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Inclusion effects of cyclomaltohexa- and heptaose (α- and β-cyclodextrins) on the acidities of several phenol derivatives

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Abstract

By means of spectrophotometry, equilibrium constants for the formation of 1:1 inclusion complexes of cyclomaltohexaose (α-cyclodextrin, α-CD) or cyclomaltoheptaose (β-CD) in aqueous solutions have been evaluated for neutral and anionic species of 3-cyanophenol, 4-cyanophenol, 3-nitrophenol, 4-nitrophenol, 4-bromophenol, and 4-methoxyphenol. Using the equilibrium constants of the neutral and anionic species, pK_a values have been determined for the phenols bound to the α- and β-CD cavities. These phenols, which are accommodated in the α-CD cavity, have been found to be stronger acids than the free, uncomplexed ones, except for 4-methoxyphenol. On the other hand, 4-cyanophenol, 3-nitrophenol, and 4-methoxyphenol bound to the β-CD cavity are weaker acids than the uncomplexed ones, although 3-cyanophenol, 4-nitrophenol, and 4-bromophenol bound to β-CD show the same trend as those bound to α-CD. The different influences of α- and β-CDs on the pK_a values are likely due to the difference in the magnitudes of the induced dipole moments of the guest caused by α- and β-CDs; depending on the magnitude of the induced dipole moment, the inclusion complexes are stabilized through the dipole–dipole interaction between the host and guest.

Keywords: Cyclomaltohexaose; Cyclomaltoheptaose; Cyclodextrins; Phenols; Equilibrium constants; pK_a; Inclusion complexes

1. Introduction

Cyclomaltooligosaccharides (cyclodextrins, CDs) are cyclic oligosaccharides consisting of six, seven, and eight D-glucose residues linked by α-(1 → 4) bonds, with the D-glucose residues in $^4C_1$ chair conformation. These CDs have a shape like a truncated cone with a hydrophobic cavity, which can accommodate a variety of organic compounds as guest molecules. The physicochemical properties of the guest molecules are varied upon the formation of inclusion complexes with CDs. Electronic absorption, fluorescence, phosphorescence, and ^{1}H NMR spectral properties for the guests are more or less varied as a result of incorporation into the CD cavities [1–7].

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Furthermore, solubilities, stabilities, chemical reactivities, etc. of the guests are changed by the incorporation into the cavities.

Although variations in pK_a with the presence of CDs have been reported for phenols [8], naphthols [9,10], carboxylic acids [8,10,11], indoles [12,13], and tetraarylporphrins [14], the effects of CDs on pK_a have not been investigated systematically with respect to substituent groups. The CD effects on pK_a are related to variations in equilibrium constants for the formation of CD inclusion complexes with neutral and anionic species of the organic compounds that possess a functional substituent such as a hydroxyl group. Thus, we investigated the effects of α- and β-CDs on the equilibrium constants for the formation of inclusion complexes of neutral and anionic phenol derivatives in aqueous solutions and the effects of α- and β-CDs on pK_a. Inclusion of the phenols by α-CD has been found to cause decreases in the pK_a values (increases in acidities) of the phenols examined except for 4-methoxyphenol. On the other hand, β-CD does not necessarily increase the acidities of the phenols.

2. Experimental

Chemicals.—α- and β-CDs were purchased from Nakalai Tesque. β-CD was recrystallized twice from water, while α-CD was used without further purification. 3-Cyanophenol, which was obtained from Tokyo Kasei Kogyo, was recrystallized twice from water. 4-Cyanophenol and 2-nitrophenol obtained from Tokyo Kasei Kogyo were recrystallized twice from hexane. 3-Nitrophenol, 4-nitrophenol, 4-bromophenol, and 4-methoxyphenol from Kasei Tokyo Kogyo, were recrystallized twice from ethanol. Phenol, from Nakalai Tesque, was used as received. Aqueous buffers of HCl–potassium chloride (pH 3.05), sodium citrate–HCl (pH 3.70–4.50), sodium citrate–NaOH (pH 4.90–5.08), potassium hydrogen phosphate–NaOH (pH 5.99–7.88), boric acid–potassim choride (pH 7.83–9.69), $NaHCO_3$–NaOH (pH 10.28–10.58), and NaOH–potassium chloride (pH 11.67–12.61) were employed for the determination of pK_a values and equilibrium constants for the formation of inclusion complexes.

A phosphate anion in buffers does not influence on an equilibrium constant of a guest in the pH range of 2–11 [15]. There are no available data for chloride, citrate, borate, and carbonate anions. For inorganic anions, however, binding constants with CDs are generally small. In addition, reported equilibrium constants for the phenols are similar to those obtained in this study in spite of different buffer anions. Consequently, the anions in buffers seem to cause a relatively small influence, if any, on the equilibrium constants for the formation of inclusion complexes with the phenols.

