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# Determination of the Stability Constants for Inclusion Complexes of Cyclodextrins with Various Drug Molecules by High Performance Liquid Chromatography[1)]

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Stability constant ($K_c$) for 1:1 inclusion complexes of $\alpha$- and $\beta$-cyclodextrins with barbiturates, phenothiazines, sulfonylamides, and sulfonylureas were determined by high performance liquid chromatography (HPLC). The retention times of the drugs following the binding to cyclodextrins in aqueous mobile phase on ion exchange support were quantitatively treated to obtain the $K_c$ values. The $K_c$ values obtained by HPLC method were in fair agreement with those obtained by other methods such as solubility and spectroscopic methods. The advantages of HPLC method developed here were that $K_c$ values could be rapidly obtained by simple procedure with minimum quantity of the drugs and reproducibility and accuracy were not less than other methods. Furthermore, this method was proved to be particularly suitable for chemically unstable compounds such as phenothiazines.

**Keywords**——determination of stability constant; high performance liquid chromatography; cyclodextrin complex; solubility method; spectroscopic method; partition coefficient; barbiturates; phenothiazines; sulfonylamides; sulfonylureas

The determination of the stability constants ($K_c$) of inclusion complexes have been reported by several authors using a variety of techniques, such as solubility,[3)] potentiometry,[4)] polarography,[5)] and spectroscopic methods.[6)] These methods, however, do not appear to be suitable for the chemically unstable compounds and for systems accompanying no spectral changes. They are also often characterized by very limited concentration ranges. In the previous paper,[7)] cyclodextrins (CyDs) complexations have been successfully applied to rapid analyses of prostaglandin derivatives by high performance liquid chromatography (HPLC). It has then been shown that the retention times of the prostaglandins decreased significantly by the addition of $\alpha$- or $\beta$-cyclodextrin ($\alpha$-CyD, $\beta$-CyD) into aqueous mobile phase on anion exchange support because of the formation of soluble complexes in the mobile phase.

In the present study, changes in retention times of various drug molecules such as barbiturates, phenothiazines, sulfonylamides, and sulfonylureas as a function of CyD concentration have been quantitatively treated to obtain the $K_c$ values. The advantages of the HPLC method described here were that $K_c$ values can be rapidly obtained by simple procedure with minimum quantity of the guest molecules even when significant spectral changes are not observed by complexation. This method was proved to be pertinent to various CyD com-

1) A part of this work was presented at 2nd Symposium of Stabilization and Evaluation Methodology of Pharmaceutical Preparations, Okayama, October 1977.
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3) J. Cohen and J.L. Lach, *J. Pharm. Sci.*, **52**, 132 (1963); Y. Hamada, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.* (Tokyo), **23**, 1205 (1975).
4) T. Miyaji, K. Kurono, K. Uekama, and K. Ikeda, *Chem. Pharm. Bull.* (Tokyo), **24**, 1155 (1976).
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6) F. Cramer, W. Saenger, and H.-Ch. Spatz, *J. Am. Chem. Soc.*, **89**, 14 (1967); A.L. Thakkar, P.B. Kuehn, J.H. Perrin, and W.L. Wilham, *J. Pharm. Sci.*, **61**, 1841 (1972); K. Uekama, F. Hirayama, Y. Yamasaki, M. Otagiri, and K. Ikeda, *Chem. Lett.*, **1977**, 1389.
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plexes with weakly acidic or basic drug molecules using a proper ion exchange support. The results were in fair agreement with those obtained by other methods such as spectroscopic and solubility methods.

