© *1991 The Chemical Society of Japan* *Bull. Chem. Soc. Jpn.*, ***64***, *1979—1981 (1991)*

Association of *p*-Halofluorobenzenes with *α*- and *β*-Cyclodextrins in Aqueous Medium

Tatsuyoshi Takuma, Toshio Deguchi, and Isao Sanemasa*
Department of Chemistry, Faculty of Science, Kumamoto University, Kurokami 2-39-1, Kumamoto 860
(Received January 14, 1991)

Synopsis. The complex formation of *α*- and *β*-cyclodextrins (CyDs) with *p*-(chloro, bromo, and iodo)fluorobenzenes has been studied in aqueous medium at 25 °C. Formation constants are compared with those of CyD–monohalobenzene systems.

The concept of microscopic binding constant (MBC concept) has been proposed by Connors and Pendergast.[1] They applied the concept to *α*-cyclodextrin (CyD) complex formations with various 1,4-disubstituted benzenes. In a system consisting of a guest substrate having two sites, X and Y, and a host with a single binding site (*α*-CyD), two isomeric 1 : 1 complexes can exist, X′Y and XY′, where the superscript prime indicates the binding site. The observed 1 : 1 formation constant, $K_{11}{}^{XY}$, is related to microscopic binding constants, $K_{X'Y}$ and $K_{XY'}$, as $K_{11}{}^{XY}=K_{X'Y}+K_{XY'}$. If the two substrate sites are identical, the equation becomes $K_1{}^{XX}=2K_{X'X}$.

We studied host–guest associations using *α*-, *β*-, and *γ*-CyDs as hosts and four monohalobenzenes,[2] X–C_6H_5, where X refers to a halogen atom, and four symmetrical *p*-dihalobenzenes,[3] X–C_6H_4–X, as guests. Based on a comparison of their 1 : 1 formation constants, we discussed the validity of the MBC concept.[3] It turned out that the equation, $K_{11}{}^{XX}=2K_{X'X}$, holds for chloro- and bromobenzene, but this is not the case for fluoro- and iodobenzene. We concluded therefore that the concept does not necessarily apply to *α*-CyD complex formations with all of symmetrical *p*-disubstituted benzenes.

The present work is concerned with *α*- and *β*-CyD complex formations with *p*-dihalobenzenes, X–C_6H_4–Y, where X and Y refer to different halogen atoms. One of the aimes of the present study is to discuss the validity of the MBC concept. There are many possible XY combinations. The formation constants of *α*- and *β*-CyD with monohalobenzenes and symmetrical *p*-dihalobenzenes increase with an increase in the size of the halogen atom.[2,3] It is therefore preferable to use either fluoro- or iodobenzene derivatives in order to make clear the difference of another halogen atom. Here we chose *p*-halofluorobenzenes.

In the case of *β*-CyD complex formations, where the MBC concept cannot be applied, it is of interest to see if there is any relationship between the 1 : 1 association constant of X–C_6H_4–Y and that of X–C_6H_5 and Y–C_6H_5. This is another incentive of the present study.

The method used in this work to determine the association constant is the same as that employed in our previous works,[2—4] and is based on the volatility of guest in aqueous solutions. Volatile guest molecules are driven out to the gas phase by introducing an inert gas at a constant flow rate into the aqueous solution. The volatilization rate is measured with and without addition of CyD; the rate decreases as a result of the association with CyD.

Experimental

Materials and Preparation of Sample Solutions. Deionized distilled water was used throughout the experiments. An appropriate amount of *α*- or *β*-CyD of guaranteed grade (Nakarai Chemical Co.), dried over phosphorus pentoxide under vacuum, was weighed and dissolved in water to prepare CyD stock solutions of desired concentrations. Three guest substances, (*p*-chloro-, *p*-bromo-, and *p*-iodo-)fluorobenzenes, were used as received; the minimum purities are 99.0, 98.0, and 98.0%, respectively, as claimed by the manufacturer (Tokyo Kasei Kogyo Co.). An aqueous stock solution of each guest was prepared by adding an excess of each *p*-dihalobenzene to water and stirring for at least 24 h in the dark. After leaving the mixture standing for at least 24 h, a portion of the saturated guest solution was transferred to a separatory funnel and the absorbance of its cyclohexane extract was measured to determine the guest concentration at the following wavelengths: *p*-chloro- at 270 (or 263), *p*-bromo- at 270, and *p*-iodo-fluorobenzene at 271.8 nm.

