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Allosteric coextraction of sodium and metal ions with calix[4]arene derivatives 2: First numerical evaluation for the allosteric effect on alkali metal extraction with crossed carboxylic acid type calix[4]arenes

Tomoaki Yoneyama, Hirotoshi Sadamatsu, Shigemasa Kuwata,
Hidetaka Kawakita, Keisuke Ohto*

Department of Chemistry and Applied Chemistry, Faculty of Science and Engineering, Saga University, 1-Honjo, Saga 840-8502, Japan

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ABSTRACT

Crossed carboxylic acid types of calix[4]arene derivatives with two longer carboxylic acids and two acetic acids at the distal position have been prepared to investigate the solvent extraction of three alkali metal ions in individual and competitive systems. These extractants selectively extracted sodium ions among other alkali ions at low pH, and the first extracted sodium ion acted as a "trigger" causing a change in extraction ability and metal selectivity. Spacer groups with different lengths induced significant differences in the extraction behavior. The extraction equilibrium constants, K_{ex1} and K_{ex2}, between the present cyclic tetramers and the extracted two alkali metal ions were estimated in order to obtain a numerical evaluation of the allosteric effect.

1. Introduction

Calixarenes obtained from the condensation of *p*-alkylphenol and formaldehyde are very attractive and interesting macrocyclic host compounds. A number of review articles have been published on their use for ion recognition [1–5]. Many researchers have been attracted by their ion recognition properties and have employed these compounds as solvent extraction reagents [6–21], and for use in chemical sensors [22–24]. Researchers have also investigated specific extraction behavior based on ion discrimination using host calixarenes containing different size cavities [25–31]. It was determined that the effect of functional groups and ring size are very important factors for both selective and effective extraction to occur [28].

Specific coextraction behavior of sodium and other metal ions with calix[4]arene carboxylic acid derivatives has been reported by Ludwig et al. [32–36], Kakoi et al. [37–39], Uezu et al. [40], and our group [41–44]. In our previous work, the mechanism was elucidated [45,46]; specifically, *p*-t-octylcalix[4]arene carboxylic acid was observed to selectively form a complex with sodium ion over lithium and potassium ions, two sodium ions were simultaneously extracted by a single molecule of the calix[4]arene derivative, with the second sodium extraction being facilitated by the uptake of the first sodium ion. (The first sodium ion was surrounded by four phenoxy oxygen atoms, three carbonyl oxygen atoms, and a carboxyl oxygen in a restricted arrangement, which formed a dehydrated metal complex exhibiting eightfold coordination; the sodium ion was subsequently extracted. Consequently, this first sodium extraction acted as a "trigger" and facilitated the coextraction with the second ion.)

Traditionally, host–guest chemistry has been termed "enzyme-mimetic" chemistry. In this context it is potentially important to obtain a proper understanding of the nature of allosteric effects exhibited by a host–guest complex, which is initially formed between an original specific host and a "trigger" guest involving both the effect of metal coordination coupled with size fitting.

Herein, individual and competitive extractions of three alkali metal ions using crossed carboxylic acid type calix[4]arene derivatives with two longer carboxylic acids and two acetic acids moieties at the distal position have been investigated. To elucidate the extraction mechanism, a study was performed of the ^{1}H NMR peak shifts for the extractants during the sodium extraction process. The extraction equilibrium constants, K_{ex1} and K_{ex2}, for the present cyclic tetramers and the two extracted alkali metal ions were also estimated in order to obtain a numerical evaluation of the allosteric effect associated with the coextraction of the first "trigger" and the second ions.

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* Corresponding author. Tel.: +81 952 28 8669; fax: +81 952 28 8669.
E-mail address: ohtok@cc.saga-u.ac.jp (K. Ohto).

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2. Experimental

2.1. Reagents

5,11,17,23-Tetrakis(1,1,3,3-tertamethylbutyl)calix[4]arene-25,26,27,28-tetrol (*^{t}Oct[4]H*) was synthesized in a similar manner to that reported in a previous paper [25].

25,26,27,28-Tetrakis(carboxymethoxy)-5,11,17,23-tetrakis(1,1,3,3-tetramethylbutyl)calix[4]arene and *25,27-bis(carboxypropoxy)-26,28-(carboxymethoxy)-5,11,17,23-tetrakis-(1,1,3,3-tetramethylbutyl)calix[4]arene* (abbreviated to extractants **1** and **2**) were synthesized using the same procedure as reported in a previous paper [25,41].

2.1.1. 25,27-Bis(ethoxycarbonylbutoxy)-26,28-dihydroxy-5,11,17,23-tetrakis-(1,1,3,3-tetramethylbutyl)calix[4]arene

Under a nitrogen stream, ^{t}Oct[4]H (12.0 g, 13.8 mmol), sodium carbonate (23.4 g, 220 mmol), and ethyl 5-bromopentanoate (34.7 g, 166 mmol) were added to 450 cm^3 of dry acetone and the mixture was refluxed for 72 h. After filtration, the solvent and the excess of ethyl 5-bromopentanoate were removed *in vacuo*. The residue was extracted with chloroform, and the organic phase was washed three times with 1 M (M = mol dm^{-3}) hydrochloric acid and twice with distilled water. After drying over anhydrous magnesium sulfate, the solution was filtered and then the solvent was removed *in vacuo*. The residue was recrystallized from ethanol; yield 75.0%, white needles, TLC (SiO_2, chloroform:hexane = 2:1, $R_f = 0.82$), ^{1}H NMR (300 MHz, δ, $CDCl_3$, TMS, 25 °C), 0.19 (18H, s, $C(CH_3)_3$), 0.75 (18H, s, $C(CH_3)_3$), 1.09 (12H, s, $C(CH_3)_2$), 1.25 (6H, t, $CH_2\underline{CH_3}$), 1.32 (12H, s, $C(CH_3)_2$), 1.58 (4H, s, CCH_2C), 1.69 (4H, s, CCH_2C), 2.05 (8H, m + m, $CH_2\underline{CH_2}\underline{CH_2}CH_2$), 2.49 (4H, t, CH_2COO), 3.32 (4H, d, *exo*-CH_2), 3.97 (4H, t, $\underline{CH_2}CH_2CH_2CH_2$), 4.16 (4H, q, $\underline{CH_2}CH_3$), 4.26 (4H, d, *endo*-CH_2), 6.82 (4H, s, ArH), 7.01 (4H, s, ArH), 7.79 (2H, s, OH).

