BIOORGANIC CHEMISTRY 10, 255–265 (1981)

# Induced Circular Dichroism of Cycloamylose Complexes with *meta*- and *para*-Disubstituted Benzenes

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*Received April 28, 1980*

Cycloamylose complexes with substituted benzenes in aqueous solutions were investigated by circular dichroism (CD) spectroscopy. The differences in CD spectra between cyclohexaamylose complexes and cycloheptaamylose complexes suggests that the orientation and disposition of the guest molecule differ in these two cycloamylose complexes. It was shown theoretically that the sign and intensity of CD are quite sensitive to the orientation of the guest chromophor in the cycloamylose cavity, but that the difference between the cyclohexaamylose complex and the cycloheptaamylose complex is only 13% if the guest molecule is included in the same geometry. Molecular ellipticity and thermodynamic parameters, which were determined by the least-squares curve-fitting procedure, indicate that the guest molecule is more closely packed in the cyclohexaamylose cavity, and that there is no stereospecificity in the complex formation between the *meta*-disubstituted benzenes and the *para*-disubstituted benzenes.

## INTRODUCTION

Cycloamyloses induce optical activity in an optically inactive chromophor by including it in the torus-shaped cavity in aqueous solution. The structure of cycloamylose complexes and the origin of induced optical activity have been studied by circular dichroism (CD) spectra (*1–4*). Theoretical calculations have shown that the rotational strength is approximately expressed in the form (*2*): $R_{oa} = A_{oa}(1 + 3\cos\theta)\mu_{oa}^2$, although the detail of $A_{oa}$ has been yet defined.

The stereospecificity in the complex formation of cycloamylose is important in relation to stereospecific catalysis (*5*). In the previous paper (*6*), we have shown that the orientation and disposition of the included guest differ with respect to the complexes with cyclohexaamylose and cycloheptaamylose. In this paper, we deal with cycloamylose complexes with disubstituted benzenes. CD spectra of these complexes with the *para* isomers and the *meta* isomers were compared to each other as well as with cyclohexaamylose and cycloheptaamylose. The theoretical approach was also pursued to elucidate the $A_{oa}$ term in the formula mentioned above. The structure and binding forces will be discussed on the basis of the thermodynamic parameters determined on the basis of the temperature-dependent CD spectra.

0045-2068/81/030255-11$02.00/0

## EXPERIMENTAL METHODS AND MATERIALS

Cycloamyloses were obtained from Tokyo Kasei Company and benzene derivatives were purchased from Nakarai Chemicals Ltd. Cycloamyloses were recrystallized three times from water, and dried *in vacuo* over phosphorous pentaoxide. Solutions were prepared with deionized and distilled water. The concentration of the guest was held to 1 m*M*. Cycloamylose concentrations were adjusted to 4, 8, and 36 m*M* for cyclohexaamylose, and 2.5, 6.5, and 12 m*M* for cycloheptaamylose. CD spectra were recorded on a JASCO J-40A spectropolarimeter with a J-DPZ data processor. The temperature was regulated by a Tokyo Rico TC-100 thermo-controller, and a water-jacketed cylindrical cell was used. The CD measurement was carried out at temperatures from 20 to 60°C with steps of 5°C.

Molecular ellipticity and thermodynamic parameters of the 1 : 1 complex were determined by the least-squares curve-fitting procedure from the equation (*7*)

$$\ln K_\mathrm{d} = \frac{\Delta H}{\mathrm{R}T_i} - \frac{\Delta S}{\mathrm{R}}, \qquad [1]$$

$$K_\mathrm{d} = \frac{ab_j\theta_\mathrm{m}}{\theta_{ij}} - a - b_j + \frac{\theta_{ij}}{\theta_\mathrm{m}}, \qquad [2]$$

where $a$ and $b_j$ are concentrations of the guest and cycloamylose, respectively, $\theta_{ij}$ is the observed CD at the temperature of $T_i$(K), and $\theta_\mathrm{m}$ is the molecular ellipticity of the complex.

