

THERMODYNAMIC PARAMETERS FOR THE MOLECULAR INCLUSION
REACTIONS OF SOME AZO COMPOUNDS WITH α -CYCLODEXTRIN

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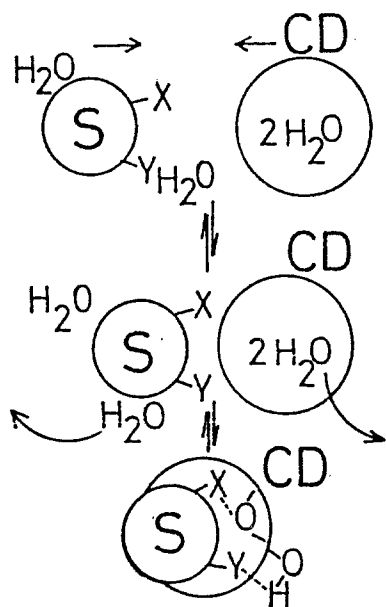
ABSTRACT. Molecular inclusion reactions of some azo compounds with α -cyclodextrin were studied in aqueous solution by means of a stopped-flow method. The forward rate constants for the inclusion reactions were found to be in the order of $10\text{-}10^4 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$. The thermodynamic activation parameters were also determined firstly in α -cyclodextrin system.

INTRODUCTION

Torus-shaped α -cyclodextrin, which is a molecule-discriminating molecule, has been used as an enzyme model, since it exhibits an enzyme-like behavior such as stereoselective acceleration leading to a stereoselective product, saturation, and inhibition.¹

The association constants (K and K') and the thermodynamic parameters (ΔH and ΔS) for the inclusion reactions with α -cyclodextrin (α -CD) have been determined for various systems. However the kinetic studies²⁻⁷ on the inclusion reactions are relatively few as compared with the equilibrium studies. This is because the signal amplitude accompanying the inclusion process is very small. Therefore, the mechanism for the inclusion process by α -cyclodextrin and the transition state in the course of the inclusion process are not clear even now.

At the present stage of the investigations about the molecular dynamics for inclusion, the following mechanism can be considered (Scheme 1). First step is the encounter between the guest molecule and α -CD. Second step contains the release of water molecules with high energy in α -CD⁸ and the breakdown of the water structure around the guest molecule.² In the third step, the intermolecular



Scheme 1

interactions (the short-range force) such as van der Waals force⁹, hydrogen-bonding¹⁰, hydrophobic interaction¹¹, and the relaxation of the conformational strain in the macrocyclic ring of α -CD are operative.

These interactions have been considered to be the driving force for inclusion. From the standpoint of the molecular dynamics for inclusion, our attention is focused on one point; which step is the rate-determining one? If the first step is rate-determining, which was observed in the inclusion reactions between α -CD and the guest molecule having no steric hindrance such as *p*-nitrophenol² and *p*-nitrophenylazosalicylic acid³, the rate constants for the association are determined in the order of 10^7 - 10^8 mol⁻¹ dm³ s⁻¹. In the interaction of α -CD with the guest molecule having a bulky substituent, the rate constants

for association decrease by a factor of 10-1000 because of the steric hindrance. Furthermore, the desolvation of the electrostrictive hydrated water molecules around the inclusion site of the guest molecule causes the decrease in the association rate constants by a factor of about 100. Recently, Turro suggested that the rate-determining step of the host-guest association is the breakdown of the water structure inside CD and/or around the guest molecule.⁶ The direction of the inclusion by CD is also important in molecular dynamics of inclusion; information about the direction of the inclusion by CD is obtained only by kinetic measurement.

In the present study, the rate constants for the association and the dissociation reactions between α -CD and some azo compounds were measured by the stopped-flow method. Activation parameters (ΔG^\ddagger , ΔH^\ddagger , and ΔS^\ddagger) were also determined.

EXPERIMENTAL

These studies were undertaken using a stopped-flow apparatus over the time range 10 - 10^{-3} s. α -Cyclodextrin (Tokyo Kasei) was used without further purification. Azo compounds were synthesized by a usual azo coupling method and purified by

cellulose column chromatography (Whatman CC 31, 1-butanol : 2 mol dm⁻³ aqueous NH₃ : ethanol = 60 : 20 : 20 v/v/v).

