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Kinetic Studies on the Inclusion Reaction of Ethylenediamine Mono-substituted α-Cyclodextrin with Sodium p-(3-t-Butyl-4-hydroxyphenylazo)-benzenesulfonate in Aqueous Solution

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Kinetics of the inclusion reactions of the title azo compound having negative charge and an α-cyclodextrin derivative with positive charge is investigated by means of stopped-flow method. A two-step inclusion mechanism is proposed.

The driving force of molecular discrimination or molecular recognition by α-cyclodextrin results from weak interactions between host and guest molecules, such as hydrogen bonding, van der Waals force, hydrophobic interactions, subsequent relaxation of conformational strain in the macrocyclic ring of host molecule, and release of partially hydrogen-bonded two water molecules with high energy from the host cavity.

However, these forces operating in the inclusion with cyclodextrin (CDx) are not always additive but complicatedly correlated with each other.[1] Furthermore, the complementary spatial requirements between host and guest molecules are crucial for effective functioning of the binding force.[2] These facts suggest that a subtle difference in size and structure of the guest and the host molecules does control the mechanism of molecular inclusion process with CDx.[3]

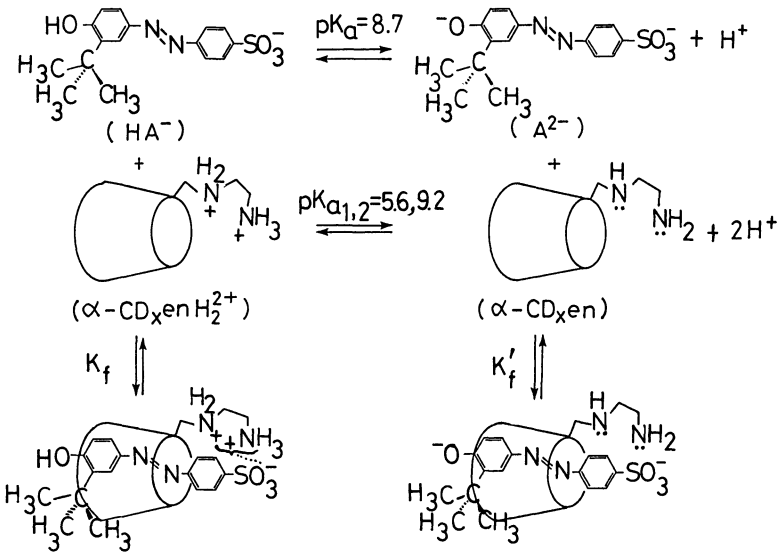
In the present communication, we propose a two-step mechanism on the basis of the data of stopped-flow method for inclusion reactions of the title guest azo molecule (3-tBu-HAB) with a positively-charged derivative of α-cyclodextrin.

The guest molecule, 3-tBu-HAB, consists of two moieties of different nature, a hydrophobic (t-Bu) and a hydrophilic ($-SO_3^-$) site; acid-dissociation constant (K_a) of the phenolic group was found to be 2.13×10^{-9} mol dm^{-3}. A charged derivative of α-cyclodextrin, mono[6-deoxy-6-N-(aminoethylamino)]-α-cyclodextrin (α-CDxen) was prepared via mono-6-p-toluenesulfonyl-α-cyclodextrin (α-CDxOTs).[4] The product was purified by column chromatography using a cation exchanger, CM-Toyopearl 650M, and 0.05 mol dm^{-3} ammonium hydrogencarbonate as eluent. The purity was checked by means of high performance liquid chromatography with an ERMA ERC 7520 RI detector (CH_3CN/H_2O; ERC-NH-1171 column).[5]

The acid-dissociation equilibria and the inclusion equilibria of the guest and the modified host molecule is illustrated in Scheme 1. The formation constants (K_f and K_f') of the inclusion complexes of the acid (HA^-) and the base form (A^{2-}) of the guest molecule were determined under acid (pH 3.4) and alkaline

(pH = 11.9) conditions, respectively. Visible spectral changes accompanying the formation of inclusion complexes, HA^--αCDx and HA^--αCDxen, are quite different from each other (Figs. 1(a) and 1(b)). Isosbestic points are observed at 371 and 421 nm for α-CDx system and at 362, 430, and 460 nm for α-CDxen system. The λ_{max} of the inclusion complex of α-CDxen (366 nm) is fairly shorter than that of unmodified α-CDx (374 nm). In the pH region between 3 and 4, α-CDxen possesses two positive charges as in α-CDx-$NH_2^+CH_2CH_2NH_3^+$, α-CDxenH_2^{2+}. Furthermore, the inclusion complex of positively charged α-CDxenH_2^{2+} is less stable than the corresponding complex of uncharged α-CDx. These facts suggest that the distinct electrostatic interaction is involved in the binding of α-CDxenH_2^{2+} and HA^- system. Since in alkaline region, α-CDxen is neutral, α-CDx-$NHCH_2CH_2NH_2$, the spectral feature and the stability of the complex formed (Table 1) is quite similar to that of the system involving uncharged α-CDx.