## Experimental

**Apparatus and Conditions of HPLC**——A liquid chromatograph instrument (FLC-A700, Jasco) was employed for liquid chromatography: at a proper flow rate (0.3—0.5 ml/min) using a stainless steel column ($500 \times 2.3$ mm i.d.) packed with an ion-exchange pellicular support (Jasco strong anion of AV-02-500 or strong cation of CV-02-500). The pH (3.0—9.7) and ionic strength ($\mu = 0.2$) of the mobile phase were adjusted to appropriate value with 0.1 M $H_3PO_4$, 0.1 M NaOH, and NaCl. Stock solutions of the drugs (1.0—2.0 mg/ml) were prepared in EtOH. The column temperature was ambient ($25 \pm 2°$) and a 2 $\mu$l of the sample was injected with 10 $\mu$l syringe (MS-G10, Termo Co.). The effluents were monitored with a double-beam spectrophotometric detector (UVIDEC-1M, Jasco) at the ultraviolet (UV) absorption maxima of the drugs. The retention time was defined as the elapsed time between injection and attainment peak by the maximum peak on chromatogram. The retention times of the drugs (final concentration of $2.0 \times 10^{-5}$ M, in general) in the absence and in the presence of excess amounts of CyDs (varied from 1.0 to $7.0 \times 10^{-3}$ M) in the mobile phase were measured.

**Materials**——Barbiturates (**1**—**17**),[8a] phenothiazines (**18**—**24**),[8b] and sulfonylamides (**25**—**36**),[8c] were same as in previous papers. Sulfonylureas (**37**—**52**)[9] were donated by Prof. S. Goto. $\alpha$- and $\beta$-CyDs were the gift of Teijin Ltd. All other materials and solvents were of analytical reagent grade, and deionized, double-distilled water was used.

**Solubility Studies**——These were carried out according to Lach *et al.*[3] Excess amounts of the drugs were added to aqueous $\alpha$- or $\beta$-CyD solutions and were shaken at $25 \pm 0.1°$. After equilibration was attained, an aliquot was centrifuged and pipetted through a cotton filter. A 0.5 ml aliquot of the sample was diluted with 0.1 M phosphate buffer (pH 7.0) and assayed spectrophotometrically. The $K_c$ values were calculated[10] on the basis of 1:1 stoichiometry[8] from the phase diagrams obtained.

**Spectroscopic Studies**——The UV absorption and circular dichroism (CD) spectral measurements were made on a Shimadzu 200 type spectrometer and a Jasco J-40 AS spectropolarimeter, respectively. All solutions were prepared in 0.1 M phosphate buffer (pH 7.0) at 25°. The $K_c$ values were calculated as previously described.[8]

## Theoretical

It was observed that the retention times of weakly acidic or basic drugs decreased significantly by the addition of $\alpha$- or $\beta$-CyD into the mobile phase on ion exchange supports. Since all the drugs used in this study have been known to form 1:1 inclusion complexes with $\alpha$- and $\beta$-CyDs in aqueous solution,[8] the retention behavior of the drug (G) and its CyD complex (G-CyD) within ion exchange column can be depicted in Chart 1. In this scheme, $D_o$, $D_c$, and $K_c$ are concentration distribution ratio of ionized G, that of G-CyD, and stability constant of 1:1 complex, respectively, as defined following equations:

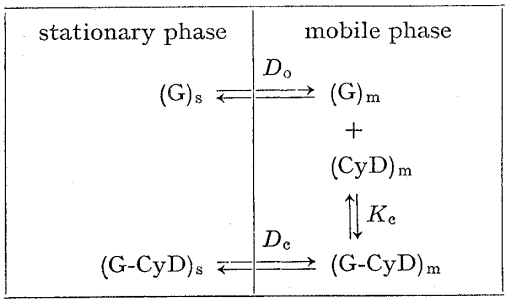


Chart 1. Schematic Representation of the Concentration Distribution Ratio of Drug (G) in the Presence of CyD

$$D_o = \frac{(G)_s}{(G)_m} \qquad \text{(Eq. 1)}$$

$$D_c = \frac{(G\text{-}CyC)_s}{(G\text{-}CyD)_m} \qquad \text{(Eq. 2)}$$

$$K_c = \frac{(G\text{-}CyD)_m}{(G)_m \cdot (CyD)_m} \qquad \text{(Eq. 3)}$$

8) *a*) M. Otagiri, T. Miyaji, K. Uekama, and K. Ikeda, *Chem. Pharm. Bull.* (Tokyo), **24**, 1146 (1976); *b*) M. Otagiri, K. Uekama, and K. Ikeda, *ibid.*, **23**, 188 (1975); *c*) K. Uekama, F. Hirayama, M. Otagiri, Y. Otagiri, and K. Ikeda, *ibid.*, **26**, 1162 (1978).
9) S. Goto, H. Yoshitomi, and M. Nakase, *Chem. Pharm. Bull.* (Tokyo), **26**, 472 (1978).
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where suffixes s and m stand for stationary phase and mobile phase, respectively, and concentrations of each species in parenthesis are in molar concentration unit. Then, the apparent concentration distribution ratio for this system, $D_{obs}$, can be expressed as follow,

