3490 © *1992 The Chemical Society of Japan* NOTES *Bull. Chem. Soc. Jpn.*, *65*, *3490—3492 (1992)* [Vol. 65, No. 12

# Complexation Property of a Novel Macrobicyclic Polyether with Two Amide Moieties toward Alkali Metal and Alkaline Earth Metal Cations

Yohji NAKATSUJI,* Toshinori INOUE, Araki MASUYAMA,
and Mitsuo OKAHARA
Department of Applied Chemistry, Faculty of Engineering, Osaka University,
Yamada-oka 2-1, Suita, Osaka 565

(Received April 18, 1992)

**Synopsis.** A new type of macrobicyclic compound, which was prepared by the reaction of 2,9-bis[(ethylamino)methyl]-15-crown-5 with sebacoyl dichloride, has shown a selective complexation property toward $K^+$ and $Ba^{2+}$ cations based on data obtained with potentiometric titration and solvent extraction. This finding was reasonably explained by considering the cooperative binding of the amide moieties and the crown ring. The coordination direction of the carbonyl oxygens was found to markedly affect its complexation property by comparing its complexing ability with those of lariat ethers having one or two amide side arms.

Crown ethers are selective complexing agents toward alkali and alkaline earth metal cations.[1] Their selectivities are generally controlled by changing the ring sizes or the donor atoms. The introduction of electron-donating side arms to the crown ring is also a promising procedure to improve their complexation properties.[2,3] In certain natural antibiotics ester or amide substituents have been skillfully used as appropriate coordination sites for specific cations.[4] Accordingly, such functional groups are potentially useful as the donor sites of synthetic ionophores. In this case, however, the direction of the coordination of the carbonyl oxygen should be suitably regulated by certain structural devices.[5]

We now report on the synthesis of a new type of macrobicyclic compound having a diamide bridge and its effective complexation property toward alkali metal and alkaline earth metal cations.

A new type of macrobicyclic compound (**1**) was prepared by the reaction of 2,9-bis[(ethylamino)methyl]-15-crown-5[6] and sebacoyl dichloride in a 22% yield using a high-dilution technique. The acylation of 2,9-bis[(hexylamino)methyl]-15-crown-5[6] and 2-[(ethylamino)methyl]-15-crown-5[7] gave **2** having plural amide side arms and **3** having an acylamino group on a side arm. The structures of all the new compounds were ascertained by $^1$H NMR, MS, IR, and elemental analysis (see Experimental).

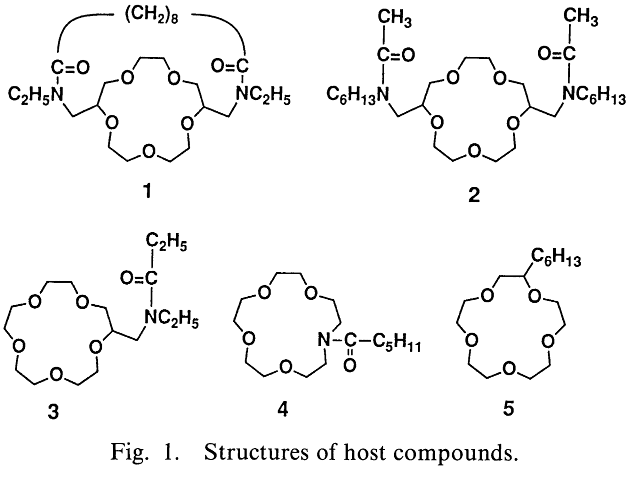

Fig. 1. Structures of host compounds.

Table 1. Stability Constants of Several Host Compounds

| Compd | log $K$(Na$^+$) | log $K$(K$^+$) | $K$(K$^+$)/$K$(Na$^+$) |
|---|---|---|---|
| **1** | 2.37 | 4.11 | 55 |
| **2** | 2.36 | 2.59 | 1.7 |
| **3** | 2.71 | 2.91 | 1.8 |
| **4** | <1 | <1 | — |
| **5**[a] | 3.2[b] | 3.0[b] | 0.9 |
| | 3.15 | 3.19 | 1.1 |
| 15-Crown-5 | 3.31[c] | 3.34[c] | 1.1 |

a) Hexyl-15-crown-5. b) Ref. 9. c) Ref. 3.