β-CDx with relatively larger cavity includes the title guest molecule so deeply as to t-Bu site where the best van der Waals contact with host cavity is attained, but the interaction site with α-CDx of the guest molecule



Scheme 1.

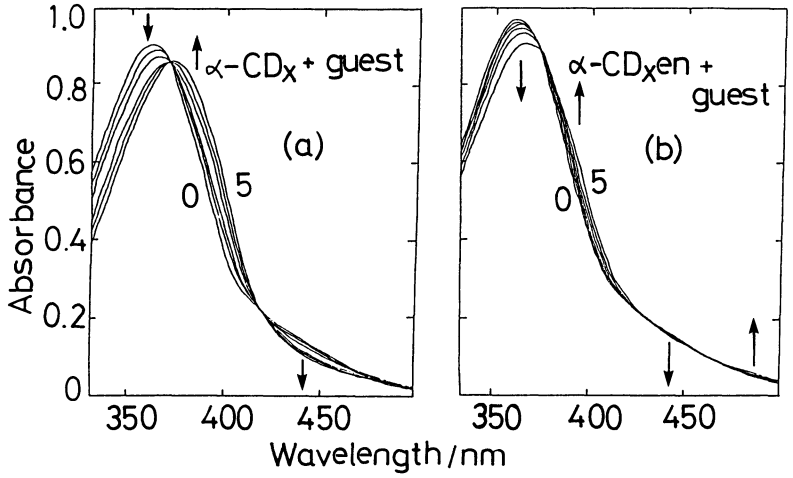


Fig. 1. Visible spectral changes on addition of α-cyclodextrin (a; pH = 4.5) and ethylenediamine mono-substituted α-cyclodextrin (b; pH = 3.4) to a 4.30 x 10^{-5} mol dm^{-3} solution of 3-tBu-HAB. The number 0 is the spectrum of the acid form (HA^-) of 3-tBu-HAB. Spectra 1-5 were obtained for the solutions having host concentrations (/10^{-4} mol dm^{-3}) of 1.09, 2.18, 6.55, 10.9, and 21.8 (a) and 1.16, 2.31, 5.78, 11.6, and 23.1 (b).

Table 1. The equilibrium and the rate constants for the inclusion reactions of 3-tBu-HAB with α-cyclodextrin and ethylenediamine mono-substituted α-cyclodextrin at 25 °C and I = 0.1 mol dm^{-3} (NaCl)

Reaction system	HA^-				A^{2-}			
	λ_{max} / nm	K_f / $mol^{-1}dm^3$	k_+ / $mol^{-1}dm^3s^{-1}$	k_- / s^{-1}	λ_{max} / nm	K_f' / $mol^{-1}dm^3$	k_+ / $mol^{-1}dm^3s^{-1}$	k_- / s^{-1}
G	363	-	-	-	468	-	-	-
G + α-CDx	374	1700	420	0.84	469	1200	270	0.48
G + α-CDxenH_2^{2+}	366	1200	k_{+2} = 1.9, k_{-2} = 0.72					
G + α-CDxen					470	1100	270	0.47

shifts towards the SO_3^- moiety resulting in the relatively shallow inclusion.[7]

Kinetic data were obtained under pseudo-first-order conditions in the presence of a large excess of the host molecule. While linear dependence of k_{obsd} on [host] is observed in HA^--αCDx, A^{2-}-αCDx, and A^{2-}-αCDxen systems (Fig. 2(a)), only in HA^--αCDxenH_2^{2+} system, a saturated-type dependence is observed (Fig. 2(b)). Generally, the linear dependence, $k_{obsd} = k_+[\alpha\text{-CDx}] + k_-$, is observed in one-step mechanism.[1,2] A saturated-type relationship as shown in Fig. 2(b) indicating a two-step mechanism (Eq. 1) is very limited.[3]

$$G + \alpha\text{-CDxen}H_2^{2+} \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} G\text{-}\alpha\text{CDxen}H_2^{2+*} \underset{k_{-2}}{\overset{k_{+2}}{\rightleftharpoons}} G\text{-}\alpha\text{CDxen}H_2^{2+}, \qquad (1)$$

where G, G-αCDxenH_2^{2+*}, and G-αCDxenH_2^{2+} denote the guest molecule, an intermediate, and a final inclusion complex, respectively. Provided that the first step proceeds rapidly compared with the second one, the dependence