$$D_{obs} = \frac{(G)_s + (G\text{-}CyD)_s}{(G)_m + (G\text{-}CyD)_m} \quad \text{(Eq. 4)}$$

Substituting Eq. 1, 2, and 3 in Eq. 4 yields:

$$D_{obs} = \frac{D_o + D_c \cdot K_c \cdot (CyD)_m}{1 + K_c \cdot (CyD)_m} \quad \text{(Eq. 5)}$$

Assuming that an addition of CyD in the mobile phase does not provide a significant changes in the void volume of the column, the relationship[11] between concentration distribution ratios and retention times can be expressed as follows,

$$D_o = \frac{T_o' - T_o}{T_o} \cdot \frac{V_m}{V_s} \quad \text{(Eq. 6)}$$

$$D_c = \frac{T_c - T_o}{T_o} \cdot \frac{V_m}{V_s} \quad \text{(Eq. 7)}$$

$$D_{obs} = \frac{T_{obs} - T_o}{T_o} \cdot \frac{V_m}{V_s} \quad \text{(Eq. 8)}$$

where $T_o$, $T_o'$, $T_c$, and $T_{obs}$ are retention time of nonretained band, that of G itself, that of G-CyD complex, and that of G at a given concentration of CyD, and $V_s$ and $V_m$ are volume of stationary phase and void volume within the column, respectively. Substituting Eq. 6, 7, and 8 in Eq. 5 yields:

$$T_{obs} = \frac{T_o' + T_c \cdot K_c \cdot (CyD)_m}{1 + K_c \cdot (CyD)_m} \quad \text{(Eq. 9)}$$

Rearranging Eq. 9:

$$\frac{(CyD)_m}{T_o' - T_{obs}} = \frac{1}{T_o' - T_c} \cdot (CyD)_m + \frac{1}{K_c \cdot (T_o' - T_c)} \quad \text{(Eq. 10)}$$

A plot of the left hand term of Eq. 10 *versus* $(CyD)_m$ gives both the $K_c$ and $T_c$ values from the slope and intercept. Since Eq. 9 is held in any concentration of CyD, the following relation can be expressed between two arbitrary selected CyD concentrations, which are designated as $(CyD)_{m1}$ and $(CyD)_{m2}$, respectively.

$$\frac{\Delta(CyD)_m}{\Delta T_{obs}} = \frac{K_c \cdot (CyD)_{m1} + 1}{T_o' - T_c} \cdot (CyD)_{m2} + \frac{K_c \cdot (CyD)_{m1} + 1}{K_c \cdot (T_o' - T_c)} \quad \text{(Eq. 11)}$$

where $\Delta T_{obs}$ is the difference of observed retention times at two sets of CyD concentrations and $\Delta(CyD)_m = (CyD)_{m2} - (CyD)_{m1}$. When $(CyD)_{m1}$ is held constant and $(CyD)_{m2}$ is varied, a linear relation should be obtained between $\Delta(CyD)_m/\Delta T_{obs}$ and $(CyD)_{m2}$, and $K_c$ is determined from the linear relationship by (Slope)/(Intercept). Equation 11 is particularly useful for the system showing long retention times even when $T_o'$ is unknown.

## Results and Discussion

### Stability Constants Determined by HPLC Method

Figure 1 shows typical liquid chromatograms of 5-ethyl-5-*n*-hexylbarbituric acid (**4**) on anion exchange support in the absence and in the presence of $\alpha$- or $\beta$-CyD. The aqueous mobile phase used was sodium phosphate buffer, since phosphate anions do not interfere with inclusion complexation.[12] A simple phosphate buffer gave extremely long retention

11) K. Uekama, F. Hirayama, and T. Irie, *Chem. Lett.*, **1978**, 661.
12) E.A. Lewis and L.D. Hansen, *J. Chem. Soc. Perkin II*, **1973**, 2081.