A portion of the saturated guest solution was transferred into a 2.5ϕ×25 cm cylindrical glass tube. An appropriate fraction of the CyD stock solution was then added, and the solution was diluted with water to 80 cm^3. The concentration ranges of host and guest are given in the footnote of Table 1.

Apparatus and Procedures. The apparatus and the experimental procedure were the same as those described in previous papers.[2,3] Nitrogen gas was bubbled into the aqueous guest solution with or without CyD placed in the cylindrical glass tube immersed in a bath thermostated at 25.0±0.1 °C, at a constant flow rate suitable for each guest volatility: *p*-chloro- at 50, *p*-bromo- at 80, and *p*-iodofluorobenzene at 100 cm^3 min^{-1}. The N_2 gas leaving the sample solution was passed through a glass column of 0.5 ϕ×23 cm filled to 8 cm in length with XAD-2 resin beads (80—150 mesh). The guest adsorbed on the resin within a fixed time was eluted out with 4 cm^3 of cyclohexane, and the amount of guest, ΔQ_ϕ, was determined by UV absorption measurements.

Results and Discussion

Determination of Formation Constants. The equation derived in a previous paper[4] was used to estimate the 1 : 1 and 2 : 1 (host : guest) association constants, K_1 and K_2:

$$\ln(C_\phi - Q_\phi V^{-1}) = -kt/(1+K_1C_{\mathrm{CyD}}+K_1K_2C^2{}_{\mathrm{CyD}}) + \ln C_\phi$$
$$= -k't + \ln C_\phi, \qquad (1)$$

where C_{CyD} and C_ϕ refer to the total concentration of host and that of guest, respectively, Q_ϕ is the sum of ΔQ_ϕ from time 0 to *t*, *V* is the volume of the aqueous solution, *k* is the rate constant for transfer of guest molecules from the aqueous to gas phase, and

$$K' = k/(1+k_1C_{\mathrm{CyD}}+K_1K_2C^2{}_{\mathrm{CyD}}). \qquad (2)$$

Rearrangement of Eq. 2 yields

$$1/k' = K_1K_2C^2_{\mathrm{CyD}}/k + K_1C_{\mathrm{CyD}}/k + 1/k. \qquad (3)$$

The plots according to Eq. 1 for all the *p*-halofluorobenzene–CyD systems examined in this work gave straight lines over the whole aeration time, during which ca. 70% of the guest molecules present initially in the sample solutions were purged. Slopes of the resulting straight lines, k' (and k), were evaluated by the least-squares method. Typical $1/k'$ vs. C_{CyD} plots are shown in Figs. 1 and 2. The plots exhibit upward curvatures for α- and β-CyDs, indicating formations of both 1 : 1 and 2 : 1 (host : guest) complexes. The K_1 and K_2 values were determined by the curve-fitting method and are summarized in Table 1. Concerning the present host–guest systems, there are no data available in the literature.

α-Cyclodextrin Complex Formation. According to the MBC concept,[1] the 1 : 1 formation constant is to be 134 for *p*-chlorofluorobenzene (abbreviation; Cl–F), 544 for *p*-bromofluorobenzene (Br–F), and 1134 $\mathrm{M^{-1}}$ for *p*-iodofluorobenzene (I–F), where 1 M=1 mol $\mathrm{dm^{-3}}$. The expected value for each guest, however, is not in agree-