2.1.2. 25,27-Bis(ethoxycarbonylbutoxy)-26,28-(ethoxycarbonylmethoxy)-5,11,17,23-tetrakis-(1,1,3,3-tetramethylbutyl)calix[4]-arene

Under a nitrogen stream, 25,27-bis(ethoxycarbonylbutoxy)-26,28-dihydroxy-5,11,17,23-tetrakis-(1,1,3,3-tetramethylbutyl) calix[4]arene (5.14 g, 4.44 mmol), sodium hydride (2.06 g, 85.8 mmol), and ethyl bromoacetate (14.1 g, 84.7 mmol) were added to 150 cm^3 of dry tetrahydrofuran; the mixture was refluxed for 24 h. After cooling, the excess sodium hydride was deactivated by a dropwise addition of ethanol. After removing the solvent, the excess of ethyl bromoacetate was removed *in vacuo*. The residue was extracted with chloroform. The solution was washed three times with 1 M hydrochloric acid and twice with distilled water. After drying over anhydrous magnesium sulfate, the solution was filtered and the solvent was then removed *in vacuo*. The residue was recrystallized from ethanol; yield 70.4%, white needles, TLC (SiO_2, chloroform:methanol = 20:1, $R_f = 0.38$), ^{1}H NMR (300 MHz, δ, $CDCl_3$, TMS, 25 °C), 0.71 (18H, s, $C(CH_3)_3$), 0.73 (18H, s, $C(CH_3)_3$), 1.09 (12H, s, $C(CH_3)_2$), 1.25 (32H, s + s + s + t + t, $C(CH_3)_2 + CCH_2C + CCH_2C + CH_2\underline{CH_3} + CH_2\underline{CH_3}$), 1.78 (8H, m, $CH_2\underline{CH_2}\underline{CH_2}CH_2$), 2.40 (4H, t, $\underline{CH_2}CH_2CH_2CH_2$), 3.18 (4H, d, *exo*-$CH_2$), 3.84 (4H, t, $CH_2CH_2CH_2\underline{CH_2}$), 4.17 (8H, q + q, $\underline{CH_2}CH_3 + \underline{CH_2}CH_3$), 4.60 (4H, d, *endo*-$CH_2$), 4.80 (4H, s, CH_2COO), 6.60 (4H, s, ArH), 6.86 (4H, s, ArH).

*2.1.3. 25,27-Bis(carboxybutoxy)-26,28-(carboxymethoxy)-5,11,17,23-tetrakis-(1,1,3,3-tetramethylbutyl)calix[4]arene (extractant **3**)*

Tetrahydrofuran (170 cm^3) was combined with 25,27-bis(ethoxycarbonylbutoxy)-26,28-(ethoxycarbonylmethoxy)-5,11,17,23-tetrakis-(1,1,3,3-tetramethylbutyl)calix[4]arene (3.95 g, 3.03 mmol), potassium hydroxide (10.9 g, 194 mmol), and distilled water 120 cm^3; the mixture was refluxed for 24 h. After cooling, the solvent was removed *in vacuo* and the residue was extracted with chloroform. The solution was washed once with 6 M hydrochloric acid, twice with 1 M hydrochloric acid, and twice with distilled water. After drying over anhydrous magnesium sulfate, the solution was filtered and the solvent was removed *in vacuo*. The residue was recrystallized from hexane; yield 85.9%, white needles, TLC (SiO_2, chloroform:methanol = 5:1, $R_f = 0.51$), ^{1}H NMR (300 MHz, δ, $CDCl_3$, TMS, 25 °C), 0.46 (18H, s, $C(CH_3)_3$), 0.77 (18H, s, $C(CH_3)_3$), 0.92 (12H, s, $C(CH_3)_2$), 1.38 (16H, s + s, $C(CH_3)_2 + CCH_2C$), 1.71 (4H, s, CCH_2C), 1.88 (8H, s, $CH_2\underline{CH_2}\underline{CH_2}CH_2$), 2.51 (4H, t, $CH_2CH_2CH_2\underline{CH_2}$), 3.25 (4H, d, *exo*-$CH_2$), 3.76 (4H, t, $\underline{CH_2}CH_2CH_2CH_2$), 4.48 (4H, d, *endo*-$CH_2$), 4.75 (4H, s, CH_2COO), 6.61 (4H, s, ArH), 7.12 (4H, s, ArH), Found: H, 9.37; C, 74.79%, Calcd for $C_{74}H_{108}O_{12}$: H, 9.68; C, 74.96%.

