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Complexing properties of two benzocrown-ether moieties arranged at a cyclobutane ring system

Seiichi Inokuma, Takashi Funaki, Shin-ichi Kondo and Jun Nishimura*

Department of Chemistry, Gunma University, 1-5-1 Tenjin-cho, Kiryu, Gunma 376-8515, Japan

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Abstract—Biscrown ethers **2a**–**c** and **3a**–**c** arranged at a cyclobutane ring were prepared by intermolecular [2+2] photocycloaddition of vinylated benzocrown ethers. The complexing behavior of **2a**–**c** toward alkali metal cations was evaluated by ESI-MS analysis, liquid–liquid extraction, and the comparison of complexing stability constant. An intramolecular sandwich-type 1:1 (host/guest) complexation was observed by ESI-MS analysis in the competitive system where **2a**-Na^+, **2b**-K^+, and **2c**-Cs^+ were formed selectively. In the liquid–liquid extraction, however, **2a** hardly extracted any cation, while both **2b** and **2c** efficiently extracted larger cations such as K^+, Rb^+, and Cs^+. It was found that the complexing stability constant of **2a**-Na^+ is lower than that of benzo-15-crown-5-Na^+ though extraordinarily high values were obtained for **2b**-K^+ and **2c**-Cs^+ complexes compared with those of 18-crown-6-K^+ and dibenzo-24-crown-8-Cs^+ complexes, respectively. Hence, the excellent complexing ability was achieved by using the cyclobutane ring, which strongly preorganized two benzocrown-ether moieties for the larger alkali metal cations.

1. Introduction

The preorganization of a host molecule toward a certain guest compound is one of the most important strategies to increase its complexing ability.[1,2] Among them the attachment of an oligo(oxyethylene) chain to a crown ether is the simplest method. Gokel and co-workers called such crown compounds lariat ethers.[3] Along the strategy, often two crown ether moieties are connected by various kinds of spacers to construct biscrown ethers,[4] since biscrown ethers are known to bind larger cations than size-fitting one to the crown unit due to sandwich complexation, and to enhance the complexing ability including ion-selectivity and ion-affinity. Those have been also widely investigated for their complexing behavior.[5] Bis(benzocrown ether)s possessing a flexible spacer forming sandwich-type complexes with alkali metal cations have been thoroughly studied by Kikukawa and co-workers.[6] Biscrown ethers as preorganized hosts having both rigid spacer and suitable geometry can selectively and efficiently form stable sandwich-type complexes with larger species, compared with conventional biscrown ethers.

Despite many examples related to biscrown ethers,[7] there is no report regarding to bis(benzocrown ether)s arranged at a cyclobutane ring system. Recently, we have successfully prepared crown compounds bridged by a cyclobutane ring by means of intramolecular [2+2] photocycloaddition of styrene derivatives possessing an oligo(oxyethylene) linkage,[8] and have reported that this cyclization is also a useful method to prepared rigid crown compounds.[9] In this paper we describe the preparation of the title compounds by intermolecular [2+2] photocycloaddition of vinylated benzocrown ethers and the examination of their specific complexation to alkali metal cations in a homogeneous phase and a liquid–liquid two-phase system.

2. Results and discussion

2.1. Synthesis of bis(benzocrown ether)s

The photodimerization of styrene[10,11] and *p*-methoxystyrene[12] offered *cis*- and *trans*-isomers in a certain ratio under conditions given. It was considered that when vinylated benzocrown ethers **1** were used as starting materials the dimerization could give us **2** and **3** which would have induced-fitting ability to make a sandwich-type complexation with larger cations. Therefore, the photodimerization of **1** was carried out by using a 400-W high-pressure mercury lamp through Pyrex filter (Scheme 1).

To obtain target compounds in good yields, the reaction was carried out with or without a template in various solvents and with cyclodextrins (CDs) in aqueous media. Precursor **1b** was chosen as a representative and the time-course of its

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Keywords: Bis(crown ether)s; Photosynthesis; Extraction experiment; Complexing ability.

* Corresponding author. Tel.: +81-277-30-1310; fax: +81-277-30-1314; e-mail address: nisimura@chem.gunma-u.ac.jp

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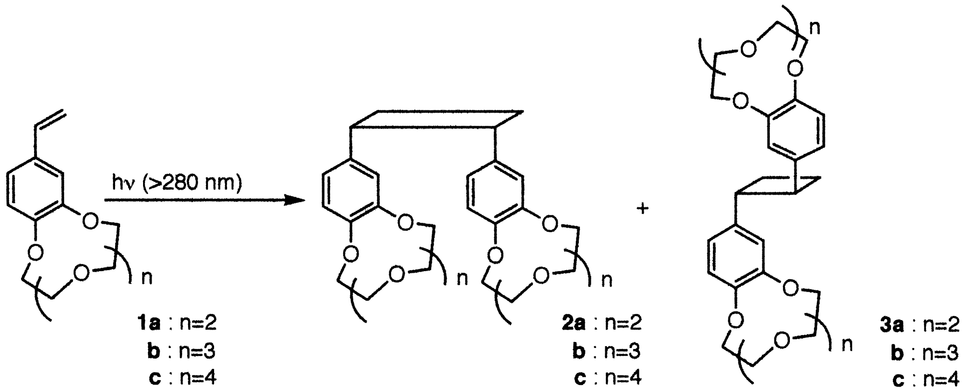


Scheme 1.