RESULTS AND DISCUSSION

a. Equilibrium Measurements

The structural formulae of the guest molecules used in this experiment are shown in Fig. 1(a) and 1(b). These azo compounds show the following protolytic equilibrium in aqueous solution,



where H denotes the phenolic proton. The values of pK_a (= -log (K_a/ mol dm⁻³)) range from 7.8 to 8.9.

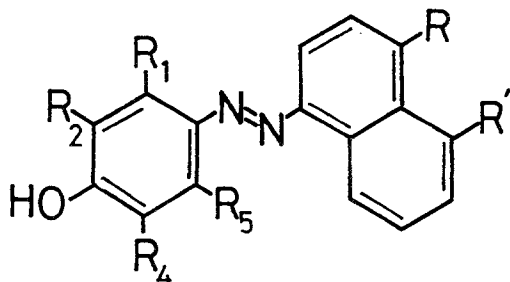


Fig. 1a (1) R₁-R₅=H, R'₁=SO₃⁻; (2) R₂=Cl, R₁-R₅=H, R₁-R₅=H, R=SO₃⁻; (3) R₂=Me, R₁-R₅=H, R=SO₃⁻; (4) R₂=Et, R₁-R₅=H, R'₁=SO₃⁻; (5) R₂=Pr, R₁-R₅=H, R'₁=SO₃⁻.

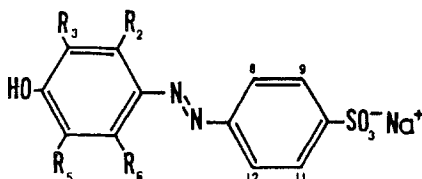
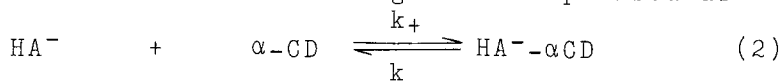


Fig. 1b (6) R₂-R₆=H; (7) R₃=Me, R₂-R₆=H; (8) R₃=Et, R₂-R₆=H; (9) R₃=Pr, R₂-R₆=H; (10) R₃=i-Pr (11) R₃=s-Bu, R₂-R₆=H; (12) R₃=t-Bu, R₂-R₆=H; (13) R₃=R₅=i-Pr, R₂=R₆=H

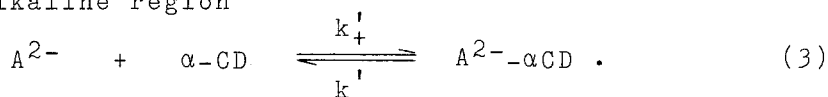
Both HA⁻ and A²⁻ form inclusion complexes at an appropriate pH region. The formation of 1 : 1 inclusion complexes was confirmed by the presence of isosbestic points in the spectral change upon varying α -CD_x concentration and by the Hildebrand-Benesi plot.⁷ The formation constants (K and K') of the α -CD inclusion complexes of (1)-(5) are much smaller than those of the inclusion complexes of (6)-(13). This instability of the α -CD inclusion complexes of (1)-(5) would be due to the steric hindrance of the naphthalene moiety in the inclusion with α -CD.

b. Rate Constants

The inclusion reaction in acidic region is expressed as



and in alkaline region



Under pseudo first order conditions the observed rate constant (k_{obsd}) is given by

$$k_{\text{obsd}} = k_+[\alpha\text{-CD}] + k_- \quad (4)$$

and

$$k_{\text{obsd}} = k'_+[\alpha\text{-CD}] + k'_- . \quad (5)$$

In the inclusion reaction of (4) with $\alpha\text{-CD}$, $k_+ = 5.5 \times 10^3 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$ and $k_- = 39 \text{ s}^{-1}$ were easily evaluated from a plot of k_{obsd} vs. $\alpha\text{-CD}$ concentration. Table 1 gives the value of the rate constants for the association and the dissociation of the $\alpha\text{-CD}$ inclusion complexes. There is a general tendency for the magnitude of the rate constants.

