

Synthesis of *N*-Octylmonoaza-15-crown-5 having a Dodecylphosphoric Acid Functional Group and the Binding Ability Toward Alkali Metal Cations

Yoichi Habata* and Sadatoshi Akabori

Department of Chemistry, Faculty of Science, Toho University, Funabashi, Chiba 274, Japan
Received July 5, 1994

A new *N*-octylmonoaza-15-crown-5 having an alkylphosphoric acid functional group (**3c**) was synthesized. It was revealed that **3c** selectively transported sodium ion under neutral source phase/acidic receiving phase condition, and selectively transported lithium ion under basic source phase/acidic receiving phase condition. From an ir and ^{13}C nmr spectral study of the lithium hydroxide and sodium thiocyanate complexes of **3c**, it is suggested that **3c** does not incorporate cations into the three dimensional cavity using the crown ring and the phosphoric acid site, but that the crown and the phosphoric acid sites act on the cations independently; only the crown ether site of **3c** significantly coordinates to the cations under neutral source phase condition, and the phosphate anion is mainly employed under basic conditions.

J. Heterocyclic Chem., **31**, 1605 (1994).

Recently, crown compounds possessing one or more side arms as an additional binding site, named lariat or armed crown ethers, have attracted much attention by chemists [1], since they have specific cation binding abilities. Especially, armed crown ethers, which have ionizable groups such as carboxylic, phenolic -OH or arylphosphonyl groups, have some advantages; rapid incorporation of cations from the basic aqueous phase to the organic phase with rapid release to the acidic aqueous phase, and an enhancement of cation selectivity by formation of a three dimensional cavity using the crown ring and the anion site of the pendant arm [2].

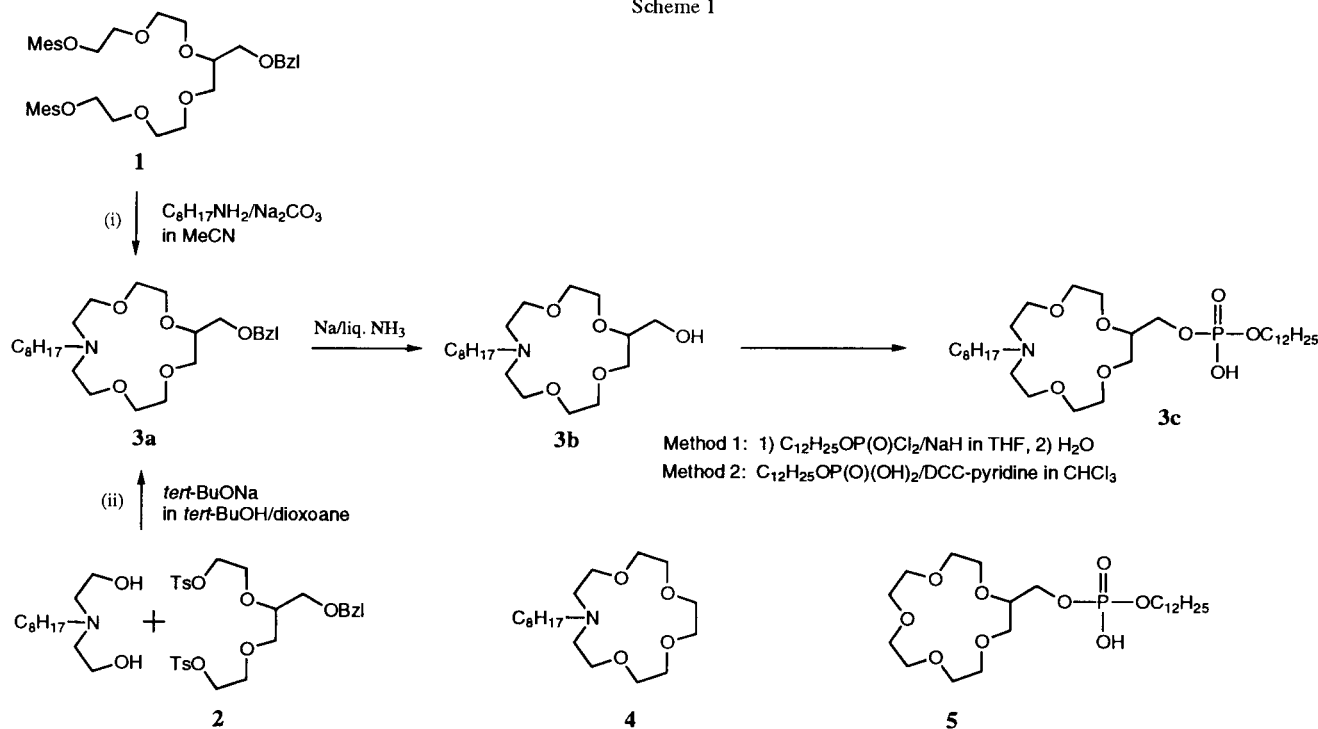
Previously, we reported [3a-d] that the crown com-

pounds, which have an alkylphosphoric acid functional group as a side arm, are selective and effective carriers for alkali metal cations in liquid membrane transport, and the structure around the bridgehead carbon bearing the pendant arm influences the selectivity of alkali metal cations in the alkylphosphoric acid armed crown-4 and crown-5 ethers. However, there is no report about the alkylphosphoric acid armed azacrown ethers and their complexing ability.

