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# Substitution Effect, Absorption, and Fluorescence Behaviors of 11,12-Benzo-1,7,10,13-tetraoxa-4-aza-cyclopentadec-11-ene (Benzoaza-15-crown-5) Derivatives upon Cation Complexation in Solvent Extraction

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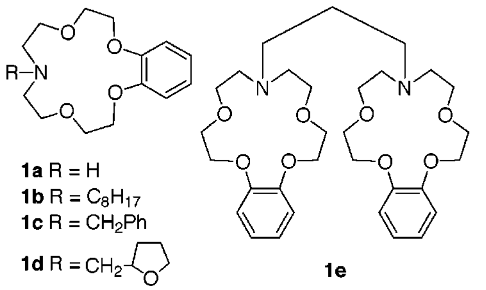
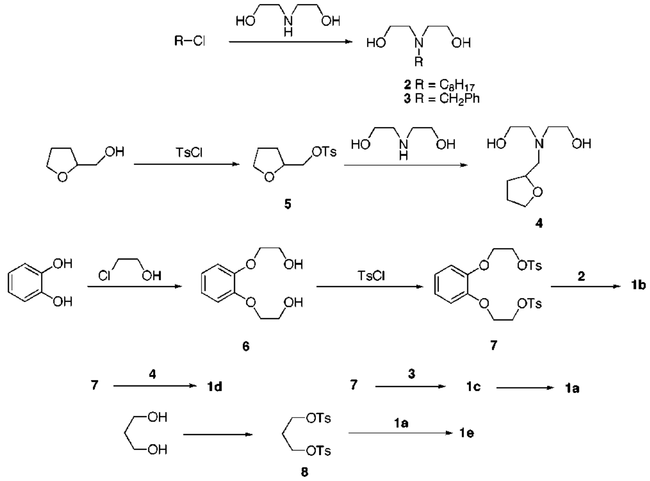
**Abstract:** Substitution effect, absorption, and fluorescence behaviors of some benzoaza-15-crown-5 derivatives upon cation complexation in solvent extraction were studied. The introduction of a substituent on the nitrogen atom in benzoaza-15-crown-5 enhanced extractabilities in the solvent extraction of aqueous alkali metal picrates. The nondonating substituents raised the cation selectivity for $Na^+$ over $K^+$, but the donating substituents reduced the cation selectivity. The absorption and fluorescence spectral behavior was different with the alkali metal cations.

Since it is known that azacrown ethers have an advantage in synthetic feasibility over all oxygen analogues, azacrown ethers with N-substituents have been designed to enhance cation binding ability and also to partly mimic the dynamic complexation exhibited by natural macrocyclic ligands.[1] Indeed, several groups have shown that some azacrown ethers with N-substituents perform generally well in cation binding and transport, compared with the parent or reference azacrown ethers.[2] However, less attention has been paid to the cation binding properties for benzoazacrown ethers. In particular, the effects of an N-substituent on the cation binding properties of, and the cation selectivity for, benzoazacrown ethers have not been studied systematically, to the best of our knowledge. Since benzoazacrown ethers have chromophores in their skeleton, the cation complexation of benzoazacrown ethers can be observed via absorption or luminescence. Recently, macrocyclic ethers have been studied extensively as cation complexing agents that are significant for chemistry and physiology.[3]

## Chart 1



## Scheme 1



In the present work, the following 11,12-benzo-1,7,10,13-tetraoxa-4-aza-cyclopentadec-11-ene (benzoaza-15-crown-5) derivatives, each with an N-substituent, were studied: benzoaza-15-crown-5 **1a**, *N*-octylbenzoaza-15-crown-5 **1b**, *N*-benzylbenzoaza-15-crown-5 **1c**, *N*-tetrahydrofurfurylbenzoaza-15-crown-5 **1d**, and *N*,*N*′-trimethylene-bis(benzoaza-15-crown-5) **1e**. Here, we discuss the cation binding abilities and cation selectivities of **1a**−**e** and the absorption and fluorescence behavior of **1e** upon cation complexation.

