# Cyclodextrin Precipitates with Naphthalene–Biphenyl Mixed Guests in Aqueous Medium

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**Synopsis.** Cyclodextrins ($\beta$- and $\gamma$-CyDs) were precipitated in an aqueous medium at 25 °C in the presence of a naphthalene (N)–biphenyl (B) mixed guest. The N/B molar ratio in the precipitates was found to be governed by $S_N \cdot K_N (S_B \cdot K_B)^{-1}$, where $S$ refers to the solubility of the guest in water and $K$ to the 1 : 1 association constant of the CyD–guest.

Cyclodextrin(CyD, host) forms inclusion complexes with a variety of molecular species (guests) in an aqueous medium. The complexes precipitate if the guest to be included exhibits low solubility in water and the CyD in water exceeds a certain concentration characteristic of the host–guest combination. The solubilities of CyDs in water in the presence of various guest substances[1,2] and the CyD : guest molar ratios in the precipitates[2—4] have been studies. Researches, on the other hand, in mixed-guest systems have received much less attention. The first attempt to prepare CyD precipitates with mixed guests was made on pentane–nonane systems.[2] The $C_5/C_9$ molar ratio in the CyD precipitate was found to be roughly proportional to the mixing ratio of the two liquid hydrocarbons.

This work is concerned with a naphthalene–biphenyl mixed-solid guest system. This system was chosen based on two criteria: the guest solubility in water and the 1 : 1 (host : guest) association constant ($K_1$). The solubility of naphthalene is 5.4-times that of biphenyl; in contrast to the $C_5$–$C_9$ system previously studied, the solubility in water of each component of the naphthalene–biphenyl mixture is independent of the mixing ratio. The $K_1$ of biphenyl is larger than that of naphthalene for the $\beta$-CyD complex, while being nearly equal for the $\gamma$-CyD complex. The object of this work was to determine what is the predominant factor governing the guest composition of the CyD precipitates prepared in the presence of two different guests.

## Experimental

Naphthalene and biphenyl, which had been roughly powdered in an agate mortar, of each ca. 1 g were dispersed together in water of ca. 100 cm$^3$ in a separatory funnel. A CyD solution of 100 to 300 cm$^3$ was placed in another separatory funnel and the CyD precipitate was prepared as described in a previous paper.[2] The content of each funnel was held constant at 25 °C by circulating water from a thermostated water bath through the jacket surrounding each funnel.

The CyD solution became turbid in most cases within 10 min after vapor-circulation of the mixed-guest hydrocarbons; it took a longer time at lower CyD concentrations. After the prescribed vapor-circulation period, a 10 cm$^3$ portion of the turbid solution was withdrawn to a centrifuge tube of 10 cm$^3$ capacity and then centrifuged. The guest hydrocarbons in the precipitate were extracted with cyclohexane and analyzed with a Shimadzu GC-14B gas chromatograph (fused-silica wide-bore capillary column of 0.53 mm×25 m, coated with polydimethyl siloxane). Anthracene was used as an internal standard. The amount of CyD in the precipitate and the CyD concentration in the supernatant aqueous solutions were determined by a Shodex Model SE-11 differential refractometer.

## Results and Discussion

**Solubility in Water of Naphthalene or Biphenyl in Mixture.** It has been shown that each component of the naphthalene–biphenyl mixture exhibits a solubility in water that is nearly equal to that of each single solute.[5] The conclusion, however, was derived from a single experimental condition: each 1 mmol of the two solid hydrocarbons was mixed. Moreover, the data were obtained by a shake-flask method: aqueous solutions saturated with solutes were prepared by adding an excess quantity of solid particles directly to water in a container equipped with a stopper and mechanically shaking the container at a constant temperature. It is necessary to confirm that the vapor-circulation method used in this work gives the same results as those obtained by the shake-flask method at various mixing ratios of the two hydrocarbons.