Measurements.—Absorption spectra were taken with a Shimadzu UV-260 spectrophotometer at 25 ± 0.1 °C. Values of pH for solutions were measured with a Horiba M-8 pH meter.

3. Results and discussion

An inclusion complex of α-CD with 4-cyanophenol.—Fig. 1 shows the pH dependence of the absorption spectrum of 4-cyanophenol (4.0×10^{-5} mol dm^{-3}) in aqueous solutions. There are two isosbestic points at 223 and 256 nm, indicating the presence of an equilibrium between a neutral species and an anion (deprotonated form of a hydroxyl group) of 4-cyanophenol. In acidic solutions, the absorption maximum of 4-cyanophenol, which exists as the neutral species, is located at 246 nm, whereas, in alkaline solution of pH 10.28, 4-cyanophenol, which exists as the anion, has an absorption maximum at 274 nm. Fig. 2 illustrates titration curves for the absorbance of 4-cyanophenol observed at the wavelengths of 245 and 272.5 nm. From the titration curves, a pK_a value of 4-cyanophenol is determined to be 7.74.

Fig. 3 exhibits absorption spectra of 4-cyanophenol (5.0×10^{-5} mol dm^{-3}) in aqueous solutions (pH 3.05) containing varying concentrations of α-CD. When α-CD is added to 4-cyanophenol solution, the

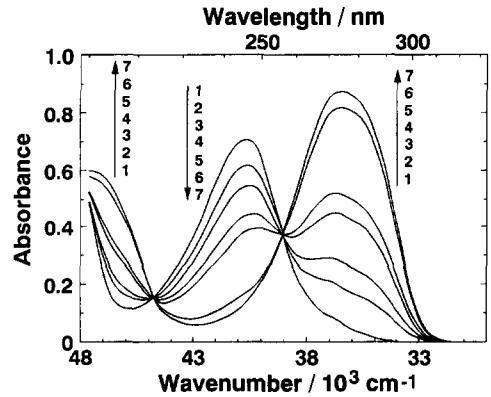

Fig. 1. pH dependence of the absorption spectrum of 4-cyanophenol (4.0×10^{-5} mol^{-1} dm^3) in aqueous solutions buffered at pH (1) 3.05, (2) 7.05, (3) 7.33, (4) 7.71, (5) 7.83, (6) 8.93, and (7) 10.28.

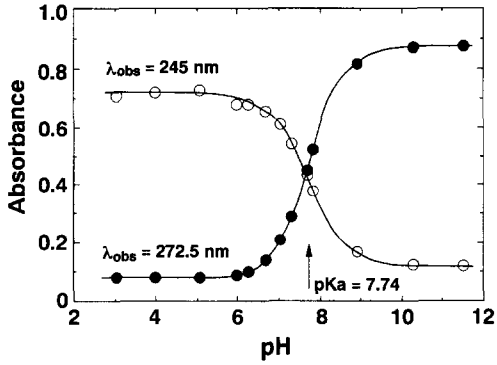

Fig. 2. Titration curves for the absorbances, of 4-cyanophenol (4.0×10^{-5} mol^{-1} dm^3), observed at 245 and 272.5 nm.

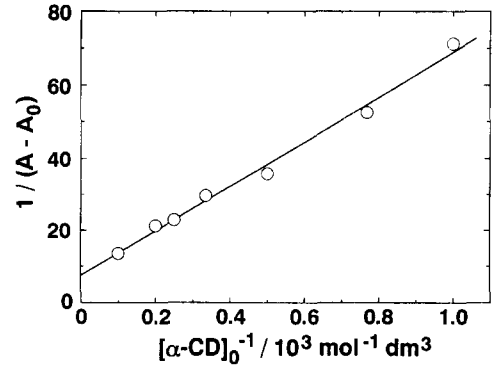

Fig. 4. Double-reciprocal plot for the system of α-CD-4-cyanophenol (5.0×10^{-5} mol^{-1} dm^3) in pH 3.05 solutions. λ_{obs} = 262.5 nm.