Table 1. Preparation of bis(benzocrown ether)s from **1b**

Solvent	Concentration (additive)	Yield (%)	
		2b	**3b**
Cyclohexane	100 mM	23	3
Benzene	100 mM	55	11
Benzene	100 mM ([KBF_4]=1.00 M)	23	8
Benzene	100 mM ([CsBr]=1.00 M)	51	12
Benzene	100 mM ([CH_3COOCs]=1.00 M)	41	7
Toluene	100 mM	51	8
Acetonitrile	100 mM	38	19
Acetonitrile	100 mM ([KBF_4]=1.00 M)	78	4
Acetonitrile	100 mM ([CsBr]=1.00 M)	40	8
Acetonitrile	100 mM ([$CH_3COOHCs$]=1.00 M)	55	11
Acetonitrile	2 mM	0	9
Acetonitrile	2 mM ([KBF_4]=60 mM)	63	2
Water	2 mM	0	0
Water	2 mM ([γ-CD]=0.5 mM, [CsBr]=20 mM)	0	0

reaction was followed by ^1H NMR and HPLC analyses. Yields of **2b** and **3b** increased with the conversion of **1b**, then reached at plateau, and decreased sharply due to formation of polymeric material which was not characterized. Hence, the irradiation should be ceased at the plateau.

It is apparent that the yields clearly depended on the polarity of solvent used as shown in Table 1. Good yields and high selectivity for **2b/3b** were recorded in benzene and toluene. Since, alkali metal cation often shows an important role as a template in crown ether syntheses,[13–15] we applied the cations in this synthesis. Remarkable template effect by potassium cation was observed in acetonitrile.

Although γ-CD can accommodate two vinyl phenyl moieties,[16] it did not effect this particular reaction.

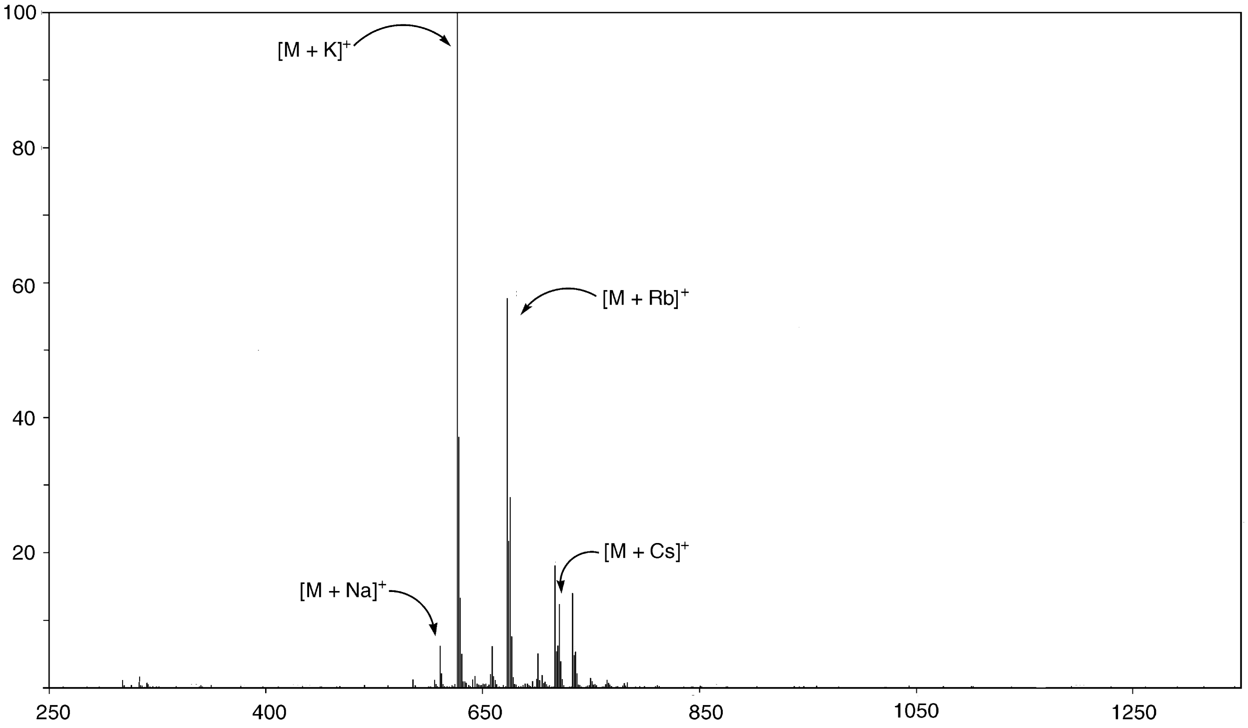


Figure 1. ESI-MS spectrum of **2b** in 4:1 (v/v) CH_3CN-H_2O containing an equimolar mixture of $LiClO_4$, $NaClO_4$, $KClO_4$, $RbClO_4$, and $CsClO_4$.

