Journal of Inclusion Phenomena and Molecular Recognition in Chemistry **28:** 349–358, 1997.

Solvent Extraction of Alkali Metal Picrates by Lipophilic Cyclodextrin Derivatives

KAZUTOSHI KOBAYASHI[1,⋆] GERHARD WENZ[2] and WOLFGANG KNOLL[1,3,⋆⋆]

[1]*Max-Planck-Institut für Polymerforschung, Ackermannweg 10, D-55128 Mainz, Germany;*
[2]*Polymer-Institut, Universität Karlsruhe, Hertz-Straße 16, D-76187 Karlsruhe, Germany;*
[3]*Frontier Research Program, The Institute of Physical and Chemical Research (RIKEN), Hirosawa 2-1, Wako-shi, Saitama 351-01, Japan.*

(Received: 2 January 1997; in final form: 28 February 1997)

Abstract. Lipophilic cyclodextrin (CD) derivatives were prepared to extract alkali metal cations from a water phase into an organic phase. The extraction equilibrium constant, K_{ex}, was determined by the solvent extraction method using UV absorption spectroscopy. Hydroxyl groups at the carbons in the 2,6-positions of CD molecules were dipropylated to add the hydrophobicity for dissolving into organic solvents, and furthermore hydroxyl groups at the carbons in the 3-position of these derivatives were acylated as complexing sites with the alkali metal cations. These CD derivatives formed a 1 : 1 complex with alkali metal cations, except for the case of Li^+, and transported the alkali metal cations from a water phase into a benzene phase. The initial concentrations of alkali metal cation and picrate anion in the water phase and that of the CD derivatives in the organic phase strongly influenced the extraction equilibrium. Extraction of the alkali metal cation by the derivative without acyl groups was not detected. K_{ex} values of these CD derivatives are of the same order of magnitude as or larger than those of crown ethers. The order of the K_{ex} values in all cases is $Li^+ < Na^+ < K^+ \simeq Rb^+ \simeq Cs^+$, although these CD derivatives have no special selectivity for the alkali metal cations. The cation extraction mechanism was interpreted by an induced-fit mechanism.

Key words: Solvent extraction, lipophilic cyclodextrin derivatives, metal picrate

1. Introduction

Cyclodextrins (CDs) together with crown ethers are well known as typical examples of organic host compounds. CD molecules are cyclic oligosaccarides containing six, seven, eight or more anhydroglucose units joined by α-1,4 glucosidic linkages, as shown in Figure 1 [1]. CD molecules are hydrophilic hosts that can include hydrophobic guest molecules in their hydrophobic cavity [2–5]. On the other hand, crown ethers consist of hydrophobic exteriors, so that they are lipophilic hosts, which can include cations, especially alkali and alkaline earth metal ions, into their cavities via an ion–dipole interaction [6–10]. Pedersen was the first to study the extraction of metal cations from a water phase into an organic phase by crown

⋆ *Present address*: Frontier Research Program, The Institute of Physical and Chemical Research (RIKEN), Hirosawa 2-1, Wako-shi, Saitama 351-01, Japan.
⋆⋆ Author for correspondence.

ethers [6]. In general, oxygen macrocycles such as crown ethers are effective for the extraction of alkali and alkaline earth metal cations but not transition metal cations. Conversely, their nitrogen analogs are effective for transition metal ions but not alkali metal cations, [11–23]. The metal cation binding properties of crown ether derivatives, studied on the basis of their solvent extraction properties, have been reported previously [6–10, 24–28]. In general the selectivity of crown ether derivatives for metal cations depends on the cavity size of the host compounds. In other words, the metal cation that fits best to the crown ether cavity is most extractable.

In previous papers we have reported a method for the synthesis of lipophilic CD derivatives together with some characterization of their properties [29–32]. The purpose of the present study is to develop a new class of CD derivatives that have better ion selectivity and/or ion transportability than crown ethers. In this paper we report the syntheses of acyl derivatives of lipophilic CD molecules and discuss their ability to form complexes with alkali metal cations, using the solvent extraction method.