Aqueous solutions saturated with naphthalene–biphenyl mixed solutes were prepared by the vapor-circulation and shake-flask methods; the apparatus used in our shake-flask method and experimental procedures were described elsewhere.[6] The results are given in Table 1. Although the solubility by the vapor-circulation method is ca. 5% (naphthalene) or 9% (biphenyl) lower than that by the shake-flask method, we can say that the solubility of each component in water is almost independent of the mixing ratio. Our previous solubility results for a single solute at 25 °C obtained by the vapor-circulation method are $2.42 \times 10^{-4}$ M (1 M≡1 mol dm$^{-3}$) (naphthalene) and $4.30 \times 10^{-5}$ M (biphenyl).[7]

In general, it is difficult in the shake-flask method to completely remove suspended micro-particulates of solid solutes from saturated solutions. In the vapor-circulation method, on the other hand, it is unnecessary to remove any excess solute phase. Moreover, aqueous solutions can be quickly saturated with solutes; the cir-

Table 1. Solubility in Water at 25 °C of the Constituent Component in the Naphthalene–Biphenyl Binary Mixture

| $X_B$[a)] | Solubility | | | |
|---|---|---|---|---|
| | Naphthalene/$10^{-4}$ mol dm$^{-3}$ | | Biphenyl/$10^{-5}$ mol dm$^{-3}$ | |
| | Method A[b)] | Method B[c)] | Method A[b)] | Method B[c)] |
| 0.0686 | 2.44±0.02 | 2.39 | 4.84±0.09 | 4.48 |
| 0.124 | 2.49±0.02 | 2.34 | 4.74±0.07 | 4.15 |
| 0.301 | 2.48±0.02 | 2.28 | 4.78±0.09 | 4.42 |
| 0.500 | 2.49±0.03 | 2.34 | 4.72±0.04 | 4.03 |
| 0.940 | 2.45±0.04 | 2.35 | 4.77±0.03 | 4.52 |

a) Mole fraction of biphenyl. b) Shake-flask method. c) Vapor-circulation method; the relative standard deviation is 2%.

cumstances are given in Fig. 1.

**Association Constants.** The $K_1$ value for each host–guest of interest was shown in a previous paper (see Table 3 in Ref. 2), except for γ-CyD–biphenyl. The $K_1$ of γ-CyD–biphenyl has been determined in this work by solubility measurements using the vapor-circulation method.[6)] At a given $C_{\mathrm{CyD}}$ (the total CyD concentration), the concentration of biphenyl dissolved in water ($[\mathrm{B}]_{\mathrm{T}}$) was measured. The $K_1$ can be determined by the following equation:

$$\begin{aligned}[\mathrm{B}]_{\mathrm{T}} &= [\mathrm{B}] + [\mathrm{CyD{\cdot}B}] = [\mathrm{B}] + K_1[\mathrm{CyD}][\mathrm{B}] \\ &= S_{\mathrm{B}}(1 + K_1 C_{\mathrm{CyD}}). \qquad (1)\end{aligned}$$

The concentration of free biphenyl ([B]) is equal to the solubility of biphenyl ($S_{\mathrm{B}}$); if [CyD·B] is negligibly small compared to $C_{\mathrm{CyD}}$, the concentration of free CyD ([CyD]) can be made equal to $C_{\mathrm{CyD}}$. In Fig. 2, $[\mathrm{B}]_{\mathrm{T}}/S_{\mathrm{B}}$ is plotted against $C_{\mathrm{CyD}}$; biphenyl does not precipitate in this $C_{\mathrm{CyD}}$ range. The $K_1$ was determined to be 130 M$^{-1}$ from the slope of the straight line.

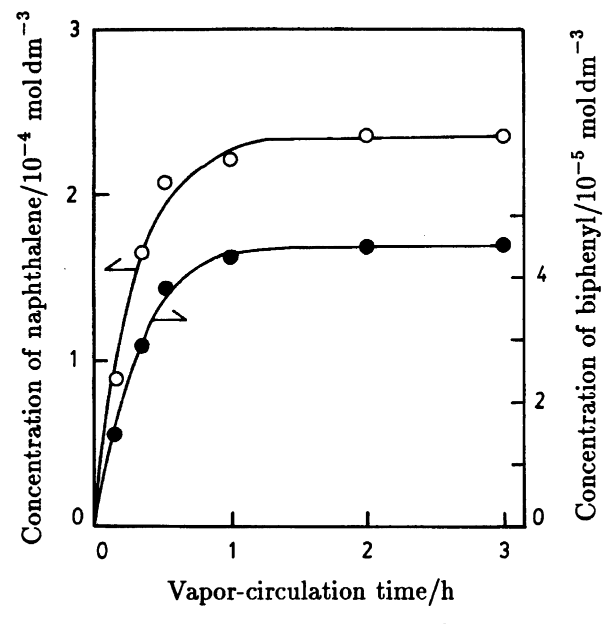

Fig. 1. Concentrations in water at 25 °C of the constituent components in the naphthalene–biphenyl binary mixture as a function of the solute vapor-circulation time.

