  Bull. Chem. Soc. Jpn., 55, 1039—1045 (1982)

Proton-transfer Reactions of 5-(*m*- and *p*-Nitrophenylazo)salicylic Acids Coupled with Inclusion Reactions with α- and β-Cyclodextrins†

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(Received August 7, 1981)

The title azo compounds, 5-(*m*- and *p*-nitrophenylazo)salicylic acids (*m*- and *p*-NPAS), were found kinetically to be included into a cavity of α- or β-cyclodextrin. The rate constants for the inclusion reactions were found to be in the order of magnitude 10^7 and 10^6 mol^{-1} dm^3 s^{-1} for α-cyclodextrin and β-cyclodextrin systems, respectively. The ^1H and ^{13}C NMR data showed that the hydrophobic nitrobenzene ring moiety of *m*- and *p*-NPAS is situated in the α- and the β-cyclodextrin cavity. The proton-transfer reactions of *m*- and *p*-NPAS were accelerated in the presence of α- and β-cyclodextrins. This indicates the possibility that the inclusion force of cyclodextrins contributes to weakening the intramolecular hydrogen bond of *m*- and *p*-NPAS.

Torus-shaped α- and β-cyclodextrins (α- and β-CD), cyclic α-1, 4-linked D-glucose polymers, have 6 and 7 glucose residues per molecule, respectively, and form a number of stereosclective inclusion complexes with azo and triphenylmethane compounds.[1] The driving force for inclusion has been attributed to hydrogen bonding,[2] van der Waals forces,[3,4] hydrophobic interactions,[5] the relaxation of the conformational strain in the cyclodextrin,[6] and the release of non-hydrogen-bonding water molecules with high energy in the cyclodextrin cavity.[4] Recently, a theoretical approach to the aspect of driving force of inclusion by α-cyclodextrin was carried out.[7]

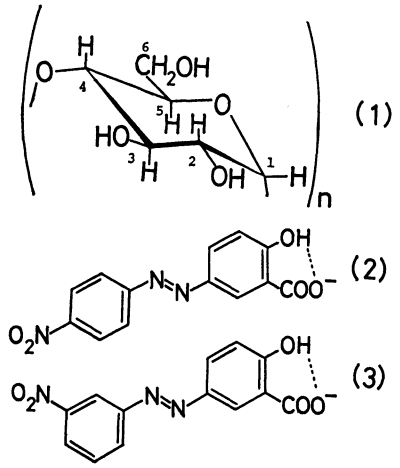


Fig. 1. Structural formulae of α-cyclodextrin ($n=6$; (1)), β-cyclodextrin ($n=7$; (1)); 5-(*p*-nitrophenylazo)salicylate anion (2) and 5-(*m*-nitrophenylazo)salicylate anion (3), HA^-.

5-(*m*- and *p*-Nitrophenylazo)salicylic acids (Fig. 1) were found to form 1 : 1 inclusion compounds with β-CD[8] and α-CD[9] from spectrophotometric and temperature-jump measurements. The ^1H and ^{13}C NMR studies showed that the nitrobenzene ring as hydrophobic portion of *m*- and *p*-NPAS is situated inside the hydrophobic β-CD cavity.[10]

† Presented in part at the 29th Annual Meeting on Coordination Chemistry, Hamamatsu, October 1, 1979, Abstract, p. 300 and 30th Annual Meeting on Coordination Chemistry, Tokyo, October 7, 1980, Abstract, p. 430.

In general the acid dissociation of azo pH indicators is facilitated or retarded by the formation of inclusion compounds with α- and β-CD.[1,8,9,11,13] The enhancement or retardation in acid dissociation has been attributed to Raumalkalität (space alkalinity) in cyclodextrin cavity,[14] topochemische Basizität (topochemical basicity) in cyclodextrin cavity,[15] dipole–ion interaction between dye molecule as nucleophile and cyclodextrin molecule as electrophile,[16] and hydrophobic microenvironment effect of cyclodextrin cavity.[13] On the other hand, it was pointed out qualitatively that the rate constants for the recombination of *m*- and *p*-NPAS with hydroxide ion increase with increasing concentrations of cyclodextrin, irrespective of enhancement or retardation in acid dissociation, namely, the intramolecular hydrogen bond of *m*- and *p*-NPAS is weakened by the formation of inclusion compounds with cyclodextrin molecules.[8,9]

The present paper deals with the detailed quantitative kinetic results on the proton-transfer reactions of *m*- and *p*-NPAS coupled with inclusion reactions with α- and β-cyclodextrins in aqueous solutions.