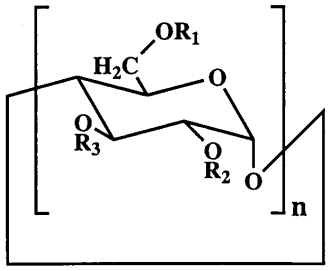
2. Experimental

2.1. Preparation of lipophilic CD derivatives

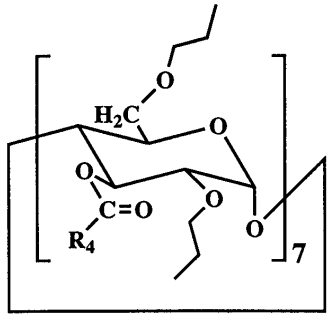
2.1.1. *General*

The structures of CDs and CD derivatives used in this study are shown in Figure 1. β-CD, **2**, was used after careful drying. Dichloromethane was freshly distilled; other reagents were used as received. The reactions were monitored by thin layer chromatography (TLC) on Silica Gel 60 (Merck), using a 6 : 4 ratio mixture of *tert*-butyl methyl ether and petroleum ether (solvent A) and a 1 : 1 mixture of *tert*-butyl methyl ether and dichloromethane (solvent B) as solvents. Detection was by charring with 5% sulfuric acid in ethanol. The crude product was fractionated and purified by liquid chromatography (overpressure 0.02 MPa) on Silica Gel 60 (40–63 μm, Merck) and aluminum oxide (active neutral, 63–200 μm, Merck) with the same solvent as TLC.

Mass spectroscopy is known to be a precise method for the detection of over- or under-alkylated CD products [33]. After the purification of CD derivatives, the fast atom bombardment mass spectra of CD derivatives were measured for this purpose by a GV-Instruments ZAB2-SE-FPD mass spectrometer. NMR spectra (^{1}H, 300.13 MHz; ^{13}C, 75.46 MHz) were obtained with a Bruker AW 300 spectrometer at 20 °C. All chemical shifts were referenced to internal TMS. The ^{13}C NMR signals were assigned by using the DEPT (distortionless enhancement by polarization transfer) technique.



1 $R_1=R_2=R_3=H$, n=6; α-CD
2 $R_1=R_2=R_3=H$, n=7; β-CD
3 $R_1=R_2=R_3=H$, n=8; γ-CD
4 $R_1=R_2$=n-propyl, $R_3=H$, n=7; DPCD



5 $R_4=CH_3$; DPACCD
6 $R_4=CH_3CH_2$; DPPRCD
7 $R_4=CH_3CH_2CH_2$; DPBUCD
8 $R_4=(CH_3)_2CH$; DPISCD

Figure 1. Molecular structures of native CDs and CD derivatives.

2.1.2. *Synthesis of Heptakis(2,6-di-O-propyl)-β-CD (DPCD),* **4**

This synthesis was basically performed as described in the previous paper [30].

2.1.3. *Syntheses of acylated CD derivatives*

Compound **4** (1 mmol) was allowed to react with acid anhydride (11 mmol) in the presence of 4-(dimethylamino)pyridine (0.35 mmol) and triethylamine (11 mmol) in 20 mL of dichloromethane solution at 40 °C under nitrogen gas for 5 days. The reagents were replenished every day. After work up, the product was subjected silica gel chromatography and aluminum oxide chromatography.

5: Heptakis(2,6-di-*O*-propyl-3-*O*-acetyl)-β-CD (DPACCD)
After the chromatography, **5** was obtained as a colorless oil (38.6%) with the R_f values of 0.09 (solvent A) and 0.22 (solvent B). ^{1}H NMR ($CDCl_3$): δ = 5.18 (t, 1H, J = 4.4), 5.01 (d, 1H, J = 2.1), 3.91 (d, 2H, J = 5.0), 3.78 (t, 1H, J = 4.2), 3.53–3.19 (m, 6H), 2.05 (s, 3H), 1.61–1.43 (m, 4H), 1.15 (t, 3H, J = 7.4), 0.86 (t, 3H, J = 7.4); ^{13}C NMR ($CDCl_3$): δ = 171.0, 98.6, 78.3, 77.3, 73.0, 72.7, 72.5, 71.1, 69.2, 22.9, 22.8, 21.0, 10.6, 10.2.