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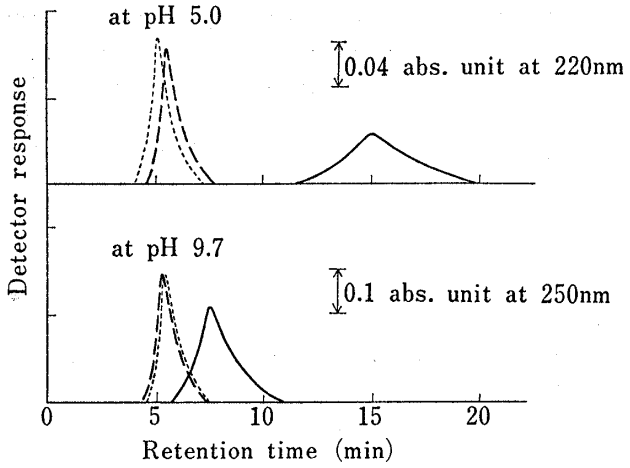


Fig. 1. Liquid Chromatograms of 5-Ethyl-5-*n*-hexylbarbituric Acid (**4**) on Anion Exchange Column in the Absence and Presence of $\alpha$- or $\beta$-Cyclodextrin ($5\times10^{-3}$ M) in the Mobile Phase

——: in the absence of CyD,
– – –: in the presence of $\alpha$-CyD,
------: in the presence of $\beta$-CyD.

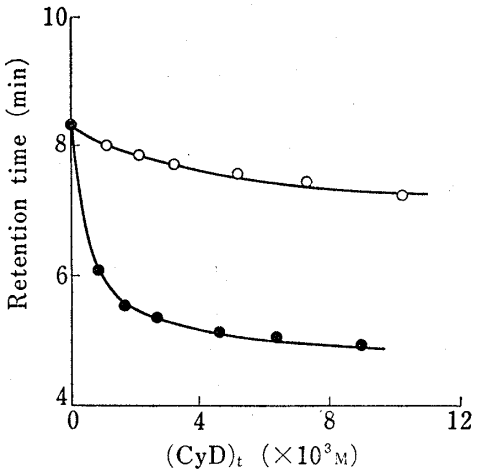


Fig. 2. Observed Retention Times for Phenobarbital with Varying Concentration of CyD in the Mobile Phase (0.1 M Phosphate Buffer: pH=5.0, $\mu$=0.2)

(○): $\alpha$-CyD system, (●): $\beta$-CyD system.

times with marked tailing because of the highly hydrophobic nature of compound **4**, as expected from its partition coefficient (Table I). When $\alpha$- or $\beta$-CyD was added to phosphate buffer, the retention times decreased significantly. Fig. 2 shows that increase in $\alpha$- or $\beta$-CyD concentration shortened the retention times of phenobarbital (**8**), indicating that increase in the solubility of **8** by the binding to CyDs. In equations 10 and 11, $(CyD)_m$ can be assumed to be equal to the added concentration of CyD, $(CyD)_t$, when concentration of CyD is largely in excess compared to that of G in the mobile phase. Assuming that $(CyD)_m$ equal to $(CyD)_t$, the data in Fig. 2 were treated according to Eq. 10. As shown in Fig. 3, linear plots were obtained for both of the $\alpha$- and $\beta$-CyDs systems, verifying 1:1 stoichiometry in Chart 1. Then, $K_c$ values were calculated from intercept and slope by a programed least squares method. Table I summarizes $K_c$ values for inclusion complexes of various barbiturates with $\alpha$- and $\beta$-CyDs. Similarly, stability constants for $\beta$-CyD complexes of phenothiazines, sulfonylamides, and sulfonylureas were obtained by HPLC method and the results are listed in Table II, III, and IV, respectively. In the case of phenothiazines, the data were treated according to Eq. 11, since retention times of the drugs were extremely long because of the highly hydrophobic nature of phenothiazine derivatives. The $K_c$ values determined by HPLC method were in fair agreement with those obtained by other methods, such as solubility and spectroscopic methods. As shown in Fig. 4, for example, $K_c$ values by HPLC method were well correlated to those by UV spectral method with a correlation coefficient of 0.998 and reproducibility and accuracy ($\pm5\%$) were not less than the latter method.

