CHEMISTRY LETTERS, pp. 703 - 706, 1984.

RATE CONSTANTS AND THERMODYNAMIC PARAMETERS FOR THE INCLUSION REACTIONS OF SOME p-HYDROXYPHENYLAZO DERIVATIVES OF SULFANILIC ACID WITH α-CYCLODEXTRIN

Noboru YOSHIDA, Akitoshi SEIYAMA, and Masatoshi FUJIMOTO*
Department of Chemistry, Faculty of Science, Hokkaido University,
Sapporo 060

Inclusion reactions of the title azo compounds with α-cyclodextrin were studied in aqueous solution by means of the stopped-flow method. The forward rate constants for the inclusion reactions were found to be in the order of magnitude 10^2 - 10^4 mol^{-1} dm^3 s^{-1}. Activation parameters were first determined for α-cyclodextrin system.

Torus-shaped α-cyclodextrin (α-CD_x), a cyclic α-1,4-linked D-glucose polymer, has six glucose residues per molecule.[1] The cavity of α-CD_x in aqueous media is relatively hydrophobic and apolar as compared with bulk solvent water.[2] Therefore, in the inclusion complexes formed in aqueous solution, regiospecific interaction with the hydrophobic moiety of a guest molecule is observed.[3] As regards the driving force for the inclusion process, a number of explanations have been presented on the basis of thermodynamic,[4] kinetic,[3,5] theoretical,[6] and X-ray structural studies.[7] However the dynamic feature of the inclusion process is still not clear even now.[3,5]

In the present study the rate constants of the inclusion process of α-CD_x with some p-hydroxyphenylazo derivatives of sulfanilic acid (Fig. 1) were measured by the stopped-flow method. Activation parameters for the inclusion process were first determined.

The guest azo compounds, p-(3-propyl-4-hydroxyphenylazo)benzenesulfonate ion (1) and p-(3,5-diisopropyl-4-hydroxyphenylazo)benzenesulfonate ion (2) show the following protolytic equilibrium in aqueous solution,

$$HA^- \overset{K_a}{\rightleftharpoons} A^{2-} + H^+, \qquad (1)$$

where H denotes the phenolic proton. The values of pK_a(= - log(K_a/mol dm^{-3})) for 1 and 2 were determined to be 8.19 and 8.19, respectively. The formation of 1 : 1 inclusion complexes was confirmed by the presence of isosbestic points in the spectral change upon varying α-CD_x concentrations and Hildebrand-Benesi plot.[3] The equilibrium for the inclusion reaction in acidic region is expressed as

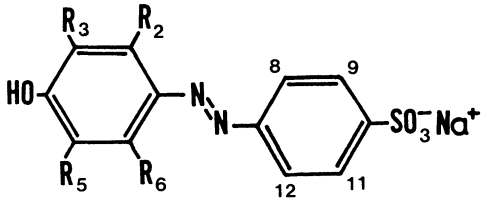

Fig. 1. Structural formula of the guest molecule.
1 R_3 = $-(CH_2)_2CH_3$, R_2 = R_5 = R_6 = H
2 R_3 = R_5 = $-CH(CH_3)_2$, R_2 = R_6 = H

$$HA^- + \alpha\text{-CD}_x \underset{}{\overset{K}{\rightleftharpoons}} HA^-\text{-}\alpha\text{CD}_x \qquad (2)$$

and in alkaline region

$$A^{2-} + \alpha\text{-CD}_x \underset{}{\overset{K'}{\rightleftharpoons}} A^{2-}\text{-}\alpha\text{CD}_x. \qquad (3)$$

The values of the stability constants, K and K′, of the inclusion complexes were spectrophotometrically determined to be in the order of magnitude 10^2 - 10^4 mol^{-1} dm^3 (Table 1). The lower stability of the inclusion complex of 2 is attributable to the steric hindrance between the rim of α-CD_x ring and the bulky isopropyl group in the guest molecule.[8] The ^1H NMR study showed that α-CD_x interacts with the azo-sulfanilate moiety,[8,9] though the interacting position of the guest molecule varies subtly with the size and the shape of R_i substituents.