6: Heptakis(2,6-di-*O*-propyl-3-*O*-propionyl)-β-CD (DPPRCD)
After the chromatography, **6** was obtained as a colorless oil (12.6%) with the R_f values of 0.16 (solvent A) and 0.26 (solvent B). ^{1}H NMR ($CDCl_3$): δ = 5.09 (t, 1H, J = 4.4), 4.89 (d, 1H, J = 2.1), 3.81 (d, 2H, J = 5.0), 3.69 (t, 1H, J = 4.2), 3.46–3.13 (m, 6H), 2.30–2.10 (m, 2H), 1.51–1.32 (m, 7H), 0.98 (t, 3H, J = 7.4), 0.75 (t, 3H, J = 7.4); ^{13}C NMR ($CDCl_3$): δ = 172.0, 98.4, 78.1, 77.1, 73.0, 72.6, 72.5, 71.1, 69.2, 27.3, 23.0, 22.8, 10.8, 10.2, 8.9.

7: Heptakis (2,6-di-*O*-propyl-3-*O*-butyryl)-β-CD (DPBUCD)
After the chromatography, **7** was obtained as a colorless oil (36.8%) with the R_f values of 0.25 (solvent A) and 0.36 (solvent B). ^{1}H NMR ($CDCl_3$): δ = 5.20 (t, 1H, J = 4.4), 5.00 (d, 1H, J = 2.1), 3.92 (d, 2H, J = 5.0), 3.80 (t, 1H, J = 4.2), 3.57–3.20 (m, 6H), 2.38–2.07 (m, 2H), l.62–1.46 (m, 6H), O.92–0.81 (m, 9H); ^{13}C NMR ($CDCl_3$): δ = 172.0, 98.3, 77.9, 77.0, 73.0, 72.5, 72.2, 71.1, 69.3, 35.9, 23.0, 22.8, 18.1, 13.6, 10.6, 10.3.

8: Heptakis(2,6-di-*O*-propyl-3-*O*-isobutyryl)-β-CD (DPISCD)
After the chromatography, **8** was obtained as a colorless oil (10.5%) with the R_f values of 0.78 (solvent A) and 0.63 (solvent B). ^{1}H NMR ($CDCl_3$): δ = 5.00 (t, 1H, J = 4.4), 4.80 (d, 1H, J = 2.1), 3.72 (d, 2H, J = 5.0), 3.60 (t, 1H, J = 4.2), 3.39–3.01 (m, 6H), 2.41–2.22 (m, 1H), l.41–l.29 (m, 4H), 1.05–0.85 (m, 6H), 0.76–0.58 (m, 6H); ^{13}C NMR ($CDCl_3$): δ = 174.5, 98.0, 80.5, 79.8, 77.0, 75.2, 72.9, 71.0, 69.6, 33.7, 23.3, 22.9, 19.1, 18.6, 10.6, 10.3.

2.2. SOLVENT EXTRACTION

Analytical grade benzene and metal picrate were used without further purification. Milli Q water was saturated with benzene, and benzene was saturated with water, in order to minimize the volume change on mixing. An aliquot of aqueous solution containing picric acid and metal hydroxide (5 mL) and 5 mL of organic solution containing lipophilic CD derivatives were mixed using a shaker for 40 min, which was found to be sufficient for extraction equilibrium at 25 °C, and the concentration of picrate anion in the aqueous phase was determined spectrophotometrically at 354 nm using a Perkin-Elmer Lambda 9 UV/Vis spectrophotometer, using a molar extinction coefficient of 1.45×10^4 cm^{-1} M^{-1} at 354 nm [7]. The amount of

picrate anion in the organic phase was calculated from the concentration difference in the aqueous phase before and after extraction. No detectable picrate anion was transferred to the organic phase in the absence of CD derivatives.