absorption peak at 246 nm is shifted to longer wavelengths, with a slight decrease in the peak absorbance. Furthermore, two isosbestic points are observed at 220 and 250 nm, suggesting the formation of a 1:1 α-CD-4-cyanophenol inclusion complex. Since at pH of 3.05 4-cyanophenol is in the neutral form, the absorption spectral changes in Fig. 3 indicate an equilibrium between neutral 4-cyanophenol and its 1:1 inclusion complex with α-CD:

$$\alpha\text{-CD} + 4\text{CP} \overset{K_1}{\rightleftharpoons} \alpha\text{-CD}\cdot 4\text{CP} \quad (1)$$

$$K_1 = \frac{[\alpha\text{-CD}\cdot 4\text{CP}]}{[\alpha\text{-CD}][4\text{CP}]} \quad (2)$$

where 4CP and α-CD · 4CP stand for neutral 4-cyanophenol and its 1:1 inclusion complex with α-CD, respectively, and K_1 is the equilibrium constant for the formation of the 1:1 inclusion complex. According to a Benesi–Hildebrand type relationship, the K_1 value can be evaluated from the absorbance changes by the addition of α-CD [16]:

$$1/(A - A_0) = 1/a + 1/(aK_1[\alpha\text{-CD}]_0) \quad (3)$$

where A, A_0, a, and $[\alpha\text{-CD}]_0$ are the absorbance in the presence of α-CD, that in the absence of α-CD, a constant including molar absorption coefficients at an observed wavelength, and the initial concentration of α-CD, respectively. Fig. 4 shows the Benesi–Hildebrand type plot (double-reciprocal plot) for the α-CD-4-cyanophenol system in aqueous solutions buffered at pH 3.05. This plot yields a good straight line, indicating that the stoichiometry is really 1:1 for the α-CD–4-cyanophenol inclusion complex. From the plot, a K_1 value of 120 ± 20 mol^{-1} dm^3 is obtained. This K_1 value is similar to that (97 mol dm^{-3}) obtained from a flow microcalorimetry [17].

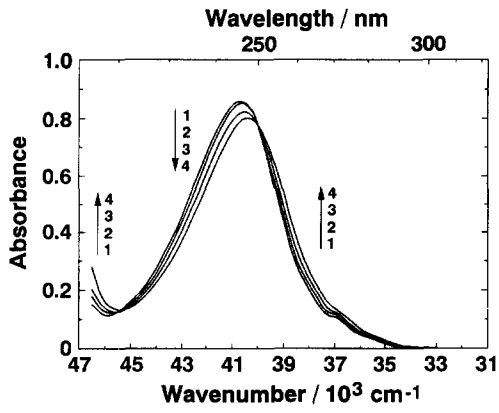

Fig. 3. Absorption spectra of 4-cyanophenol (5.0×10^{-5} mol^{-1} dm^3) in aqueous solutions (pH 3.05) containing varying concentrations of α-CD. Concentration of α-CD: (1) 0, (2) 1.0×10^{-3}, (3) 3.0×10^{-3}, and (4) 1.0×10^{-2} mol^{-1} dm^3.

The pK_a value of α-CD is 12.1–12.3 [18–20]. To investigate the interactions between 4-cyanophenol anion and neutral α-CD, therefore, we have selected aqueous solutions buffered at pH 10.28, at which 4-cyanophenol and α-CD are exclusively present as an anionic and a neutral species, respectively. When α-CD was added to the pH 10.28 solutions of 4-cyanophenol, the absorption maximum at 274 nm was shifted to longer wavelengths accompanied by isosbestic points at 231 and 281 nm (not shown), indicating the formation of a 1:1 α-CD–4-cyanophenolate anion inclusion complex:

$$\alpha\text{-CD} + 4\text{CP}^- \overset{K_2}{\rightleftharpoons} \alpha\text{-CD}\cdot 4\text{CP}^- \quad (4)$$

$$K_2 = \frac{[\alpha\text{-CD}\cdot 4\text{CP}^-]}{[\alpha\text{-CD}][4\text{CP}^-]} \quad (5)$$

where $4CP^-$ and α-CD · $4CP^-$ represent the 4-cyanophenolate anion and the 1:1 α-CD–4-cyanophenolate anion inclusion complex, respectively, and K_2 is the equilibrium constant for the formation of the 1:1 inclusion complex. A double-reciprocal plot based on Eq. (3) gave 580 ± 50 mol^{-1} dm^3 as a K_2 value for 4-cyanophenol. Like the K_1 value, the K_2 value of 4-cyanophenol is similar to a literature value (630 mol^{-1} dm^3) [17]. The finding that the K_2 value is 4.8-fold greater than the K_1 value definitely indicates that 4-cyanophenolate much favorably binds to the α-CD cavity compared to neutral 4-cyanophenol.

The acid dissociation constant, K_a, of free 4-cyanophenol is expressed by

$$K_a = \frac{[4CP^-][H_3O^+]}{[4CP][H_2O]}. \quad (6)$$

Similarly, the acid dissociation constant, K'_a, of 4-cyanophenol complexed with α-CD is given as

$$K'_a = \frac{[\alpha\text{-CD} \cdot 4CP^-][H_3O^+]}{[\alpha\text{-CD} \cdot 4CP][H_2O]}. \quad (7)$$

Combining Eqs. (2), (5)–(7) we can derive the following equation:

$$K'_a = \frac{K_2}{K_1} K_a. \quad (8)$$

Taking the logarithm of Eq. (8), it is transformed to

$$pK'_a = pK_a + \log\frac{K_1}{K_2}. \quad (9)$$

According to Eq. (9), therefore, a pK'_a value for 4-cyanophenol is estimated to be 7.06 from the values of pK_a (7.74), K_1 (120 ± 20 mol^{-1} dm^3), and K_2 (580 ± 50 mol^{-1} dm^3) obtained in this study. The smaller pK'_a value than the pK_a value implies that the acidity of 4-cyanophenol bound to the α-CD cavity is stronger than that of free, uncomplexed 4-cyanophenol.

