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Selective Recognition of Alkanoates by a β-Cyclodextrin Flexibly Capped with a Chromophore

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The association between 6-deoxy-6-(*p*-hydroxy-*m*-nitrophenacylthio)-β-cyclodextrin **1** and sodium *n*-alkanoate, sodium 2,2-dimethylpropionate, or sodium 3,3-dimethylbutyrate was investigated. Host–guest association was measured by means of electronic spectroscopy and circular dichroism spectroscopy and ascertained to be 1:1. The inclusion of 2,2-dimethylpropionate or butanoate marginally affected the circular dichroism spectrum of **1**. The inclusion of 3,3-dimethylbutyrate, hexanoate, octanoate, decanoate, or dodecanoate, however, dramatically affected the spectrum of **1**. The plots of molecular ellipticities of the inclusion complexes against the carbon number of the *n*-alkanoates were sigmoid. From these observations, the effective size of the guest molecule to push the chromophore in the cavity to the capping position was estimated. From the similarity of the spectrum of the octanoate-**1** complex to that of 1-adamantanecarboxylate-**1** complex, the carbon chain of octanoate appears to be folded in the cavity of the cyclodextrin.

INTRODUCTION

Modeling of enzyme function has been extensively and successfully studied by the use of cyclodextrins and their derivatives (*1, 2*). Although conformational changes of enzymes upon substrate binding are an important aspect of enzyme catalysis (*3*), there have been few studies on modeling of substrate-induced conformational changes (*2*). Recently, we reported the substrate-induced conformational change of a modified cyclodextrin **1**,6-deoxy-6-(*p*-hydroxy-*m*-nitrophenacylthio)-β-cyclodextrin (*4*). From the changes of electronic, nmr, and circular dichroism spectra as well as pK_a of **1** upon binding of 1-adamantanecarboxylate, the conformational change around the chromophore-moiety of the cyclodextrin as shown in Scheme 1 was strongly suggested.

It is reasonably expected from this mechanism (Scheme 1) that the size of the guest molecule will affect the degree of the conformational change around the chromophore. Moreover, comparison of the change caused by inclusion of a rigid guest with that of a flexible guest would bring knowledge about the structure of the flexible guest included in the cyclodextrin cavity. In this paper, we report that **1** can recognize the difference of the size of the guest molecule, sodium *n*-alkanoate,

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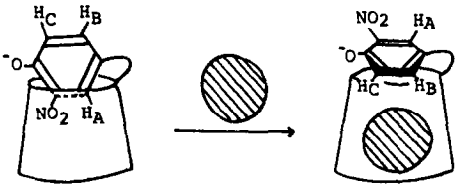

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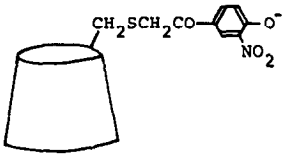
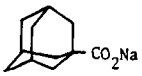


1

$CH_3(CH_2)_nCO_2Na$

2a ; n = 2
b ; n = 4
c ; n = 6
d ; n = 8
e ; n = 10



3

$(CH_3)_3CCO_2Na$

4

$(CH_3)_3CCH_2CO_2Na$

5

SCHEME 1

TABLE 1

ASSOCIATION CONSTANTS BETWEEN MODIFIED CYCLODEXTRIN (1) AND GUEST MOLECULES[a]

Guest	K_a of Modified cyclodextrin (M^{-1})
$CH_3(CH_2)_2CO_2Na$ (**2a**)	10
$CH_3(CH_2)_4CO_2Na$ (**2b**)	45
$CH_3(CH_2)_6Co_2Na$ (**2c**)	240
$CH_3(CH_2)_8CO_2Na$ (**2d**)	530
$CH_3(CH_2)_{10}CO_2Na$ (**2e**)	1370(1240)[b]
$(CH_3)_3CCO_2Na$ (**4**)	59[c]
$(CH_3)_3CCH_2CO_2Na$ (**5**)	500[c]

[a] Unless otherwise noted, the constants were estimated on the basis of the electronic absorption change in phosphate buffer (pH 11.0) at 25°C.

[b] The constant was estimated on the basis of the circular dichroism spectral change in phosphate buffer (pH 11.0) at 25°C.

[c] Reference (*4*).