3. Results and Discussion

The picrate anion is widely used as a counteranion for cation extraction experiments using crown ether derivatives. This is because a complex of crown ether with a metal picrate is more easily extracted into an organic phase due to the high affinity of the picrate anion for the organic solvent. The concentration of the extracted picrate complex can easily be determined by UV spectroscopy due to the colored anion [7–10].

The extraction equilibrium between an aqueous phase containing alkali metal cation (M^+), picrate counter anion (P^-), and an organic phase containing CD derivatives can be formulated as

$$M^+_w + P^-_w + CD_o \overset{K_{ex}}{\rightleftharpoons} [MCDP]_o \tag{1}$$

where K_{ex} is the extraction equilibrium constant; MCDP is an ion pair between a CD-cation complex (MCD^+) and P^-; subscripts 'w' and 'o' denote a water phase and an organic phase, respectively.

The equilibrium constant, K_{ex}, in Equation (1) is defined as

$$K_{ex} = \frac{[MCDP]_o}{[M^+]_w[P^-]_w[CD]_o} \tag{2}$$

where square brackets indicate molar concentrations of these species. When a polar solvent is used as an organic solvent, we should take into account the following dissociation equilibrium in the organic phase,

$$MCDP_o \overset{K_d}{\rightleftharpoons} MCD^+_o + P^-_o \tag{3}$$

where K_d is the dissociation equilibrium constant. It is, however, more complicated to analyze the extraction equilibrium since the dissociation of an ion pair in an organic solvent is not negligible. Thus benzene was chosen as an organic solvent because of its nonpolarity, and (in addition) the high solubility of CD derivatives in it. All the activity coefficients of the chemical species mentioned here are assumed to be unity [10]. No detectable picrate anion was transferred to the organic phase in the absence of CD derivatives, so that the concentration of hydroxide ion in an aqueous phase could be neglected. The $[P^-]_w$ value is easily determined by the spectrophotometric method, and then $[M^+]_w$, $[CD]_o$, and $[MCDP]_o$ can be obtained from the mass balance.

In Figure 2, log ($D_M/[P^-]_w$) values are plotted against $-\log [CD]_o$ values for the complexes of **7** with alkali metal picrates in the benzene–water system. D_M is