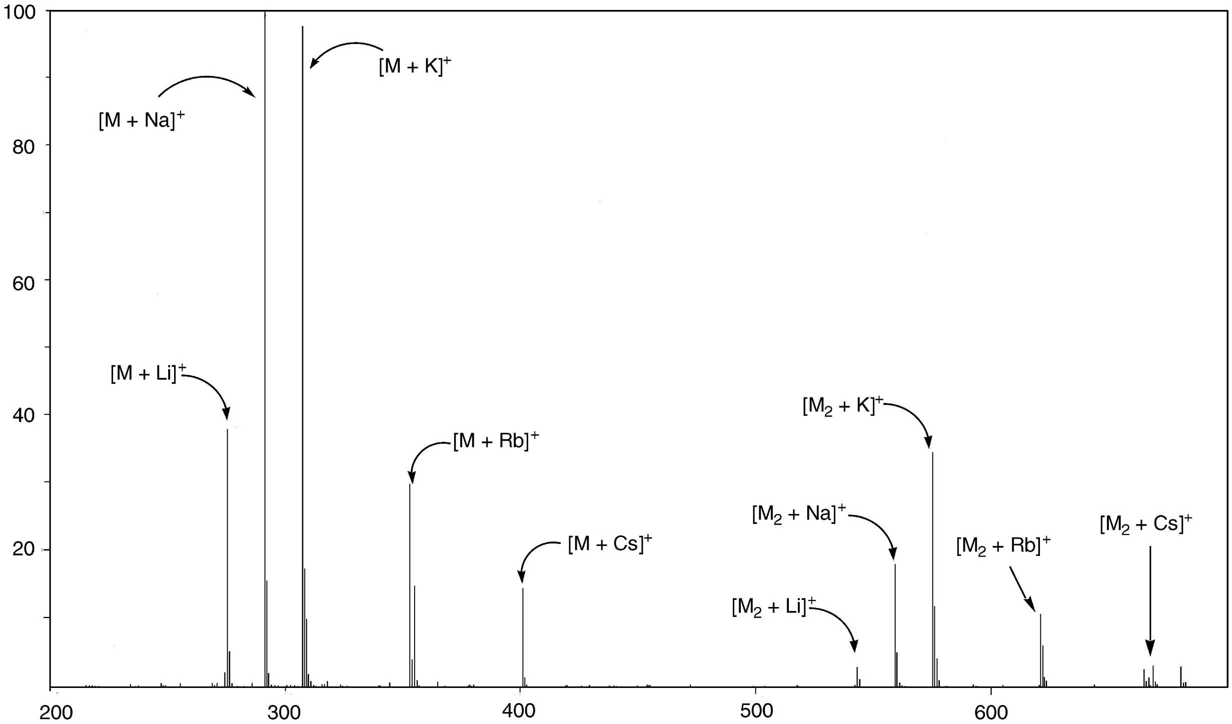


Figure 2. ESI-MS spectrum of **5** in 4:1 (v/v) CH_3CN-H_2O containing an equimolar mixture of $LiClO_4$, $NaClO_4$, $KClO_4$, $RbClO_4$, and $CsClO_4$.

2.2. Complexing behavior of bis(benzocrown ether)s

Complexing ability of relatively rigid compounds **2a–c** was evaluated by the liquid–liquid extraction, electrospray ionization mass spectroscopy (ESI-MS) and equilibrium stability in homogeneous systems as described in the following.

2.2.1. Complexation of bis(benzocrown ether)s with alkali metal cations in homogeneous solution. ESI-MS is one of the most simple and useful methods to disclose the complexing behavior of host compounds with cations in a polar homogeneous system.[17–19] The interaction between the bis(benzocrown ether)s and alkali metal perchlorates