## APPLICATION OF THE KIRKWOOD–TINOCO METHOD

The Kirkwood–Tinoco equation for the rotational strength of a strong electric dipole transition interacting with far-ultraviolet transitions in perturbing groups is given by (*8*)

$$R_\mathrm{oa} = \pi\nu_\mathrm{a}\mu_\mathrm{oa}{}^2 \sum_i \frac{\nu_i{}^2(\alpha_{33} - \alpha_{11})_i(\mathrm{GF})_i}{c(\nu_i{}^2 - \nu_\mathrm{a}{}^2)}, \qquad [3]$$

$$(\mathrm{GF})_i = \frac{1}{r_i{}^2}\,[(\hat{e}_\mathrm{a} \cdot \hat{e}_i) - 3(\hat{e}_\mathrm{a} \cdot \hat{e}_{\mathrm{o}i})\,(\hat{e}_i \cdot \hat{e}_{\mathrm{o}i})]\,(\hat{e}_\mathrm{a} \times \hat{e}_i) \cdot \hat{e}_{\mathrm{o}i}, \qquad [4]$$

where $\hat{e}_\mathrm{a}$ is the unit vector in the direction of the electric dipole moment ($\mu_\mathrm{oa}$) of the transition from o to a with a frequency of $\nu_\mathrm{a}$; $\hat{e}_i$ is the unit vector of the *i*th bond with a transition frequency of $\nu_i$; $r_i$ is the distance from the electric dipole moment to the *i*th bond with the unit vector of $\hat{e}_{\mathrm{o}i}$; $\alpha_{33}$ and $\alpha_{11}$ are electric polarizabilities parallel and perpendicular to the unit vector of the *i*th bond. If we put the origin at the center of the cycloamylose cavity as shown in Fig. 1, each unit vector can be expressed as

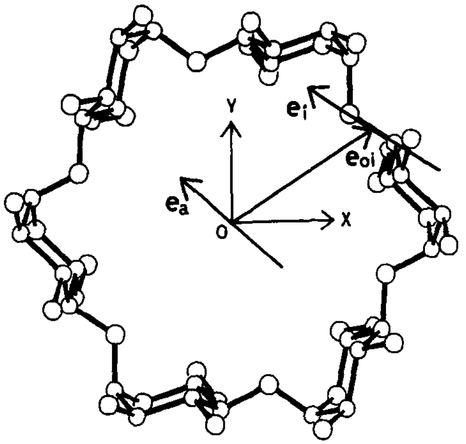

FIG. 1. Schematic representation of coordinate system.

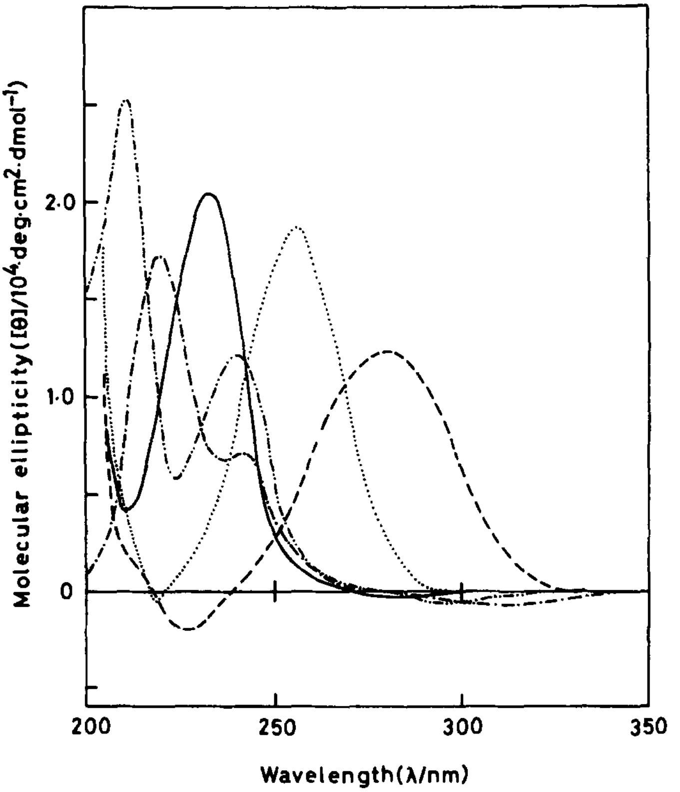

FIG. 2. CD spectra of cyclohexaamylose complexes with benzoic acid (——), *p*-aminobenzoic acid (– – –), *p*-hydroxybenzoic acid (· · ·), *m*-aminobenzoic acid (–·–·–), and *m*-hydroxybenzoic acid (–··–··–). $10^4$ deg · cm$^2$ · dmol$^{-1}$ = 0.1745 rad · m$^2$ · mol$^{-1}$.