The inclusion complex of α-CD with 3-cyanophenol.—Fig. 5 shows the pH dependence of the absorption spectrum of 3-cyanophenol (3.0×10^{-4} mol^{-1} dm^3) in aqueous solution. In aqueous solution of pH 3.05, the absorption maximum is located at 291.5 nm, while it is at 319 nm at pH 12.61. 3-Cyanophenol in acidic solutions exclusively exists as a neutral species. On the other hand, the anion of 3-cyanophenol is predominantly present in alkaline solutions of pHs greater than 12.61. At a pH of about 10, therefore, 3-cyanophenol is partly in the neutral form, although

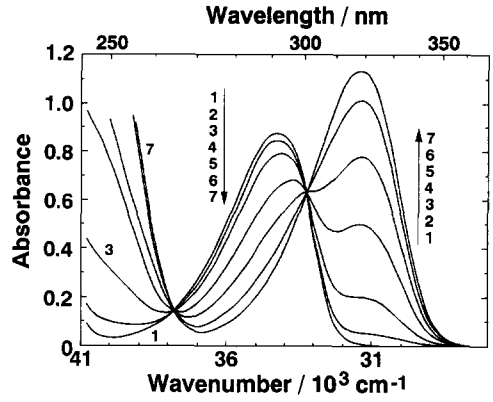

Fig. 5. pH dependence of the absorption spectrum of 3-cyanophenol (3.0×10^{-4} mol^{-1} dm^3) in aqueous solutions buffered at pH (1) 3.05, (2) 7.01, (3) 7.78, (4) 8.49, (5) 8.98, (6) 10.29, and (7) 12.61.

it mainly exists as the anion. From a titration curve for the absorbance observed at 320 nm (not shown), a pK_a value of 3-cyanophenol has been evaluated to be 8.66, which is greater than that of 4-cyanophenol.

Addition of α-CD to aqueous 3-cyanophenol solution of pH 3.05 resulted in a red-shift of the absorption maximum accompanied by isosbestic points at 251 and 300 nm (not shown). In contrast to 4-cyanophenol, the absorbance at the maximum was slightly increased with an increase in the α-CD concentration. A K_1 value of 3-cyanophenol was evaluated to be 110 ± 30 mol^{-1} dm^3 from a double-reciprocal plot based on Eq. (3).

Fig. 6 illustrates absorption spectra of 3-cyanophenol (2.78×10^{-4} mol^{-1} dm^3) in aqueous solutions (pH 8.98) containing varying concentrations of α-CD. As stated previously, in the pH region at

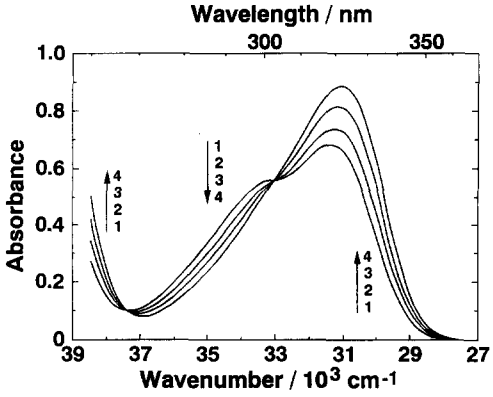

Fig. 6. Absorption spectra of 3-cyanophenol (2.78×10^{-4} mol^{-1} dm^3) in aqueous solutions (pH 8.98) containing varying concentrations of α-CD. Concentration of α-CD: (1) 0, (2) 1.0×10^{-3}, (3) 3.0×10^{-3}, and (4) 1.0×10^{-2} mol^{-1} dm^3.

which α-CD exclusively exists as a neutral species, both anionic and neutral species of 3-cyanophenol are present. Consequently, we cannot employ a double-reciprocal plot based on Eq. (3) in the determination of a reliable K_2 value of 3-cyanophenol.