Experimental

Materials. Water was deionized and distilled. The azo compounds, *m*- and *p*-NPAS, were synthesized by the usual azo coupling method and purified by cellulose column chromatography (Whatman CC 31, 1-butanol : 2 mol dm^{-3} aqueous NH_3 : ethanol=60 : 20 : 20, v/v/v). The monosodium salts of NPAS were acidified with HCl and washed thoroughly with water. The free acids thus obtained were recrystallized from ethanol–water. Found: C, 54.32; H, 3.18; N, 14.41% for *m*-NPAS and C, 54.46; H, 3.23; N, 14.74% for *p*-NPAS. Calcd for $C_{13}H_9N_3O_5$: C, 54.36; H, 3.16; N, 14.63%. Cyclodextrins, α- and β-CD (Tokyo Kasei), were purified by the method of Cramer and Henglein using *p*-cymene, cyclohexane, and fluorobenzene.[17]

A Hitachi-Horiba pH-meter F7-ss was used for the determination of pH values. Acid-dissociation constants were determined spectrophotometrically with a Hitachi recording spectrophotometer Model EPS-3T. The absorption spectra of acid and base forms of *m*- and *p*-NPAS at varying CD concentrations showed isosbestic points at constant pH and ionic strength ($I=0.1$ mol dm^{-3} (KNO_3) at 25 °C). The wavelength of the absorption maximum (λ_{max}) of the absorption spectrum of a solution of NPAS–CD system was dependent on the concentration of CD except for A^{2-} of *m*-NPAS, showing a red shift.[9] Kinetic measurements were carried out with a

Union Giken co-axial-cable temperature-jump apparatus Model RA-105. The reactions were followed on the screen of an oscilloscope Tektronix Type 545 B at a wavelength in the range 350—500 nm.

Deuterium oxide (99.9%) and 40% sodium hydroxide-*d* solution were purchased from E. Merck, Ltd. The NMR spectra of degassed samples (13 mg cm^{-3} *m*-NPAS, 13—180 mg cm^{-3} CD for ^{1}H NMR and 50 mg cm^{-3} *m*-NPAS, 180 mg cm^{-3} CD for ^{13}C NMR in 0.9 mol dm^{-3} NaOD) were obtained in 5 mm spinning tube at 25±2 °C. The 100 MHz ^{1}H NMR spectra were taken on a JEOL JNM-FX 100 PFT NMR spectrometer with sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an external reference. The ^{13}C NMR spectra were measured by the PFT NMR spectrometer operating at 25.1 MHz using a deuterium lock. The chemical shifts (measured accuracy approx. ±0.05 ppm) were referred to internal dioxane ($\delta_{TMS} = 67.4 + \delta_{dioxane}$).[18] The assignments of ^{13}C NMR spectra of *m*- and *p*-NPAS were based on proton decoupling, the substituent effects, the additivity rule, and the proton off-resonance irradiation. The theoretical values of chemical shift of *m*- and *p*-NPAS were obtained by the equation δ(substituted benzene)=δ(benzene)+$\sum\Delta\delta$, where $\sum\Delta\delta$ is the sum of the substituent chemical shift.[18] The value of $\Delta\delta$ for azo group of *m*- and *p*-NPAS can be assumed to be approximately equal to that for Ph–N=N– group of azobenzene.[19]

Results and Discussion

Equilibria of the Inclusion Reactions. The formation of 1 : 1 inclusion compounds of *m*- and *p*-NPAS with cyclodextrins in aqueous solutions is confirmed by the presence of isosbestic points in the spectral change. Figure 2 shows the spectral change of *p*-NPAS on addition of α-CD. The equilibria for inclusion reaction in neutral region are expressed as

$$HA^- + \alpha\text{-CD} \underset{K}{\rightleftharpoons} HA\text{-}\alpha CD^-, \quad (1)$$

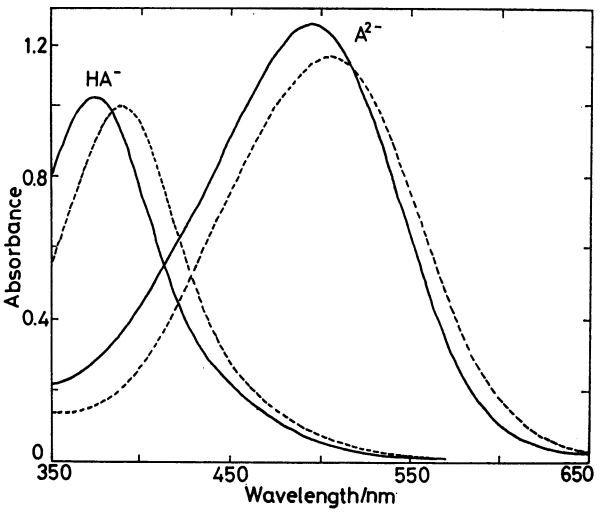


Fig. 2. Absorption spectra of HA^- and A^{2-} forms of *p*-NPAS (full lines) and their inclusion complexes (broken lines).
HA^-: $C_{HA^-}=4.32\times10^{-5}$ mol dm^{-3} and $C_{\alpha\text{-CD}}=(0—6.86)\times10^{-3}$ mol dm^{-3} at pH 7.34. A^{2-}: $C_A=4.32\times10^{-5}$ mol dm^{-3} and $C_{\alpha\text{-CD}}=(0—7.00)\times10^{-3}$ mol dm^{-3} at pH 11.80. At 25 °C and I=0.1 mol dm^{-3} (KNO_3).

