axis.

Finally, the calculation of the rotational strengths of these complexes were carried out by putting the electric dipole moment at the origin.

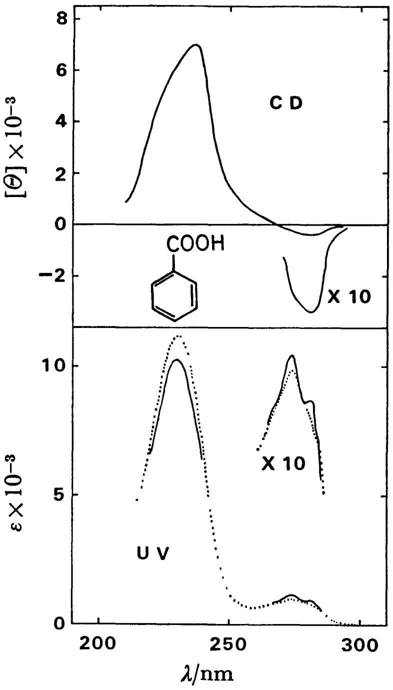


Fig. 5. CD (upper) and UV absorption (lower) spectra of β-CDx complex with benzoic acid in 0.1 M aqueous HCl at room temperature. Dotted line; in the absence of β-CDx, solid line; β-CDx (1.46×10^{-2} M) +benzoic acid (1.29×10^{-4} M).

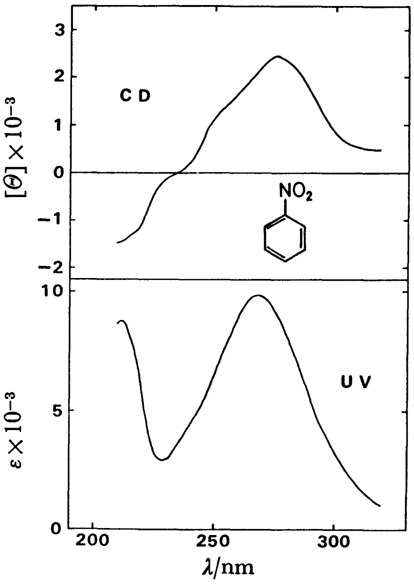


Fig. 7. CD (upper) and UV absorption (lower) spectra of β-CDx complex with nitrobenzene in aqueous solution at room temperature; β-CDx (1.63×10^{-2} M)+ nitrobenzene (1.20×10^{-4} M).

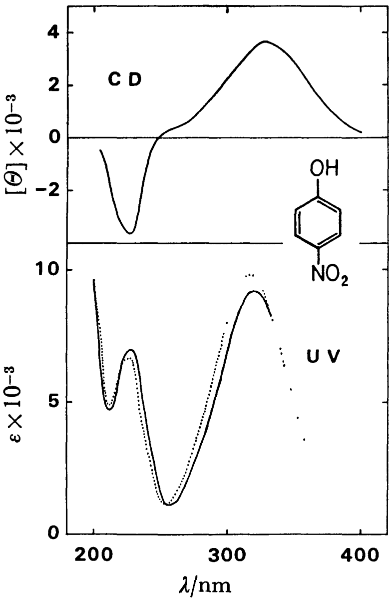


Fig. 6. CD (upper) and UV absorption (lower) spectra of β-CDx complex with p-nitrophenol in 0.1 M aqueous HCl at room temperature. Dotted line; in the absence of β-CDx, solid line; β-CDx (1.37×10^{-2} M) +p-nitrophenol (1.33×10^{-4} M).

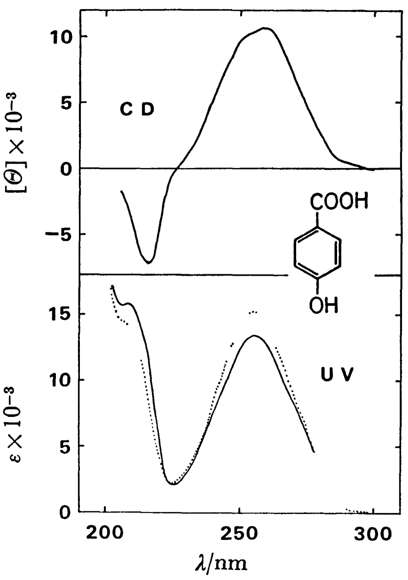


Fig. 8. CD (upper) and UV absorption (lower) spectra of β-CDx complex with p-hydroxybenzoic acid in 0.1 M aqueous HCl at room temperature. Dotted line; in the absence of β-CDx, solid line; β-CDx (1.21×10^{-2} M)+p-hydroxybenzoic acid (8.17×10^{-5} M).