**Preparation of Materials.** The benzoaza-15-crown-5 derivatives employed in this work are illustrated in Chart 1 and were prepared according to Scheme 1. The corresponding chlorides were permitted to react with diethanolamine to give *N*-octyldiethanolamine **2** and *N*-benzyldiethanolamine **3**. *N*-Tetrahydrofurfuryldiethanolamine **4** was prepared by reaction of diethanolamine with tetrahydrofurfuryl tosylate **5** given from tetrahydrofurfuryl alcohol and toluenesulfonyl chloride. 2,2′-(*o*-Phen-

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(3) For example, see: (a) Hayashita, T.; Taniguchi, S.; Tanamura, Y.; Uchida, T.; Nishizawa, S.; Teramae, N.; Jin, Y. S.; Lee, J. C.; Bartsch, R. A. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1003. (b) Ji, H. F.; Dabestani, R.; Brown, G. M.; Hettich, R. L. *Photochem. Photobiol.* **1999**, *69*, 513. (c) Kollmannsberger, M.; Rurack, K.; Resch-Genger, U.; Daub, J. *J. Phys. Chem. A* **1998**, *102*, 10211. (d) Prodi, L.; Bolletta, F.; Zaccheroni, N.; Watt, C. I. F.; Mooney, N. J. *Chem. Eur. J.* **1998**, *4*, 1090. (e) Cielen, E.; Tahri, A.; Heyen, K. V.; Hoornaert, G. J.; Schryver, F. C.; Boens, N. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1573. (f) Alonso, M. T.; Brunet, E.; Hernandez, C.; Rodriguez-Ubis, J. C. *Tetrahedron Lett.* **1993**, *34*, 7465. (g) Sousa, L. R.; Son, B.; Trehearne, T. E.; Stevenson, R. W.; Ganion, S. J.; Beeson, B. E.; Barnell, S.; Mabry, T. E.; Yao, M.; Chakrabarty, C.; Bock, P. L.; Yoder, C. C.; Pope, S. Synthesis and Study of Crown Ethers with Alkali-Metal-Enhanced Fluorescence. In *Fluorescent Chemosensors for Ion and Molecular Recognition*; Czarnik, A. W., Ed.; ACS Symposium Series 538; American Chemical Society: Washington, DC, 1992; pp 10−24.

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**Table 1. Extraction of Metal Picrates[a] and Crown Ether Distribution Coefficients ($K_d$)**

| | extractability (%)[b] | | | | | $K_d$ |
|---|---|---|---|---|---|---|
| | $Li^+$ | $Na^+$ | $K^+$ | $Rb^+$ | $Cs^+$ | |
| **1a** | 0.3 | 1.4 | 0.5 | 0.3 | 0.3 | 0.047 |
| **1b** | 1.5 | 24.6 | 2.7 | 2.4 | 2.0 | 0.005 |
| **1c** | 0.5 | 9.5 | 1.3 | 0.8 | 0.4 | 0.010 |
| **1d** | 33.9 | 43.8 | 27.0 | 13.3 | 7.3 | 0.019 |
| **1e** | 3.9 | 21.5 | 25.8 | 20.8 | 5.4 | 0.015 |

[a] Aqueous phase: [MOH] = 10 mM, [picric acid] = 3 mM. Organic phase: [ligand unit] = 3 mM, dichloromethane. Temperature: 25 °C. [b] Extractability was defined as the percent picrate extracted into the organic phase.

ylenedioxy)diethanol **6** was synthesized in the reaction of catechol with 2-chloroethanol under an alkaline medium and tosylated to 2,2′-(*o*-phenylenedioxy)diethanol ditosylate **7**. The ditosylate **7** was allowed to react with **2** to give **1b** in a 9% yield, with **3** to give **1c** in a 32% yield, and with **5** to give **1d** in a 7% yield. Parent benzoazacrown **1a** was derived from **1c** in a 71% yield. Compound **1e** was prepared in a 21% yield by reaction of **1a** with 1,3-propanediol ditosylate **8** derived from 1,3-propanediol.