Case I

$$k_+ \gg k'_+ \quad \text{and} \quad k_- \gg k'_- \quad (6)$$

It appears that the rate constants of the formation and the dissociation of $A^{2-}\text{-}\alpha\text{CD}$ is smaller than those of the formation and the dissociation of $HA^-\text{-}\alpha\text{CD}$. This decrease in the formation and the dissociation rate constants is due to the desolvation of the electrostrictive hydrated water molecules around the $-O^-$ group of the guest molecules, (4) and (5).

Case II

$$k_+ \approx k'_+ \quad \text{and} \quad k_- \approx k'_- \quad (7)$$

This case is observed in the formation of the $\alpha\text{-CD}$ inclusion complexes with (7)-(13). Strictly speaking, the deprotonation of the $-OH$ group has a slight influence on the rate constants (k_+ and k_-). This kinetic results suggest that the inclusion site is far from the phenolic moiety and the inclusion by $\alpha\text{-CD}$ takes place from the $-\text{SO}_3^-$ moiety of the guest molecule.

The decrease in the rate constants (k_+ and k'_+) accounts for such an increase in steric hindrance around the OH group. However, the following two situations are encountered in two types of the inclusion reaction. In the first type of inclusion reactions (1)-(5) with $\alpha\text{-CD}$, the decrease in k_+ and k'_+ is due to the steric hindrance between the inside of CD cavity and the alkyl substituents of the guest molecule. In the second type of the inclusion reactions (6)-(13) with $\alpha\text{-CD}$, the decrease in k_+ and k'_+ is attributable to the steric hindrance between the rim of the $\alpha\text{-CD}$ ring and the alkyl substituent of the guest molecule.

Table 1. Rate and Association Constants for The Inclusion Reactions with α -Cyclodextrin

Guest	R_i	k_+ $\text{mol}^{-1} \text{dm}^3 \text{s}^{-1}$	k_- s^{-1}	K $\text{mol}^{-1} \text{dm}^3$	k'_+ $\text{mol}^{-1} \text{dm}^3 \text{s}^{-1}$	k'_- s^{-1}	K' $\text{mol}^{-1} \text{dm}^3$
(1)	H	a	a	391 ^b	a	a	211 ^b
(2)	Cl	a	a	280 ^b	7.8×10^2	1.7	460
(3)	Me	a	a	211 ^b	2.3×10^2	1.3	180
(4)	Et	5.5×10^3	39	220	43	0.06	219 ^b
(5)	Pr	1.4×10^4	60	230	58	0.18	320

(6)	H	a	a	6200 ^b	a	a	5800 ^b
(7)	Me	7.0×10^5	77	9100	9.3×10^3	2.0	4700
(8)	Et	2.1×10^4	6.5	3200	8.1×10^3	2.1	3900
(9)	Pr	2.2×10^4	5.1	4300	8.9×10^3	2.6	3400
(10)	i-Pr	1.2×10^4	9.4	1300	-	-	-
(11)	s-Bu	1.1×10^4	14.0	790	-	-	-
(12)	t-Bu	4.6×10^2	0.55	840	-	-	-
(13)	(i-Pr) ₂	5.4×10^2	0.7	770	3.5×10^2	0.5	700

a) Too rapid to measure by the stopped-flow method. b) Determined spectrophotometrically. Others are obtained as the ratios of k_+/k_- or k'_+/k'_- .

The most striking aspect of the present kinetic result is that the rate constants (k_+ and $k_+^!$) of (4) are larger than those of (5), which is probably due to the more hydrophobic property of Pr group. It can be seen from the CPK model that the difference in size of Me and Et groups is very large but that of Et and Pr groups would be small.

c. Activation Parameters

The mechanism for the inclusion reactions of (1)-(5) and (6)-(13) with α -CD are illustrated in Schemes 2 and 3, respectively. When the thermodynamic parameters for the inclusion reaction are interpreted in detail, we should clarify the direction and/or the orientation in the inclusion of the guest molecule by α -CD as shown in Schemes 2 and 3.