$$\hat{e}_a = (\sin\theta\cos\phi, \sin\theta\sin\phi, \cos\theta), \quad [5]$$

$$\hat{e}_i = (x_i, y_i, z_i), \quad [6]$$

$$\hat{e}_{oi} = (x_{oi}, y_{oi}, z_{oi}). \quad [7]$$

The angle of $\theta$ is made by the unit vector of $\hat{e}_a$ and the z axis. The rotation of the electric dipole moment around the z axis is defined by the angle of $\phi$. If we assume a $N$-fold symmetry in the cycloamylose molecule, by substituting Eqs. [5]–[7] for Eq. [4], we obtain

$$\begin{aligned}(\mathrm{GF})_i = \frac{1}{4r_i^2}\Big[ & NZ_{ai}(z_i - 3Z_{bi})(1 + 3\cos 2\theta) \\ & + \{X_{ai}(x_i - 3X_{bi}) - Y_{ai}(y_i - 3Y_{bi})\}(1 - \cos 2\theta)\sum_{m=1}^{N}\cos\left(2\phi + \frac{4m\pi}{N}\right) \\ & + \{X_{ai}(y_i - 3Y_{bi}) + Y_{ai}(x_i - 3X_{bi})\}(1 - \cos 2\theta)\sum_{N=1}^{N}\sin\left(2\phi + \frac{4m\pi}{N}\right) \\ & + \{Z_{ai}(x_i - 3X_{bi}) + X_{ai}(z_i - 3Z_{bi})\}\sin 2\theta\sum_{m=1}^{N}\cos\left(\phi + \frac{2m\pi}{N}\right) \\ & + \{Z_{ai}(y_i - 3Y_{bi}) + Y_{ai}(z_i - 3Z_{bi})\}\sin 2\theta\sum_{m=1}^{N}\sin\left(\phi + \frac{2m\pi}{N}\right)\Big], \end{aligned} \quad [8]$$

with

$$\begin{aligned} X_{ai} &= y_i z_{oi} - z_i y_{oi}, \\ Y_{ai} &= z_i x_{oi} - x_i z_{oi}, \\ Z_{ai} &= x_i y_{oi} - y_i x_{oi}, \end{aligned} \quad [9]$$

$$\begin{aligned} X_{bi} &= x_{oi}(x_i x_{oi} + y_i y_{oi} + z_i z_{oi}), \\ Y_{bi} &= y_{oi}(x_i x_{oi} + y_i y_{oi} + z_i z_{oi}), \\ Z_{bi} &= z_{oi}(x_i x_{oi} + y_i y_{oi} + z_i z_{oi}). \end{aligned} \quad [10]$$

Since $\Sigma\cos\left(2\phi + \frac{4m\pi}{N}\right) = 0$, $\Sigma\sin\left(2\phi + \frac{4m\pi}{N}\right) = 0$, $\Sigma\cos\left(\phi + \frac{2m\pi}{N}\right) = 0$, and $\Sigma\sin\left(\phi + \frac{2m\pi}{N}\right) = 0$, Eq. [8] is reduced to a quite simple form:

$$(\mathrm{GF})_i = \frac{NZ_{ai}}{4r_i^2}(z_i - 3Z_{bi})(1 + 3\cos 2\theta). \quad [11]$$

Therefore, by substituting Eq. [11] for Eq. [3], we obtain

$$R_{oa} = \pi N\nu_a\mu_{oa}^2(1 + 3\cos 2\theta)\sum_i \frac{\nu_i^2(\alpha_{33} - \alpha_{11})_i Z_{ai}(z_i - 3Z_{bi})}{4r_i^2 c(\nu_i^2 - \nu_a^2)}. \quad [12]$$