**Solvent Extraction.** When a $CH_2Cl_2$ solution of **1a** (3.0 mol/dm$^3$) and an aqueous solution of alkali metal cations were shaken together for 30 min at 25 °C, **1a** preferably extracted $Na^+$, which was a size-matched cation to the hole cavity of **1a**, at 24.8%. As shown in Table 1, the extractability of **1a** for the alkali metal cations decreased in the following order: $Na^+ > K^+ > Rb^+ \approx Cs^+ \approx Li^+$. Compounds **1b** and **1c** also effectively extracted $Na^+$. Derivative **1d** gave the highest extractabilities for $Li^+$, $Na^+$, $K^+$, and $Cs^+$ among the benzoazacrown derivatives. In the solvent extraction of **1e**, the extractability for size-mismatched larger $K^+$ was higher than that for size-matched $Na^+$.

It should be noted that the introduction of a nondonating *n*-octyl group in **1b** remarkably raised the extractability for size-matched $Na^+$, while the extractabilities for size-mismatched cations increased only slightly. Similar results appeared for the benzyl group in **1c**. In contrast, **1d** and **1e**, possessing donating sites in the tetrahydrofurfuryl and *N*-trimethylene-benzoaza-15-crown-5 moieties, respectively, yielded higher extractabilities for the alkali metal cations employed in the present work. These results indicate that nondonating N-substituents such as *n*-octyl and benzyl groups are more favorable for $Na^+$ binding and that the oxygen atom of the tetrahydrofurfuryl group in **1d** is an effective donor site for alkali metal cations. The higher extractabilities for size-mismatched larger cations in **1e** were attributable to the biscrown effect reported previously.[4]

Table 1 also exhibits the distribution coefficients ($K_d$) of **1** between the aqueous and organic phases (cf. Experimental Section). The introduction of an N-substituent remarkably suppressed the partition of the benzoazacrown ethers to the aqueous phase compared with the parent benzoazacrown ether **1**.

The overall extraction equilibrium between an aqueous (aq) phase containing alkali metal picrates (MA) and an organic (org) phase containing ligands (L) is expressed by eq 1,[5]

$$M^+_{aq} + A^-_{aq} + nL_{org} \rightleftarrows (ML_nA)_{org} \qquad (1)$$

where *n* gives the ligand:cation ratio.

The overall extraction equilibrium constants ($K_{ex}$) are given by eq 2.

$$K_{ex} = D_M/[A^-]_{aq}[L]_{org}{}^n \qquad (2)$$

The distribution coefficient of alkali metal ions ($D_M$) and the concentration of free ligands in the organic phase ($[L]_{org}$) after the establishment of the equilibrium are calculated by eqs 3 and 4, respectively,

$$D_M = [ML_nA]_{org}/[M^+]_{aq} \qquad (3)$$

$$[L]_{org} = ([L]_i - n[ML_nA]_{org})/(1 + K_d) \qquad (4)$$

where $[L]_i$ represents the initial concentration of ligands dissolved in the organic phase, and $K_d$ is the distribution coefficient of ligands between the aqueous and organic phases ($K_d = [L]_{aq}/[L]_{org}$). Equation 2 can be modified to eq 5.

$$\log(D_M/[A^-]_{aq}) = n\log[L]_{org} + \log K_{ex} \qquad (5)$$

A plot of $\log(D_M/[A^-]_{aq})$ versus $\log[L]_{org}$ gives a straight line of slope *n* determined by complex stoichiometry. The overall extraction $K_{ex}$ is calculated from the intercept.[6]

In the present work, the quantitative solvent extraction experiments with aqueous sodium and potassium picrates were performed in the range of $1.0-5.0 \times 10^{-3}$ mol/dm$^3$ crown concentrations. Figure 1 shows plots of the extraction data for **1a**−**e** according to eq 2. The extractions of $Na^+$ and $K^+$ gave straight lines of unit slopes, and this clarified the formation of a stoichiometric 1:1 complex with $Na^+$ and $K^+$ for **1a**−**e**.

Table 2 summarizes the calculated log $K_{ex}$ values as well as relative cation selectivities for $Na^+$ over $K^+$ calculated from $K_{ex}$. An N-substitution for a hydrogen atom on the nitrogen atom in **1a** raised the log $K_{ex}$ value for the size-matched cation $Na^+$; the log $K_{ex}$ values of **1b**−**e** for $Na^+$ were considerably larger than that of **1a**. Compounds **1d** and **1e**, in which the N-substituents performed donating ligation, enhanced the log $K_{ex}$ values for the size-mismatched larger cation $K^+$ as well as $Na^+$. On the other hand, the introduction of a nondonating substituent on the nitrogen atom in **1a** slightly increased the log $K_{ex}$ values of **1b** and **1c** for $K^+$ compared with that of **1a**.