Therefore, we have used the following procedure. At a wavelength where only 3-cyanophenolate ($3CP^-$) and its inclusion complex absorb light, the absorbance is expressed by

$$A = \varepsilon_0^a[3CP^-]d + \varepsilon_1^a[\alpha\text{-CD} \cdot 3CP^-]d \quad (10)$$

where ε_0^a, ε_1^a, and d are the molar absorption coefficient of the free anion, that of the α-CD–3-cyanophenolate inclusion complex, and the path length (1 cm) of a quartz cell, respectively. Using a relationship analogous to Eq. (5), Eq. (10) becomes

$$A = (\varepsilon_0^a + \varepsilon_1^a K_2[\alpha\text{-CD}])[3CP^-] \quad (11)$$

The initial concentration of 3-cyanophenol, $[3CP]_0$, is represented by

$$[3CP]_0 = [3CP] + [\alpha\text{-CD} \cdot 3CP] + [3CP^-] + [\alpha\text{-CD} \cdot 3CP^-]. \quad (12)$$

Substitution of $[\alpha\text{-CD} \cdot 3CP]$ and $[\alpha\text{-CD} \cdot 3CP^-]$ by terms including K_1 and K_2, respectively, gives

$$[3CP]_0 = (1 + K_1[\alpha\text{-CD}])[3CP] + (1 + K_2[\alpha\text{-CD}]) \times [3CP^-] \quad (13)$$

The concentration ratio, x, of [3CP] to $[3CP^-]$ remains constant irrespective of the presence of α-CD since a pH value of buffer is unchanged even if α-CD is added:

$$x = \frac{[3CP]_i}{[3CP^-]_i} = \frac{[3CP]}{[3CP^-]} \quad (14)$$

where $[3CP]_i$ and $[3CP^-]_i$ stand for the concentrations of neutral and anionic species in the absence of α-CD, respectively. Since, under our experimental conditions, the concentrations of the inclusion complexes of 3CP and $3CP^-$ are negligible relative to the initial α-CD concentration, the concentration of free α-CD, [α-CD], is approximated to $[\alpha\text{-CD}]_0$. Using Eqs. (13) and (14), therefore, Eq. (11) is transformed to

$$A = \frac{(\varepsilon_0^a + \varepsilon_1^a K_2[\alpha\text{-CD}]_0)[3CP]_0}{(1 + K_1[\alpha\text{-CD}]_0)x + (1 + K_2[\alpha\text{-CD}]_0)} \quad (15)$$

As a consequence, we can simulate the observed absorbance as a function of the initial concentration of α-CD by employing ε_1^a and K_2 as parameters.

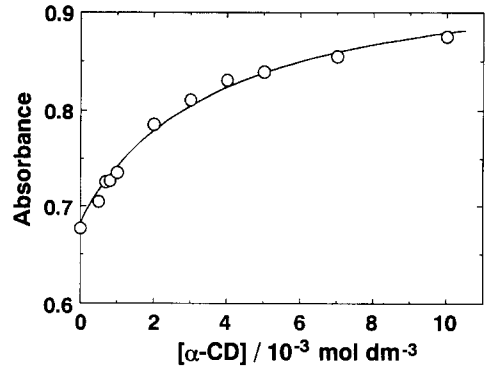

Fig. 7. The best-fit curve simulated for the absorbances (320 nm) of 3-cyanophenol (2.78×10^{-4} mol dm^{-3}) in pH 8.98 solutions containing varying concentrations of α-CD. The simulation curve was calculated with known values of $K_1 = 110$ mol^{-1} dm^3 and $\varepsilon_0^a = 3730$ dm^3 mol^{-1} cm^{-1} and with parameters $K_2 = 360$ mol^{-1} dm^3 and $\varepsilon_1^a = 3960$ dm^3 mol^{-1} cm^{-1}.

Fig. 7 depicts the best fit curve for the observed absorbances at 320 nm, which has been calculated with $\varepsilon_0^a = 3730$ mol^{-1} dm^3 cm^{-1} and $x = 0.483$. From the simulation, 360 mol^{-1} dm^3 and 3960 mol^{-1} dm^3 cm^{-1} are obtained as the K_2 and ϵ_1^a values, respectively. The K_2 value for 3-cyanophenol is more than three times greater than its K_1 value, indicating that 3-cyanophenolate is much favorably incorporated into the α-CD cavity compared to neutral 3-cyanophenol. This inclusion behavior of 3-cyanophenol is similar to that of 4-cyanophenol. According to Eq. (9), a pK_a' value is estimated to be 8.15. Consequently, the acidity of 3-cyanophenol bound to the α-CD cavity is stronger than that of free 3-cyanophenol.