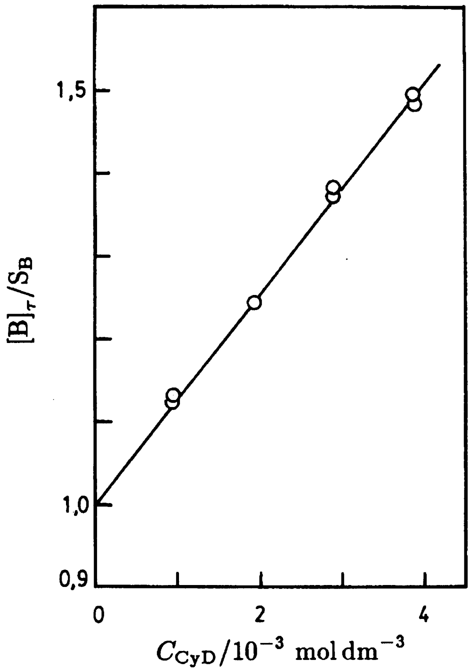

Fig. 2. $[\mathrm{B}]_{\mathrm{T}}/S_{\mathrm{B}}$ vs. $C_{\mathrm{CyD}}$ plots. $[\mathrm{B}]_{\mathrm{T}}$ and $S_{\mathrm{B}}$ refer, respectively, to the concentration of biphenyl in the presence and absence of γ-CyD.

Table 2 summarizes the solubility of naphthalene and biphenyl and the $K_1$ of each host–guest system. The $K_1$ of β-CyD–naphthalene reported in the literature ranges from 630 to 900 M$^{-1}$.

Table 2. Solubility and Association Constant at 25 °C

| Guest | Solubility in water[a)]/mol dm$^{-3}$ | Association constant (1 : 1) /mol dm$^{-3}$ |
|---|---|---|
| Naphthalene | $2.34\times10^{-4}$ | β (630, 685, 730, 850, 900)[b)]<br>γ (130)[8)] |
| Biphenyl | $4.32\times10^{-5}$ | β (2100)[c)] γ (130)[d)] |

a) The mean value determined in this work using vapor-circulation method for the naphthalene–biphenyl binary mixture. b) Cited from Ref. 6. c) I. Sanemasa, unpublished data. d) Determined in this work.

Table 3. Composition of Cyclodextrin (CyD), Naphthalene (N), and Biphenyl (B) in CyD Precipitates Prepared in the Presence of N and B at 25 °C

| Vapor-circulation time | Amount of CyD in precipitate | Amount of guest in precipitate $/10^{-3}$ mmol | | Molar ratio in precipitates | |
|---|---|---|---|---|---|
| /h | $/10^{-3}$ mmol | N | B | (N+B)/CyD | N/B |
| β-CyD precipitate: | | | | | |
| Initial concentration of CyD; $3.91\times10^{-3}$ mol dm$^{-3}$ | | | | | |
| 0.5 | 7.9 | 6.6 | 1.2 | 0.99 | 5.5 |
| 1 | 16 | 13 | 2.3 | 0.96 | 5.7 |
| 5 | 25 | 16 | 4.0 | 0.80 | 4.0 |
| 8 | 27 | 17 | 4.4 | 0.79 | 3.9 |
| 24 | 32 | 17 | 5.4 | 0.70 | 3.1 |
| Initial concentration of CyD; $1.98\times10^{-3}$ mol dm$^{-3}$ | | | | | |
| 0.5 | 5.8 | 5.3 | 1.5 | 1.2 | 3.5 |
| 1 | 11 | 9.6 | 3.1 | 1.1 | 3.1 |
| 5 | 13 | 9.5 | 3.4 | 0.99 | 2.8 |
| 8 | 13 | 8.3 | 3.2 | 0.88 | 2.6 |
| 24 | 14 | 8.3 | 3.4 | 0.84 | 2.4 |
| Initial concentration of CyD; $7.89\times10^{-4}$ mol dm$^{-3}$ [a] | | | | | |
| 2 | 6.1 | 2.8 | 1.5 | 0.70 | 1.9 |
| 5 | 7.2 | 3.6 | 1.8 | 0.75 | 2.0 |
| 10 | 8.1 | 4.7 | 2.4 | 0.88 | 2.0 |
| 24 | 8.8 | 4.0 | 2.1 | 0.69 | 1.9 |
| γ-CyD precipitate: | | | | | |
| Initial concentration of CyD; $9.49\times10^{-3}$ mol dm$^{-3}$ | | | | | |
| 0.25 | 3.5 | 4.6 | 0.7 | 1.5 | 6.6 |
| 0.5 | 7.0 | 8.3 | 1.4 | 1.4 | 5.9 |
| 1 | 15 | 21 | 3.5 | 1.6 | 6.0 |
| 5 | 59 | 85 | 16 | 1.7 | 5.3 |
| 7 | 86 | 120 | 23 | 1.7 | 5.2 |
| 24 | 92 | 120 | 23 | 1.6 | 5.2 |
| Initial concentration of CyD; $4.96\times10^{-3}$ mol dm$^{-3}$ | | | | | |
| 0.5 | 6.1 | 8.6 | 1.7 | 1.7 | 5.1 |
| 1 | 10 | 18 | 3.4 | 2.1 | 5.3 |
| 4 | 40 | 69 | 14 | 2.1 | 4.9 |
| 7 | 49 | 82 | 16 | 2.0 | 5.1 |
| 25 | 49 | 79 | 14 | 1.9 | 5.6 |