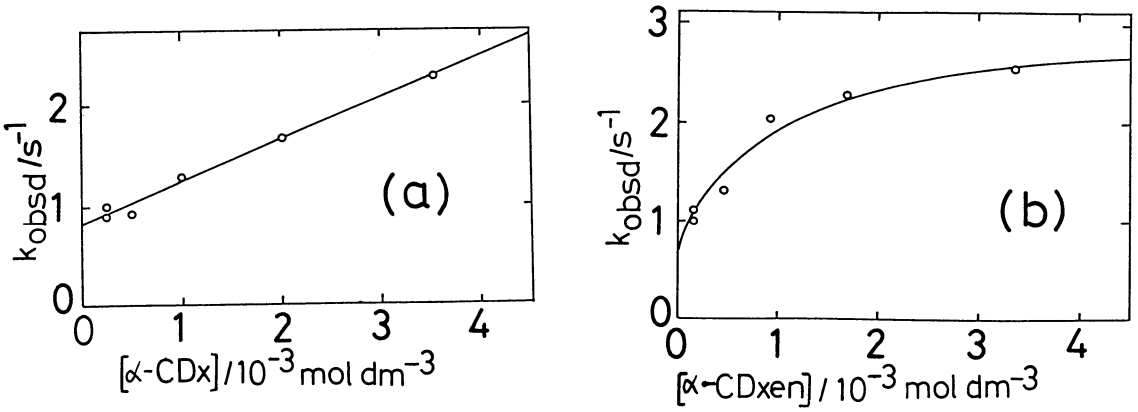


Fig. 2. Plots of the observed rate constant, k_{obsd}, vs. the concentration of α-CDx (a) and α-CDxenH_2^{2+} (b) at pH = 3.5 (HCl-phosphate buffer) and I = 0.1 mol dm^{-3} (NaCl). $[3\text{-tBu-HAB}]_{final}$ = 1.77 x 10^{-5} mol dm^{-3}.

of the rate constants on [α-CDxenH_2^{2+}] can be expressed as follows,[3)]

$$k_{fast} = k_{+1}[\alpha\text{-CDxen}H_2^{2+}] + k_{-1} \quad (2)$$

and

$$k_{slow} = k_{-2} + k_{+2}[\alpha\text{-CDxen}H_2^{2+}]/(K_{-1} + [\alpha\text{-CDxen}H_2^{2+}]), \quad (3)$$

where $K_{-1} = k_{-1}/k_{+1}$. The values of k_{+2} and k_{-2} in Table 1 are obtained by curve-fitting method. The K_{+1} value is determined to be $(1.5 \pm 1.0) \times 10^3$ mol^{-1} dm^3.

The preferential binding of α-CDx with the sulfanilate site in 3-tBu-HAB was already confirmed by kinetic method.[3)] This directional binding is also applicable to the inclusion reaction investigated here. The fast process observed in acid region would be attributed to the formation of an intermediate in which the electrostatic interaction between a negative $-SO_3^-$ site in the guest molecule and a positive $-[NH_2CH_2CH_2NH_3]^{2+}$ site in the host molecule is operated. This fast process was not detected by the stopped-flow method due to an immeasurably fast change or to a very small absorbance change. Since such electrostatic interaction disappears in alkaline region, no saturated-type dependence is observed in A^{2-}-αCDx$[NHCH_2CH_2NH_2]^0$ system.

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5) R_f = 0.62 ($CHCl_3$/CH_3COOH/H_2O = 10:80:30(v/v/v); Silicagel 70 Plate-Wako). ^{1}H-NMR; δ(D_2O) = 5.1 (6H, CH(1)), 3.5-4 (36H, CH(2),(3),(4),(5),(6a),(6b)), 3.3 (4H, NCH_2).
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7) The difference in the interaction site of α-CDx and β-CDx system will be discussed in the following papers in this issue.

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