2.1.4. 25,27-Bis(ethoxycarbonylpentoxy)-26,28-dihydroxy-5,11,17,23-tetrakis-(1,1,3,3-tetramethylbutyl)calix[4]arene

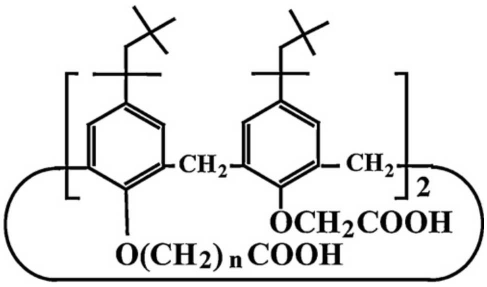
Under a nitrogen stream, ^{t}Oct[4]H (10.1 g, 11.6 mmol), sodium carbonate (29.7 g, 281 mmol), and ethyl 6-bromohexanoate (34.7 g, 181 mmol) were added to 500 cm^3 of dry acetone and the mixture was refluxed for 120 h. After filtration, the solvent and the excess ethyl 6-bromohexanoate were removed *in vacuo*. The residue was extracted with chloroform, and the organic solution was washed three times with 1 M hydrochloric acid and twice with distilled water. After drying over anhydrous magnesium sulfate, the solution was filtered and the solvent was removed *in vacuo*. The residue was recrystallized from ethanol; yield 61.8%, white needles, TLC (SiO_2, chloroform:hexane = 2:1, $R_f = 0.80$), ^{1}H NMR (300 MHz, δ, $CDCl_3$, TMS, 25 °C), 0.19 (18H, s, $C(CH_3)_3$), 0.75 (18H, s, $C(CH_3)_3$), 1.23 (12H, s, $C(CH_3)_2$), 1.32 (18H, s + t, $C(CH_3)_2 + CH_2\underline{CH_3}$), 1.76 (16H, s + m + m + m, $CCH_2C + CH_2\underline{CH_2}\underline{CH_2}\underline{CH_2}CH_2$), 2.03 (4H, s, CCH_2C), 2.39 (4H, t, CH_2COO), 3.30 (4H, d, *exo*-CH_2), 3.95 (4H, t, $\underline{CH_2}CH_2CH_2CH_2CH_2$), 4.12 (4H, q, $\underline{CH_2}CH_3$), 4.24 (4H, d, *endo*-CH_2), 6.82 (4H, s, ArH), 7.01 (4H, s, ArH), 7.85 (2H, s, OH).

2.1.5. 25,27-Bis(ethoxycarbonylpentoxy)-26,28-(ethoxycarbonylmethoxy)-5,11,17,23-tetrakis-(1,1,3,3-tetramethylbutyl)calix[4]-arene

Under a nitrogen stream, 25,27-bis(ethoxycarbonylpentoxy)-26,28-dihydroxy-5,11,17,23-tetrakis-(1,1,3,3-tetramethylbutyl) calix[4]arene (1.01 g, 0.86 mmol), sodium hydride (0.42 g, 17.5 mmol), and ethyl bromoacetate (2.74 g, 16.4 mmol) were added to 30 cm^3 of dry tetrahydrofuran and the mixture was refluxed for 24 h. After cooling, the excess sodium hydride was deactivated by a dropwise addition of ethanol. After removing the solvent, the excess ethyl bromoacetate was removed *in vacuo*. The residue was extracted with chloroform. The solution was washed three times with 1 M hydrochloric acid and twice with distilled water. After drying over anhydrous magnesium sulfate, the solution was filtered, and the solvent then removed *in vacuo*. The residue was recrystallized from methanol; yield 71.1%, white needles, TLC (SiO_2, chloroform:methanol = 20:1, $R_f = 0.38$), ^{1}H NMR (300 MHz, δ, $CDCl_3$, TMS, 25 °C), 0.63 (18H, s, $C(CH_3)_3$), 0.74 (18H, s, $C(CH_3)_3$), 0.93 (12H, s, $C(CH_3)_2$), 1.46 (22H, s + t + s, $CH_2\underline{CH_3} + CCH_2C + C(CH_3)_2$), 1.67 (10H, t + s, $CH_2\underline{CH_3} + CCH_2C$), 1.90 (12H, m, $CH_2\underline{CH_2}\underline{CH_2}\underline{CH_2}CH_2$), 2.36 (4H, t, $\underline{CH_2}CH_2CH_2CH_2CH_2$), 3.18 (4H, d, *exo*-$CH_2$), 3.80 (4H, t, $\underline{CH_2}CH_2CH_2CH_2CH_2$), 4.20 (8H, q + q, $\underline{CH_2}CH_3 + \underline{CH_2}CH_3$), 4.63 (4H, d, *endo*-$CH_2$), 4.86 (4H, s, CH_2COO), 6.53 (4H, s, ArH), 6.92 (4H, s, ArH).

*2.1.6. 25,27-Bis(carboxypentoxy)-26,28-(carboxymethoxy)-5,11,17,23-tetrakis-(1,1,3,3-tetramethylbutyl)calix[4]arene (extractant **4**)*

Tetrahydrofuran (100 cm^3) was combined with 25,27-bis(ethoxycarbonylpentoxy)-26,28-(ethoxycarbonylmethoxy)-5,11,17,23-tetrakis-(1,1,3,3-tetramethylbutyl)calix[4]arene (1.01 g,



1 : n = 1 **3** : n = 4
2 : n = 3 **4** : n = 5

Fig. 1. Chemical structures of the extractants.

0.78 mmol), KOH (2.64 g, 47.0 mmol), and distilled water 40 cm^3 and the mixture was refluxed for 24 h. After cooling, the solvent was removed *in vacuo* and the residue was extracted with chloroform. The solution was washed once with 6 M hydrochloric acid, twice with 1 M hydrochloric acid and twice with distilled water. After drying over anhydrous magnesium sulfate, the solution was filtered, and the solvent was removed *in vacuo*. The residue was recrystallized from hexane; yield 40.6%, white needles, TLC (SiO_2, chloroform:methanol = 5:1, $R_f = 0.31$), ^{1}H NMR (300 MHz, δ, $CDCl_3$, TMS, 25 °C), 0.47 (18H, s, $C(CH_3)_3$), 0.77 (12H, s, $C(CH_3)_2$), 0.91 (18H, s, $C(CH_3)_3$), 1.44 (20H, s + m + m, $C(CH_3)_2 + CCH_2C + CH_2CH_2CH_2\underline{CH_2}CH_2$), 1.76 (12H, s + m + m, $CCH_2C + CH_2\underline{CH_2}CH_2CH_2CH_2 + CH_2CH_2\underline{CH_2}CH_2CH_2$), 2.41 (4H, t, $CH_2\underline{CH_2}COO$), 3.25 (4H, d, *exo*-CH_2), 3.78 (8H, t, $\underline{CH_2}CH_2\underline{CH_2}CH_2CH_2$), 4.33 (4H, d, *endo*-$CH_2$), 4.67 (4H, s, CH_2COO), 6.61 (4H, s, ArH), 7.12 (4H,s,ArH).