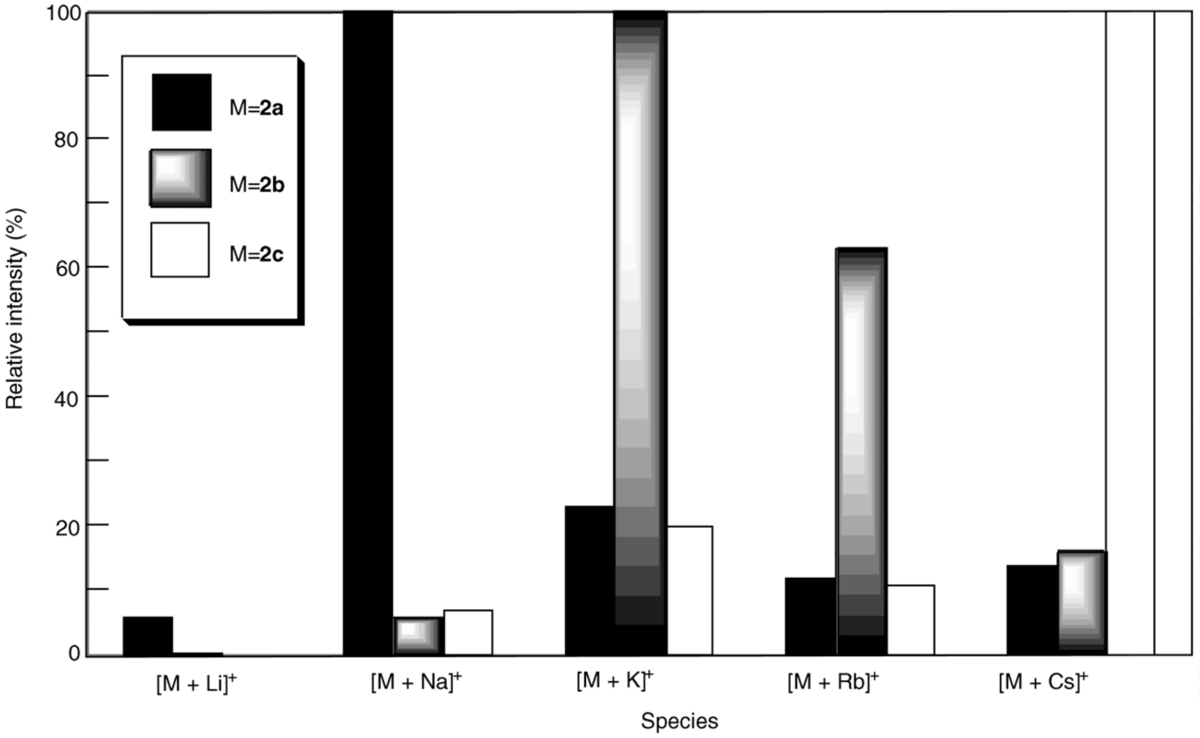


Figure 3. Relative intensity of alkali metal cations complexed with **2a**, **2b**, and **2c** in ESI-MS analysis.

were investigated in a competitive system in CH_3CN-H_2O (4:1, v/v) solution.

As shown in Figure 1, **2b** was completely consumed by complexation so that the molecular ion was not detected at all. Not only **2b** but also both **2a** and **2c** formed exclusively the 1:1 complex with each cation, indicating that these host molecules incorporated the cation by intramolecular sandwich-type complexation. In contrast with **2**, conventional benzo-12-crown-4 (**4**) and benzo-15-crown-5 (**5**) formed both 1:1 and 2:1 (host:guest) complexes with all alkali metal cations. Figure 2 illustrates the spectrum of **5**, as a representative monobenzocrown ether.

Note that bis(benzocrown ether)s **2** showed unique complexing behavior. To stress the selectivity the relative intensity along cations complexed with **2a**, **2b**, and **2c** is illustrated in Figure 3.

Biscrown **2a** showed extraordinarily high Na^+-selectivity. This is apparently due to a strong sandwich-type complexation, since the 12-crown-4 moiety has been well known to exhibit relatively high affinity toward Li^+ compared with other alkali metal cations. Biscrown **2b** showed relatively high K^+-selectivity. It is noteworthy that the crown ether with 15-crown-5 moieties showed the low affinity toward Na^+ as well as Li^+, although **5** shows the highest affinity toward Na^+ among alkali metal cations (Fig. 2). The fact suggests that the formation of intramolecular sandwich-type complexes occurred, preferring to the 1:1 complexation due to size fitting between the cation diameter and cavity diameter. For example, compound **2c** showed exceedingly high Cs^+-selectivity. The arrangement of two crown ethers like **2c** is quite suitable for the intramolecular sandwich-type complexation with Cs^+, since benzo-18-crown-6 (**6**) itself exhibits relatively the low affinity toward Cs^+ and does not form any sandwich-type complexes with any alkali metal cations as shown in Figure 4.

All series of the bis(benzocrown ether)s preferentially and efficiently formed intramolecular sandwich-type complexes with large cations. These results suggest that the bis(benzocrown ether)s make the complexes stable and cation-selective due to the preorganized and fixed structure by the cyclobutane ring as a spacer, which is different from other bis(benzocrown ether)s as mentioned in Section 2.2.3.