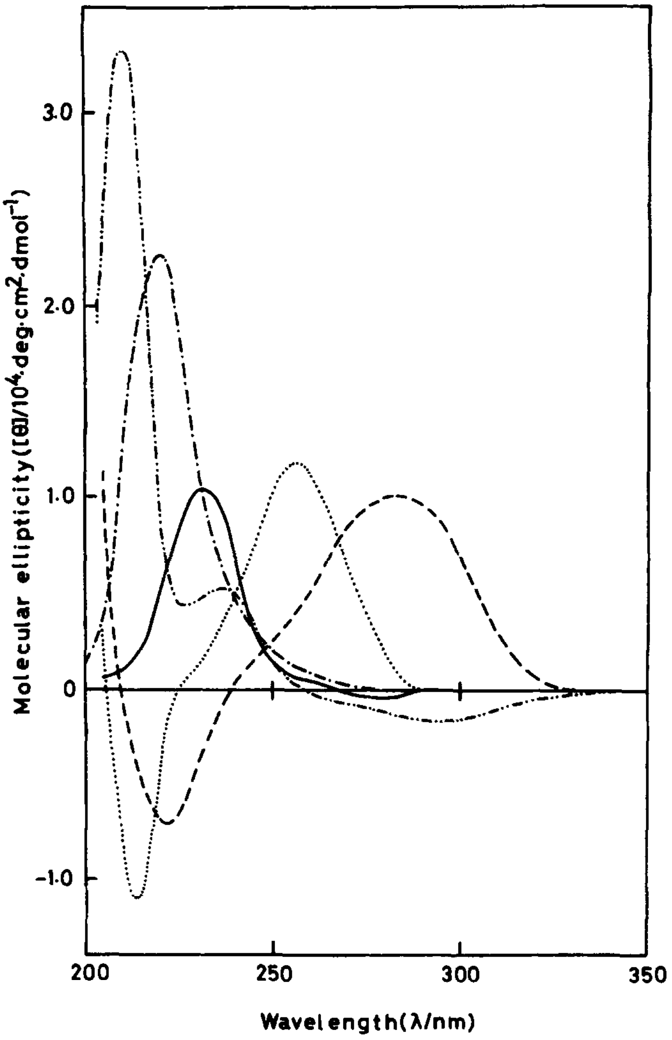

FIG. 3. CD spectra of cycloheptaamylose complexes with benzoic acid (——), *p*-aminobenzoic acid (– – –), *p*-hydroxybenzoic acid (· · ·), *m*-aminobenzoic acid (– · – · –), and *m*-hydroxybenzoic acid (– · · – · · –). $10^4$ deg · cm$^2$ · dmol$^{-1}$ = 0.1745 rad · m$^2$ · mol$^{-1}$.

## RESULTS

Induced CD spectra of cycloamylose complexes with substituted benzenes are shown in Figs. 2–5. In the cyclohexaamylose complexes, benzoic acid and its *meta*-substituted derivatives give a weak and negative-signed CD in the wavelength region from 270 to 350 nm (Fig. 2). The benzoic acid complex shows a large and positive-signed CD at 232 nm, while the complexes with *m*-hydroxybenzoic acid and *m*-aminobenzoic acid give two positive CD peaks in the 200- to 250-nm