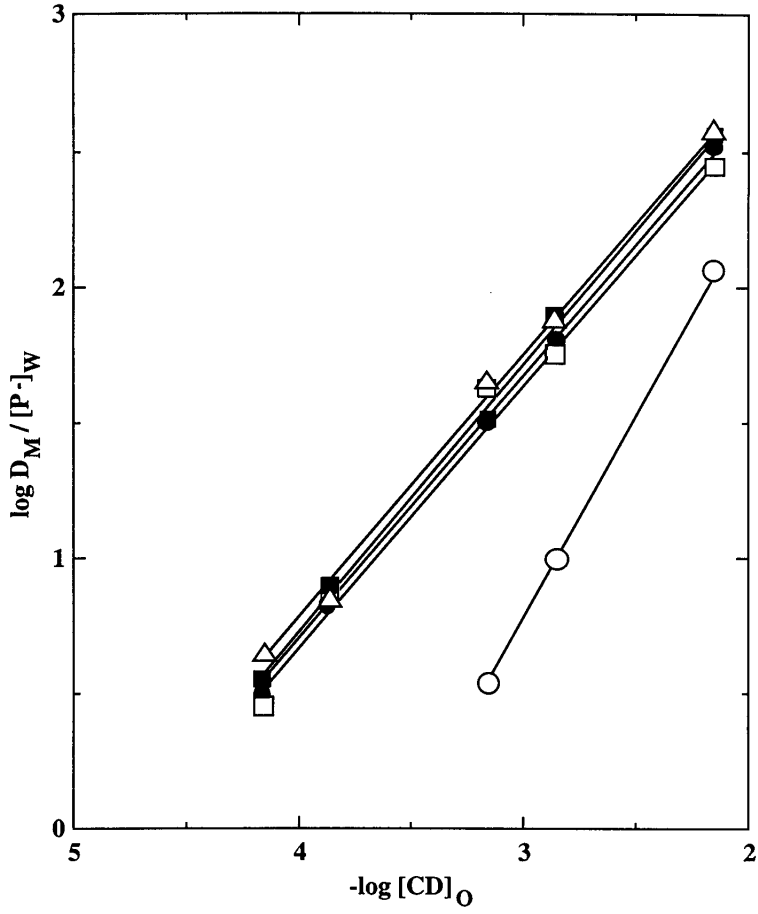


Figure 2. Plots of $\log(D_M/[P^-]_w)$ against $-\log[CD]_o$ for the extraction of univalent metal picrate by DPBUCD in the benzene–water system at 25 °C. The concentration of the metal cation and the picrate anion are 1×10^{-4} M and 7×10^{-5} M, respectively. ○: Li, ●: Na, ■: K □: Rb, △: Cs.

the extraction ratio of the metal picrate by CD derivatives from an aqueous phase into an organic phase; it is therefore defined as

$$D_M = \frac{[M^+]_{o,t}}{[M^+]_{w,t}} \tag{4}$$

where $[M^+]_{o,t}$ and $[M^+]_{w,t}$ represent the total metal cation concentrations in the organic phase and the water phase, respectively; $[M^+]_{o,t}$ and $[M^+]_{w,t}$ in this case are the same as $[MCDP]_o$ and $[M^+]_w$, respectively, because the dissociation of $[MCDP]_o$ in an organic phase and the association of $[M^+]_w$ in a water phase are negligible. Figure 2 shows a linear relationship in a log–log plot with a slope of 1 in every case, except for the case of the **7**–Li^+ complex, indicating that **7** forms