Inclusion complexes of α-CD with 3-nitrophenol, 4-nitrophenol, 4-bromophenol, and 4-methoxyphenol. —When α-CD was added to acidic aqueous solutions of these phenols, absorption maxima of the phenols were shifted to longer wavelengths. With an increase in the α-CD concentration, the absorbances at the maxima were decreased for 3- and 4-nitrophenols whereas those for 4-bromophenol and 4-methoxyphenol were increased. 3-Nitrophenol, 4-nitrophenol, and 4-bromophenol, as well as 3- and 4-cyanophenols, have an electron-withdrawing substituent, whereas 4-methoxyphenol has an electron-donating substituent. For 4-nitrophenol, a pK_a value has been evaluated to be 7.10 from a titration curve concerning the absorbance (not shown). This pK_a value is the smallest of the phenols examined in this study, indicating that a nitro group is the strongest electron-withdrawing group. Using the double-re-

ciprocal plot, values of K_1 (pH 3.70 buffer) and K_2 (pH 10.28 buffer) for 4-nitrophenol have been determined to be 170 ± 20 and 1910 ± 80 mol^{-1} dm^3, respectively. The K_2 value is an order of magnitude greater than the K_1 value. On the basis of Eq. (9), a pK'_a value has been calculated to be 6.05, which is considerably less than the observed pK_a value. These findings imply that 4-nitrophenolate is much favorably bound to the α-CD cavity compared to neutral 4-nitrophenol and that the acidity of 4-nitrophenol buried within the α-CD cavity is significantly greater than that of uncomplexed one. Similar K_1 (160 and 220 ± 20 mol^{-1} dm^3) and K_2 (1590 and 1800 ± 300 mol^{-1} dm^3) values have been reported for 4-nitrophenol [17,21].

Employing the double reciprocal plot, values of K_1 (pH 3.05 buffer) and K_2 (pH 10.3 buffer) for 3-nitrophenol were evaluated to be 140 ± 60 and 300 ± 40 mol^{-1} dm^3, respectively. Reported K_1 (124 ± 5 mol^{-1} dm^3) and K_2 (202 ± 3 mol^{-1} dm^3) values are analogous to our values [21]. The smaller K values of 3-nitrophenol than those of its 4-nitro isomer seem to be due to the steric hindrance in the complexation processes. Since a pK_a value of 3-nitrophenol has been reported to be 8.09 [22], a pK'_a value of 7.76 has been estimated using the K_1 and K_2 values determined. As in the cases of 3- and 4-cyanophenols and 4-nitrophenol, the acidity of 3-nitrophenol bound to the α-CD cavity is greater than that of uncomplexed one.

In the case of 4-bromophenol, a pK_a value of 9.28 was evaluated from a titration curve for the absorbance (not shown). A K_1 value was determined to be 250 ± 30 mol^{-1} dm^3 according to Eq. (3). Because of the relatively large pK_a value, the experimental conditions that 4-bromophenol exists as an anion but α-CD exists as a neutral species cannot be met in the entire pH range. Consequently, we could not estimate a K_2 value from a usual procedure using the double-reciprocal plot. Thus, a simulation method, which was utilized in determining the K_2 value of 3-cyanophenol, was applied to the evaluation of the K_2 value for 4-bromophenol in pH 9.69 buffers. The K_2 value has been evaluated to be 953 mol^{-1} dm^3, which is about 3.8-fold greater than the K_1 value of 4-bromophenol, indicating that the incorporation of its anion into the α-CD cavity is favored to a great degree relative to its neutral species. Consequently, a pK'_a value (8.70) of 4-bromophenol is less than the pK_a value, indicating the stronger acidity of 4-bromophenol bound to the α-CD cavity compared to the uncomplexed one.

Among the phenol derivatives examined in the present study, only 4-methoxyphenol has an electron-donating substituent. For 4-methoxyphenol, a pK_a value of 10.72 has been evaluated from a titration method similar to that applied for the other phenols (not shown). This pK_a value is the largest of the phenols examined, indicative of the weakest acidity. The largest pK_a value is due to the electron-donating nature of the methoxyl group. A K_1 value of 33 ± 10 mol^{-1} dm^3 has been estimated from the double reciprocal plot for pH 3.99 solutions of 4-methoxyphenol. This K_1 value is significantly less than those of the other phenols. The significantly small K_1 value may imply that a methoxyl group is more hydrophillic than cyano, nitro, and bromo groups and that the hydrophobic interaction is weak between α-CD and the guest carrying a methoxyl group. As in the cases of 3-cyanophenol and 4-bromophenol, a reliable K_2 value could not be estimated employing the double-reciprocal plot, since α-CD is partly deprotonated under the conditions that 4-methoxyphenolate is exclusively present. Using a simulation method similar to that applied for 3-cyanophenol and 4-bromophenol, we evaluated the K_2 value for 4-methoxyphenol to be 31 mol^{-1} dm^3 at pH 10.58, which is identical to its K_1 value within experimental error. Therefore, the acidity of 4-methoxyphenol is not affected by the complexation with α-CD.