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(4) Jeong, K. S.; Pyun, S. Y. *Tetrahedron Lett.* **1994**, *35,* 7041. He, G. X.; Kikukawa, K.; Nishiyama, N.; Ohe, H.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3785. Kikukawa, K.; He, G. X.; Abe, A.; Goto, T.; Arata, R.; Ikeda, T.; Wada, F.; Matsuda, T. *J. Chem. Soc., Perkin Trans. 2* **1987**, 135. Kimura, K.; Sakamoto, H.; Koseki, Y.; Shono, T. *Chem. Lett.* **1985**, 1241.

(5) The formation of benzoazacrown ether−cation complexes in an aqueous phase was neglected throughout this work because the distribution of these benzoazacrown ethers into water is minimal. For example, the complex association constants ($K_a$) of 15-crown-5 in water have been shown to be around 5, which is 3−4 orders of magnitude lower than those in organic solvents. See: de Jong, F.; Reingoubt, D. N. *Stability and Reactivity of Crown Ether Complexes*; Academic Press: London, 1981; p 25 and the reference cited therein.

(6) Tsukube, H.; Furuta, H.; Odani, A.; Takeda, Y.; Kudo, Y.; Inoue, Y.; Liu, Y.; Sakamoto, H.; Kimura, K. Determination of Stability Constants. In *Comprehensive Supramolecular Chemistry;* Davies, J. E. D., Ripmeester, J. A., Eds.; Pergamon Press: Elmsford, NY, 1996; Vol. 8, p 425.

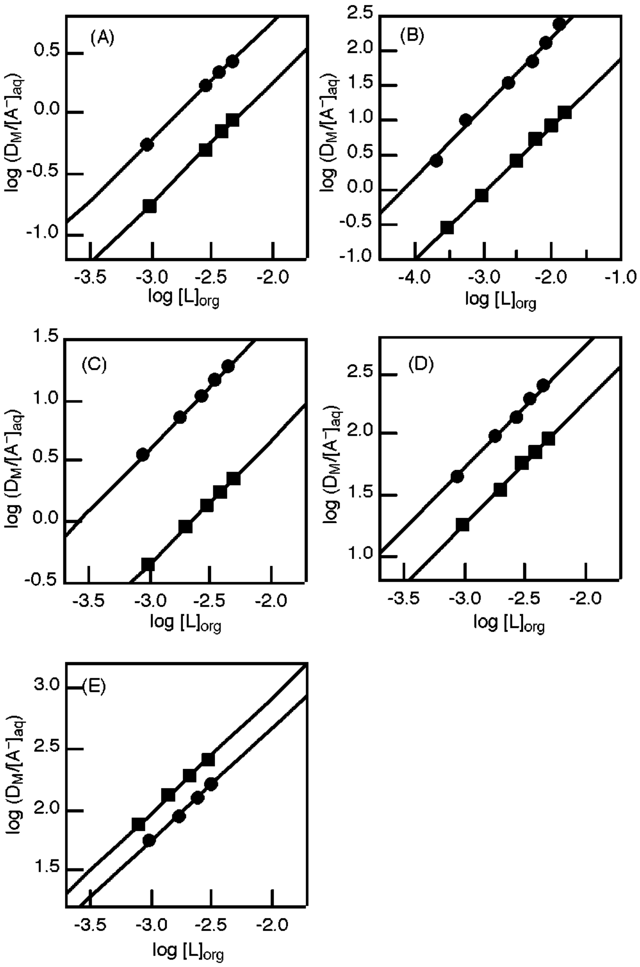

**Figure 1.** Plots of log($D_M$/[A]$_{aq}$) versus log[**1**]$_{org}$ obtained in solvent extraction for (A) **1a**, (B) **1b**, (C) **1c**, (D) **1d**, and (E) **1e**. Closed circle: $Na^+$. Closed square: $K^+$.