2.2.2. Liquid–liquid extraction of alkali metal picrates by bis(benzocrown ether)s.

Extraction experiments were carried out in $H_2O-CH_2Cl_2$ systems. In contrast to the data obtained from the ESI-MS analysis, **2a** hardly extracted any cations under the conditions used in this experiment. The low extractability is in accord with its low complexing stability constants for those cations (see Tables 3 and 4). Bis(benzocrown ether) **2b** efficiently extracted larger cations than Na^+, but the selectivity was not so high compared with that expected from the ESI-MS analysis. The efficiency, however, was higher than that of **5**. Compound **2c** also showed high extractability toward larger cations, especially extracting Cs^+ two-times larger than **6**. Thus, the two-phase liquid–liquid extraction evaluated the present ionophores differently from those of ESI-MS analysis in homogeneous media. The liquid–liquid extraction is often affected by the distribution coefficient between the two phases in addition to the complexation constant between the ligand and cation. Since the complexing ability of bis(crown ether)s showed the high selectivity in homogeneous phase as observed in ESI-MS data, the efficient extractability of **2b**

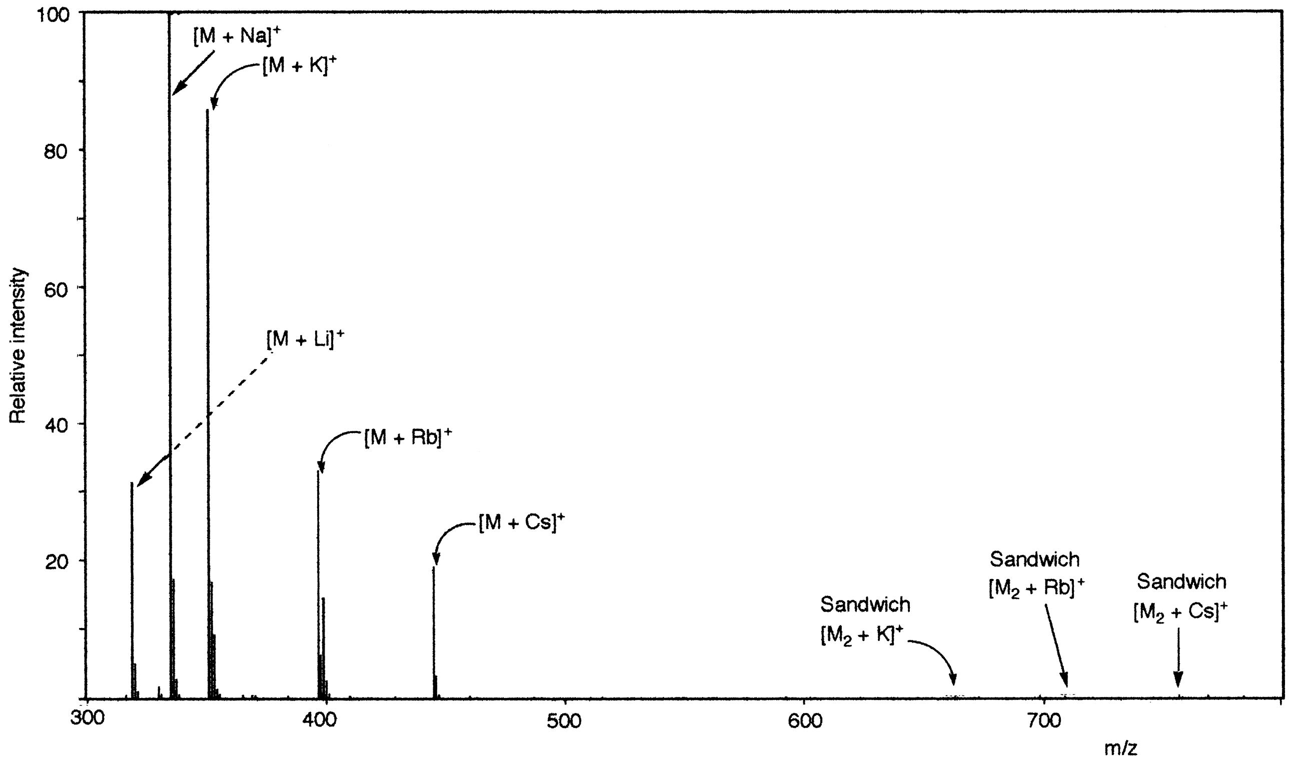


Figure 4. ESI-MS spectrum of **6** in 4:1 (v/v) CH_3CN-H_2O containing an equimolar mixture of $LiClO_4$, $NaClO_4$, $KClO_4$, $RbClO_4$, and $CsClO_4$.

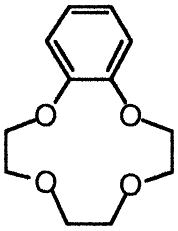
Table 2. Liquid–liquid extraction of metal picrate by crown compounds[a]

Ligand	Percent extraction				
	Li^+	Na^+	K^+	Rb^+	Cs^+
2a[b]	0	1	0	1	1
2b[b]	16	26	73	69	62
2c[b]	1	19	68	60	67
3a[b]	1	1	0	1	1
3b[b]	1	7	17	9	6
3c[b]	1	9	74	49	27
4[b]	1	1	1	1	1
4[c]	1	2	1	1	1
5[b]	2	4	6	5	3
5[c]	1	6	13	8	5
6[b]	1	5	56	38	21
6[c]	2	7	76	54	31

[a] Extraction conditions: Aqueous phase; [MOH]=0.1 M, [picric acid]=5.0×10^{-5} M, 5 mL. Organic phase; CH_2Cl_2, 5 mL.

[b] [ligand]=5.0×10^{-5} M.