The structures of the extractants utilized in the present work are shown in Fig. 1.

2.2. Distribution study

The individual extraction of three alkali ions (lithium, sodium, and potassium ions) was carried out using a conventional batchwise method. The aqueous solution was prepared by dissolving each alkali hydroxide in 0.1 M HEPES (2-[4-(2-hydroxyethyl)-1-piperazinyl]-ethanesulfonic acid) buffer solution to maintain the alkali concentration constant at 0.1 M. The pH was arbitrarily adjusted by adding 0.1 M hydrochloric acid (also to maintain the alkali concentration constant at 0.1 M). The organic solution was prepared by diluting the extractant in chloroform to 5 mM. Equal volumes (5 cm^3) of both phases were added to a test tube and the mixture was shaken at 303 K for 24 h. The pH value of the aqueous solution was measured after the extraction. Furthermore, the equilibrated organic solution (1 cm^3) was again mixed with fresh 1.2 M hydrochloric acid (5 cm^3) in a Teflon-coated bottle. The mixture was shaken at 303 K for 24 h to completely strip the extracted sodium ion. After phase separation, the concentration of sodium ions stripped into the aqueous phase was measured using an atomic absorption spectrometer, AAS (Seiko Instruments SAS-7500).

The sodium extraction was also monitored by ^{1}H NMR spectrophotometry. Experimental conditions were nearly the same as those mentioned above except for the use of deuterated chloroform. After equilibrium was reached, the NMR peaks for the extractant used in the organic phase were recorded (using Jeol, JNM-GX300 spectrometer).

The competitive extraction of the three alkali metal ions (lithium, sodium, and potassium ions) was also investigated. An aqueous solution was prepared by dissolving these alkali hydroxides in a 0.1 M HEPES solution, with the concentration of each alkali ion being 0.1 M. Subsequent procedures were preformed in a similar manner to those described for the individual extractions.

3. Results and discussion

3.1. Extraction study

The effects of pH on the percentage of loaded alkali metals on the extractant were investigated. The loading percentage, loading %, was defined as:

$$\text{Loading}\ \% = \frac{\text{amount of alkali metal ion extracted}}{\text{total amount of the extractant}} \times 100. \qquad (1)$$

The effects of pH on the loading percentage of alkali metal ions on extractants **1**–**4** in individual system are shown in Fig. 2(1)–(4), respectively. Those in competitive system are shown in Fig. 3(1)–(4), respectively. Figs. 2(1) and 3(1) are taken from the previous paper [46] for comparison. Although extractant **2** exhibited high selectivity towards sodium ion among the three alkali ions, the extractability was lower than for extractant **1**, compared from Fig. 2(1) and (2). It was also confirmed that lithium was extracted at a lower pH than potassium due to the narrowing of the coordination site by substituting to longer groups. Extractant **1** extracted sodium ion in a complementary fashion using four equivalent acetic acids together with phenoxy oxygen moieties (all carboxylic acids had the same spacer length). In the case of extractant **2**, carbonyl oxygen atoms located next to a longer spacer were not as strongly involved in the coordination because a charge of sodium ion was neutralized by one shorter acetic acid group with lower pK_a value and four phenoxy oxygen atoms coordinate; thus, it appears likely that the sodium ion did not completely dehydrate. Mismatching of the coordination donor sites associated with decreased complementarily by introducing two longer spacer groups results in the extraction being depressed. Furthermore, because the longer groups in extractant **2** allow them to come closer together, this will result in steric hindrance, and hence lithium was extracted at lower pHs compared to potassium.

From Fig. 3(2), sodium ions were extracted to higher than 100% (based on 1:1 complexation) due to the further extraction of a second sodium ion by extractant **2**. The effects of the extraction in this competitive system compared to the corresponding individual systems were significantly different. The loaded percentage of sodium ion in the competitive system was suppressed by the potassium added as a competitive ion. Potassium ion was extracted at pH 4.0 in the individual system case but was extracted at a pH value as low as 2.2 in the competitive system, although its loaded percentage was still low. Very little lithium and only a small amount of potassium were extracted in the competitive system.

As shown in Figs. 2(3) and 3(3), differences in selectivity (Na > Li > K, where lithium is selected over potassium) were observed in both systems with extractant **3** compared with extractant **2** (Na > Li = K in individual system). In view of this, an extraction study using even longer binding moieties, extractant **4**, was performed to examine the influence of the spacer length on the coextraction behavior.

A difference in selectivity was also observed in the individual extraction of the alkali metals with extractant **4** compared with extractant **2**. In competitive extraction, there was no difference in the extraction of potassium when extractant **4** was compared to extractant **2** at low pH.