a) The contents of two centrifuge tubes collected at each vapor-circulation time were combined and analyzed.

**CyD Precipitates in Mixed Guests.** The molar ratios of naphthalene (N)/biphenyl (B) in β- and γ-CyD precipitates are given in Table 3 together with those of the total guest (the sum of N and B)/CyD. These ratios were not affected by the initial mixing ratio of the solid naphthalene and biphenyl. It is noteworthy that, at higher initial concentrations of β-CyD, the N/B and (N+B)/CyD values gradually decrease with the vapor-circulation time. This is probably due to an aging effect of the CyD precipitates. At higher CyD concentrations, the guest (N), the solubility of which is larger than that of another guest (B), is preferentially taken into the precipitates. With aging, the guest (N) in the precipitates is gradually replaced by the guest (B), the $K_1$ of which is larger than that of the guest (N). The aging effect was not observed at a low β-CyD concentration. In this case, the precipitation occurs after one hour of vapor-circulation, and the amount of the precipitates is very small. We take a value of 2.0 as the N/B in β-CyD precipitates. This value can be derived by the following equation:

$$\text{N/B molar ratio in CyD precipitates} = S_{\mathrm{N}}\cdot K_{\mathrm{N}}(S_{\mathrm{B}}\cdot K_{\mathrm{B}})^{-1}, \tag{2}$$

where $S_{\mathrm{N}}$ and $S_{\mathrm{B}}$ refer to the solubility of the guests in water and $K_{\mathrm{N}}$ and $K_{\mathrm{B}}$ to the 1 : 1 association constant of the CyD–guest. Equation 2 gives, if we take 630 or 900 $\mathrm{M}^{-1}$ as $K_{\mathrm{N}}$, 1.6 or 2.3, respectively.

As for precipitates with γ-CyD, the N/B value was found to be almost constant, irrespective of the initial CyD concentration and vapor-circulation time. We take a value of 5.5 (the mean of 11 data) as N/B for the γ-CyD precipitates. Since there is no difference in the

$K_1$ value between the associations of $\gamma$-CyD with the two guests, N/B is determined by the solubility ratio, $S_N/S_B$ (=5.4).

In a previous study,[2] we determined the CyD concentration in a supernatant solution, $[\mathrm{CyD}]_{\mathrm{super}}$, after centrifugation of the CyD phase precipitated in water saturated with a given guest hydrocarbon. The $[\mathrm{CyD}]_{\mathrm{super}}$ are as follows: $2.9\times10^{-4}$ ($\beta$-naphthalene), $9.4\times10^{-4}$ ($\beta$-biphenyl), $2.5\times10^{-4}$ ($\gamma$-naphthalene), and $6.3\times10^{-3}$ ($\gamma$-biphenyl).[2] In an aqueous solution saturated with a given guest, CyD begins to precipitate if its concentration exceeds $[\mathrm{CyD}]_{\mathrm{super}}$. We expected that a selective precipitation might occur if we use a suitable CyD concentration. Let us take $\beta$-CyD as an example. When the initial concentration of $\beta$-CyD was set so as to be larger than $2.9\times10^{-4}$, but lower than $9.4\times10^{-4}$ M, only naphthalene might be precipitated with $\beta$-CyD. This expectation, however, was not realized for both $\beta$- and $\gamma$-CyDs (see Table 3). We then measured the $[\mathrm{CyD}]_{\mathrm{super}}$ in the mixed-guest precipitates, and found that $[\mathrm{CyD}]_{\mathrm{super}}$ was almost equal to the lower one, that is, the $[\mathrm{CyD}]_{\mathrm{super}}$ of $\beta$- or $\gamma$-naphthalene precipitate.

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