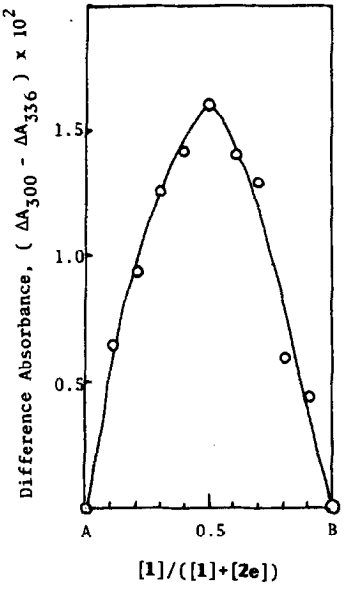


FIG. 1. Job's continuous variation plot for **1**–**2e** system in phosphate buffer (pH 11.0). A, **1** (1.03×10^{-4} *M*); B, **2e** (1.03×10^{-4} *M*).

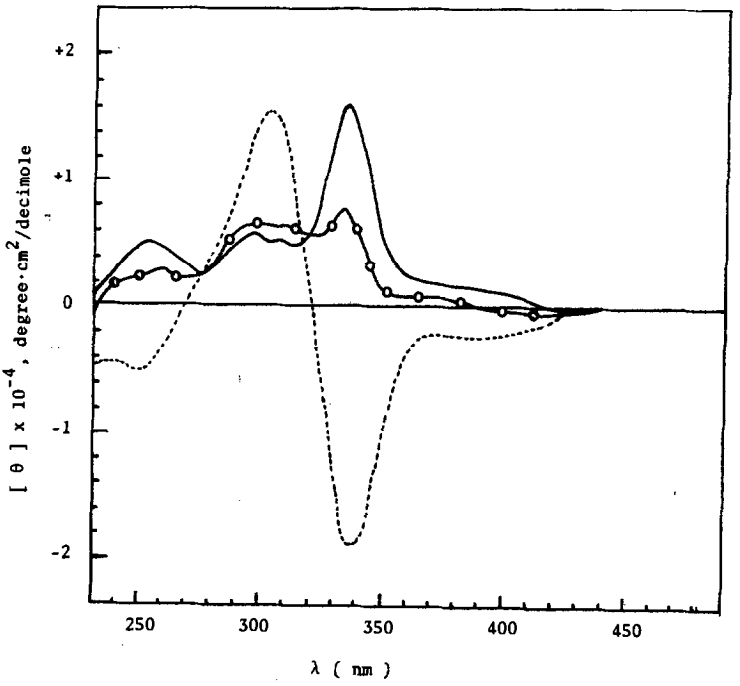


FIG. 2. Circular dichroism spectra of **1** (—), and inclusion complexes of **1** with sodium 1-adamantanecarboxylate (---), or with sodium 3,3-dimethylbutyrate (o) in phosphate buffer (pH 11.0) at 25°C. The spectrum of the complex of **1** with sodium 2,2-dimethylpropionate was very similar to that of **1** alone.

in its inclusion and that the alkanoate seems to possess a folded structure in the cavity of the cyclodextrin.

RESULTS AND DISCUSSION

The chromophore-modified cyclodextrin **1** was prepared as described elsewhere (*4*). The electronic spectrum of **1** in a phosphate buffer (pH 11.0) had absorptions at 396 and 323 nm (*4*). Addition of sodium alkanoate (**2a–e**) caused a blue shift of the absorptions of **1**. On treatment of the spectral data by the Scatchard method (*4, 5*), the formation of 1 : 1 host guest association was evidenced, and the association constant was estimated under the condition where the guest concentration was less than its critical micelle concentration (Table 1). The 1 : 1 host–guest association was also ascertained by Job's treatment (*6*) of the electronic spectral change for the inclusion of **2e** by **1** (Fig. 1). Inclusion of sodium alkanoate **2a–e, 3–5** caused a change of circular dichroism (CD) spectrum of **1** depicted in Figs. 2 and