**Table 2. Extraction Equilibrium Constants ($K_{ex}$) and Cation Selectivities**[a]

| | log $K_{ex}$ | | selectivity[b] |
|---|---|---|---|
| | $Na^+$ | $K^+$ | $Na^+/K^+$ |
| **1a** | 2.77 | 2.26 | 3.2 |
| **1b** | 4.19 | 2.96 | 17 |
| **1c** | 3.61 | 2.66 | 8.9 |
| **1d** | 4.73 | 4.26 | 3.0 |
| **1e** | 4.72 | 4.96 | 0.6 |

[a] In a dichloromethane–water system at 25 °C. [b] Calculated from extraction equilibrium constants ($K_{ex}$).

The introduced N-substituent dramatically affected the relative cation selectivity for $Na^+$ over $K^+$. A specific enhancement of the cation selectivity appeared with **1b** having an *n*-octyl group. The log $K_{ex}$ value of **1b** for the size-mismatched cation $K^+$ slightly increased, contrary to the large enhancement of the log $K_{ex}$ value for $Na^+$, thus yielding a higher relative selectivity for $Na^+$ compared with the parent **1a**. Compounds **1d** and **1e** enhanced the log $K_{ex}$ values for $K^+$ as well as those for $Na^+$, and thus the relative selectivities were almost unchanged or lower than that of **1a**.

Since bisbenzoazacrown ether **1e** forms a stoichiometric 1:1 complex with $K^+$, as suggested by the plot in Figure 1, and substantially extracts size-mismatched larger cations in the solvent extraction, it follows that **1e** probably forms a sandwich-type complex, which has been proposed by many groups, with a size-mismatched larger cation.[7]

We previously investigated the log $K_{ex}$ values and cation selectivities of some aza-15-crown-5 ethers, each having an N-substituent.[8] Although the log $K_{ex}$ (= 4.28) value of *N*-octylaza-15-crown-5 ether for $Na^+$ was nearly equal to that of **1b**, the log $K_{ex}$ (= 3.72) value of *N*-octylaza-15-crown-5 for $K^+$ was higher than that of **1b**. This means that the benzoaza-15-crown-5 skeleton is unfavorable for complexation with the larger cation $K^+$ compared with the aza-15-crown-5 skeleton. The introduction of a benzene ring to the aza-15-crown-5 skeleton can reduce the flexibility of aza-15-crown-5 for complexation with $K^+$; the enthalpic loss upon complexation with $K^+$ for benzoaza-15-crown-5 is larger than that for aza-15-crown-5.[9] As a consequence, benzoaza-15-crown-5 exhibits a higher cation selectivity for $Na^+$ than does aza-15-crown-5.

**Absorption and Fluorescence Spectra of 1e.** The absorption spectrum of **1e** changed with the addition of alkali metal cations. Figure 2 shows the absorption spectral changes of **1e** in acetonitrile in the presence of alkali metal cations. The absorption maximum of **1e** appeared at 275 nm and shifted slightly to a shorter wavelength with the addition of sodium and potassium perchlorates (Figures 2A and B, respectively). The optical density at 275 nm decreased as the concentrations of $Na^+$ and $K^+$ increased. Similar decreases in absorbance appeared in the cases of $Rb^+$ and $Cs^+$. In contrast, no absorption spectral changes were observed in the presence of $Li^+$ (Figure 2C); thus, **1e** is capable of distinguishing $Li^+$ from other alkali metal cations via absorption.

The absorption behavior reflects the manner of complexation. Since the metal cation withdraws the nonbonding electrons of the two oxygen atoms connected to the benzene ring upon complexation, this process reduces the electron-donating character of the oxygen to the benzene ring. As a consequence, the absorption maximum shifts to a shorter wavelength. The absence of a spectral change in absorption for $Li^+$ indicates that the complexing power with $Li^+$ is much smaller than that with other cations.