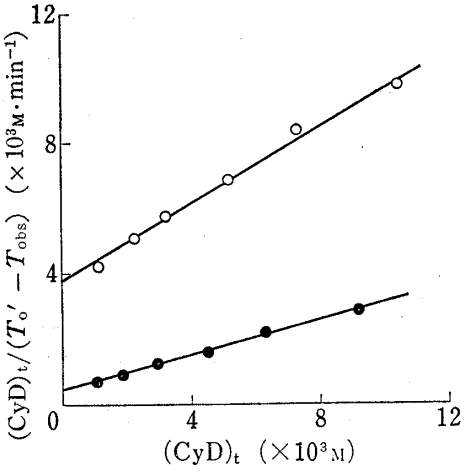


Fig. 3. Determination of $K_c$ from Retention Time Data (Fig. 2) of Phenobarbital-CyD Complexes According to Eq. 10

(○): $\alpha$-CyD system, (●): $\beta$-CyD system.

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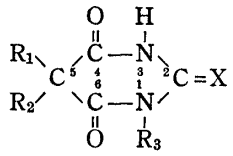
Table I. Stability Constants of Various Barbiturate-Cyclodextrin Complexes determined by HPLC Method



| | Compound | PC[a] | Stability constant ($M^{-1}$) α-CyD system | | β-CyD system | |
|---|---|---|---|---|---|---|
| | | | At pH 5.0[b] | At pH 9.7[c] | At pH 5.0[b] | At pH 9.7[c] |
| (1) | 5-Ethyl-5-*n*-propyl-BA[d] | 2.00 | 530 | 220 | 130 (180)[f] | 110 (70)[f] |
| (2) | 5-Ethyl-5-*n*-butyl-BA | 9.67 | 430 | 220 | 480 (390) | 140 (130) |
| (3) | 5-Ethyl-5-*n*-pentyl-BA | 38.6 | 870 | 450 | 1300 (1200) | 340 (350) |
| (4) | 5-Ethyl-5-*n*-hexyl-BA | 78.5 | 2420 | 680 | 2860 (2150) | 890 (820) |
| (5) | 5-Ethyl-5-*n*-heptyl-BA | 334 | 4150 | 850 | 5190 (2950) | 1720 (960) |
| (6) | 5-Ethyl-5-(1-methylbutyl)-BA (Pentobarbital) | 28.0 | 410 | 110 | 1570 (1040) | 350 (390) |
| (7) | 5-Ethyl-5-isopentyl-BA (Amobarbital) | 28.3 | 140 | 200 | 1750 (1190) | 380 (410) |
| (8) | 5-Ethyl-5-phenyl-BA (Phenobarbital) | 4.40 | 170 | 120 | 1860 (1650) | 170 (160) |
| (9) | 5-Ethyl-1-methyl-5-phenyl-BA (Mephobarbital) | 191 | 250 | 120 | 1660 (1580) | 230 (130) |
| (10) | 5-Cyclohexenyl-1,5-dimethyl-BA (Hexobarbital) | 153 | 220 | 220 | 1530 (1280) | 390 (380) |
| (11) | 5,5-Diethyl-TBA[e] | 11.1 | 500 | —[g] | 300 (290) | — |
| (12) | 5-Ethyl-5-*n*-propyl-TBA | 27.9 | 750 | 240 | 540 (300) | 130 (120) |
| (13) | 5-Ethyl-5-*n*-butyl-TBA | 103 | 600 | 260 | 690 (760) | 150 (210) |
| (14) | 5-Ethyl-5-*n*-pentyl-TBA | 306 | 1850 | 480 | 2110 (2380) | 480 (520) |
| (15) | 5-Ethyl-5-*n*-hexyl-TBA | 926 | 2870 | 960 | 4830 (3150) | 1120 (1400) |
| (16) | 5-Ethyl-5-(1-methylbutyl)-TBA (Thiopental) | 326 | 280 | 230 | 2400 (2700) | 430 (340) |
| (17) | 5-Ethyl-5-phenyl-TBA (Thiophenobarbital) | 63.9 | 3300 | — | 3540 (3900) | — |