Results and Discussion

Figures 3—10 show the CD (upper) and UV (lower) spectra of β-CDx complexes with various substituted benzenes. The β-CDx complex with phenol (in Fig. 3) showed positive and negative ICD bands at 224 and at 275 nm, respectively. These ICD bands were assigned to the $^1A_1 \leftarrow ^1A_1$ and $^1B_2 \leftarrow ^1A_1$ transitions, respectively, from the results calculated by use of the PPP method in Table 2. The β-CDx–aniline complex (Fig. 4) and the β-CDx–benzoic acid complex (Fig. 5) exhibited ICD bands similar to the bands of the β-CDx–phenol complex.

On the other hand, as shown in Fig. 6, the β-CDx complex with *p*-nitrophenol showed negative and positive ICD bands at 227 and at 329 nm. These bands were attributed to the $^1B_2 \leftarrow ^1A_1$ and $^1A_1 \leftarrow ^1A_1$ transitions, respectively. Each sign of the ICD spectra of β-CDx with nitrobenzene (Fig. 7) and *p*-hydroxybenzoic acid (Fig. 8) is the same as that of the β-CDx–*p*-nitrophenol complex.

Two negative ICD bands of β-CDx–*p*-nitroaniline complex observed at 230 and 296 nm were assigned to the $^1B_2 \leftarrow ^1A_1$ transitions, and the lowest positive ICD band was attributed to the $^1A_1 \leftarrow ^1A_1$ transition (Fig. 9).

As seen from each figure, the ICD bands of these inclusion complexes were observed at the absorption of benzene derivatives. In addition, from the assignment based on the SCF-MO calculation by the PPP method, it was found that the electronic transitions which are polarized along the long axis of substituted benzenes showed positive ICD, while the sign of the ICD of short-axis polarized transitions are negative.

In Table 3, formation constants, *K*, and UV and CD spectral data of β-CDx inclusion complexes are summarized.

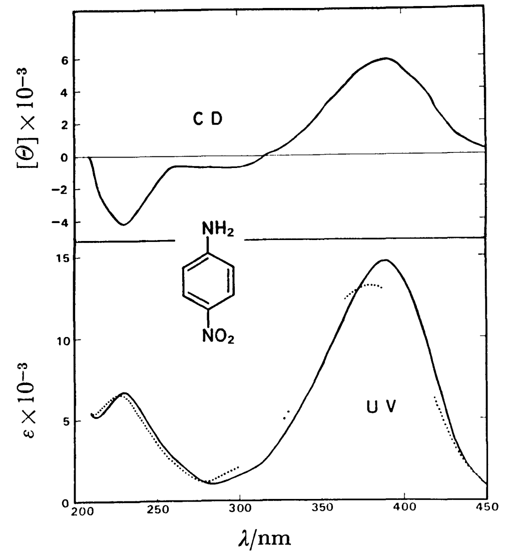


Fig. 9. CD (upper) and UV absorption (lower) spectra of β-CDx complex with *p*-nitroaniline in aqueous solution at room temperature. Dotted line; in the absence of β-CDx, solid line; β-CDx (1.47×10^{-2} M) +*p*-nitroaniline (8.41×10^{-5} M).

Figure 10 illustrates Job's continuous variation plots for β-CDx and benzoic acid systems. From this figure, it can be seen that the composition ratio of β-CDx to benzoic acid is 1:1.

The observed and calculated rotational strengths of β-CDx complexes with benzene derivatives are compared in Table 4. It is seen from Table 4 that the values calculated by assuming the axial inclusion (I) are in fairly good agreement with the experimental values. On the contrary, the signs of the calculated rotational strengths for equatorial inclusion (II) disagree with the experimental results. Therefore, the orientation of the guest molecule which is included in the β-CDx cavity can be regarded as the axial inclusion (I).

Finally, the effects of the translation and rotation of the guest molecules in the β-CDx cavity on the signs and magnitudes of the calculated rotational

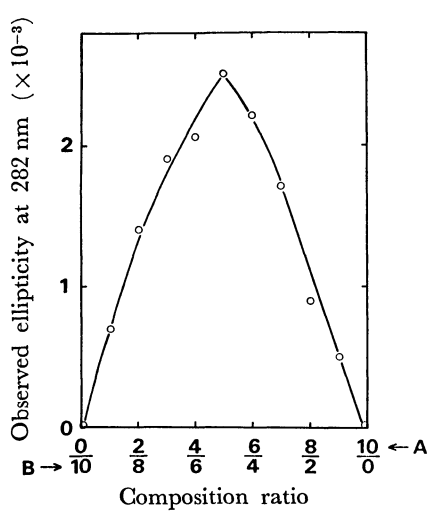


Fig. 10 Job's continuous variation plots for β-CDx (A)–benzoic acid (B) system in 0.1 M aqueous HCl. A; β-CDx (1.646×10^{-2} M), B; benzoic acid (1.646×10^{-2} M).