[c] [ligand]=1.0×10^{-4} M.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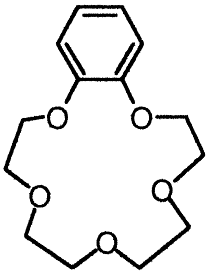
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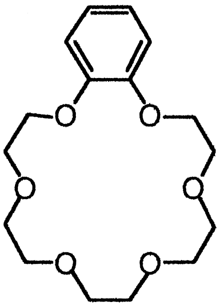
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and **2c** for larger cations without selectivity is most likely due to the large distribution coefficients for large cations into CH_2Cl_2.

The extraction efficiency and selectivity of bis(benzocrown ether)s **3a**, **3b**, and **3c** are similar to those of **4**, **5**, and **6**, respectively, suggesting that the 1:1 (cation-crown) complexes are formed (Table 2).

2.2.3. Determination of stability constants (K_a). To assess the binding ability of the bis(benzocrown ether)s **2a–c**, ^{1}H NMR titration with alkali metal cations was carried out in acetonitrile-d_3 (Table 3) and in acetonitrile-d_3–D_2O (Table 4) at 25 °C.

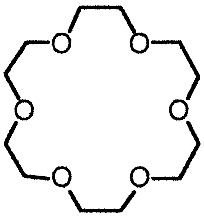
Table 3 shows the stability constants of the bis(benzocrown ether)s and reference compounds with alkali metal cation in acetonitrile-d_3. Biscrown ether **2a** showed higher stability constant toward Na^+ among alkali metal cations, though the value is lower than that of **5**. An extremely high value was obtained for **2b** with K^+ and **2c** with Cs^+. Since these values are too large to accurately assess by a curve fitting method based on the ^{1}H NMR titration in acetonitrile-d_3, we performed the titration in acetonitrile-d_3–D_2O (4:1 v/v). Biscrown ether **2b** showed high selectivity toward K^+ and the value of **2b** with K^+ was not only large compare with

Table 3. Stability constants of the bis(benzocrown ether)s with alkali metal cation in CD_3CN

Ligand	log K_a		
	Na^+	K^+	Cs^+
2a	3.22	2.40	2.31
2b	3.99	6.51	5.78
2c	4.40	4.53	8.19
5	4.19	2.48	–
6	–	4.84	–

Table 4. Stability constants of the bis(benzocrown ether)s with alkali metal cation in CD_3CN–D_2O (4:1 v/v)

Ligand	log K_a		
	Na^+	K^+	Cs^+
2a	0.78	–	–
2b	2.60	4.63	3.33
2c	3.11	4.21	5.15
5	1.79	1.92	1.75
6	2.60	3.67	2.42
7	–	4.29	–
8	1.04	2.30	2.75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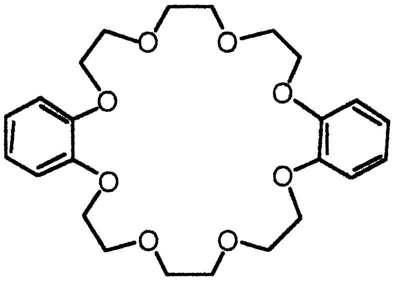
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that of **6** with K^+ (Tables 3 and 4) but also that of 18-crown-6 (**7**) with K^+ (Table 4) which is the champion datum in a series of crown ethers containing biscrown compounds[20] and lariat ethers except for Nakatsuji's C-pivot lariat ether with alkali metal cation.[21]

The stability constants in 90% methanolic aqueous solution and the extractability in a $H_2O-CH_2Cl_2$ system for a series of bis(benzo-15-crown ether)s possessing a flexible spacer with potassium cation were reported by Kikukawa and co-workers. According to their data, all bis(benzo-15-crown ether)s show K^+-selectivity and the stability constant of bis(benzo-15-crown-5) possessing triethylene glycol chain spacer ($\log K=4.64$) as well as that possessing octamethylene chain spacer ($\log K=4.17$), which show higher extractability than bis(benzo-15-crown-5) possessing ethylene chain spacer, is lower than that of **6** ($\log K=4.75$). As mentioned above biscrown ether **2b** showed higher stability constant for K^+ than not only **6** but also that of **7**, obviously indicating that complexing ability of **2b** is higher than bis(benzo-15-crown-5) possessing ethylene chain spacer because its extractability for K^+ (53.2%) is lower than that of **6** (54.1%) as well as bis(benzo-15-crown-5) possessing triethylene glycol chain spacer (86.7%).[6] Thus, it was found that the replacement of ethylene spacer by rigid cyclobutane ring spacer results in the efficient sandwich-type complexation structure by fixed *cis*-form of the bis(benzocrown). This 'biscrown effect'[22] is remarkably observed by complexation of **2c** with Cs^+. The stability constant of **2c** is higher than that of any bis(benzocrown ether)s reported by Kikukawa.[6] In acetonitrile-d_3–D_2O (4:1 v/v), the Cs^+-complexing stability of **2c** was higher than that of dibenzo-24-crown-8 (**8**) by about 250 times, which shows the highest Cs^+-affinity in the single looped crown ethers.[5] Thus, it was found that a ligand showing extraordinarily high affinity to Cs^+ is easily obtained by using the cyclobutane ring spacer to bis(benzo-18-crown-6).