From the temperature-dependency of the rate constants for the inclusion reaction, the activation parameters are determined (Table 2). The large contribution of enthalpy of activation to the free energy of activation is observed in both the association and the dissociation processes. The entropy term, ΔS_+^\ddagger , contributes unfavorably to the Gibbs energy term, ΔG_+^\ddagger . This fact suggests that the hydrophobic interaction ($\Delta S_+^\ddagger > 0$) does not play an important role in the transition state and/or overshadowed by ΔS^\ddagger contributions from other intermolecular force.

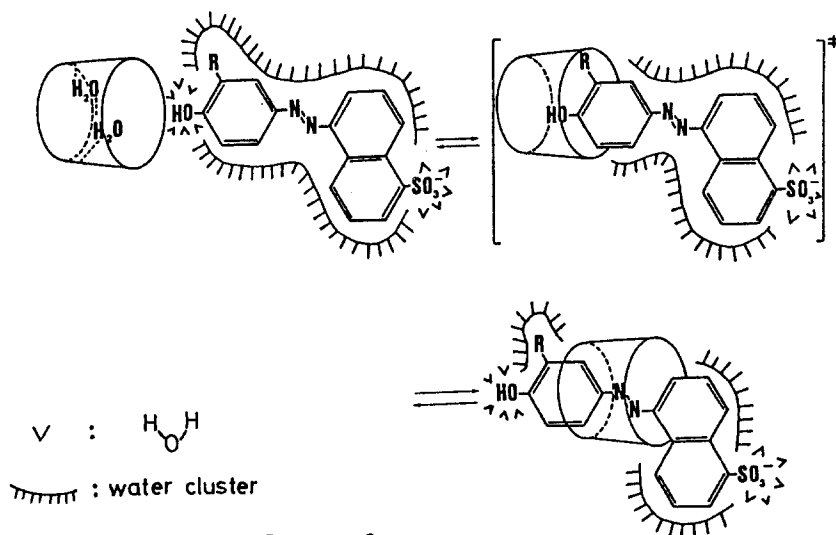
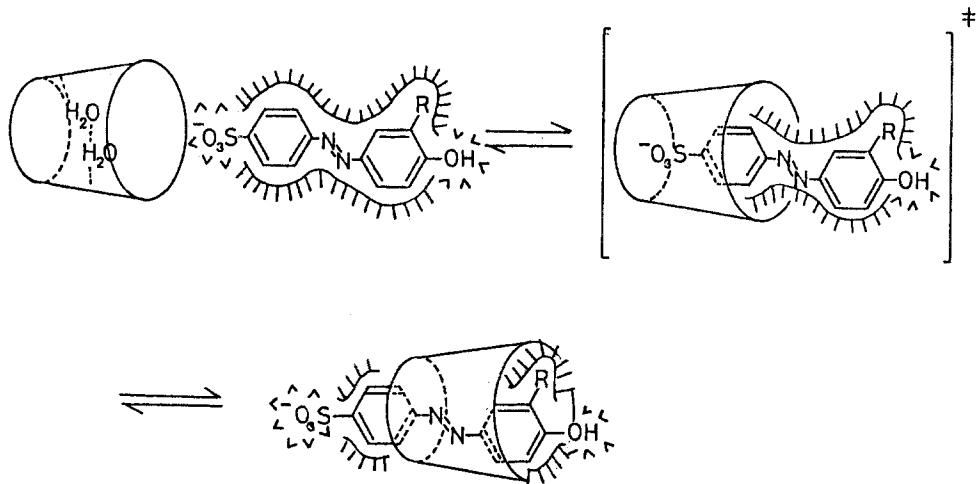


Table 2. Thermodynamic Parameters for the Inclusion Reactions by α -Cyclodextrin^a