Effects of α-CD on the pK_a values of the phenol derivatives.—Table 1 summarizes the values of K_1, K_2, pK_a, and pK'_a for 3-cyanophenol, 4-cyanophenol, 3-nitrophenol, 4-nitrophenol, 4-bromophenol, and 4-methoxyphenol, along with available literature data. With respect to α-CD, the K_2 values are significantly greater than the K_1 values, except for 4-methoxyphenol. As noted previously, this finding means that the acidity of the guest complexed with α-CD is considerably higher than that of the corresponding free one. Reported values of K_1 and K_2 are similar to our values obtained in the present study.

Because a cyano group is hydrophobic unlike a hydroxyl group, a cyano group in 4-cyanophenol is bound to the hydrophobic α-CD cavity [23]. Similarly, neutral and anionic 4-nitrophenol penetrate the α-CD cavity a nitro group first from the side of the secondary hydroxyl groups (wider rim), with a hydroxyl group and a deprotonated hydroxyl group pointing out into the bulk solution, respectively [24–26]. It has been revealed that α-CDs accommodating water and 4-nitrophenol have dipole moments of 9.4

Table 1
pK_a values of the phenol derivatives, their K_1 and K_2 values, and pK'_a values of the phenol derivatives complexed with α- and β-CDs

	α-CD				β-CD		
	pK_a	K_1 (mol^{-1} dm^3)	K_2 (mol^{-1} dm^3)	pK'_a	K_1 (mol^{-1} dm^3)	K_2 (mol^{-1} dm^3)	pK'_a
3-Cyanophenol	8.66	110 ± 30	360	8.15	36 ± 20	491	7.53
4-Cyanophenol	7.74	120 ± 20	580 ± 50	7.06	330 ± 30	230 ± 30	7.90
		97[a]	630[a]				
2-Nitrophenol	7.05[b]	–[c]	–	–	145 ± 10[d]	100 ± 5[d]	7.21
3-Nitrophenol	8.09[b]	140 ± 60	300 ± 40	7.76	130 ± 10[d]	75 ± 10[d]	8.46
		124 ± 5[e]	202 ± 3[e]		274 ± 27[e]	117 ± 19[e]	
4-Nitrophenol	7.10	170 ± 20	1910 ± 80	6.05	220 ± 50	320 ± 60	6.94
	6.90[b]	160[a]	1590[a]		130 ± 15[d]	410 ± 40[d]	
		220 ± 20[e]	1800 ± 300[e]		350 ± 50[e]	570 ± 25[e]	
4-Bromophenol	9.28	250 ± 30	953	8.70	310 ± 10	1090	8.73
4-Methoxyphenol	10.72	33 ± 10	31	10.75	80 ± 40	22	11.28
Phenol	9.82[b]	–[c]	–	–	129 ± 5[d]	15 ± 1[d]	10.75

[a]Ref. [17].
[b]Ref. [22].
[c]The absorbance changes were too small to evaluate a K_1 value.
[d]Ref. [37].
[e]Ref. [21].

and 13.5 D, respectively [27,28]. The dipole moments of the α-CDs are directed from the side of the primary hydroxyl groups (narrower rim) towards the side of the secondary hydroxyl groups. Consequently, it is reasonable that neutral 4-nitrophenol is incorporated into the α-CD cavity with the nitro group pointing inward, first, since the antiparallel orientation of the dipole moments of the host and guest is energetically most stabilized. In addition, the hydrophobic interaction between the host and guest contributes to the stabilization of the CD inclusion complex.

The dipole moment of α-CD causes an induced dipole in 4-nitrophenol bound to the α-CD cavity, whose direction is identical to that of the intrinsic dipole moment of neutral 4-nitrophenol, whereas an induced dipole in 4-nitrophenolate is reversed relative to the direction of the net, intrinsic dipole moment of the guest hydroxyl oxanion. This induced dipole moment increases and decreases the apparent dipole moments of the bound neutral and anionic species, respectively. Consequently, the inclusion by α-CD would exert the 'electron-polarizing' effect on the incorporated guest molecule. The 'electron-polarizing' effect of α-CD on the guest most likely reduces the electron densities around the protons on the benzene ring of the guest. Upon the addition of α-CD to deuterium oxide solutions of neutral and anionic 4-nitrophenol, proton signals in ^1H NMR spectra of the guests are shifted to lower fields relative to those of the free guests, indicating the deshielding effect of α-CD [29–32]. The deshielding effect seems to be interpreted in terms of the 'electron-polarizing' effect of α-CD. The deshielding effect of α-CD has been observed for other organic compounds as well as phenols [33–35]. Since the deshielding effect of α-CD has been observed for 4-nitrophenolate, it is unlikely that the negative charge on a deprotonated hydroxyl group flows towards a benzene ring upon the inclusion. This suggests that the dipole–dipole stabilization occurs between α-CD and the nitrobenzene moiety of 4-nitrophenolate, although the interaction may be weaker than that for the neutral species.