*a*) Partition coefficient, between $CHCl_3$ and aqueous pH 5.0 buffer.
*b*) At pH 5.0 barbiturates are substantially in free form.
*c*) At pH 9.7 barbiturates are substantially ionized.
*d*) BA: barbituric acid.
*e*) TBA: thiobarbituric acid.
*f*) Values in parenthesis were determined by UV spectroscopic method.
*g*) Could not be determined with accuracy due to the small changes of retention times.

Table II. Stability Constants of β-Cyclodextrin–Phenothiazine Complexes at 25°

| | Compound | PC[a] | Stability constant ($M^{-1}$) HPLC method[b] | UV method[c] | CD method[c] |
|---|---|---|---|---|---|
| (18) | Chlorpromazine | 10.9 | 8310 | 12000 | 7900 |
| (19) | Chlorpromazine sulfoxide | 0.04 | 480 | 500 | —[d] |
| (20) | Methopromazine | 1.38 | 8060 | 13000 | 8000 |
| (21) | Promethazine | 3.21 | 2020 | 2100 | 1400 |
| (22) | Levomepromazine | 5.97 | 16400 | 25000 | 16000 |
| (23) | Propericiazine | 0.11 | 4230 | 5300 | — |
| (24) | Prochlorperazine | 29.0 | 40800 | 34000 | 25000 |

*a*) Partition coefficient, between cyclohexane+*n*-octanol (9:1) and aqueous pH 5.0 buffer at 25°.
*b*) In 0.1 M phosphate buffer (pH 7.0), using cation exchange column.
*c*) In 0.1 M phosphate buffer (pH 7.0).
*d*) Could not be determined with accuracy due to the small changes of CD spectra.

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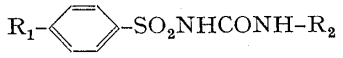
Table III. Stability Constants of β-Cyclodextrin–Sulfonamide Complexes at 25°

| | Compound | PC[a] | p$K_a$[b] | Stability constant ($M^{-1}$) HPLC method[c] | Solubility method[d] | UV method[e] |
|---|---|---|---|---|---|---|
| (25) | Sulfapyridine | 0.74 | 8.56 | 450 | 500 | 480 |
| (26) | Sulfadiazine | 0.58 | 6.37 | 340 | 340 | 140 |
| (27) | Sulfamerazine | 2.53 | 6.85 | 220 | 150 | 170 |
| (28) | Sulfamonomethoxine | 6.84 | 6.05 | 380 | 310 | 250 |
| (29) | Sulfadimethoxine | 36.8 | 5.98 | 340 | 180 | 110 |
| (30) | Sulfisomidine | 0.42 | 7.47 | 140 | 130 | 130 |
| (31) | Sulfamethomidine | 3.26 | 7.06 | 300 | 220 | 150 |
| (32) | Sulfisomezole | 9.05 | 5.72 | 860 | 760 | 600 |
| (33) | Sulfisoxazole | 6.52 | 4.79 | 730 | 460 | 320 |
| (34) | Sulfathiazole | 1.02 | 7.23 | 1860 | 1800 | 1650 |
| (35) | Sulfamethizole | 3.07 | 5.22 | 1270 | 1070 | 550 |
| (36) | Sulfaphenazole | 38.9 | 5.87 | 420 | 230 | 110 |

a) Partition coefficient, between $CHCl_3$ and aqueous pH 7.0 buffer at 25°.
b) Dissociation of amide proton (see ref. 13).
c) In 0.1 M phosphate buffer (pH 3.0), using cation exchange column.
d) In distilled water.
e) In 0.1 M phosphate buffer (pH 7.0).