Bisbenzoazacrown **1e** fluoresced in acetonitrile and reached its fluorescence maximum at 310 nm with excitation of 260 nm light. The fluorescence spectrum of **1e** also changed with the addition of the alkali metal cations, and distinct values could be found by the effects of $Na^+$, $K^+$, and $Li^+$.[10] As shown in Figure 3A, the fluorescence intensity slightly increased as the concentration of $Na^+$ increased. The addition of potassium perchlorate decreased the fluorescence intensity (Figure 3B). No spectral changes were observed in the presence of $Li^+$ (Figure 3C). The fluorescence of **1e** illustrated the

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(7) For example, see: Inoue, Y.; Nakagawa, K.; Hakushi, T. *J. Chem. Soc., Dalton Trans.* **1993**, 2279. Markovskii, L. N.; Rudkevich, D. M.; Kal'chenko, V. I. *J. Gen. Chem. USSR (Engl. Transl.)* **1992**, *62*, 306. Koudelka, P. H. J.; Belohradsky, M.; Stibor, I.; Zavada, J. *Collect. Czech. Chem. Commun.* **1991**, *56*, 6, 1482. Tanaka, T.; Mizufune, H.; Shono, T. *Chem. Lett.* **1990**, 1419. He, G. X.; Kikukawa, K.; Ikeda, T.; Wada, F.; Matsuda, T. *J. Chem. Soc., Perkin Trans. 2* **1988**, 719.

(8) Unpublished data.

(9) Nakagawa, K.; Inoue, Y.; Hakushi, T. *J. Chem. Res. Miniprint* **1990**, 2625. Takeda, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 931. Takeda, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2040.

(10) The fluorescence spectra were observed at a 260 nm excitation wavelength at which the absorption optical density of **1e** barely changed with the addition of metal perchlorates.

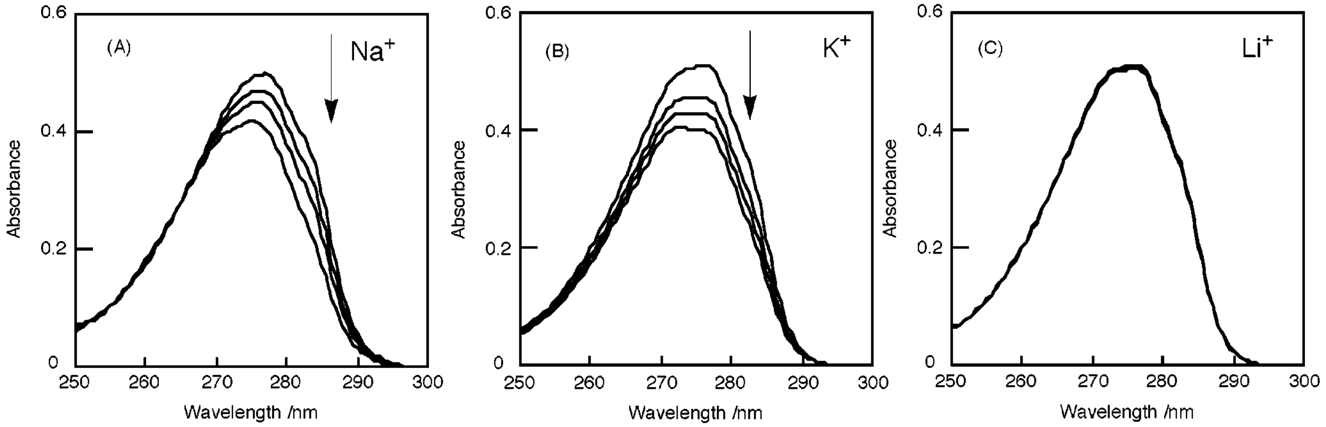

**Figure 2.** Absorption spectral change of **1e** ($1 \times 10^{-4}$ mol/dm$^3$ in acetonitrile) in the presence of alkali metal cations ($0-5 \times 10^{-4}$ mol/dm$^3$): (A) Na$^+$, (B) K$^+$, and (C) Li$^+$.