The stability constants of macrobicyclic compound (**1**) toward $Na^+$ and $K^+$ were measured in methanol at 25 °C[8] and are summarized in Table 1 along with the data for reference compounds. Potentiometric titration data demonstrate that all compounds examined in this study mainly form 1 : 1 complexes with $Na^+$ and $K^+$.[8] As expected from the previously reported extraction data,[5] *N*-hexanoyl-1,4,7,10-tetraoxa-13-monoazacyclopentadecane (**4**) showed remarkably low stability constants toward $Na^+$ and $K^+$. The introduction of an alkyl group without any donor atoms aids in reducing the stability constants toward $Na^+$ and $K^+$ (see **5**).[9] The stability constants of carbon-pivot lariat ethers containing a 15-crown-5 ring are generally lower than those of the corresponding unsubstituted compound,[2] though evidence for side-arm participation had been obtained through a $^{13}$C NMR $T_1$ measurement[10] or a lanthanoid shift reagent study.[11] The introduction of one or two acylamino group(s) on the 15-crown-5 ring as the side chain also decreased their stability constants toward $Na^+$ and $K^+$ (see **2** and **3**); the extent of the decrease is not as conspicuous compared with those of **4**. On the other hand, a remarkable increase in the stability constant toward $K^+$ without raising that toward $Na^+$ was observed in the case of **1**. This is unequivocal evidence of the effective coordination of the amide moieties to $K^+$. The $K^+/Na^+$ selectivity of this compound is relatively high, and almost equal to that of 18-crown-6 ($K(K^+)/K(Na^+)=52$).[3]

The solvent-extraction method is another excellent procedure for estimating the complexation properties. This is the method used by Gokel et al., who first found the cooperative binding of the electron-donating side

Table 2. Solvent Extraction of Alkali Metal and Alkaline Earth Metal Picrates by Several Host Compounds[a)]

| Compd | $Na^+$ | $K^+$ | $Ca^{2+}$ | $Ba^{2+}$ |
|---|---|---|---|---|
| **1** | 25 | 55 | 8 | 26 |
| **2** | 21 | 27 | 11 | 18 |
| **5** | 26 | 13 | 2 | 4 |

a) Organic phase ($CH_2Cl_2$, 10 $cm^3$)/aqueous phase (10 $cm^3$): $[MNO_3]=5\times10^{-2}$ mol dm$^{-3}$, [extractant]=[picric acid]=$5\times10^{-4}$ mol dm$^{-3}$ or $[M(NO_3)_2]=5\times10^{-2}$ mol dm$^{-3}$, [extractant]=$5\times10^{-4}$ mol dm$^{-3}$, [picric acid]= $10^{-3}$ mol dm$^{-3}$.

arm and the crown ring in the complexation of lariat ethers with alkali metal cations.[12)] Extraction data for several host compounds with picrates of $Na^+$, $K^+$, $Ca^{2+}$, and $Ba^{2+}$ cations are summarized in Table 2. In order to measure the extraction ability toward alkaline earth metal cations, strong basic conditions must be avoided because of the formation of precipitates; thus, metal nitrates were chosen in the place of metal hydroxides.[13)] Compound **2**, having plural amide side chains, effectively extracts $K^+$ compared with hexyl-15-crown-5 (**5**), thus suggesting the participation of the acylamino groups in complexation. As for the extraction of alkaline earth metal cations, both **1** and **2** extracted far more cations than did **5**; the function of the acylamino groups is evident. As for the $Ba^{2+}/Ca^{2+}$ selectivity, macrobicyclic compound **1** is superior to **2**, which has two acylamino groups as the side arm of the crown ring. The extraction data for **1** with a series of alkali metal cations were estimated by a method using metal hydroxide[14)] to be less than 1% for $Li^+$, 23% for $Na^+$, 60% for $K^+$, 35% for $Rb^+$, and 10% for $Cs^+$. These data again showed the good $K^+$ selectivity of the macrobicyclic compound. Macrobicyclic polyethers with carbon bridgeheads have been shown to possess a selectivity for alkali metal cations corresponding to their cavity sizes.[15)] An examination of the Corey–Pauling–Koltun molecular model suggests that the cavity size of **1** is suitable for the size of $K^+$.