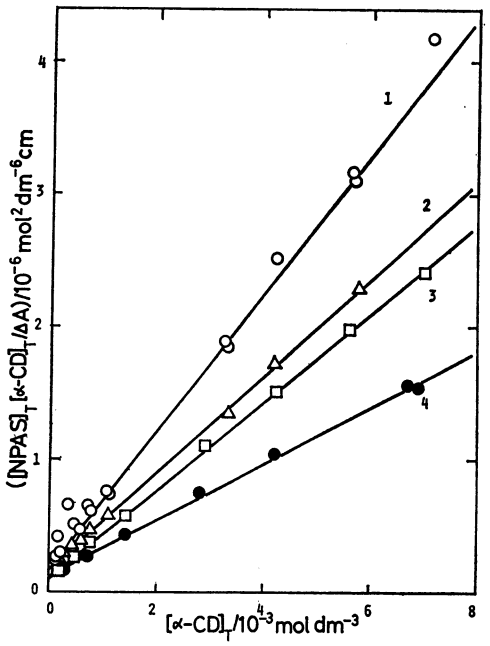


Fig. 3. Plots of $[NPAS]_T[\alpha\text{-CD}]_T/\Delta A$ against $[\alpha\text{-CD}]_T$. (1) A^{2-} of *m*-NPAS at 454 nm, (2) HA^- of *m*-NPAS at 370 nm, (3) A^{2-} of *p*-NPAS at 490 nm, (4) HA^- of *p*-NPAS at 400 nm.

and in alkaline region

$$A^{2-} + \alpha\text{-CD} \underset{K'}{\rightleftharpoons} A\text{-}\alpha CD^{2-} \quad (2)$$

where $K=[HA][\alpha\text{-CD}]/[HA\text{-}\alpha CD]$ and $K'=[A][\alpha\text{-CD}]/[A\text{-}\alpha CD]$, and charges are omitted. A plot of $[NPAS]_T[\alpha\text{-CD}]_T/\Delta A$ against $[\alpha\text{-CD}]_T$ gave a straight line (Fig. 3), where ΔA denotes the change in absorbance of a solution of NPAS-αCD system on addition of α-CD and [ ]$_T$ the total concentration.[8,9,13] The values of the dissociation constants of inclusion compounds, K and K', are determined from the slope and the intercept of Fig. 3.[8,9] The *m*- and *p*-NPAS inclusion complexes with α-CD are 2—7 times more stable compared to those with β-CD (Table 3).

^{1}H NMR and ^{13}C NMR Spectra of Inclusion Compounds. NMR spectroscopy is an effective technique to study the structure in solution of the inclusion complexes.[20] ^{1}H NMR spectra were obtained for A^{2-} form of *m*-NPAS (Fig. 4). No ^{1}H NMR data of HA^- form of *m*-NPAS are available owing to the poor solubility of HA^- form in D_2O. Figure 5 shows ^{1}H chemical shifts of A^{2-} form of *m*-NPAS on addition of β-CD. By the inclusion into β-CD cavity, most of nitrobenzene ring

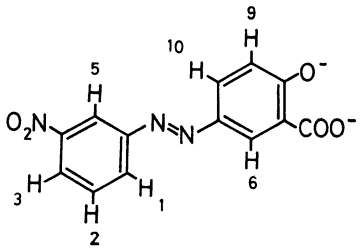


Fig. 4. Structure of the *m*-NPAS bivalent anion (A^{2-}) with the numbering for the protons in nitrobenzene and salicylic acid moieties.

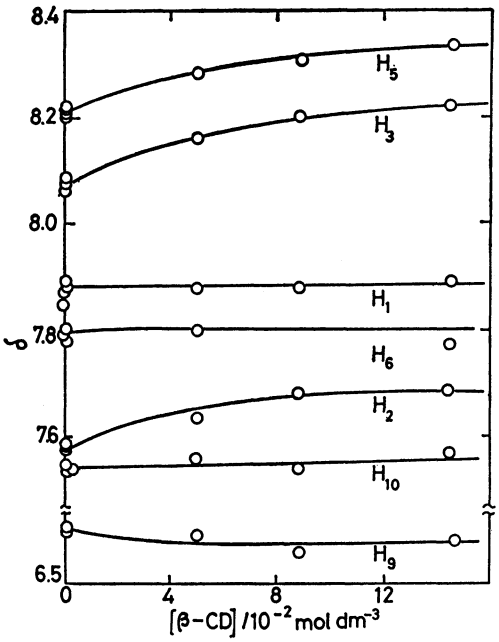


Fig. 5. Chemical shift as a function of β-CD concentration for solutions of the *m*-NPAS–βCD system.