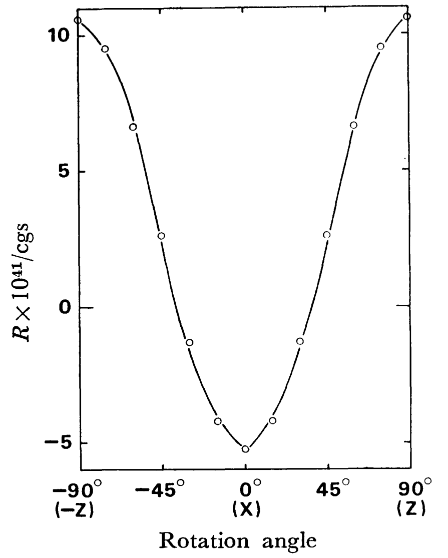


Fig. 11. Dependence of calculated rotational strength of the $^1B_2 \leftarrow ^1A_1$ transition of phenol on the rotation of the electric transition moment in the x-z plane.

TABLE 3. THE FORMATION CONSTANTS (K), UV ABSORPTION BANDS, AND INDUCED CD BANDS OF β-CYCLODEXTRIN COMPLEXES WITH BENZENE DERIVATIVES IN AQUEOUS SOLUTION

Benzene derivative	$\frac{K}{\text{M}^{-1}}$	$\frac{\lambda_{\text{max}}}{\text{nm}}$	UV $\frac{\varepsilon\times10^{-3}}{(\text{M}\cdot\text{cm})^{-1}}$	$\frac{\lambda_{\text{max}}}{\text{nm}}$	CD $\frac{\Delta\varepsilon\times10^{-2}}{(\text{M}\cdot\text{cm})^{-1}}$
Phenol	99	212.5	5.28	224	0.17
		271.5	1.62	275	−0.18
Aniline	184	231.5	7.82	238	0.26
		282	1.55	288	−0.10
Nitrobenzene	—	268.5	9.82	275	0.75[b)]
p-Nitrophenol[a)]	244	229	7.02	227	−1.57
		321	9.24	329	1.42
p-Nitroaniline	312	230	6.71	230	−1.58
				296	−0.22
		389	14.66	390	2.24
Benzoic acid[a)]	604	230.5	10.35	238	2.28
		274	1.05	282	−0.13
		281	0.87		
p-Hydroxybenzoic acid[a)]	158	208.5	15.96	216	−2.41
		256	13.44	259	3.61

a) In 0.1 M aqueous HCl. b) $\Delta\varepsilon$ of β-CDx complex with nitrobenzene was estimated by assuming that all the molecules of nitrobenzene in the solution form complexes because of the insolubility of nitrobenzene itself in water.

TABLE 4. COMPARISON OF THE OBSERVED AND CALCULATED ROTATIONAL STRENGTH (R) OF β-CYCLODEXTRIN COMPLEXES WITH BENZENE DERIVATIVES

Benzene derivative	Assignment	$\frac{\lambda_{\text{max}}}{\text{nm}}$	$R\times10^{40}$/cgs		
			Experiment	Calculation	
				(I) Axial	(II) Equatorial
Phenol	B_2	275	−0.34	−0.53	1.06
	A_1	224	0.16	7.92	−3.96
Aniline	B_2	288	−0.24	−0.42	0.83
	A_1	238	0.55	8.33	−4.16
Nitrobenzene	B_2			−0.17	0.34
	A_1	275	2.97	9.51	−4.75
	B_2			−0.13	0.25
	B_2		− (large)	−2.30	4.61
p-Nitrophenol	A_1	329	7.50	12.28	−6.14
	B_2	227	−3.83	−4.37	8.73
p-Nitroaniline	A_1	390	9.14	13.05	−6.52
	B_2	296	−0.52	−0.08	0.17
	B_2	230	−5.37	−7.78	15.55
	A_1			0.20	−0.10
Benzoic acid	A′	282	−0.15	0.08	0.18
	A′	238	5.69	10.18	−4.86
p-Hydroxy-benzoic acid	A′	259	11.17	16.34	−8.13
	A′	216	−3.08	−9.16	18.85

strengths were investigated. The sign of the calculated rotational strength was unchanged by the translations of the guest molecules along the x-, y-, and z-axes, while their magnitudes were affected by the translation and became maxima when the center of the guest molecule was placed on the point about 2 Å away from the origin along the z-axis. The rotation of the guest molecule in the x-y plane had no influence on the calculated rotational strengths. On the other hand, the calculated rotational strengths were very sensitive to the rotation of the guest molecules in the x-z plane, as demonstrated in Fig. 11.

In conclusion, when the direction of the electric dipole moment is known, we can estimate the orientation of the chromophore which is included in the cavity of β-CDx.

Finally, it is stated that the measurements of ICD spectra in combination with the theoretical calculation of rotational strengths are quite useful for the investigations of the structure of these inclusion complexes.

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