In conclusion, the acylamino groups were successfully used as effective donating sites for alkali metal and alkaline earth metal cations in the design of new types of synthetic multidentates. The results obtained in this study clearly show that the coordination direction of the carbonyl oxygen must be suitably regulated for optimal participation in complexation.

## Experimental

$^1H$ NMR spectra at 100 MHz or 400 MHz were taken on a JEOL JNM-PS-100 spectrometer or JEOL JNM-GSX-400 spectrometer using tetramethylsilane as an internal standard. IR spectra were obtained on a Hitachi 260-10 spectrometer. The mass spectra were measured with a JEOL JMS-DS 303 HF spectrometer at an ionization potential of 70 eV. *N*-hexanoyl-1,4,7,10-tetraoxa-13-monoazacyclopentadecane (**4**),[5)] 2-[(ethylamino)methyl]-15-crown-5,[7)] 2,9-bis[(ethylamino)methyl]-15-crown-5,[6)] and 2,9-bis[(hexylamino)methyl]-15-crown-5[6)] were prepared according to a method described in the literature.

**3,4-Diethyl-17,20,23,25,28-pentaoxa-3,14-diazabicyclo-[14,7,6]nonacosane-4,13-dione (1).** To a stirred solution of triethylamine (8.08 g, 0.08 mol) in dichloromethane (500 $cm^3$) was simultaneously added 2,9-bis[(ethylamino)methyl]-15-crown-5 (6.68 g, 0.02 mol) in dichloromethane (500 $cm^3$) and sebacoyl dichloride (6.11 g, 0.026 mol) in dichloromethane (500 $cm^3$) over a period of 8 h at room temperature. After the mixture was stirred for another 10 h, the solvent was removed. Water (200 $cm^3$) was added to the residue and extracted with dichloromethane (200 $cm^3\times3$). The combined organic layer was concentrated and purified on an alumina column (benzene/dioxane=4/1 (v/v)) to give compound **1** as a slightly yellow viscous oil (2.20 g, 22%). IR(neat) 2930, 1650, 1480, 1130 cm$^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=1.0—1.2 (m, 6H), 1.2—1.4 (m, 8H), 1.5—1.8 (m, 4H), 2.2—2.5 (m, 4H), 3.0—4.1 (m, 26H); MS *m/z* (rel intensity) 500 ($M^+$; 21), 268 (14), 226 (22), 84 (22), 58 (100), 45 (20).

Found: C, 62.16; H, 9.64; N, 5.56%. Calcd for $C_{26}H_{48}O_7N_2$: C, 62.37; H, 9.66; N, 5.60%.

***N,N′*-Diacetyl-*N,N′*-dihexyl-1,4,7,10,13-pentaoxacyclopentadecane-2,9-dimethanamine (2).** To a stirred solution of 2,9-bis[(hexylamino)methyl]-15-crown-5 (3.35 g, 7.5 mmol) and triethylamine (3.03 g, 30 mmol) in dichloromethane (100 $cm^3$) acetyl chloride (2.95 g, 37.5 mmol) in dichloromethane (30 $cm^3$) was dropwise added over a period of 1 h at room temperature. The mixture was stirred for another 24 h at that temperature and the solvent was removed under reduced pressure. Water (200 $cm^3$) was added to the residue and extracted with dichloromethane (100 $cm^3\times3$). The combined organic layer was concentrated and distilled in a Kugelrohr apparatus (210 °C/5.3 Pa) to give **2** as a slightly yellow oil (3.08 g, 78%). IR (neat) 2940, 2800, 1640, 1450, 1350, 1110 cm$^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=0.88 (t, 6H), 1.1—1.8 (m, 16H), 2.08, 2.12 (s+s, 6H), 3.0—4.0 (m, 26H); MS *m/z* (rel intensity) 530 ($M^+$; 7), 487 (29), 374 (100), 156 (29), 114 (84).

Found: C, 63.19; H, 10.26; N, 5.40%. Calcd for $C_{28}H_{54}O_7N_2$: C, 63.36; H, 10.26; N, 5.28%.