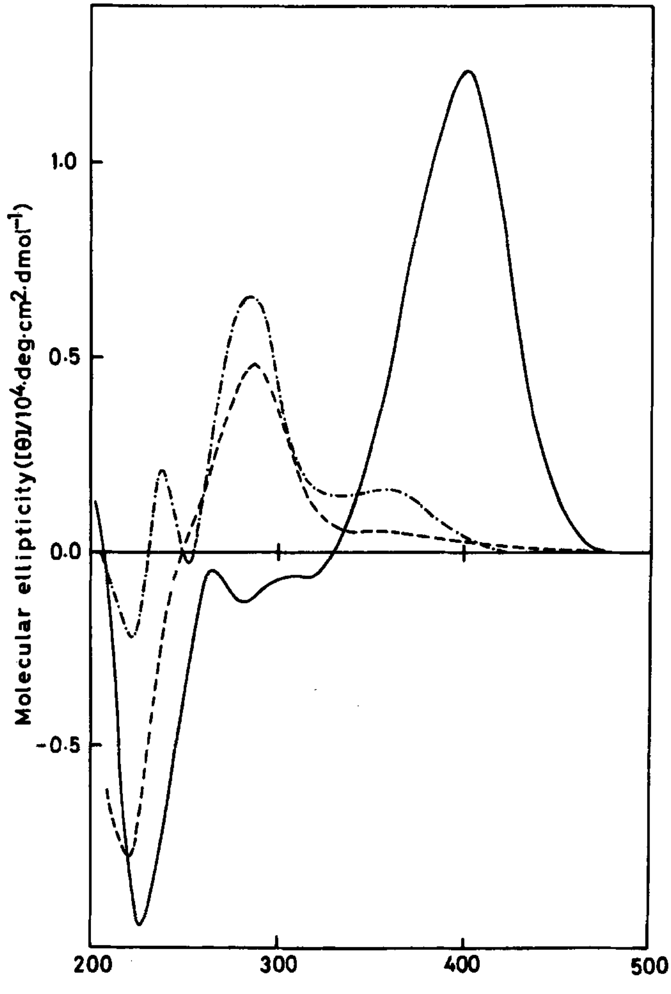

FIG. 4. CD spectra of cyclohexaamylose complexes with *p*-nitroaniline (——), *m*-nitroaniline (– – –), and *m*-nitrophenol (– · – · –). $10^4$ deg · cm$^2$ · dmol$^{-1}$ = 0.1745 rad · m$^2$ · mol$^{-1}$.

region. Cyclohexaamylose complexes with *p*-aminobenzoic acid and *p*-hydroxybenzoic acid have a large positive-signed CD band at longer wavelength region and a small negative CD in the shorter wavelength region (200–250 nm).

CD spectra of cycloheptaamylose complexes with substituted benzoic acids are largely similar in shape to those of the cyclohexaamylose complexes, but their intensity differs considerably (Fig. 3). The intensity of positive CD of the cycloheptaamylose complexes with *p*-aminobenzoic acid and *p*-hydroxybenzoic acid is smaller than the corresponding intensity of the cyclohexaamylose complexes, but the intensity of the negative CD in the 200- to 250-nm region is remarkably increased. In the complexes with *meta*-substituted isomers, in

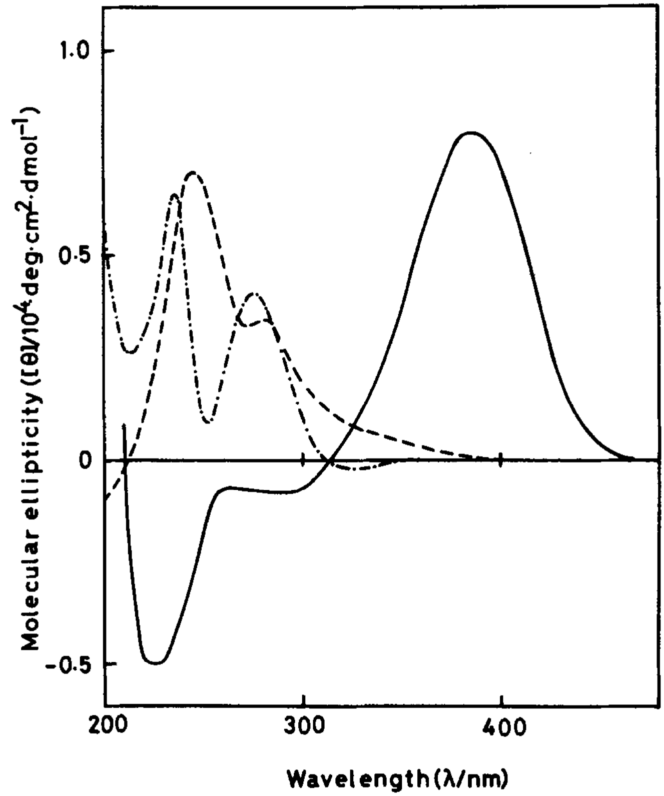

FIG. 5. CD spectra of cycloheptaamylose complexes with *p*-nitroaniline (——), *m*-nitroaniline (– – –), and *m*-nitrophenol (– · – · –). $10^4$ deg · cm$^2$ · dmol$^{-1}$ = 0.1745 rad · m$^2$ · mol$^{-1}$.

comparison with the cyclohexaamylose complex, the CD intensity at 245 nm is decreased while the intensity of the 200- to 250-nm band is enhanced.