In previous work on individual alkali metal extraction with extractant **1**, it was reported that the first-extracted sodium ion acted as an allosteric trigger for "self-coextraction" of sodium ions. This means that the first sodium ion facilitated the extraction of the second sodium and percentage loading of **1** continuously increased up to 200%. At higher pH regions compared to the sodium study

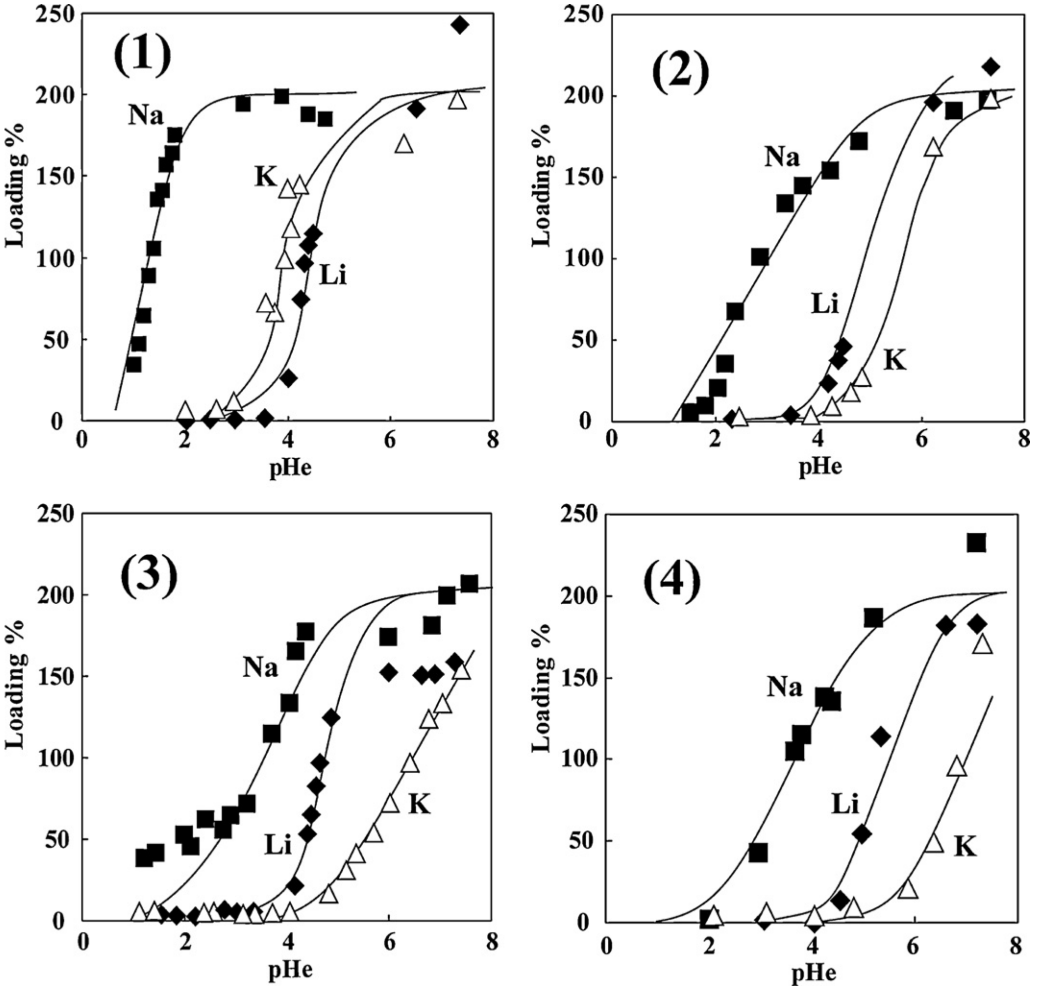


Fig. 2. Effect of pH on the loading percentage of alkali metal ions on extractant **1** (1), extractant **2** (2), extractant **3** (3), and extractant **4** (4) in individual system. [metal chloride] = 0.1 M, [extractant] = 5 mM, 0.1 M HCl–0.1 M HEPES.

with extractants **2**–**4**, percentage loadings of lithium and potassium ions also attained 200%, not in a stepwise manner but continuously shown in Fig. 2(2)–(4), respectively. Coextraction can be classified into two categories: the first is facilitated coextraction associated with allosteric effects based on a basicity change (*e.g.*, in the case of extractant **1**, carbonyl oxygen atoms, coordinated to the sodium ion and the second dissociation was facilitated, consequently two sodium ions were simultaneously extracted) and the second is general coextraction, which may be associated with the breaking of intramolecular hydrogen bonds. The uptake of the second ion took place by a simple ion-exchange mechanism. Although it was difficult to decide which types of coextraction took place, the "self-coextractions" of lithium and potassium with extractants **1**–**4** seem likely to be examples of a general coextraction.

3.2. *Estimation of extraction equilibrium constants for alkali metals with calix[4]arene derivatives for numerical evaluation of the allosteric effect*

The first and second extraction reactions of the individual alkali metal ions are defined by Eqs. (2) and (3):

$$\mathrm{RH_4} + \mathrm{M^+} \xleftrightarrow{K_{\mathrm{ex1}}} \mathrm{RH_3M} + \mathrm{H^+}, \tag{2}$$

$$\mathrm{RH_3M} + \mathrm{M^+} \xleftrightarrow{K_{\mathrm{ex2}}} \mathrm{RH_2M_2} + \mathrm{H^+}, \tag{3}$$

where RH_4 and M represent the carboxylic acid extractant and the alkali metal, respectively. (RH_4 means that each extractant can release four protons. Based on their pK_a values, two protons from the two acetic acid groups would be dissociated first before those of the two longer carboxylic acids.)