Table IV. Stability Constants of β-Cyclodextrin–Sulfonylurea Complexes at 25°



| | $R_1$ | $R_2$ | PC[a] | p$K_a$[b] | Stability constant ($M^{-1}$) HPLC method[c] | Solubility method[d] |
|---|---|---|---|---|---|---|
| (37) | $CH_3$– | $-CH_3$ | 8.91 | 5.24 | 200 | 250 |
| (38) | $CH_3$– | $-CH_2CH_3$ | 13.8 | 5.37 | 220 | 260 |
| (39) | $CH_3$– | $-CH_2CH_2CH_2CH_3$ (Tolbutamide) | 331 | 5.27 | 250 | 320 |
| (40) | $CH_3$– |  | 4.47 | 5.95 | 640 | 770 |
| (41) | $CH_3$– |  | 21.9 | 5.71 | 210 | 200 |
| (42) | $CH_3$– |  | 794 | 5.50 | 1500 | 1000 |
| (43) | $CH_3$– |  | 1290 | 4.38 | 230 | 470 |
| (44) | Cl– | $-CH_3$ | 14.5 | 4.77 | 220 | 220 |
| (45) | Cl– | $-CH_2CH_3$ | 61.7 | 4.84 | 210 | 180 |
| (46) | Cl– | $-CH_2CH_2CH_3$ (Chlorpropamide) | 186 | 4.92 | 210 | 200 |
| (47) | Cl– | $-CH_2CH_2CH_2CH_3$ | 646 | 4.92 | 230 | 240 |
| (48) | Cl– |  (Chlorpentazaide) | 6.92 | 5.68 | 530 | 490 |
| (49) | Cl– |  | 2400 | 4.94 | 1340 | 1100 |
| (50) | Cl– |  | 4070 | 3.97 | 200 | 260 |
| (51) | $CH_3CO$– |  (Acetohexamide) | 275 | 4.63 | 1100 | 610 |
| (52) | $NH_2$– | $-CH_2CH_2CH_2CH_3$ (Carbutamide) | 10.2 | 5.96 | 180 | 130 |

a) Partition coefficient (by S. Goto *et al.*, see ref. 9).
b) Dissociation of sulfonamide proton (by S. Goto *et al.*, see ref. 9).
c) In 0.1 M phosphate buffer (pH 7.0), using anion exchange column.
d) In distilled water.

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## Physicochemical Properties and Stability Constants

It is noteworthy that the HPLC method developed here was applicable to weak interaction systems which generally do not accompany a significant spectral changes by complexation, particularly for α-CyD system.[8a] Figure 5 shows the relationship between $K_c$ for complexes of α-CyD-barbiturates and number of carbon atoms in 5-C substituents of the drugs. Sigmoidal correlations obtained in Fig. 5 may be the reflection of steric requirement in guest-host interaction, *i.e.*, smaller or larger substituents at 5-C is rather unfavorable toward α-CyD cavity to form stable complex. In Fig. 6, the sigmoidal correlations between $K_c$ and partition coefficient of guest molecule were also observed for the barbiturates having aliphatic chains at 5-C. While the drugs bearing cyclic or bulky substituents such as amobarbital (**7**), phenobarbital (**8**), mephobarbital (**9**), hexobarbital (**10**), and thiopental (**16**) showed negative deviations from the general correlation curves. Although similar results were obtained in β-CyD system,[8a] a steric requirement of inclusion complexation was much more strict in α-CyD-barbiturates. Importance of spacial relationship between host and guest molecules was further found in Table IV. For example, cyclohexyl derivatives (**42**, **49**, and **51**) showed significantly large