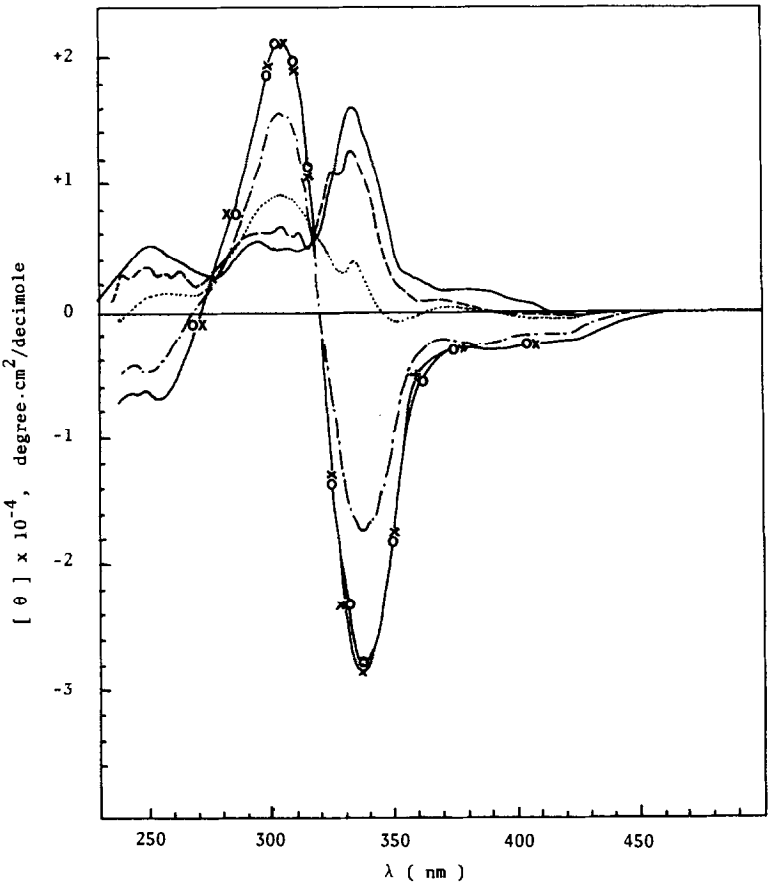


FIG. 3. Circular dichroism spectra of **1** (—) and inclusion complexes of **1** with **2a** (---), with **2b** (···), with **2c** (–·–), with **2d** (○), and with **2e** (×) in phosphate buffer (pH 11.0) at 25°C.

3, where the spectra of the inclusion complexes were estimated by calculation from the CD spectra of the partial (~50–80%) inclusion complex formation of **1** on the basis of the association constants (Table 1). Since complete saturation of **1** with a guest would need a higher concentration of the guest than the critical micell concentration and since such a high concentration of a guest would alter the nature of the aqueous solution, the present estimate was adopted to obtained the complete saturation spectrum. From the CD spectral change by guest inclusion, the association constant between **1** and **2e** was also estimated by the Scatchard method (Table 1), showing a good agreement with the corresponding value obtained from the electronic spectral change.

Interestingly, 1 : 1 host–guest association, even for dodecanoate (**2e**), was observed in the present case. On the other hand, the mole ratio of β-cyclodextrin to the associated dodecanoic acid was already estimated to be 4.5 from the effect of β-cyclodextrin on the solubility of dodecanoic acid in water (*7*). This difference in the mole ratio (host–guest) between the present result with **1** and the above result