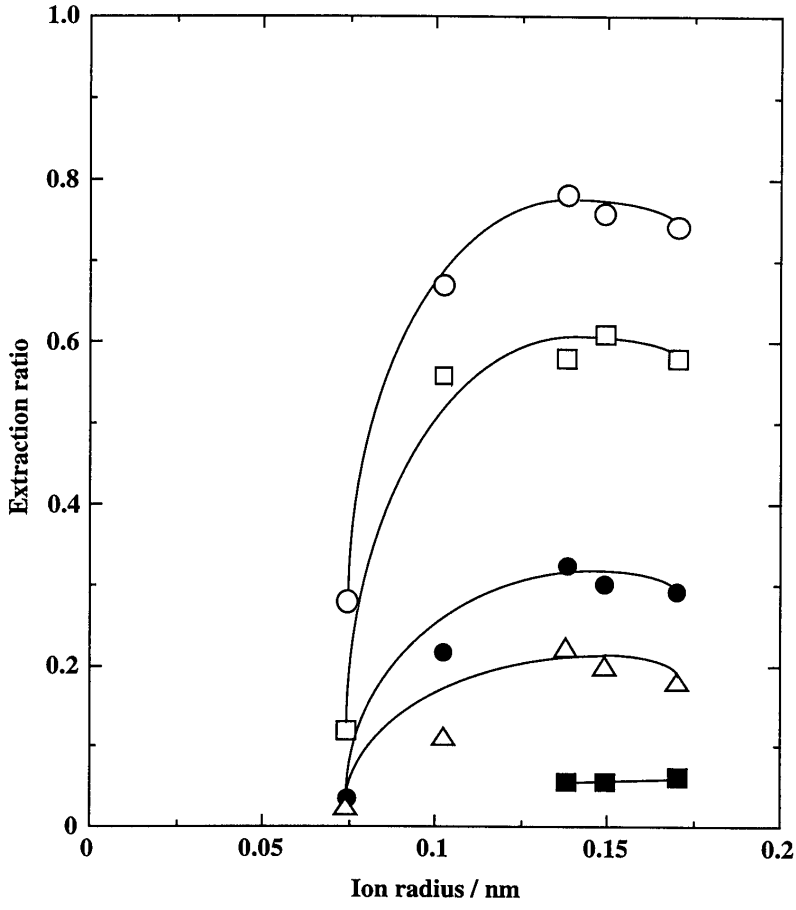


Figure 3. The metal cation concentration effect on the extraction of metal picrate into a benzene phase by DPPRCD against the radii of alkali metal cation (Li^+: 0.074 nm, Na^+: 0.102 nm, K^+: 0.138 nm, Rb^+: 0.149 nm, Cs^+: 0.170 nm). The concentrations of the picrate cation and DPPRCD are 7×10^{-5} M and 7×10^{-4} M, respectively. ○: 1×10^{-1} M, □: 5×10^{-2} M, ●: 1×10^{-2} M, △: 5×10^{-3} M, ■: 1×10^{-3} M.

a 1 : 1 complex with the alkali metal cation. The slope for the case of **7**–Li^+ was 1.5. One possible explanation for this value is that this **7**–Li^+ complex comprises equimolar mixtures of 1 : 1 and 2 : 1 complexes. Another possible explanation is that **7** forms a 3 : 2 complex with Li^+, although such a complex is not likely due to the asymmetric (trapezoidal) shape of CD molecule.

Figure 3 shows the metal cation concentration effect on the solvent extraction by CD derivatives into a benzene phase under the same conditions for metal picrate and CD derivatives concentrations. The order of the extraction ratio was $Li^+ < Na^+ < K^+ \simeq Rb^+ \simeq Cs^+$, regardless of the metal cation concentration. The extraction ratio of metal cation into the organic phase by CD derivatives strongly depends on the metal cation concentration.

Figure 4 shows the extraction constants, K_{ex}, as a function of the radius of the alkali metal cations which are transported by various kinds of CD derivatives into the benzene phase. Extraction of alkali metal cations by **4** could not be detected, which indicates that this CD cavity has only a poor binding potential to the alkali metal cations. On the other hand, CD derivatives having acyl groups could transport the alkali metal cations into the benzene phase. Therefore, it is clear that acyl groups in CD derivatives are needed to interact, include, and transport the alkali metal cations. Among the K_{ex} values of CD derivatives that of **5** is slightly lower, indicating that the cavity size of **5** might be slightly larger than those of **6** and **7**. Extraction of the metal cation by **8** could not be detected. One reason might be that the pore size of **8** is not large enough to include the alkali metal cation into the cavity due to steric hindrance of the bulky substituted group. The other is that **8** could make a complex with the alkali metal cation; however, this **8**–cation complex could not interact with a picrate anion due to steric hindrance of the bulky substituted group. Therefore, this CD–cation complex could not be extracted into the organic phase because it has to be extracted with a co-anion (picrate ion) at the same time because of the charge neutralization on extraction. The level of the K_{ex} values of CD derivatives is quite high and is either the same order of magnitude as or higher than that of crown ethers [10]. The order of the K_{ex} values in all cases is $Li^+ < Na^+ < K^+ \simeq Rb^+ \simeq Cs^+$, which is quite similar to the results obtained for dibenzo-24-crown-8 [28]. In general, the selectivity of crown ether derivatives for metal cations in solvent extraction systems depends largely on the relation between the sizes of the metal cation and of the cavity of the crown ether; in other words, the metal cation which fits the crown ether cavity best is most extractable [10]. Therefore, such a graph has one local maximum when the K_{ex} values are plotted against the ion radii. CD derivatives have no special selectivity for alkali metal cations, as shown in Figure 4. (The reason for this is discussed below.) The shapes of the active sites of some enzymes (e.g. carboxypeptidase A, yeast hexokinase, etc.) are profoundly modified, undergoing large structural changes only after the substrate is bound. This process of recognition is called an induced fit [34]. Ueno *et al.* reported that the attachment of a naphthalene moiety to γ-CD enables this modified γ-CD to become a good host for small molecules, due to an induced fit-type of complexation, i.e., the space regulating effect of the appended naphthalene moiety [35].