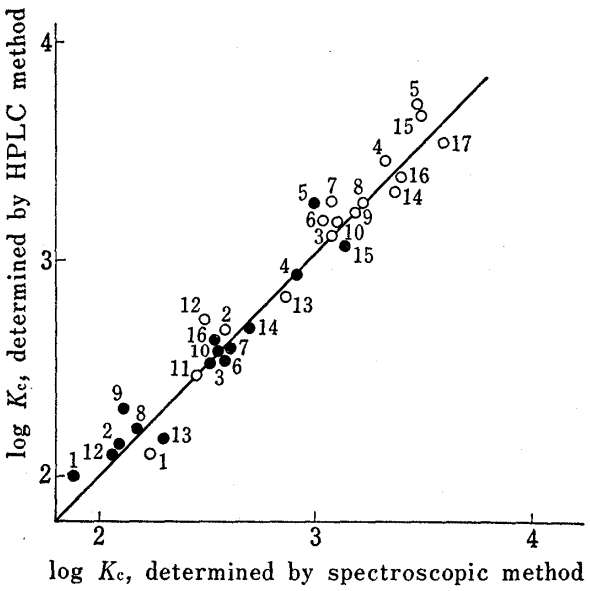


Fig. 4. Relationship between Stability Constants of Barbiturate-β-CyD Complexes determined by HPLC Method and Those determined by Spectroscopic Method

Numbers refer to compounds in Table I.
(○): at pH 5.0, (●): at pH 9.7.

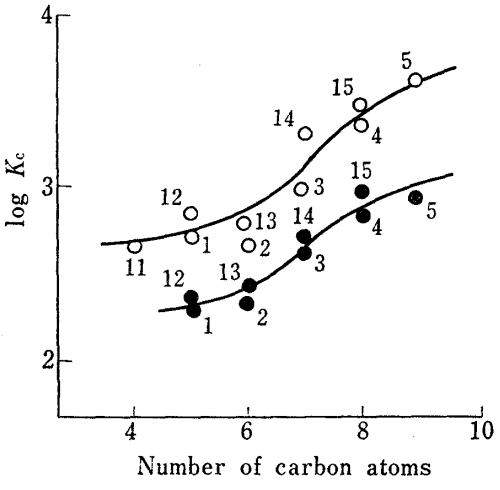


Fig. 5. Relationship between Stability Constants of α-CyD Complexes and Number of Carbon Atoms in 5-Substituents of Barbiturates

Numbers refer to compounds in Table I.
(○): at pH 5.0, (●): at pH 9.7.

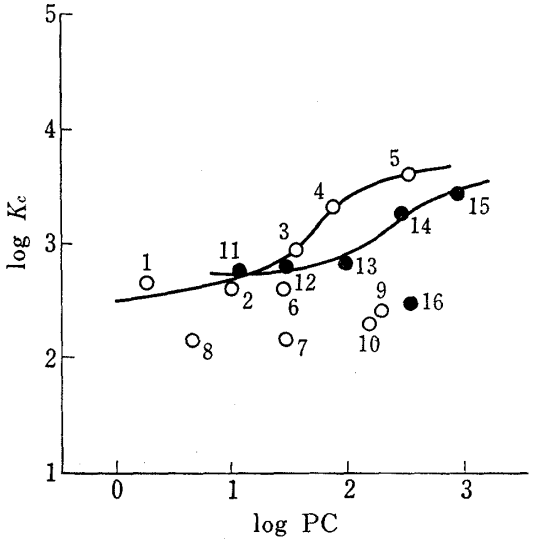


Fig. 6. Relationship between Stability Constants of α-CyD Complexes at pH 5.0 and Partition Coefficients of Their Guest Molecules

Numbers refer to compounds in Table I.
(○): barbituric acid derivatives,
(●): thiobarbituric acid derivatives.

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$K_c$ values in the series of sulfonylureas, indicating a favorable fitness of cyclohexyl moiety within the cavity of $\beta$-CyD.

It is interesting to note that the drugs with sulfur containing substituents, such as thiobarbiturates in Table I, sulfathiazole (**34**) sulfamethizole (**35**) in Table III showed larger $K_c$ values. Furthermore, $K_c$ values for phenothiazines were the largest among the drugs studied. Favorable inclusion of these drugs may be due to the relatively large hydrophobic property,[14] as expected from their partition coefficients, in general. In sulfonylamides and sulfonylureas, however, no linear correlations between $K_c$ values and partition coefficients as well as $pK_a$ were generally found, which may be ascribed to the heterogeneous character of the substituents of the drugs.

As mentioned above, all results suggest that steric and hydrophobic factors of the guest molecules were largely responsible for these complexations.

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