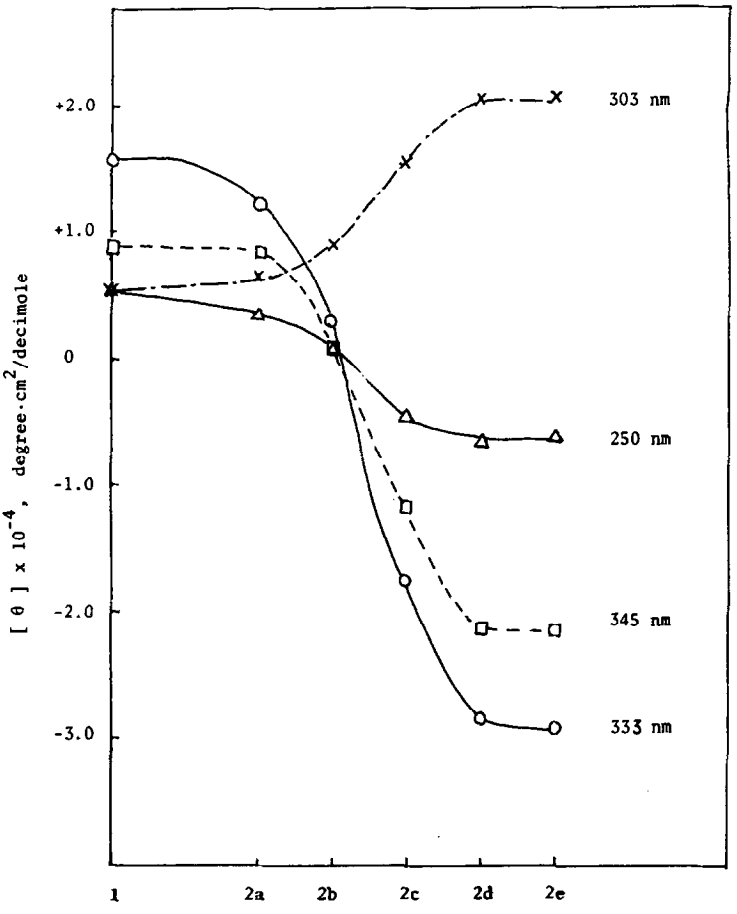


FIG. 4. Dependency of molecular ellipticity of inclusion complex (**1–2a–e**) on carbon atom number of **2a–e** at 25°C.

with β-cyclodextrin seems to be due to the capping effect of the chromophore at the primary side in **1**.

Although the inclusion of 1-adamantanecarboxylate **3** by **1** caused a dramatic change of the CD spectrum of **1** (*4*), the inclusion of 2,2-dimethylpropionate **4** did not affect the spectrum of **1**. The effect of 3,3-dimethylbutyrate **5** on the CD spectrum fell between those of **3** and **4** (Fig. 2), suggesting that the degree of spectral change is dependent on the size of the alkanoate. This trend is more clearly demonstrated by the effects of some *n*-alkanoates (Fig. 3). The molecular ellipticities of the inclusion complex at some wavelengths were plotted against the number of carbons in the alkanoate (Fig. 4). Although the small guest (**2a**) slightly affected the ellipticities of **1**, the larger guests (**2b–e**) affected those of **1** dramatically. The sigmoid dependency of the ellipticities on the size of the alkanoate is shown in Fig. 4, suggesting that a certain molecular length of the alkanoate is enough to push the chromophore-moiety in the cavity to the capping position. Also, this indicates that there are several conformations of the host molecule which vary with the size of the guest molecule. The conformation (**1″**) shown in Scheme 1 is one of them.

While the alkanoate **2c** has a flexible structure, **3** has a completely rigid structure. Therefore, it is quite interesting to note that the complex of **2c** showed practically the same CD spectrum as that of **3**. This similarity seems to indicate that the methylene chain of **2c** in the cyclodextrin cavity of **1** might be folded so as to simulate the shape of **3**. This proposal seems to be supported by the observation that the CD spectrum of the inclusion complex of **2b** having a flexible chain of six carbons was similar to that of **5** having a branched chain of four carbons. Moreover, the steady increase of the association constant from **2a** to **2e** (Table 1) also strongly supports the folded structures of the included alkanoates. Thus, flexible guests, *n*-alkanoates, would not be extended but folded in the cavity of the flexibly capped cyclodextrin **1**. This is consistent with the 1 : 1 host–guest association between **1** and *n*-alkanoate **2a–e**.

SUMMARY AND CONCLUSION

The present chromophore cap can maintain the host–guest association ratio as 1 : 1 and recognize the difference of numbers of methylenes in *n*-alkanoates **2a–e**. The flexible guest in the inclusion state is suggested to assume a folded form.

EXPERIMENTAL

General Notes

Electronic spectra and circular dichroism spectra were obtained on a Hitachi 557 double-wavelength double-beam spectrophotometer (or a Hitachi Model 200-10 spectrophotometer) and a Jasco 20C spectrophotometer, respectively.

Association Constants between 1 and Guest Molecules

The difference electronic spectrum for the estimation of association constants was taken between **1** (5×10^{-5} *M*) alone and **1** (5×10^{-5} *M*) in the presence of a guest in phosphate buffer (pH 11.0) at 25°C. The guest concentration ranges from 9.8×10^{-3} to 5.89×10^{-2} *M* for **2a**, from 1.99×10^{-3} to 8.38×10^{-3} *M* for **2b**, from 1.63×10^{-3} to 6.90×10^{-3} *M* for **2c**, from 7.5×10^{-4} to 3.36×10^{-3} *M* for **2d**, or from 8.5×10^{-4} to 3.84×10^{-3} *M* for **2e**, respectively. The association constant between **1** and **2e** was also estimated by means of circular dichroism spectra, where the concentration of **1** and **2e** were 2×10^{-4} and 2.31×10^{-4} to 1.73×10^{-3} *M*, respectively. These spectral data were treated by the Scatchard method (*5*).

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