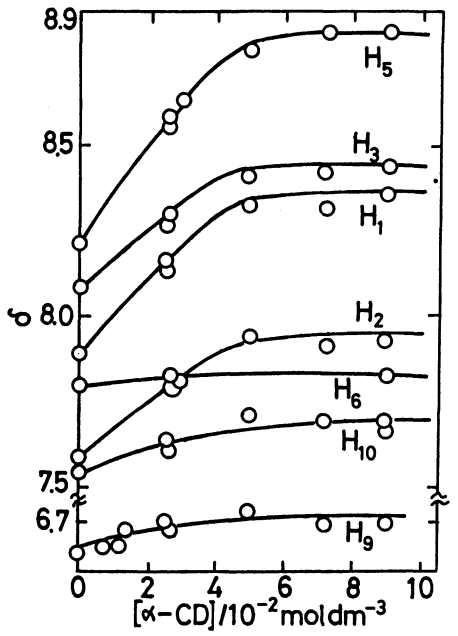


Fig. 6. Chemical shift as a function of α-CD concentration for solutions of the *m*-NPAS–αCD system.

moiety protons showed a downfield shift, while the signals of the hydrophilic moiety protons (H_9, H_{10}, and H_6) changed a little or showed an upfield shift, indicating that the hydrophobic moiety (nitrobenzene ring) of *m*-NPAS is preferentially included into β-CD cavity. Figure 6 shows ^1H chemical shifts of A^{2-} form of *m*-NPAS on addition of α-CD.[21] Figure 7 shows ^{13}C spectra of A^{2-} form of *m*-NPAS. The chemical shifts of carbon atoms are shown in Table 1. Nitrobenzene ring moiety carbons show a downfield shift except for C_5, while the hydrophilic moiety carbons an upfield shift. This fact indicates that the nitrobenzene ring moiety of *m*-NPAS preferentially enters the β-CD cavity.[22]

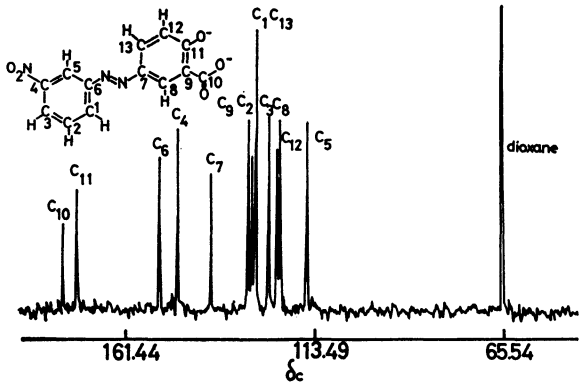
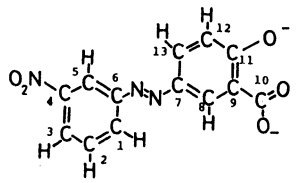


Fig. 7. Carbon-13 NMR spectrum for A^{2-} form of *m*-NPAS in D_2O.

Table 1. Carbon-13 chemical shift (ppm) of *m*-NPAS in the presence and absence of β-cyclodextrin in D_2O



	Without β-CD		With β-CD	
	δ_{calcd}	δ_{obsd}	δ'_{obsd}	$\delta'_{obsd}-\delta_{obsd}$
"Singlet carbon"				
C_{10}	177.96	178.00	177.88	−0.12
C_6	153.4	153.41	153.55	0.14
C_4	148.8	148.84	149.06	0.22
C_7	138.9	140.35	140.52	0.17
C_9	128.6	130.86	130.68	−0.18
C_{11}	171.3	174.33	174.25	−0.08
"Doublet carbon"				
C_5	117.4	115.90	115.80	−0.10
C_1	128.7	128.98	128.98	0.00
C_2	129.6	129.98	130.07	0.09
C_3	125.4	125.70	126.02	0.32
C_8	125.6	123.53	123.32	−0.21
C_{12}	120.6	122.89	122.85	−0.04
C_{13}	127.6	128.98	128.66	−0.32

In the case of smaller molecules such as *m*-nitroaniline as compared with *m*-NPAS, the α-CD ring is found by X-ray analysis to include the nitrophenyl group, while the amino group protrudes outside from the secondary hydroxyl group side of α-CD and is hydrogen-bonded to a primary hydroxyl group of α-CD molecules.[23] As for the inclusion compounds in solution of *p*-nitrophenol with α- and β-CD, the similar preferential inclusion of hydrophobic group (nitro group) was confirmed by ^1H and ^{13}C NMR methods.[24]