From Eqs. (2) and (3), respective stepwise extraction equilibrium constants were obtained using Eqs. (4) and (5):

$$K_{\mathrm{ex1}} = \frac{[\mathrm{RH_3M}][\mathrm{H^+}]}{[\mathrm{RH_4}][\mathrm{M^+}]}, \tag{4}$$

$$K_{\mathrm{ex2}} = \frac{[\mathrm{RH_2M_2}][\mathrm{H^+}]}{[\mathrm{RH_3M}][\mathrm{M^+}]}. \tag{5}$$

Furthermore, total concentrations of the extractant, $[H_4R]_T$, and alkali metal ion, $[M^+]_T$ are given by Eqs. (6) and (7), respectively.

$$[\mathrm{RH_4}]_\mathrm{T} = [\mathrm{RH_4}] + [\mathrm{RH_3M}] + [\mathrm{RH_2M_2}], \tag{6}$$

$$[\mathrm{M^+}]_\mathrm{T} = [\mathrm{M^+}] + [\mathrm{RH_3M}] + 2[\mathrm{RH_2M_2}]. \tag{7}$$

The calculated lines of the loaded percentage of alkali metal ions versus pH calculated by giving appropriate values to the stepwise extraction equilibrium constants, K_{ex1} and K_{ex2} were fitted with plots of the experimental data for four extractants (without consideration of the influence of the third and fourth acid dissociation steps). The calculated lines are given on the plots in Fig. 2(1)–(4). In case of the competitive system, the second extraction equilibrium constants were also estimated by the substitution of appropriate

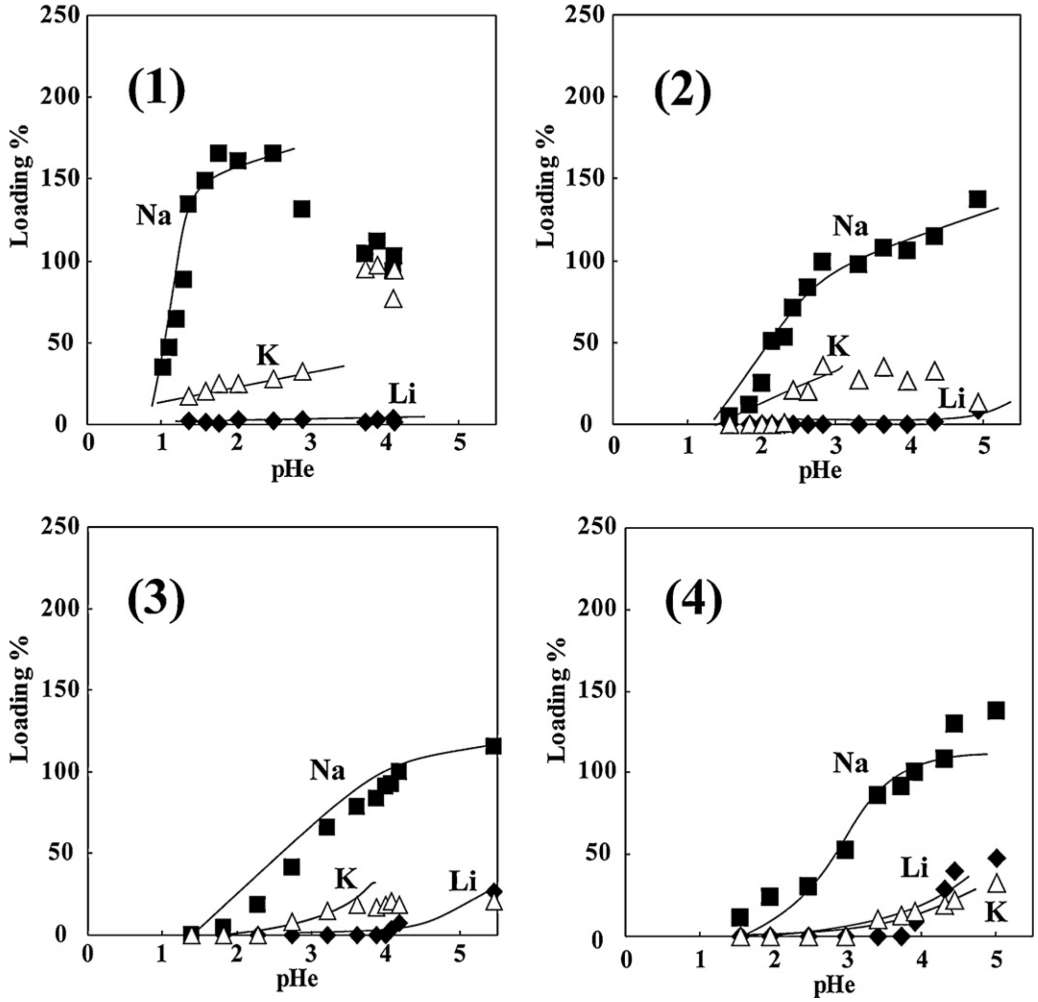


Fig. 3. Effect of pH on the loading percentage of alkali metal ions on extractant **1** (1), extractant **2** (2), extractant **3** (3), and extractant **4** (4) in competitive system. Each [metal chloride] = 0.1 M, [extractant] = 5 mM, 0.1 M HCl–0.1 M HEPES.

values to the stepwise extraction equilibrium constants; this was based on the reliable assumption that the first loaded metal ion was sodium, and K_{ex3} and K_{ex4} were sufficiently low and negligible in terms of estimating K_{ex1} and K_{ex2}. Furthermore, because the extraction abilities of the crossed type extractants **2**–**4** were sufficiently low compared to **1**, and the second metal uptake was not drastically facilitated by the first sodium uptake, it was assumed that the extraction took place by a stepwise mechanism. The calculated lines of the loaded percentage are drawn on the plots in Fig. 3(1)–(4). The stepwise extraction equilibrium constants and separation factors in the individual and competitive systems are summarized in Table 1(a) and (b), respectively. For extractant **1**, the stepwise extraction equilibrium constants, K_{ex1} and K_{ex2}, for two sodium ions were estimated to be 0.316 and 0.791 in our prior study [46].