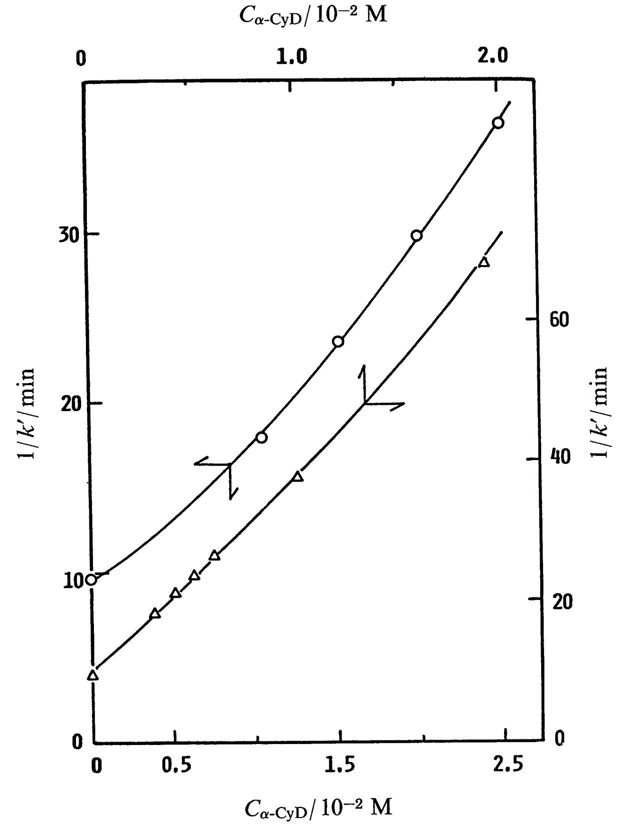

Fig. 1. Plots of $1/k'$ vs. C_{CyD}. α-CyD–*p*-chlorofluorobenzene (○). –*p*-bromofluorobenzene (△).

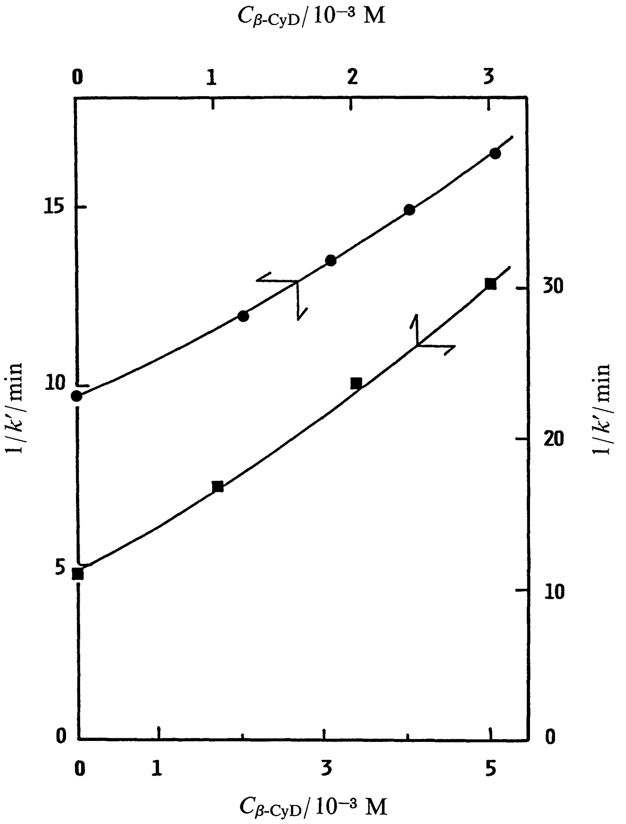

Fig. 2. Plots of $1/k'$ vs. C_{CyD}. β-CyD–*p*-chlorofluorobenzene (●), –*p*-iodofluorobenzene (■).

Table 1. Formation Constants, K_1 (1 : 1) and K_2 (2 : 1) of (Cyclodextrin: *p*-Halofluorobenzene) Complexes at 25 °C[a]

Guest (*p*-Halofluorobenzene)	Host (Cyclodextrin)	Formation constant	
		K_1 $\mathrm{M^{-1}}$	K_2 $\mathrm{M^{-1}}$
p-Chlorofluorobenzene	α-CyD	65±4	29±6
	β-CyD	120±2	30±10
p-Bromofluorobenzene	α-CyD	250±7	9±2
	β-CyD	180±40	50±50
p-Iodofluorobenzene	α-CyD	980±30	50±30
	β-CyD	510±20	50±10

a) The total concentration of guest and that of host are as follows: *p*-chlorofluorobenzene ((4.53—4.68)×10^{-4} M) -α-CyD ((1.06—2.51)×10^{-2} M) and -β-CyD ((2.01—5.09)×10^{-3} M); *p*-bromofluorobenzene (2.70—2.82)×10^{-4} M) -α-CyD ((3.01—19.2)×10^{-3} M) and -β-CyD ((1.00—8.03)×10^{-3} M); *p*-iodofluorobenzene ((1.69—2.32)×10^{-6} M) -α-CyD ((0.258—2.04) ×10^{-3} M) and -β-CyD ((1.01—3.02)×10^{-3} M).

ment with the corresponding experimental value.