Kinetic data were obtained under pseudo-first-order conditions in the presence of a large excess of α-CD_x. The observed rate constants, k_{obsd}, in the reactions 2 and 3 are expressed as $k_{obsd} = k_+[\alpha\text{-CD}_x] + k_-$ and $k'_{obsd} = k'_+[\alpha\text{-CD}_x] + k'_-$, where $k_+(k'_+)$ and $k_-(k'_-)$ are the forward and backward rate constants, respectively. The plot of k_{obsd} against the total concentration of α-CD_x, $[\alpha\text{-CD}_x]$, gave a straight line with a slope k_+ and an intercept k_- (Fig. 2). The values of the rate constants are summarized in Table 1. The stability constants, K and K′, determined kinetically as the ratios of k_+/k_- and k'_+/k'_-, respectively, were in fairly good agreement with those determined spectrophotometrically. A remarkable effect of the substituents R_i on the rate constants was observed. If the inclusion takes place at the phenol moiety, the value of k'_+ should be almost 2 - 3 orders of magnitude smaller than that of k_+.[5a,10] In the systems investigated here, all values of k'_+ are smaller only slightly than those of k_+.[11] This kinetic result supports the inclusion of the sulfanilate moiety of the guest molecules into α-CD_x cavity.

Table 1. Stability and Rate Constants for the Inclusion Reactions of 1 and 2 with α-CD_x

Guest Molecule	t [a] / °C	K [b] / $mol^{-1}dm^3$	k_+ / $mol^{-1}dm^3$ s^{-1}	k_- / s^{-1}	K' [b] / $mol^{-1}dm^3$	k'_+ / $mol^{-1}dm^3$ s^{-1}	k'_- / s^{-1}
1	13.0	14500	1.3×10^4	2.0	13700	5.6×10^3	1.1
	25.0	8260	2.2×10^4	5.1	7250	8.9×10^3	2.6
	36.5	5000	2.8×10^4	10.1	5000	1.5×10^4	6.8
2	12.0	1250	3.0×10^2	0.28	1170	1.8×10^2	0.18
	25.0	885	5.4×10^2	0.69	787	3.5×10^2	0.48
	37.0	649	9.1×10^2	1.5	585	6.0×10^2	1.0

a) ± 0.1 °C. b) Determined from the equilibrium measurements at I = 0.1 mol dm^{-3} (NaCl).

Thermodynamic parameters for the inclusion reactions were determined from the temperature-dependency of K and K . Van't Hoff plots, RT lnK vs. T^{-1}, show always a good linear relationship over the temperature range 12 - 37 °C. As shown in Table 2, all $\Delta H^{\ominus}$ and $\Delta S^{\ominus}$ values are negative and in the same order of magnitude as those reported previously for the various α-CD_x inclusion complexes.[12] The inclusion equilibria are almost enthalpy-controlled; the entropy change ($\Delta S^{\ominus} < 0$) contributes unfavorably to the formation of the α-CD_x inclusion complexes. This indicates that the hydrophobic interaction is not predominant in the formation of the inclusion complexes[12] or the $\Delta S^{\ominus}$ for the hydrophobic interaction ($\Delta S^{\ominus} > 0$) is overshadowed by $\Delta S^{\ominus}$ contributions from the other intermolecular processes.

From the temperature-dependency of the rate constants for the inclusion reactions 2 and 3, activation parameters, $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$, were determined. The contribution of the entropy of activation, $\Delta S^{\ddagger}_{+}$, to the Gibbs energy of activation, $\Delta G^{\ddagger}_{+}$, in the forward reaction is much larger than that of $\Delta S^{\ddagger}_{-}$ to $\Delta G^{\ddagger}_{-}$ in the backward reaction. The entropy term, $\Delta S^{\ddagger}_{+}$, contributes unfavorably to the Gibbs energy term, $\Delta G^{\ddagger}_{+}$. This fact suggests that the hydrophobic interaction does not play an important role in the transition state of the inclusion process.[13]