3. Conclusion

Bis(benzocrown ether)s arranged at a cyclobutane ring were conveniently synthesized by means of intermolecular [2+2] photocycloaddition of vinylated benzocrown ethers. From the ESI-MS analysis and the comparison of the stability constant, host molecule **2a** having four ethereal oxygens atoms, **2b** having five ethereal oxygens atoms, and **2c** having six ethereal oxygens atoms in the crown ether moiety were found to show excellent Na^+-, K^+-, and Cs^+-selectivity, respectively, due to their sandwich-type complexation.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on a JEOL α-500 FT NMR spectrometer. HPLC analysis was performed with a Shimadzu LC-6A pump, LC-6A UV detector, and RC-4A data processor. Mass spectra (HRMS) were determined by a JEOL JSM-BU25. UV–vis spectra were recorded by a Hitachi U-3210 spectrophotometer. Electrospray ionization mass spectra (ESI-MS) were obtained on a Perkin–Elmer Sciex API-100 electrospray ionization mass spectrometer under the following conditions: A sample solution was sprayed at a flow rate of 2 $\mu L\ min^{-1}$ at the tip of a needle biased by a voltage of 4.5 kV higher than that of a counter electrode. Toluene and benzene were distilled over Na after a prolonged reflux under a nitrogen atmosphere. Guaranteed reagent grade cyclohexane, acetonitrile, and CH_2Cl_2 were distilled before use.

Vinylbenzocrown ether **1a–c** were prepared by the reported method.[23] Reagent grade benzo-12-crown-4 **4**, benzo-15-crown-5 **5**, benzo-18-crown-6 **6**, 18-crown-6 **7**, and dibenzo-24-crown-8 **8** were used without further purification. Commercially available highest grade of alkali metal hydroxides and alkali metal perchlorates were used. Picric acid was purified by recrystallization from acetone. All aqueous solutions were prepared with distilled, deionized water.

4.2. Preparation of bis(benzocrown ether)s 2a–c and 3a–c

Into a 500 mL Pyrex flask with a magnetic stirrer and N_2 inlet was placed a solution of vinylbenzocrown ether **1** (100 mmol) in acetonitrile (10 mL) and nitrogen was bubbled for 15 min. The solution was irradiated by a 400-W high-pressure mercury lamp. The reaction was monitored by HPLC. After irradiation for 9 h, the reaction mixture was evaporated. The residue was purified by silica gel column chromatography with a gradient solution of benzene–acetone to afford the bis-(benzocrown ether)s.

4.2.1. Compound 2a. Isolated yield, 29%; viscous liquid. ^1H NMR ($CDCl_3$); 6.73 (2H, d, $J=7.9$ Hz), 6.75 (2H, dd, $J=7.9$, 2.2 Hz), 6.49 (2H, d, $J=2.2$ Hz,), 4.07–4.06 (4H, m), 3.95–3.93 (4H, m), 3.90–3.87 (2H, m), 3.79–3.77 (4H, m), 3.74–3.71 (12H, m), 2.42–2.36 (2H, m), 2.35–2.30 (2H, m). ^{13}C NMR ($CDCl_3$); 149.71, 148.36, 136.18, 121.99, 118.20, 117.17, 71.55, 71.45, 70.98, 70.86, 69.74, 69.57, 44.79, 24.18. HRMS(EI) calcd for $C_{28}H_{36}O_8$ (M^+): 500.2410. Found, 500.2418.

4.2.2. Compound 2b. Isolated yield, 54%; White solid. Mp 97.1–97.9 °C (acetone–hexane). ^1H NMR ($CDCl_3$); 6.64 (2H, d, 8.3), 6.50 (2H, dd, $J=8.3$, 1.9 Hz), 6.40 (2H, d, 1.9), 4.04–4.02 (4H, m), 3.90–3.72 (30H, m), 2.44–2.38 (2H, m), 2.34–2.29 (2H, m). ^{13}C NMR ($CDCl_3$); 148.38, 147.18, 134.88, 120.71, 114.85, 113.54, 70.97, 70.92, 70.50, 69.65, 69.55, 69.14, 69.00, 44.90, 24.46. HRMS(EI) calcd for $C_{32}H_{44}O_{10}$ (M^+): 588.2935. Found, 588.2930.

4.2.3. Compound 2c. Isolated yield, 40%; viscous liquid. ^1H NMR ($CDCl_3$); 6.65 (2H, d, 8.3 Hz), 6.52 (2H, d, 8.3 Hz), 6.39 (2H, s), 4.05 (4H, t, 4.6), 3.90–3.85 (6H, m), 3.75–3.67 (32H, m), 2.41–2.38 (2H, m), 2.33–2.29 (2H, m). ^{13}C NMR ($CDCl_3$); 148.16, 146.93, 134.83, 120.61, 114.65, 113.44, 70.67, 69.68, 69.56, 68.97, 68.92, 44.83, 24.47. HRMS(EI) calcd for $C_{36}H_{52}O_{12}$ (M^+): 676.3459. Found, 676.3435.