Although the values of K_{ex2} for the sodium ion with all extractants listed in Table 1(a) should correspond to those in Table 1(b), some variation is apparent. This may be attributed to uncertainties associated with the stepwise mechanism for the second metal extraction. Regardless, it was still possible to draw some conclusions from the data. Sodium ion was employed as a templating one in the original preparation of calix[4]arene; in agreement with this the first extraction equilibrium constants for sodium ion with all of the extractants were extremely high compared to the values for lithium and potassium. Among the extractants, **1** showed remarkably high sodium extractability compared to the other extractants. The extraction equilibrium constants for sodium ion decreased with increase of the methylene spacer length connecting two of the carboxylic acid groups in each extractant. Extractant **1** had the advantage of four equivalent and complementary acetic acid groups compared to the crossed type extractants **2**–**4**, which have the disadvantage of having no preorganized groups and a flexible geometry. The successive acid constants K_1, K_2, K_3, *etc.*, were proposed to occur in the relative ratios $1{:}10^{-5}{:}10^{-10}$:*etc.* for the oxygen acids by Pauling, respectively [47]. Although the present calixarene derivatives cannot be classified as simple oxygen acids, all relative ratios of K_{ex1} to K_{ex2} in the present work were extremely high (not like $1{:}10^{-5}$) for the individual extraction of lithium, sodium, potassium ions with **1**, and those of lithium with **2** and **3**. Thus, the self-coextraction was strongly facilitated by allosteric effects caused by the first metal uptake. In terms of selectivity and separation efficiency, all the extractants showed sodium selectivity. Extractant **1** gave the selectivity, Na ≫ K > Li, whereas the selectivity order for the crossed type extractants **2**–**4** was Na ≫ Li > K. The data in Table 1(b) show that the separation factors of potassium over lithium in the second extraction decrease with an increase of the spacer length. Because calixarenes are vice-like compounds, the introduction of long substituents (not too long to be flexible) at the lower rim is expected to lead to selectivity for smaller guests. In previous work, it was reported that the first sodium ion was strongly extracted due to the size fitting of this cation to the coordination site of calix[4]arene, while the binding of the second ion

Table 1
Stepwise extraction equilibrium constants of alkali metals with the present extractants.

Extractant		Li	Na	K	$\beta_{Na/Li}$	$\beta_{K/Na}$	$\beta_{K/Li}$
(a) Individual system							
1	K_{ex1}	2.85×10^{-4}	0.316	1.05×10^{-3}	1110	0.00332 (301)	3.68
	K_{ex2}	5.44×10^{-4}	0.791	1.35×10^{-3}	1450	0.00171 (586)	2.48
2	K_{ex1}	1.42×10^{-4}	0.068	4.53×10^{-5}	479	0.000666 (1500)	0.319 (3.14)
	K_{ex2}	2.52×10^{-4}	1.12×10^{-3}	1.82×10^{-5}	4.44	0.0163 (61.5)	0.0722 (13.8)
3	K_{ex1}	1.34×10^{-4}	0.019	2.90×10^{-5}	142	0.00153 (655)	0.216 (4.62)
	K_{ex2}	2.46×10^{-4}	7.50×10^{-4}	5.20×10^{-7}	3.05	0.000693 (1440)	0.00211 (473)
4	K_{ex1}	9.10×10^{-5}	0.011	4.52×10^{-6}	121	0.000411 (2430)	0.0500 (20.1)
	K_{ex2}	1.21×10^{-5}	3.40×10^{-4}	2.14×10^{-7}	28.1	0.000629 (1590)	0.0177 (56.5)
(b) Individual system							
1	K_{ex1}	–	0.316	–			
	K_{ex2}	9.97×10^{-5}	0.451	0.188	4520	0.417	1890
2	K_{ex1}	–	0.068	–			
	K_{ex2}	2.36×10^{-5}	2.08×10^{-4}	6.98×10^{-3}	8.81	33.6	296
3	K_{ex1}	–	0.019	–			
	K_{ex2}	2.80×10^{-5}	2.03×10^{-5}	6.10×10^{-4}	0.725	30	21.8
4	K_{ex1}	–	0.011	–			
	K_{ex2}	3.48×10^{-4}	1.82×10^{-4}	2.52×10^{-4}	0.523	1.38	0.72

The values in parentheses represents inverse ones.

corresponded to just an ion-exchange reaction. However, because the alkali metal selectivity for the extractants changed, the second metal uptake may not have corresponded to a simple ion-exchange mechanism due to for example plural dehydration.

3.3. *Relationship between loading and shifted percentages in pH dependency*

As an example, the ^{1}H NMR spectra for the aryl peaks of extractant **2** after complexation with sodium ions are shown in Fig. 4. The original peak at 6.61 ppm shifted to lower field on high sodium loading and correspondingly a new peak appeared at 7.02 ppm. The extent of the shift increased with increasing pH. It was concluded that the cavity converted from its original oval shape to a nearly round shape after the loading of the first sodium ion because the presence of the spherical sodium ion resulted in the two aryl proton peaks more closer together.

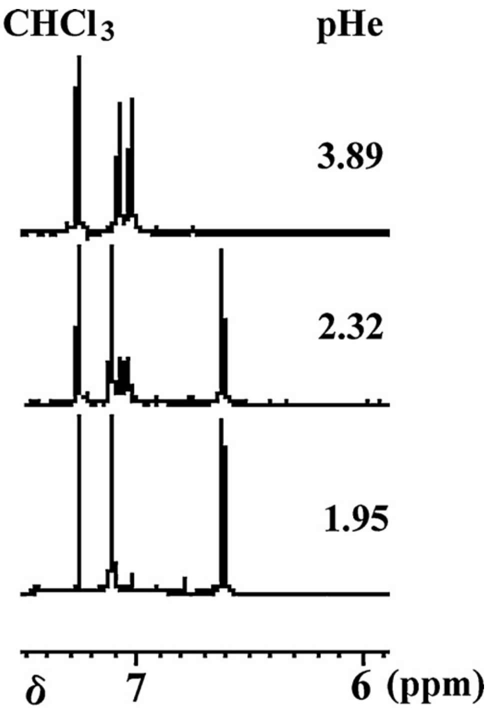


Fig. 4. Partial ^{1}H NMR spectra of extractant **2** complexed with sodium ion.