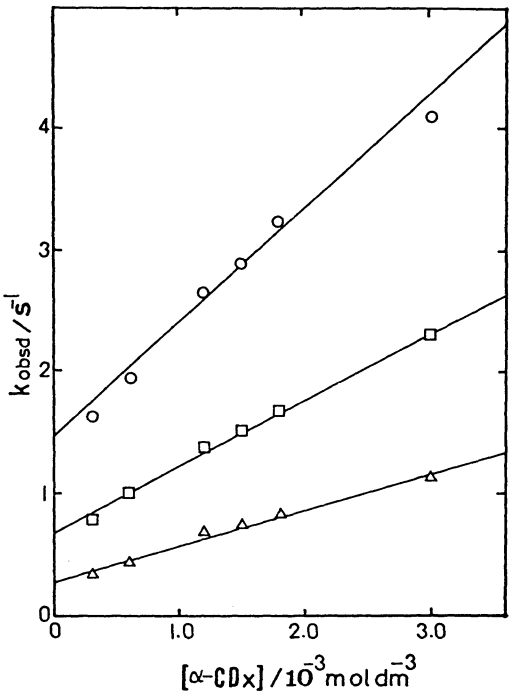

Fig. 2. Plots of the observed rate constant, k_{obsd}, vs. the concentration of α-CD_x at pH 4.6 (phosphate buffer) and I = 0.1 mol dm^{-3} (NaCl) with [1] = 3.00 x 10^{-5} mol dm^{-3}. At 37(○), 25(□), and 12(△) °C.

Table 2. Thermodynamic Parameters for the Inclusion Reactions of 1 and 2 with α-CD_x at 25 °C

Inclusion Reaction	$\Delta G^{\ominus}$ a)	$\Delta H^{\ominus}$ a)	$\Delta S^{\ominus}$ a)	$\Delta G^{\ddagger}_{+}$	$\Delta H^{\ddagger}_{+}$	$\Delta S^{\ddagger}_{+}$	$\Delta G^{\ddagger}_{-}$	$\Delta H^{\ddagger}_{-}$	$\Delta S^{\ddagger}_{-}$
1 HA^{-} + α-CD_x	- 22.5	- 33.3	- 36.0	48.4	22.5	- 87.0	69.1	49.6	- 65.3
1 A^{2-} + α-CD_x	- 22.2	- 31.8	- 32.0	50.3	29.8	- 68.7	70.4	56.0	- 48.4
2 HA^{-} + α-CD_x	- 16.4	- 19.6	- 10.8	57.4	33.0	- 81.9	74.0	49.5	- 82.1
2 A^{2-} + α-CD_x	- 16.6	- 21.9	- 17.9	58.5	35.1	- 76.5	74.9	50.5	- 81.9

a) $\Delta G^{\ominus}$, $\Delta H^{\ominus}$, and $\Delta S^{\ominus}$ were determined from equilibrium measurements. The signs of $\Delta G^{\ominus}$, $\Delta H^{\ominus}$, and $\Delta S^{\ominus}$ refer to the formation reaction of the inclusion complexes. $\Delta G^{\ominus}$, $\Delta G^{\ddagger}_{+}$, $\Delta G^{\ddagger}_{-}$, $\Delta H^{\ominus}$, $\Delta H^{\ddagger}_{+}$, $\Delta H^{\ddagger}_{-}$ in kJ mol^{-1}. $\Delta S^{\ominus}$, $\Delta S^{\ddagger}_{+}$, $\Delta S^{\ddagger}_{-}$ in J K^{-1} mol^{-1}.

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8) There would be the steric hindrance between the secondary hydroxyl group of α-CD_x and the bulky isopropyl group in the guest molecule. The azo linkage was found to be included into α-CD_x cavity as revealed by the change in chemical shift of the ring proton of α-CD_x. It is noteworthy that no inclusion was confirmed in the α-CD_x system of p-(2,6-dimethyl-4-hydroxyphenylazo)-benzenesulfonate ion by the uv-vis absorption and ^1H NMR spectroscopy.
9) For example, in the case of 2, the downfield shift by the inclusion into α-CD_x cavity of the signals H_8, H_9, H_{11}, and H_{12} protons was very large as compared with that of H_2 and H_6.
10) N. Yoshida and M. Fujimoto, 31st Annual Meeting on Coordination Chemistry, Sendai, September 14, 1981, Abstract, p. 252.
11) The value of k′ is slightly affected by the negative charge of the phenolate ion ($-O^-$) situated apart from the inclusion site.
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13) The activation entropy, $\Delta S_+^{\ddagger}$, would be divided mainly into 4 terms, (1) the freeze of motional freedoms of the guest molecule, (2) the desolvation around the $-SO_3^-$ group, (3) the release of two water molecules from the α-CD_x cavity and the subsequent transformation of them into bulk water, and (4) the partial collapse of the water cluster around the apolar site of the guest molecule. The terms (1) and (2) are negative and the terms (3) and (4) are positive. The discussion about $\Delta S_+^{\ddagger}$ and $\Delta S_-^{\ddagger}$ is too speculative at present. A detailed evaluation of the activation entropy is now in progress.

(Received February 13, 1984)