4.2.4. Compound 3a. Isolated yield, 19%; viscous liquid. ^1H NMR ($CDCl_3$); 6.90 (2H, d, 8.1 Hz), 6.82–6.78 (4H, m), 4.16–4.14 (8H, m), 3.86–3.83 (8H, m), 3.80 (8H, s), 3.42–3.38 (2H, m), 2.26–2.24 (2H, m), 2.08–2.05 (2H, m). ^{13}C NMR ($CDCl_3$); 150.31, 148.68, 139.27, 120.44, 118.03, 116.17, 71.90, 71.43, 71.01, 70.92, 69.81, 69.79, 47.75, 25.62. HRMS(EI) calcd for $C_{28}H_{36}O_8$ (M^+): 500.2410. Found, 500.2405.

4.2.5. Compound 3b. Isolated yield, 15%; White solid. Mp 99.1–100.0 °C (acetone–hexane). ^{1}H NMR ($CDCl_3$); 6.79 (2H, d, J=8.2 Hz), 6.73 (2H, dd, J=8.0, 1.9 Hz), 6.71 (2H, d, J=1.9 Hz), 4.12–4.08 (8H, m), 3.90–3.88 (8H, m), 3.75 (16H, s), 3.39–3.36 (2H, m), 2.24–2.22 (2H, m), 2.06–2.05 (2H, m). ^{13}C NMR ($CDCl_3$); 148.97, 147.42, 137.96, 119.10, 114.10, 112.67, 70.98, 70.53, 70.51, 69.67, 69.61, 69.20, 68.97, 48.15, 25.57. HRMS(EI) calcd for $C_{32}H_{44}O_{10}$ (M^+): 588.2935. Found, 588.2905.

4.2.6. Compound 3c. Isolated yield, 18%; viscous liquid. ^{1}H NMR ($CDCl_3$); 6.81 (2H, d, J=8.6 Hz), 6.74–6.73 (4H, m), 4.14–4.11 (8H, m), 3.92–3.90 (8H, m), 3.77–3.75 (8H, m), 3.72–3.68 (8H, m), 3.63 (8H, s), 3.40–3.34 (2H, m), 2.25–2.23 (2H, m), 2.06–2.04 (2H, m). ^{13}C NMR ($CDCl_3$); 148.79, 147.26, 137.96, 119.12, 114.21, 112.84, 70.73, 70.70, 70.68, 69.67, 69.64, 69.20, 69.05, 48.00, 25.62. HRMS(EI) calcd for $C_{36}H_{52}O_{12}$ (M^+): 676.3459. Found, 676.3430.

4.3. Solvent and additive effects on photodimerization

The yields for photodimerization were measured under a variety of conditions. The 15 mL Pyrex test tubes containing a solution of the precursor olefin with or without additive in a degassed solvent were set around a 400-W high-pressure mercury lamp. After irradiation for the prescribed period, the conversion and the yields of products were determined by HPLC and ^{1}H NMR spectroscopy.

4.4. ESI-MS analysis

The sample solution was 4:1 (v/v) $MeCN-H_2O$ containing the same concentration of the bis(benzocrown ether) and five alkali metal perchlorates (1×10^{-4} mol dm^{-3} each).

4.5. Liquid–liquid extraction of alkali metal picrates

The bis(benzocrown ether)s were used as extractants for alkali metal picrates in a liquid–liquid system together with reference compounds. A CH_2Cl_2 solution of the host compound (5×10^{-5} mol dm^{-3} or 1×10^{-4} mol dm^{-3}, 5 mL) and an aqueous metal picrate solution ([MOH]=0.1 mol dm^{-3}, [picric acid]=1×10^{-5} mol dm^{-3}, 5 mL) were shaken in a 20-mL test tube equipped with a ground glass stopper at room temperature (20–22 °C) for 2 h. After two liquid phase were separated, percent extraction of metal picrates was measured by UV–vis spectroscopy.

4.6. ^{1}H NMR titration of the bis(benzocrown ether)s with alkali metal

A solution of the bis(benzocrown ether)s (1 mmol dm^{-3}) was prepared, and its 500 μL portions were placed in an NMR tube, and the solvent level was marked. A second solution was made in acetonitrile-d_3 with the metal perchlorate. An initial spectrum was recorded, then an appropriate volume of the salt solution was added to the NMR tube and the solvent level was reduced by evaporation to the mark. The spectrum was then recorded again. This procedure was repeated until the salt concentration is reached 10 equiv. to the crownophane. The chemical shifts of the aromatic proton of the bis(benzocrown ether)s before and after each addition of the guest solution were used for calculation of the association constants (K_a). The constants were determined by nonlinear least-squares fitting method of the titration curves for 1:1 complexation, which was monitored by the ESI-MS analysis.

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