The *p*-nitroaniline complex with cyclohexaamylose gives a positive CD at 401 nm and a negative one at 217 nm. These CD intensities are reduced to about 60% in the complex with cycloheptaamylose (Figs. 4 and 5). A remarkable change in spectral shape is observed in the 200- to 300-nm region of the complexes with *m*-nitroaniline and *m*-nitrophenol. In their cyclohexaamylose complexes, a negative-signed CD peak is found at 210 nm; but in the cycloheptaamylose complexes the corresponding CD peak is not observed but instead a large positive CD appears in the 220- to 230-nm region.

From Eq. [10], the CD intensity ratio against the intensity of cyclohexaamylose complex was theoretically estimated. If we assume the same disposition and orientation of the guest molecule in the cycloamylose cavity and neglect the small difference in $\hat{e}_{0i}$, the rotational strength is a function of $N$, $\theta$, and $r_i$. Therefore, the ratio of the rotational strength between cyclohexaamylose and cycloheptaamylose complexes is approximately expressed as follows:

$$\frac{R_{\text{oa}}(\text{cycloheptaamylose})}{R_{\text{oa}}(\text{cyclohexaamylose})} \approx \frac{7l^2(\text{cyclohexaamylose})}{6l^2(\text{cycloheptaamylose})}, \qquad [13]$$

TABLE 1

COMPARISON OF ROTATIONAL STRENGTH IN CYCLOAMYLOSE COMPLEXES

|  | $N$ | $l$ (Å) | $l^2$ / $l^2$(cyclohexaamylose) | $R_{0a}$ / $R_{0a}$(cyclohexaamylose) |
|---|---|---|---|---|
| Cyclohexaamylose | 6 | 4.4 | 1 | 1 |
| Cycloheptaamylose | 7 | 5.1 | 1.35 | 0.87 |
| Cyclooctaamylose | 8 | 5.7 | 1.68 | 0.80 |

where $l$ is the radius of cycloamylose ring and is taken from the distance between the origin and the center of the C(4)–O(4) bond. As shown in Table 1, the CD intensity reduces to 87% in the cycloheptaamylose complex and to 80% in the cyclooctaamylose complex, compared with the cyclohexaamylose complex.

Thermodynamic parameters for the 1 : 1 complex formation were determined by the least-squares technique from Eq. [1] on the basis of the temperature-dependent CD intensity. To examine the validity of the method and the 1 : 1 stoichiometry of the complex, the molecular ellipticity and dissociation constant at each temperature were estimated from Eq. [2]. Temperature dependence was not observed in the molecular ellipticity, and the CD data were well fitted to the equilibrium formula of the 1 : 1 complex formation. The thermodynamic parameters and molecular ellipticity are given in Table 2.

TABLE 2

MOLECULAR ELLIPTICITY AND THERMODYNAMIC PARAMETERS[a]

| Guest | $\lambda$ (nm) | $[\theta_m]$[b] ($10^4$ deg · cm$^2$ dmol$^{-1}$) | $\Delta G$(298 K) (kcal · mol$^{-1}$) | $\Delta H$ (kcal · mol$^{-1}$) | $\Delta S$ (cal · K$^{-1}$ · mol$^{-1}$) |
|---|---|---|---|---|---|
|  |  | Cyclohexaamylose complexes |  |  |  |
| Benzoic acid | 232 | 20.2(0.1) | −3.45 | −9.99(0.23) | −22.0(0.7) |
| *m*-Hydroxybenzoic acid | 240 | 12.1(0.1) | −3.32 | −11.32(0.20) | −26.9(0.6) |
| *p*-Hydroxybenzoic acid | 256 | 18.6(0.1) | −3.60 | −9.72(0.21) | −20.6(0.7) |
| *m*-Aminobenzoic acid | 220 | 17.2(0.2) | −2.36 | −7.77(0.08) | −18.1(0.2) |
| *p*-Aminobenzoic acid | 280 | 12.3(0.1) | −3.82 | −10.42(0.18) | −22.1(0.6) |
| *m*-Nitrophenol | 284 | 6.3(0.1) | −2.90 | −8.44(0.10) | −18.6(0.3) |
| *p*-Nitrophenol[c] | 342 | 9.4(0.1) | −3.15 | −7.62(0.14) | −15.0(0.4) |
| *m*-Nitroaniline | 288 | 4.8(0.2) | −2.55 | −6.89(0.06) | −14.6(0.2) |
| *p*-Nitroaniline | 401 | 12.3(0.1) | −3.64 | −10.11(0.08) | −21.7(0.2) |
|  |  | Cycloheptaamylose complexes |  |  |  |
| Benzoic acid | 231 | 10.4(0.1) | −3.45 | −5.34(0.08) | −6.3(0.2) |
| *m*-Hydroxybenzoic acid | 241 | 5.6(0.1) | −3.35 | −6.60(0.08) | −10.9(0.3) |
| *p*-Hydroxybenzoic acid | 256 | 11.8(0.1) | −3.71 | −6.11(0.10) | −8.1(0.3) |
| *m*-Aminobenzoic acid | 219 | 22.6(0.1) | −2.46 | −2.09(0.08) | +1.3(0.3) |
| *p*-Aminobenzoic acid | 285 | 10.2(0.1) | −3.68 | −5.59(0.09) | −6.4(0.3) |
| *m*-Nitrophenol | 235 | 6.5(0.1) | −2.72 | −4.11(0.08) | −4.7(0.2) |
| *p*-Nitrophenol[c] | 330 | 4.8(0.1) | −3.10 | −3.81(0.14) | −2.4(0.4) |
| *m*-Nitroaniline | 282 | 3.4(0.3) | −2.17 | −2.65(0.14) | −1.6(0.4) |
| *p*-Nitroaniline | 386 | 8.0(0.1) | −3.42 | −4.69(0.08) | −4.3(0.3) |