Acid-dissociation Equilibria in the Presence of Cyclodextrins. The acid-dissociation equilibria coupled with the inclusion equilibria can be expressed as follows,

$$\begin{array}{ccc} HA^- + \alpha\text{-CD} & \overset{K_a}{\rightleftharpoons} & A^{2-} + \alpha\text{-CD} + H^+ \\ \Big\downarrow\Big\uparrow K & & \Big\downarrow\Big\uparrow K' \\ HA\text{-}\alpha CD^- & \overset{K_a'}{\rightleftharpoons} & A\text{-}\alpha CD^{2-} + H^+, \end{array} \qquad (3)$$

where $K_a=[A][H]/[HA]$ and $K_a=[A\text{-}\alpha CD][H]/[HA\text{-}\alpha CD]$ are the acid-dissociation constants of HA^- and $HA\text{-}\alpha CD^-$, and $K=[HA][\alpha\text{-CD}]/[HA\text{-}\alpha CD]$ and $K'=[A][\alpha\text{-CD}]/[A\text{-}\alpha CD]$ the dissociation constants for inclusion compounds of HA^- and A^{2-} with α-CD, respectively. The apparent acid-dissociation constants, $\bar{K}_a$, was determined from the pH-dependence of the absorbance of NPAS solution at each α-CD concentration. At each α-CD concentration the isosbestic point was observed in the pH-dependent spectral change. The absorbance, A, for the system expressed by Scheme 3 is given by

$$A = \varepsilon'_{HA}[HA] + \varepsilon'_{A}[A], \quad (4)$$

where $\varepsilon'_{HA}=\varepsilon_{HA}+\varepsilon_{HA\text{-}\alpha CD}[\alpha\text{-CD}]/K$ and $\varepsilon'_{A}=\varepsilon_{A}+\varepsilon_{A\text{-}\alpha CD}[\alpha\text{-CD}]/K'$. The terms, ε_{HA}, ε_{A}, $\varepsilon_{HA\text{-}\alpha CD}$, and $\varepsilon_{A\text{-}\alpha CD}$, are the molar absorption coefficients for corresponding species. Since the sum of [HA] and [A] is a constant at each α-CD concentration, there must be isosbestic points in the pH-dependent spectral change at the wavelength where $\varepsilon'_{HA}=\varepsilon'_{A}$, even though four absorbing species exist.[25] The apparent acid-dissociation constant, $\bar{K}_a$, at each [α-CD] is expressed as follows,[8,11,12]

$$\bar{K}_a = K_a(1+[\alpha\text{-CD}]/K')/(1+[\alpha\text{-CD}]/K), \quad (5)$$

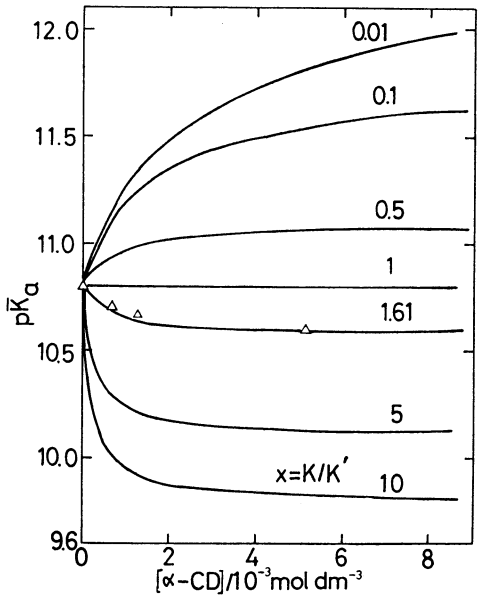


Fig. 8. The dependence of $p\bar{K}_a$ on α-CD concentrations in case of *m*-NPAS–αCD system. $K=4.95\times10^{-4}$ mol dm^{-3} and $\bar{K}_a=1.59\times10^{-11}$ mol dm^{-3}. At $I=0.1$ mol dm^{-3} (KNO_3) and 25 °C. Experimental points are indicated by triangles.

that is, the $\bar{K}_a$ value can be determined by the ratio $x=K/K'$. Figure 8 shows the theoretical curve for the dependence of $p\bar{K}_a$ on α-CD concentrations in case of *m*-NPAS–αCD system. The apparent acid-dissociation constants at each [α-CD] were determined in both *m*-NPAS–αCD and *p*-NPAS–αCD systems (Table 2). The value of $p\bar{K}_a$ decreases with increase in α-CD concentrations, namely, α-CD molecule exerts an enhancement effect on the acid dissociation of *m*- and *p*-NPAS. The quantity $\Delta pK_a=pK'_a-pK_a$ in *p*-NPAS–αCD system is more negative and larger than that in *m*-NPAS–αCD system. The change in $\bar{K}_a$ with increase of α-CD concentrations is larger as compared with the corresponding change for β-CD system.