In previous work, the ratio of the integral ratios between the original and the shifted peaks was reported to be related to the loaded percentage of sodium ions by the extractant. The ratio expressed as the shifted percentage for aryl protons in the extractant, was defined by:

$$\text{Shifted}\,\% = \frac{\text{shifted integral ratio of aryl protons}}{\text{total integral ratio of aryl protons}} \times 100.$$

However, it was not clear whether the sodium-loaded crossed type extractants facilitated further metal extraction, and if so, what the mechanism was. For this purpose, the shifted percentage of aryl protons estimated from the data of ^{1}H NMR spectra was correlated with the loading percentage of sodium ion by the extractant estimated from the data of AAS. As an example, the effects of pH on both the shifted and loaded percentages of sodium ion by **2** are shown in

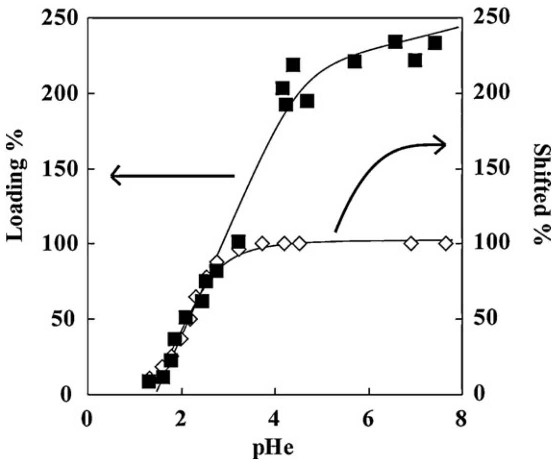


Fig. 5. Effect of pH on the loading percentage of sodium ions and the chemically shifted percentage for aryl protons on extractant **2**. *Filled square*: loading percentage of sodium ions measured by AAS. *Open diamond*: shifted percentage of the extractant measured by ^{1}H NMR spectrometer; [extractant **2**] = 5 mM.

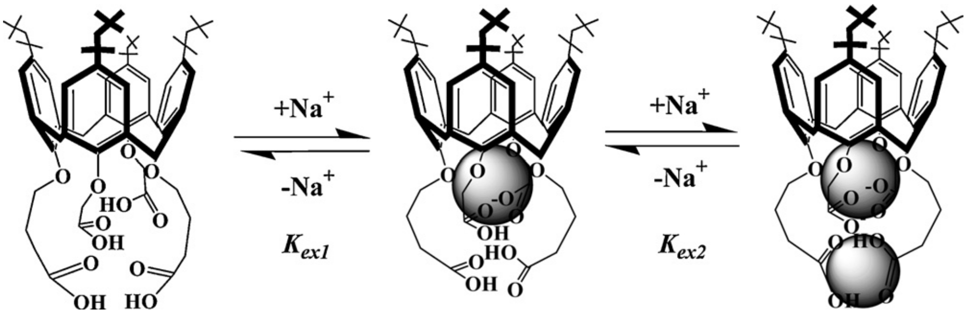


Fig. 6. Stepwise extraction mechanism of the sodium ion with extractant **2**.

Fig. 5. Both percentages for extractant **2** closely corresponded with up to 100%, then only the loaded percentage approaches to 200% with keeping the shifted percentage to be 100%; this suggested that only the first sodium uptake was related to the peak shift, reflecting a corresponding structural change; the second sodium uptake was not accompanied by a ^{1}H NMR spectra change. The results also suggest that the first and second sodium ions are extracted stepwise by a single molecule of the extractant. This mechanism was clearly different from the simultaneous extraction mechanism by extractant **1** reported in our previous papers, indicating that the shifted percentage of extractant **1** was nearly half compared to the loading percentage over the whole pH range under the same conditions [45,46]. The stepwise process proposed is illustrated in Fig. 6. The extraction of the second sodium ion took place after the extractant was occupied by the first sodium ion inside the calix[4]arene cavity, resulting in the observed NMR peak shift. On extraction, the first sodium ion was surrounded by four phenoxy oxygen atoms, a carbonyl oxygen atom, and a carboxyl oxygen atom. The sodium ion was thus dehydrated in a six coordinate structure. In contrast, the second sodium ion was bound by an ion-exchange reaction with loss of only a single proton from one of the remaining carboxylic acid groups. Because formation of the first sodium-loaded extractant **2** did not greatly facilitate the second sodium uptake, the sodium "self-coextraction" mechanisms can be considered to be dominantly (but not completely) taking place by a general coextraction process, which consisted of the breaking of intramolecular hydrogen bonds as described above.

4. Conclusions

Crossed carboxylic acid type of calix[4]arene derivatives with different spacer lengths at the distal position have been prepared in order to investigate the individual extraction of three alkali metals. Each exhibits high selectivity towards sodium ion among three alkali ions, although their extraction abilities were lower than those of the previously studied extractant **1**. Lithium was extracted at a lower pH region than potassium due to steric hindrance and the narrowing of the coordination site resulting from the introduction of longer substituents. The effects of pH on the loaded percentage of alkali metal ions in the competitive system with extractant **2** showed a significant difference from those in the individual system. Sodium ion was extracted up to a loading percentage that was higher than 100% in the competitive system, while only a small amount of potassium was coextracted; this coextraction behavior of potassium ion along with the first sodium ion, however, decreased with an increase in the spacer length. Allosteric effects caused by the first loaded sodium were numerically evaluated by the estimation of K_{ex1} and K_{ex2}. The sodium-loaded extractants acted differently compared to the original metal-free extractant and based on the evaluation of the allosteric effect extraction ability and separation efficiency, the optimization of the extraction of these metal ions could conceivably be controlled by altering the spacer length of related calixarene extractants in certain extraction media containing some metals.

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