Guest	ΔG	ΔH	ΔS	ΔG^{\ddagger}_{+}	ΔH^{\ddagger}_{+}	ΔS^{\ddagger}_{+}	ΔG^{\ddagger}_{-}	ΔH^{\ddagger}_{-}	ΔS^{\ddagger}_{-}
(2)-A ²⁻	- 15.1	- 27.0	- 39.6	56.6	24.8	-106.6	71.7	51.7	- 67.0
(3)-A ²⁻	- 12.7	- 44.5	-107.2	59.4	31.6	- 93.4	72.1	76.1	13.8
(4)-HA ⁻	- 11.3	- 24.6	- 46.1	51.3	32.5	- 63.1	62.6	57.1	-17.0
(4)-A ²⁻	- 13.1	- 18.8	- 19.4	65.4	57.8	- 25.7	78.5	76.6	- 6.3
(5)-HA ⁻	- 13.5	- 20.4	- 23.1	49.2	13.3	-120.5	62.7	33.7	- 97.4
(5)-A ²⁻	- 14.4	- 17.9	- 11.8	62.9	73.0	33.9	77.3	90.9	45.7
(7)-HA ⁻	- 22.7	- 35.2	- 42.1	39.6	15.3	- 81.5	62.3	50.5	- 39.4
(7)-A ²⁻	- 20.3	- 17.5	9.3	50.4	23.1	- 91.7	70.7	40.6	- 101
(8)-HA ⁻	- 20.0	- 20.1	- 0.4	48.5	23.0	- 85.3	68.4	43.1	- 84.9
(8)-A ²⁻	- 20.2	- 30.2	- 33.2	50.8	21.7	- 97.2	71.0	51.9	- 64.0
(9)-HA ⁻	- 22.5 ^b	- 33.3 ^b	- 36.0 ^b	48.4	22.5	- 87.0	69.1	49.6	- 65.3
(9)-A ²⁻	- 22.5 ^b	- 31.7 ^b	- 32.0 ^b	50.3	29.8	- 68.7	70.4	56.0	- 48.4
(13)-HA ⁻	- 16.4 ^b	- 19.6 ^b	- 10.8 ^b	57.4	33.0	- 81.9	74.0	49.5	- 82.1
(13)-A ²⁻	- 16.6 ^b	- 21.6 ^b	- 17.9 ^b	58.5	35.1	- 78.5	74.9	50.5	- 81.9

a) $G/kJ\ mol^{-1}$, $H/kJ\ mol^{-1}$, and $S/J\ mol^{-1}\ K^{-1}$ at 25 °C. ΔG , ΔH , and ΔS are obtained as ΔG^{\ddagger}_{+} - ΔG^{\ddagger}_{-} , ΔH^{\ddagger}_{+} - ΔH^{\ddagger}_{-} , and ΔS^{\ddagger}_{+} - ΔS^{\ddagger}_{-} , respectively. b) Determined by the equilibrium measurements.



Scheme 3

The following relationships are obtained.

$$\Delta H_{+}^{\ddagger} \ll \Delta H_{-}^{\ddagger} \quad \text{for (2)-(5), (7)-(9), and (13)} \quad (8)$$

$$\Delta H_{+,HA^{-}}^{\ddagger} \ll \Delta H_{+,A^{2-}}^{\ddagger} \quad \text{for (4) and (5)} \quad (9)$$

$$\Delta H_{-,HA^{-}}^{\ddagger} \ll \Delta H_{-,A^{2-}}^{\ddagger} \quad \text{for (4) and (5)} \quad (10)$$

$$\Delta S_{+,HA^{-}}^{\ddagger} \ll \Delta S_{+,A^{2-}}^{\ddagger} \quad \text{for (4) and (5)} \quad (11)$$

$$\Delta S_{-,HA^{-}}^{\ddagger} \ll \Delta S_{-,A^{2-}}^{\ddagger} \quad \text{for (4) and (5)} \quad (12)$$

$$\Delta S_{+,HA^{-}}^{\ddagger} \approx \Delta S_{+,A^{2-}}^{\ddagger} \approx \Delta S_{-,HA^{-}}^{\ddagger} \approx \Delta S_{-,A^{2-}}^{\ddagger} \quad \text{for (8), (9), and (13)} \quad (13)$$

The increase in ΔS^{\ddagger} and ΔH^{\ddagger} in eqs. 9, 10, 11, and 12 is attributable to the desolvation around the O^{-} group. This increase in ΔH^{\ddagger} is largely compensated for by the increase in ΔS^{\ddagger} as shown in Table 2. There is a general tendency in the inclusion reactions investigated here for enthalpies of activation and entropies of activation to compensate to each other, so that the changes in free energy of activation are much smaller in the systems (2)-(5).

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