Kinetics of the Inclusion Reactions. Kinetic study of inclusion reaction of azo compounds with α-CD was investigated for the first time by Cramer *et al.*[26] They indicated that the dissociation constant of inclusion complex (K and K') are almost in the same orders of magnitude, while the rate constants (k_+, k'_+, k_-, and k') varies considerably over the range of 1—8 orders of magnitude. Very recently Ise *et al.* determined the rate constants $\vec{k}$ and $\overleftarrow{k}$ of the inclusion reactions of phenolphthalein to be 1.45×10^5 mol^{-1} dm^3 s^{-1} and 1.30×10^3 s^{-1}, 3.66×10^7 mol^{-1} dm^3 s^{-1} and 1.18×10^3 s^{-1}, and 2.95×10^7 mol^{-1} dm^3 s^{-1} and 1.19×10^3 s^{-1} for α-CD, β-CD, and poly-βCD systems, respectively.[27] Eyring

$$HA^- + CD \underset{\overleftarrow{k}}{\overset{\vec{k}}{\rightleftharpoons}} H_2A\text{-}CD \quad (6)$$

et al. measured the rate constants of inclusion reactions of some inorganic anions with β-CD using ultrasonic relaxation technique.[28]

The kinetic data were obtained under pseudo-first-order conditions using a large excess of α-CD and β-CD. The rate of inclusion reaction was followed at λ_{max} of the inclusion species. The inclusion reaction of α-CD system in neutral region is

$$HA^- + \alpha\text{-CD} \underset{k_-}{\overset{k_+}{\rightleftharpoons}} HA\text{-}\alpha CD^-, \quad (7)$$

and in alkaline region,

$$A^{2-} + \alpha\text{-CD} \underset{k'_-}{\overset{k'_+}{\rightleftharpoons}} A\text{-}\alpha CD^{2-}. \quad (8)$$

The observed relaxation time, τ, for Reactions 7 and 8 can be expressed as

$$\tau^{-1} = k_+[\alpha\text{-CD}] + k_- \quad (9)$$

and

$$\tau^{-1} = k'_+[\alpha\text{-CD}] + k'_-, \quad (10)$$

Table 2. Acid-dissociation constants of *m*- and *p*-NPAS in the presence of α-CD

[α-CD] / mol dm^{-3}	*m*-NPAS $\bar{K}_a(p\bar{K}_a)$		*p*-NPAS $\bar{K}_a(p\bar{K}_a)$	
	Obsd	Calcd	Obsd	Calcd
0	1.59×10^{-11} (10.80)	—	2.06×10^{-11} (10.65)	—
6.47×10^{-4}	1.98×10^{-11} (10.70)	2.14×10^{-11} (10.67)	3.12×10^{-11} (10.51)	3.34×10^{-11} (10.48)
1.29×10^{-3}	2.17×10^{-11} (10.66)	2.29×10^{-11} (10.64)	3.98×10^{-11} (10.40)	3.79×10^{-11} (10.42)
5.18×10^{-3}	2.50×10^{-11} (10.60)	2.48×10^{-11} (10.61)	4.45×10^{-11} (10.35)	4.39×10^{-11} (10.36)
∞	—	2.56×10^{-11} (10.59)	—	4.70×10^{-11} (10.33)

Table 3. Rate and equilibrium constants for the inclusion reactions of *m*- and *p*-NPAS in α-CD and β-CD system

Equilibrium and rate constants	α-CD		β-CD	
	m-NPAS	*p*-NPAS	*m*-NPAS	*p*-NPAS
(1) k_+/mol^{-1} dm^3 s^{-1}	9.3×10^6	6.1×10^7	3.3×10^6	3.2×10^6
(2) k_-/s^{-1}	3.0×10^3	4.1×10^4	4.0×10^3	1.1×10^4
(3) $K=(k_-/k_+)$/mol dm^{-3}	3.2×10^{-4}	6.7×10^{-4}	1.2×10^{-3}	3.4×10^{-3}
(4) K(spectr)/mol dm^{-3}	4.95×10^{-4}	6.80×10^{-4}	9.22×10^{-4}	1.37×10^{-3}
(5) k'_+/mol^{-1} dm^3 s^{-1}	9.0×10^6	2.3×10^7	1.4×10^6	1.5×10^6
(6) k'_-/s^{-1}	2.0×10^3	8.0×10^3	2.2×10^3	4.0×10^3
(7) $K'=(k'_-/k'_+)$/mol dm^{-3}	2.2×10^{-4}	3.5×10^{-4}	1.6×10^{-3}	2.7×10^{-3}
(8) K'(spectr)/mol dm^{-3}	3.07×10^{-4}	2.98×10^{-4}	2.16×10^{-3}	1.12×10^{-3}

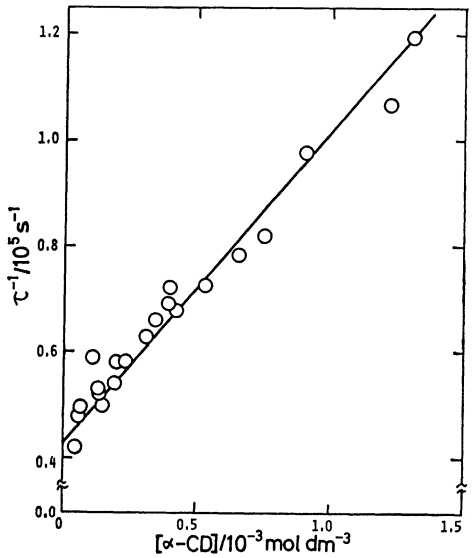


Fig. 9. A plot of Eq. 9 for the inclusion reaction of HA$^-$ form of *p*-NPAS with α-CD.

respectively. The plot of Eq. 9 gave a straight line with a slope k_+ and an intercept k_- (Fig. 9). The values of rate constants, k_+, k_-, k'_+, and k'_- for α-CD and β-CD systems are summarized in Table 3.