[a] Values in parentheses are estimated standard deviations.

[b] $10^4$ deg · cm$^2$ · dmol$^{-1}$ = 0.1745 rad · m$^2$ · mol$^{-1}$.

[c] See Ref (6).

## DISCUSSION

The shape and intensity of the induced CD spectra of the cyclohexaamylose complex and the cycloheptaamylose complex are quite different. This may be mainly ascribed to the different orientation and/or disposition of the guest molecule in the cycloamylose cavity. The theoretical elucidation of the rotational strength on the basis of the Kirkwood–Tinico model gives some interesting indications of the geometrical basis. The rotational strength is independent of the rotation of the guest molecule around the symmetry axis of cycloamylose, but quite sensitive to the angle of $\theta$, which is made by the symmetry axis and the direction of the electric dipole moment of the guest. Therefore, the rotational strength is a function of $1 + 3\cos 2\theta$, which has also been derived from the numerical approach (*2*), and the CD sign changes at $\theta = 54.7°$. The rotational strength also increases with the number of glucose residues, but decreases with the second power of the radius of cycloamylose ring. As shown in Table 1, the CD intensity of the cycloheptaamylose complex is expected to be 87% of the CD intensity of the cyclohexaamylose complex, even if the orientation and disposition of the guest chromophor are the same in both the cycloamylose rings. The CD change due to the translation of the chromophor along the $z$ axis is rather complicated; and as shown in the earlier paper (*2*), the maximum intensity is expected when the guest molecule is located near the center of the cycloamylose cavity.

Thermodynamic parameters given in Table 2 show that the free energy does not significantly differ between the cyclohexaamylose complex and the cycloheptaamylose complex, but values of enthalpy and entropy of the cyclohexaamylose complex are remarkably larger than those of the cycloheptaamylose complex. This indicates that cycloheptaamylose has a larger complexing ability at higher temperature. A strong compensation relation is observed between enthalpy and

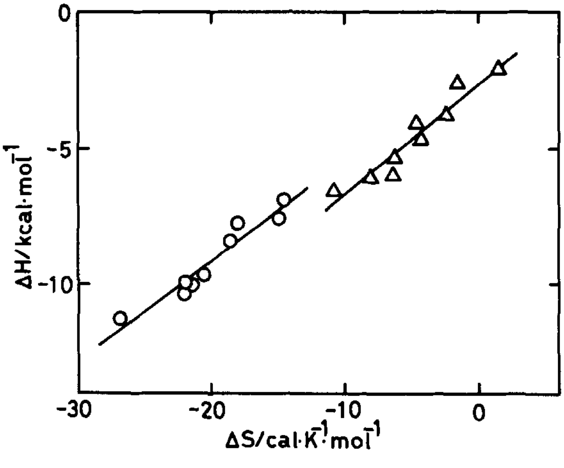

FIG. 6. Plot of $\Delta H$ against $\Delta S$ in cyclohexaamylose complex (○) and cycloheptaamylose complex (△).