Enthalpy changes, ΔH, for the inclusion of neutral and anionic 4-nitrophenols by α-CD are -25.8 ± 0.4 and -40.9 ± 0.9 kJ mol^{-1}, respectively, and the corresponding entropy changes, ΔS, are -42 ± 2 and -75 ± 3 J K^{-1} mol^{-1}, respectively [21]. The negatively greater ΔH value of 4-nitrophenolate causes the greater K_2 value than the K_1 value, despite the unfavorably large ΔS value in negative sign compared to neutral 4-nitrophenol. Since the ΔS value for anionic 4-nitrophenol is negatively greater than that for neutral 4-nitrophenol, the inclusion complex of 4-nitrophenolate has a more rigid structure compared to that of neutral 4-nitrophenol. This may imply the strong solvation around a hydroxyl oxanion or its hydrogen bonding with water molecules.

Within the α-CD cavity, 3-nitrophenol adopts the same molecular orientation as those of 4-nitrophenol

and 4-cyanophenol; the penetration of a nitro group first from the wider rim of the cavity [36]. In the inclusion complexes with α-CD, the molecular dispositions of the other phenols examined are most likely similar to that of 4-nitrophenol. For all the phenols except for 4-methoxyphenol, therefore, energetic situations analogous to that for 4-nitrophenol are expected. As a consequence, the phenols bound to the α-CD cavity are stronger acids than the free phenols.

In contrast to the other neutral phenols, the dipole moment of 4-methoxyphenol is reversely directed from a methoxyl group to a hydroxyl group. Consequently, the dipole–dipole interactions between α-CD and 4-methoxyphenol rather destabilize the inclusion complexation and facilitate the dissociation to a free host and a free guest. For 4-methoxyphenolate, the 'electron-polarizing' effect of α-CD is not effective because of the presence of an electron-donating methoxyl substituent. Consequently, the energy lowering by the water hydration is canceled by the large destabilization caused by the parallel dipole moments, of the host and guest, with the same directions, leading to nearly the same K_2 value as the K_1 value.

Inclusion complexation of β-CD with the phenol derivatives.—We also investigated the inclusional complexation of β-CD with 3-cyanophenol, 4-cyanophenol, 4-nitrophenol, 4-bromophenol, and 4-methoxyphenol. For these phenols, absorption spectral changes by the addition of β-CD were similar to those by the addition of α-CD. The K_1 values of the phenols were evaluated on the basis of double-reciprocal plots regarding the absorbance. The K_2 values for 4-cyanophenol and 4-nitrophenol were similarly estimated from the double-reciprocal plots. For 3-cyanophenol, 4-bromophenol, and 4-methoxyphenol, the K_2 values were evaluated using the simulation method applied to the estimation of the K_2 values for α-CD. These K_1 and K_2 values are summarized in Table 1, together with literature values for phenol and 2-, 3-, and 4-nitrophenols [21,37].

In the cases of 3-cyanophenol, 4-nitrophenol, and 4-bromophenol, the results that the K_2 value is greater than the K_1 value for β-CD are parallel to the relationship of those for α-CD. In contrast, for 4-cyanophenol, 2-nitrophenol [37], 3-nitrophenol [21,37], 4-methoxyphenol, and phenol [37], the K_2 value is less than the K_1 value, indicating that the guest bound to the β-CD cavity is a weaker acid than an uncomplexed one. In the β-CD inclusion complexes, the dimensions of a phenol derivative molecule do not snugly fit the cavity size in contrast to the α-CD cavity, resulting in a loose contact between the β-CD cavity wall and the guest compared to α-CD. Consequently, the induced dipole moment and the relevant 'electron-polarizing' effect caused by β-CD are smaller than those of α-CD. Because of these weaker effects, the β-CD-phenolate inclusion complex is destabilized compared to the α-CD–phenolate inclusion complex. Consequently, the K_1 value is conversely greater than the K_2 value in contrast to α-CD, as seen for 4-cyanophenol, 2-nitrophenol [37], 3-nitrophenol [21,37], 4-methoxyphenol, and phenol [37]. In the cases of 3-cyanophenol, 4-nitrophenol, and 4-bromophenol, however, other effects such as hydrogen bonding between β-CD and the bound guest may remarkably contribute to the stabilization of the anionic inclusion complexes, leading to the greater K_2 value compared to the K_1 value. In contrast to α-CD, chemical shift differences between bound and free guests are not always positive in sign for the guest protons of β-CD inclusion complexes. In one case, the chemical shift differences of the guest protons are positive in sign and in other cases are negative [38–40]. These facts suggest the weak 'electron-polarizing' effect of β-CD compared to α-CD, supporting our interpretation for the difference in the magnitudes of K_1 and K_2 between α-CD and β-CD.

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