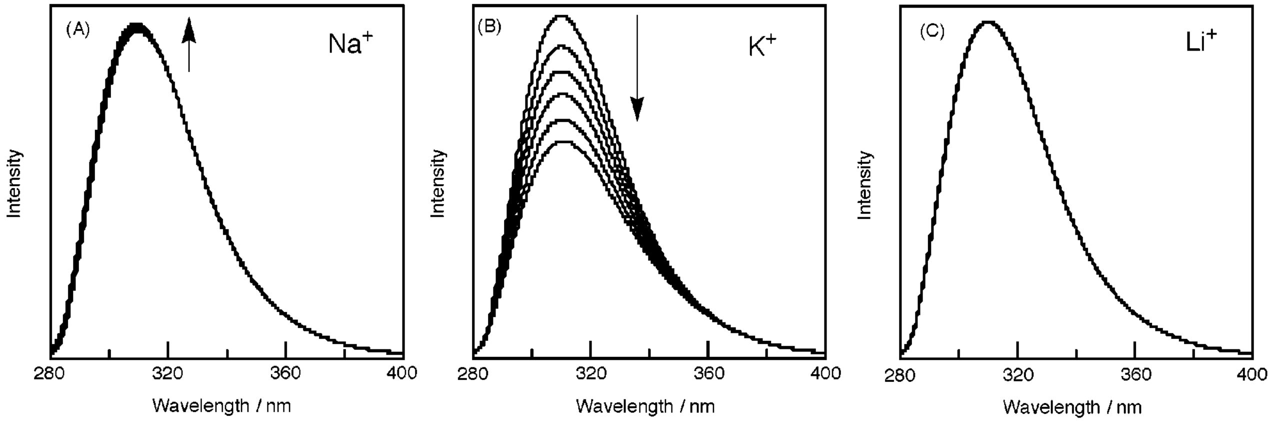

**Figure 3.** Fluorescence spectral change of **1e** ($1 \times 10^{-4}$ mol/dm$^3$ in acetonitrile) in the presence of alkali metal cations: (A) Na$^+$ ($0-5 \times 10^{-4}$ mol/dm$^3$), (B) K$^+$ ($0-1 \times 10^{-3}$ mol/dm$^3$), and (C) Li$^+$ ($0-5 \times 10^{-4}$ mol/dm$^3$).

complexing difference between Na$^+$ and K$^+$, which cannot be distinguished via absorption.

Although the fluorescence intensity of **1e** decreased with increasing concentration of K$^+$, Sousa et al. reported that the fluorescence intensity of dimethylene-bis(naphthoazacrown) increased with increasing concentration of metal cations.[3g] They stated that the nonbonding electrons on nitrogen atoms intramolecularly quench the fluorescence under the free condition and that the complexation with metal cations decreases this intramolecular quenching because the nonbonding electrons of the nitrogen atom are consumed in coordination. In our system, the fluorescence enhancement in **1e**–Na$^+$ is due to a similar mechanism. On the contrary, the decrease in fluorescence intensity in **1e**–K$^+$ cannot be explained by this mechanism. Further investigation of the fluorescence behavior of **1e** is needed. The following is a plausible explanation at present. As **1e** forms a sandwich-type complex, in which the two benzene rings are close to each other, with K$^+$, intramolecular quenching by the nonfluorescing benzene ring probably occurs and surpasses the fluorescence enhancement due to complexation with K$^+$. Since the linker length and the crown-ring size of dimethylene-bis(naphthoazacrown) are different from those of **1e**, two naphthyl rings probably form an unquenchable conformation in a sandwich-type complex with K$^+$.

The introduction of a substituent on the nitrogen atom in **1a** enhanced extractabilities in the solvent extraction of aqueous alkali metal picrates. The nondonating substituents in **1b** and **1c** raised the cation selectivity for Na$^+$ over K$^+$ relative to that of **1a**, but the donating substituents in **1d** and **1e** reduced the cation selectivity relative to that of **1a**. The nondonating substituents in **1b** and **1c** induced more a favorable conformation for size-matched Na$^+$, and the oxygen atoms of the substituents in **1d** and **1e** are effective donor sites for not only Na$^+$ but also other alkali metal cations. The absorption and fluorescence spectral behavior of **1e** was different with the alkali metal cations. Bisbenzoazacrown **1e** was capable of discriminating between Li$^+$, Na$^+$, and K$^+$ via absorption and fluorescence.

**Supporting Information Available:** Experimental procedures for solvent extraction, determination of ligand distribution coefficients, and the preparations of compounds **1**–**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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