In the inclusion processes of *m*- and *p*-NPAS with α-CD, one can expect that the rate constant, k_+ (k'_+), decreases owing to the smaller α-CD cavity.[29] However, the higher stability of inclusion complex with α-CD may be attributed to the increase in k_+ (k'_+).[30] Actually in our investigations, the rate constant k_+ (or k'_+) of α-CD system was considerably larger than that of β-CD system, showing that α-CD exerts the inclusion force more strongly than β-CD does. The value of k_+ in α-CD system was found to depend on the position of the nitro group on *m*- and *p*-NPAS, *i.e.*, the values of k_+ of *m*- and *p*-NPAS was fairly different from each other compared to the case of the β-CD system. Larger steric hindrance of the nitro group in *m*-NPAS contributes to decreasing the rate constants k_+ (or k'_+). This indicates that the inclusion process takes place at the hydrophobic site (nitrobenzene moiety).

The value of k^+ is reported to be almost 2—3 orders of magnitude larger than that of k'_+ when a hydrophilic group such as hydroxyl group is included into α-CD cavity.[26,31] In the present kinetic study, however, the value of k_+ and k'_+ were found to be in the same order of magnitude ($\simeq10^6$ mol^{-1} dm^3 s^{-1} for *m*-NPAS and 10^7 mol^{-1} dm^3 s^{-1} for *p*-NPAS).[32] This fact kinetically supports the inclusion of hydrophobic site of *m*- and *p*-NPAS as a guest molecule into α-CD cavity.

Kinetics of Proton-transfer Reactions Coupled with the Inclusion Reactions. Kinetic data on the proton-transfer reaction coupled with the inclusion reaction with α-CD interpreted in terms of the following scheme,

$$\begin{array}{ccc} HA^- + \alpha\text{-CD} + OH^- & \underset{k_r}{\overset{k_f}{\rightleftharpoons}} & A^{2-} + \alpha\text{-CD} + H_2O \\ k_+ \uparrow\downarrow k_- & & k'_+ \uparrow\downarrow k'_- \\ HA\text{-}\alpha CD^- + OH^- & \underset{k'_r}{\overset{k'_f}{\rightleftharpoons}} & A\text{-}\alpha CD^{2-} + H_2O. \end{array} \quad (11)$$

As mentioned above, it was concluded that the inclusion process takes place at the hydrophobic site (nitrobenzene ring moiety). The apparent rate constants, $\bar{k}_f$ and $\bar{k}_r$, at each α-CD concentration were obtained under pseudo-first-order conditions using a large excess of hydroxide ion. The observed relaxation time, τ, for the proton-transfer reaction can be expressed as

$$\tau^{-1} = \bar{k}_f[\overline{OH}] + \bar{k}'_r, \quad (12)$$

where $[\overline{OH}]$ denotes the equilibrium concentration of hydroxide ion determined from pH-meter readings. The plot of τ^{-1} against $[\overline{OH}]$ gave a straight line at each α-CD concentration. The values of $\bar{k}_f$ and $\bar{k}_r$ at each α-CD concentration are summarized in Table 4. Because of the strong intramolecular hydrogen bond[33] of *m*- and *p*-NPAS, the k_f value (10^7 mol^{-1} dm^3 s^{-1}) is three orders of magnitude smaller as compared with that of diffusion-controlled proton-transfer reactions (10^{10} mol^{-1} dm^3 s^{-1}). Since the interior of α-CD cavity contains a ring of C–H groups, a ring of glycosidic oxygen, and another ring of C–H groups, the interior of α-CD cavity is relatively hydrophobic and apolar as compared with bulk solvent water.[1] Then, the recombination rate constant with OH^- ion, $\bar{k}_f$, should decrease provided the reaction site (–COO$^-$···HO–) of the proton-transfer reaction is included into hydrophobic α-CD cavity,[33] where the dielectric constant is probably small compared with that of the bulk solvent water. As shown in Table 4, $\bar{k}_f$ value increased with increase in α-CD concentrations, which suggests that the reaction site (–COO$^-$···HO–) in the proton-transfer reaction is situated outside the hydrophobic α-CD cavity, and the inclusion force exerts a weakening effect to

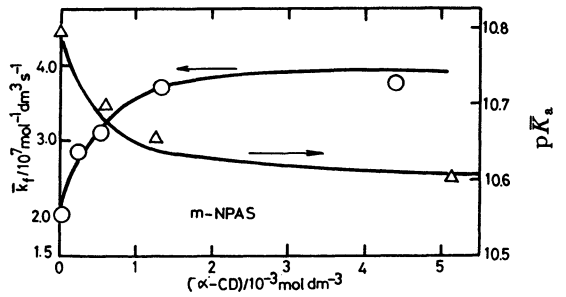


Fig. 10. The dependence of p$\bar{K}_a$ and $\bar{k}_f$ on α-CD concentrations in case of *m*-NPAS–αCD system at I=0.1 mol dm^{-3} (KNO_3) and 25 °C.

the intramolecular hydrogen bond.