Of halogen atoms, iodine with the van der Waals radius of 2.2 Å best fits to the cavity of α-CyD. The van der Waals contact area within the cavity decreases in going from iodine to fluorine atom. This is the reason that the K_1 of iodobenzene is much larger than that of fluorobenzene.[2] When α-CyD associates with the I–F guest, the host molecule is expected to associate preferentially with the iodine atom of this guest. Under the present experimental conditions where CyD molecules are always in large excess of guest molecules, there are many chances for CyD molecules to come into contact with the fluorine atom side of I–F. Nevertheless, it does not seem that the association with the fluorine atom contributes to the K_1 of I–F, because this value is almost equal to the K_1 of iodobenzene itself.

It is noteworthy that the K_1 of Cl–F or Br–F is considerably smaller than that of chlorobenzene or bromobenzene itself. This is in conflict with the MBC concept and is difficult to explain even if the association with the fluorine atom of Cl–F or Br–F is assumed not to occur. Here we postulate that the fluorine atom has a negative contribution to α-CyD complex formations, that is, the presence of this atom reduces the K_1 of Cl–F or Br–F (or I–F) that would be expected from the corresponding mono(chloro, bromo, or iodo)benzene. This assumption is made based on the fact that symmetrical *p*-difluorobenzene has a much smaller K_1 value than that of monofluorobenzene itself. The addition of an F atom to the para-position of the benzene ring might render the guest molecule somewhat hydrophilic (not the guest molecule as a whole, but locally, probably at around the F atom), which is unfavorable to the association with CyD.

When a substituent is the methyl group, a typical hydrophobic group, the MBC concept holds. For instance, as was pointed out in a previous paper,[3] the toluene ($K_1=33\pm3$)-*p*-xylene ($K_1=72\pm7$ M^{-1})[4] system supports the concept.

Connors and Pendergast derived an equation which correlates 2:1 (host:guest) formation constants to microscopic binding constants.[1] In the present paper, however, we are not concerned with this point, because K_2 values are in general less reliable than K_1 values.

β-Cyclodextrin Complex Formation. Since β-CyD can include a benzene ring as a whole, the MBC concept is not applicable to 1,4-disubstituted benzenes unless the substituent groups are not so large as to hinder the approach of a β-CyD molecule to the benzene ring.

We see an interesting relationship between the K_1 of Cl–F, Br–F, or I–F and that of the corresponding monohalobenzene. Namely, the K_1 of Cl–F, Br–F, or I–F is neary equal to half the sum of the K_1 of fluorobenzene and that of chloro-, bromo-, or iodobenzene, respectively. It should be mentioned here that this relationship does not hold for the toluene ($K_1=140\pm10$) -*p*-xylene ($K_1=240\pm10$ M^{-1})[4] system; in this case, the K_1 of *p*-xylene is approximately twice that of toluene. A further study is necessary using various kinds of both symmetrical and unsymmetrical 1,4-disubstituted benzenes as guests to see whether this arithmetic mean is a general rule for unsymmetrical guests or only applicable to the *p*-dihalobenzene series.

References

1) K. A. Connors and D. D. Pendergast, *J. Am. Chem. Soc.*, **106**, 7607 (1984).

2) T. Takuma, T. Deguchi, and I. Sanemasa, *Bull. Chem. Soc. Jpn.*, **63**, 1246 (1990).

3) T. Takuma, T. Deguchi, and I. Sanemasa, *Bull. Chem. Soc. Jpn.*, **64**, 480 (1991).

4) I. Sanemasa and Y. Akamine, *Bull. Chem. Soc. Jpn.*, **60**, 2059 (1987).