The extraction behaviors of **5**, **6**, and **7**, shown in Figure 4, could be interpreted by a similar induced fit mechanism to that mentioned above, providing that the CD derivatives undergo structural changes due to the flexibility of the complexing site when the alkali metal cation is included into the cavity. Extraction of cations by crown ethers largely depends on the size fit, as mentioned above. Extraction of cations by CD derivatives used in this study, however, depends not only on the size fit, but also on the ion–dipole interaction between the acyl groups and the cations, steric (depth) effect of the cavity, space-regulating effect (induced fit), etc. Cation extraction in this system is interpreted as an induced fit mechanism due to

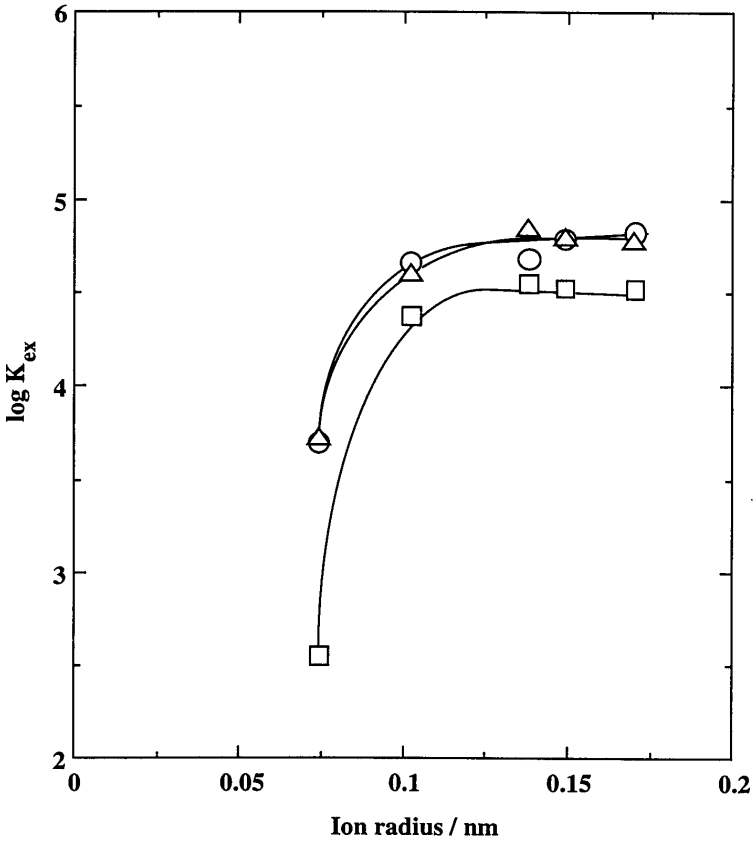


Figure 4. Plots of the extraction constants, K_{ex}, against the radii of alkali metal cation (Li^+: 0.074 nm, Na^+: 0.102 nm, K^+: 0.138 nm, Rb^+: 0.149 nm, Cs^+: 0.170 nm) in a benzene–water system at 25 °C. The concentrations of CD, M^+, and P^- are 7×10^{-4} M, 1×10^{-2} M, and 7×10^{-5} M, respectively. □: DPACCD, △: DPPRCD, ○: DPBUCD.

the flexibility of the complexing site. Therefore, the complex formation between CD derivatives and cations could be considered as a model of the formation of an enzyme–substrate complex in enzymatic catalysis.

Acknowledgments

We would like to thank Mr. Jürgen Thiel for his technical assistance. β-CD was kindly provided by Wacker Chemie GmbH, Munich, Germany. This work was partially supported by the Schlössmann Stiftung.

References

1. D. French: *Adv. Carbohydr. Chem.* **12**, 189 (1957).
2. J. Szejtli: *Cyclodextrins and Their Inclusion Complexes*, Akademiai Kiado, Budapest (1982).