The rate constant, $\bar{k}_f$, and p$\bar{K}_a$ of *m*-NPAS thus obtained in the present experiment were plotted against α-CD concentrations in Fig. 10. A definite correlation was observed between the [α-CD]-dependence of $\bar{k}_f$ and p$\bar{K}_a$, that is, with an increase of α-CD concentrations the p$\bar{K}_a$ value decreases and the $\bar{k}_f$ value increases particularly in the α-CD concentration range (0—2)$\times 10^{-3}$ mol dm^{-3}; about 91% of HA^- form of *m*-NPAS is included by α-CD at [α-CD]$=2\times10^{-3}$ mol dm^{-3}. By forming an inclusion compound with *m*-NPAS, α-CD is capable of altering the reactivity of the recombination site in the proton-transfer reaction. Similar observations were made for the proton-transfer reactions of *p*-NPAS in the presence of α-CD and β-CD (Table 4).

TABLE 4. RATE CONSTANTS FOR THE PROTON-TRANSFER REACTIONS OF *m*- AND *p*-NPAS IN THE PRESENCE OF α-CD AT 25 °C AND I=0.1 mol dm^{-3} (KNO_3)

[α-CD] / mol dm^{-3}	$\bar{k}_f$ / mol^{-1} dm^3 s^{-1}	$\bar{k}_r$ / s^{-1}	K_b^c [a] / mol^{-1} dm^3	p$\left(\frac{\bar{K}_a^c(k)}{\text{mol dm}^{-3}}\right)$ [b]
		m-NPAS		
0	2.0×10^7	3.5×10^4	570	10.97
2.11×10^{-4}	2.9×10^7	3.5×10^4	830	10.81
5.55×10^{-4}	3.1×10^7	3.0×10^4	1000	10.73
1.33×10^{-3}	3.7×10^7	3.1×10^4	1200	10.65
4.44×10^{-3}	3.7×10^7	2.9×10^4	1300	10.62
		p-NPAS		
0	2.1×10^7	1.9×10^4	1100	10.69
5.55×10^{-4}	3.4×10^7	2.2×10^4	1500	10.55
1.33×10^{-3}	3.5×10^7	1.8×10^4	1900	10.45
4.44×10^{-3}	3.9×10^7	1.7×10^4	2300	10.37

a) $K_b^c=k_f/k_r$. b) The values of kinetic pK_a^c(k) were evaluated from the relation, $K_a^c(k)=K_b^c\cdot K_w^c$. K_w^c denotes the apparent ionic product of water.[31]

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21) The observed chemical shift (δ_{obsd}) associated with Reaction 2 will be given by

$$\delta_{obsd} = \frac{[A]}{[A]_T}\delta_A + \frac{[A\text{-}\alpha CD]}{[A]_T}\delta_{A\text{-}\alpha CD}$$
$$= \frac{1}{[A]_T}\{[A]_T\delta_A + (\delta_{A\text{-}\alpha CD}-\delta_A)[A\text{-}\alpha CD]\},$$

with

$$[A\text{-}\alpha CD] = [Q-\sqrt{Q^2-4[A]_T[\alpha\text{-}CD]_T}]/2,$$

and

$$Q = [A]_T + [\alpha\text{-}CD]_T + K',$$

where δ_A, $\delta_{A\text{-}\alpha CD}$, $[\alpha\text{-}CD]_T$, and $[A]_T$ are the chemical shifts of A and A-αCD species and the total concentrations of α-CD and *m*-NPAS anion. The theoretical curves are obtained by plotting δ_{obsd} against $[\alpha\text{-}CD]_T$.

22) Assignments of α-CD and β-CD ^{13}C spectra by Kuge *et al.* were applied to these systems. See, K. Takeo, K. Hirose, and T. Kuge, *Chem. Lett.*, **1973**, 1233. Upon binding to CD of NPAS, CD carbons showed an upfield shift. The order of upfield shifts was $C_4>C_2\gtrsim C_1>C_3\gtrsim C_5\gg C_6$ in *m*-NPAS–βCD system, $C_1\gtrsim C_2>C_3\gtrsim C_4>C_5\gg C_6$ in *p*-NPAS–βCD system, $C_6\gtrsim C_2\gtrsim C_4>C_5>C_1\gg C_3$ in *m*-NPAS–αCD system,

and $C_1 \gtrsim C_2 > C_4 > C_5 > C_3 > C_6$ in *p*-NPAS–αCD system, indicating that the inclusion into CD cavity takes place from the secondary hydroxyl group side.

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