***N*-Ethyl-*N*-propanoyl-1,4,7,10,13-pentaoxacyclopentadecane-2-methanamine (3).** To a stirred solution of 2-[(ethylamino)methyl]-15-crown-5 (2.77 g, 10 mmol) and triethylamine (1.21 g, 12 mmol) in benzene (35 $cm^3$) propanoyl chloride (1.11 g, 12 mmol) in benzene (5 $cm^3$) was added dropwise over a period of 1 h at room temperature. After the mixture was stirred for another 24 h at that temperature, the solvent was removed under reduced pressure. The residue was passed through a silica gel column (acetone/hexane=1/9 (v/v)) to give a slightly yellow oil (2.80 g, 84%). IR (neat) 2930, 2860, 1640, 1450, 1110 cm$^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=1.10 (t, 3H), 1.14 (t, 3H), 2.08—2.68 (m, 2H), 2.82—4.06 (m, 23H); MS *m/z* (rel intensity) 333 ($M^+$; 14), 276 (22), 219 (12), 114 (27), 87 (100), 58 (90), 45 (37).

Found: C, 57.35; H, 9.53; N, 4.15%. Calcd for $C_{15}H_{31}O_6N$: C, 57.64; H, 9.37; N, 4.20%.

**Measurement of Stability Constants.** All of the stability constants were determined using Toko $Na^+$ 1100 and Toko $K^+$ 1200 electrodes for NaCl and KCl, respectively, in anhydrous MeOH at 25 °C. The emf was measured with a Beckman 4500 digital pH meter. The procedures used were those described by Frensdorff.[8)] The data are summarized in Table 1.

**Extraction Procedure.** A mixture of an aqueous solution (10 $cm^3$) of alkali metal nitrate or alkaline earth metal nitrate ($5\times10^{-2}$ mol dm$^{-3}$) and picric acid (for alkali metal cation, $5\times10^{-4}$ mol dm$^{-3}$; for alkaline earth metal cation, $10^{-3}$ mol dm$^{-3}$) and a dichloromethane solution (10 $cm^3$) of an appropriate extractant ($5\times10^{-4}$ mol dm$^{-3}$) was shaken at 22 °C for 9 h. In the case of extraction under basic conditions,[14)] alkali metal hydroxide ($5\times10^{-2}$ mol dm$^{-3}$) was used in place of the nitrate. The extraction ability was obtained by a calculation based on the adsorption of picrate anion in the aqueous phase at 354 nm in the UV spectrum. The data are summarized in Table 2.

## References

1) R. M. Izatt, K. Pawlak, J. S. Bradshaw, and R. L. Bruening, *Chem. Rev.*, **91**, 1721 (1991).

2) D. M. Dishong, C. J. Diamond, M. I. Cinoman, and G. W. Gokel, *J. Am. Chem. Soc.*, **105**, 586 (1983).

3) Y. Nakatsuji, T. Nakamura, M. Yonetani, H. Yuya, and M. Okahara, *J. Am. Chem. Soc.*, **110**, 531 (1988), and references cited therein.

4) G. R. Painter and B. C. Pressman, *Top. Curr. Chem.*, **101**, 83 (1982).

5) Y. Nakatsuji, H. Kobayashi, M. Okahara, and K. Matsushima, *Chem. Lett.*, **1982**, 1571.

6) H. Maeda, T. Kikui, Y. Nakatsuji, and M. Okahara, *Synthesis,* **1983**, 185.

7) H. Maeda, T. Kikui, Y. Nakatsuji, and M. Okahara, *J. Org. Chem.*, **47**, 5167 (1982).

8) H. K. Frensdorff, *J. Am. Chem. Soc.*, **93**, 600 (1971).

9) I. Ikeda, S. Yamamura, Y. Nakatsuji, and M. Okahara, *J. Org. Chem.*, **45**, 5355 (1980).

10) A. Kaifer, H. D. Durst, L. Echegoyen, D. M. Dishong, R. A. Schultz, and G. W. Gokel, *J. Org. Chem.*, **47**, 3195 (1982).

11) A. Kaifer, L. Echegoyen, and G. W. Gokel, *J. Org. Chem.*, **49**, 3029 (1984).

12) G. W. Gokel, D. M. Dishong, and C. J. Diamond, *J. Chem. Soc., Chem. Commun.*, **1980**, 1053.

13) Y. Takeda, *Bull. Chem. Soc. Jpn.*, **52**, 2501 (1979).

14) C. J. Pedersen, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **27**, 1305 (1968).

15) Y. Nakatsuji, T. Mori, and M. Okahara, *J. Chem. Soc., Chem. Commun.*, **1984**, 1045.