3. W.L. Hinze: *Sep. Purif. Methods* **10**, 159 (1981).
4. M.L. Bender and M. Komiyama: *Cyclodextrin Chemistry*, Springer-Verlag, New York (1978).
5. G. Wenz: *Angew. Chem. Int. Ed. Engl.* **33**, 803 (1994).
6. C.J. Pedersen: *J. Am. Chem. Soc.* **89**, 7017 (1967).
7. H.K. Frensdorff: *J. Am. Chem. Soc.* **93**, 4684 (1971).
8. C.J. Pedersen and H.K. Frensdorff: *Angew. Chem. Int. Ed. Engl.* **11**, 16 (1972).
9. Y. Takeda, Y. Wada, and S. Fujisawa: *Bull. Chem. Soc. Jpn.* **54**, 3727 (1981).
10. Y. Takeda: in F. Vögtle and E. Weber (eds.), *The Solvent Extraction of Metal Ions by Crown Compounds*, Host–Guest Complex Chemistry III, Topics in Current Chemistry, Springer-Verlag, Berlin (1984), pp. 1–38.
11. M. Kodama, E. Kimura, and S. Yamaguchi: *J. Chem. Soc. Dalton Trans.* 2536 (1980).
12. A. Bencini, A. Bianchi, M. Micheloni, P. Paoletti, E. Garcia-Espana, and M.A. Nino: *J. Chem. Soc. Dalton Trans.* 1171 (1991).
13. L.Y. Martin, C.R. Sperati, and D.H. Busch: *J. Am. Chem. Soc.* **99**, 2968 (1977).
14. R. Nagai and M. Kodama: *Inorg. Chem.* **23**, 4184 (1984).
15. M. Kato and T. Ito: *Inorg. Chem.* **24**, 504 (1985).
16. M. Kato and T. Ito: *Inorg. Chem.* **24**, 509 (1985).
17. H. Tsukube: *J. Chem. Soc., Chem. Commun.* 970 (1983).
18. H. Tsukube, K. Takagi, T. Higashiyama, T. Iwachido, and N. Hayama: *J. Chem. Soc. Perkin Trans. 2*, 1541 (1985).
19. H. Tsukube: *J. Coord. Chem.* **16**, 101 (1987).
20. R.M. Izatt, R.L. Bruening, B.J. Tarbet, L.D. Griffin, M.L. Bruening, K.E. Krakowiak, and J.S. Bradshaw: *Pure Appl. Chem.* **62**, 1115 (1990).
21. D. Cordier and M.W. Hosseini: *New J. Chem.* **14**, 611 (1990).
22. H. Tsukube: *J. Chem. Soc. Perkin Trans. I* 615 (1985).
23. H. Tsukube, Y. Kubo, T. Toda, and T. Araki: *J. Polym. Sci.: Polym. Lett. Ed.* **23**, 17 (1985).
24. M. Zhao and W.T. Ford: *J. Incl. Phenom.* **17**, 53 (1994).
25. Y. Takeda and C. Takagi: *J. Incl. Phenom.* **17**, 93 (1994).
26. Y. Takeda: *Bull. Chem. Soc. Jpn.* **53**, 2393 (1980).
27. Y. Takeda and H. Goto: *Bull. Chem. Soc. Jpn.* **52**, 1920 (1979).
28. Y. Takeda: *Bull. Chem. Soc. Jpn.* **52**, 2501 (1979).
29. G. Wenz, E.v.d. Bey, and L. Schmidt: *Angew. Chem. Int. Ed. Engl.* **31**, 783 (1992).
30. G. Wenz: *Carbohydr. Res.* **214**, 257 (1991).
31. G. Wenz, F. Wolf, M. Wagner, and S. Kubik: *New J. Chem.* **17**, 729 (1993).
32. G. Wenz and E.v.d. Bey: in O. Huber and J. Szejtli (eds.), *Proceedings of the 4th International Symposium on Cyclodextrins*, Kluwer, Dordrecht, Netherlands (1988), pp. 133–138.
33. T. Irie, K. Fukunaga, J. Pitha, K. Uekama, H.M. Fales, and E.A. Sokolowski: *Carbohydr. Res.* **192**, 167 (1989).
34. L. Stryer: *Biochemistry*, 3rd edition, W.H. Freeman and Company, New York, pp.187, 218, 365, 384 (1988).
35. A. Ueno, Y. Tomita, and T. Osa: *J. Chem. Soc., Chem. Commun.* 976 (1983).