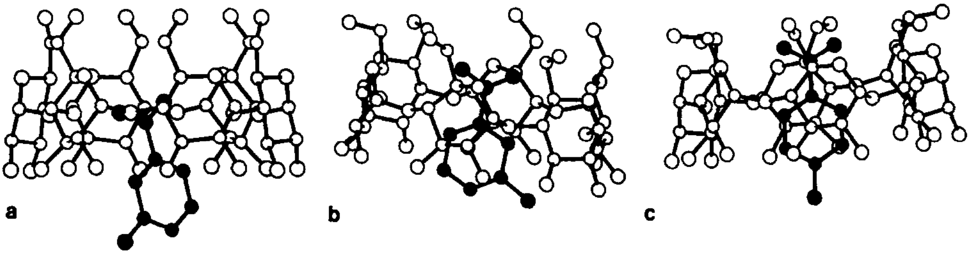

FIG. 7. Structures of cyclohexaamylose complexes found in the crystalline state; *m*-nitrophenol (a), *m*-nitroaniline (b), and *p*-nitrophenol (c).

entropy (Fig. 6). The compensation temperature is 376 ± 37 K in the cyclohexaamylose complex and 407 ± 36 K in the cycloheptaamylose complex. Similar compensation phenomena have been observed in the cycloamylose complexes with substituted cinnamic acids and cinnamates (*9*). But in that case the compensation temperature of the cyclohexaamylose (427 K) is higher than that of the cycloheptaamylose complex (302 K). On the other hand, the temperature of 311 ± 44 K has been observed in the cycloheptaamylose complexes with substituted naphthalenes (*7*).

From the thermodynamic data, no stereospecificity difference is indicated between *para*-disubstituted benzenes and their *meta* isomers. In the complexes with hydroxybenzoic acids and nitrophenols, the *meta* isomer gives larger negative enthalpy than the *para* isomer. But, an opposite tendency is observed in the complexes with aminobenzoic acids and nitroanilines. The X-ray analysis of the cyclohexaamylose complexes with *m*-nitrophenol (*10*) and *p*-nitrophenol (*11*) has shown that *p*-nitrophenol has deeply penetrated into the cyclohexaamylose cavity, while in the *m*-nitrophenol complex only the nitro group is inserted (Fig. 7). NMR studies have suggested that *p*-nitrophenol is included in a manner similar to that found in the crystalline state but penetrates only partially (*12, 13*). The theoretical estimation of enthalpy in aqueous solution on the basis of the X-ray data has shown that the enthalpy value of the *p*-nitrophenol complex is about three times greater than that of the *m*-nitrophenol complex (*10*). The smaller enthalpy value of the *m*-nitrophenol complex is mainly derived from the weak van der Waals interaction owing to the shallow inclusion. On the other hand, the present thermodynamic data suggest that both the *meta* and *para* isomers are included in a similar fashion. This is supported by our recent X-ray study of the cyclohexaamylose—*m*-nitroaniline complex (*14*). As shown in Fig. 7, the nitrophenyl group of *m*-nitroaniline is located at the same position as that found in the *p*-nitrophenol complex. Therefore, the deep penetration of *meta* isomer into the cyclohexaamylose ring is more plausible in aqueous solution. The thermodynamic behavior of both *meta* and *para* isomers is also quite similar to each other in the cycloheptaamylose complexes. In the crystalline state, cycloheptaamylose complexes with *p*-iodophenol (*15*) and *m*-cresol (*16*), and both guests are included in the same orientation and the same disposition in the cavity. Therefore, both *meta* and *para* isomers can be included in the same manner in aqueous solution.

Enthalpy and entropy values of the cycloheptaamylose complex are considerably smaller than those of the cyclohexaamylose complex. As suggested in a previous paper (*6*), these characteristics in the thermodynamic parameters may be ascribed to the size of the cycloamylose cavity. In the smaller cyclohexaamylose cavity, the guest molecule is more tightly fixed. The tight packing gives not only the large van der Waals interaction energy but also unfavorable negative entropy change by imposing restrictions on the conformational freedom of cycloamylose and the translational and rotational freedom of the guest molecule.

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