Here we report the synthesis and the binding ability of *N*-octylmonoaza-15-crown-5 having a dodecylphosphoric acid functional group for alkali metal cations.

The synthetic route is summarized in Scheme 1. The

Scheme 1



starting material **3a** was prepared *via* two routes; (i) the reaction of the dimesylate of the pentaethylene glycol derivative with *n*-octylamine in the presence of sodium carbonate, and (ii) the reaction of the ditosylate of the triethylene glycol derivative with *N*-octyldiethanolamine. The yield of the cyclization reaction in route (i) was higher than that of route (ii). The debenzoylation of **3a** with sodium in liquid ammonia produced the hydroxymethyl crown ether **3b**. The introduction of the dodecylphosphoric acid functional group to **3b** was carried out by the use of two manners; (Method 1) the reaction of **3b** with dichlorododecylphosphate in the presence of sodium hydride followed by hydrolysis, and (Method 2) the reaction of **3b** with dodecylphosphate in the presence of dicyclohexylcarbodiimide-pyridine.

Competitive transport experiments with **3c** for alkali metal cations were performed under the conditions described in the experimental section. The results are summarized in Table 1 along with those of *N*-octylmonoaza-15-crown-5 (**4**) and phosphoric acid armed 15-crown-5 (**5**). When the source phase was about pH 5.6, all hosts effectively transported sodium ion (Run 1-3). On the other hand, when the source phase was about pH 11, compound **3c** showed a unique selectivity for lithium ion despite possessing a cavity which fits the diameter of sodium ion (Run 4). The azacrown ether **4** did not transport any cation (Run 5), and the transport rate of potassium ion with **5** was comparable to sodium ion (Run 6).

Table 2, there were remarkable differences in the ir spectra on the phosphate site absorptions between **3c** and its lithium ion complex. For example, in the lithium ion complex, the PO-H stretching bands at 2625 and 2300 cm^{-1} regions disappeared, and the P-OC stretching band at the 970 cm^{-1} region of **3c** was shifted to a higher frequency by about 10 cm^{-1} . In addition, the new P=O stretching band, which arises from a $(\text{RO})_2\text{PO}_2^-$ type compound, appeared at 1105 cm^{-1} [7]. On the other hand, there was a slight shift changes on the phosphate site absorptions between **3c** and its sodium thiocyanate complex. For example, in the sodium thiocyanate complex, the P=O stretching band was shifted to a lower frequency by about 10 cm^{-1} , although the PO-H and P-OC stretching bands did not shift at all. These results indicate that the phosphoric acid site of **3c** form a phosphate with lithium ion, while the phosphoric acid site does not interact with the sodium ion incorporated in the crown moiety of the complexed sodium thiocyanate.

Further information on cation-binding behavior of **3c** was obtained *via* ^{13}C nmr spectroscopy in deuterioacetonitrile/deuteriochloroform (4/1). The ring carbons attached to the oxygen and nitrogen atoms shifted +1.4 ~ +0.2 and -0.9 ppm, respectively, with the addition of sodium thiocyanate, indicating that sodium ion was bound by the crown ring. In contrast, there was no shift change at the ring carbons attached to the oxygen with the addition of lithium hydroxide, although there was a slight shift at the ring NCH_2 carbons about +0.6 ppm. These results

Table 1
Competitive Transport of **3c**, **4** and **5** for Alkali Metal Cations

Run	Compound	Counter anion	pH of source phase	Transport rate ($\times 10^6$ mole/h)			Li ⁺ / Na ⁺	Selectivity Li ⁺ / K ⁺	Na ⁺ / K ⁺
				Li ⁺	Na ⁺	K ⁺			
1	3c	SCN ⁻	5.6	<0.01	0.16	0.04	-	-	4.0
2	4	SCN ⁻	5.6	<0.01	0.04	0.02	-	-	2.0
3	5	SCN ⁻	5.6	<0.01	0.13	0.03	-	-	4.0
4	3c	OH ⁻	11.0	0.14	0.09	0.08	1.6	1.7	1.1
5	4	OH ⁻	11.0	<0.01	<0.01	<0.01	-	-	-
6	5	OH ⁻	11.0	0.33	0.47	0.52	0.7	0.6	0.9

Table 2
IR Spectra of **3c** and its Lithium Hydroxide and Sodium Thiocyanate Complexes

Additive salt	$\nu(\text{PO-H})$	$\nu(\text{P-OC})$	$\nu(\text{P=O})$
None	2625, 2330	970	1250
LiOH complex	-	980	1240, 1105
NaSCN complex	2625, 2330	970	1240

Since **3c** gave lithium hydroxide and sodium thiocyanate selective transport under the basic and neutral source phase conditions, respectively, the cation binding behavior of **3c** for lithium hydroxide and sodium thiocyanate were investigated by means of ir spectroscopy. As shown in

may indicate that the sodium ion of the sodium thiocyanate complex is incorporated in the crown ring alone, while the lithium ion of the phosphate loosely interacts or does not interact with the crown ether site.

Recently, we reported [6] that the phosphoric acid armed crown ether **5** could not favorably form the three dimensional cavity which fits sodium ion using the phosphate anion of the side arm and oxygens of the crown ring. An examination of the CPK molecular model and the computer modeling as shown in Figure 1 (Chem 3D was used as a computer modeling software. Minimization of the crown ring and the side arm were carried out using the Chem 3D parameter) suggested that the phosphate anion of the pendant arm of **3c** could not bear the crown ring by

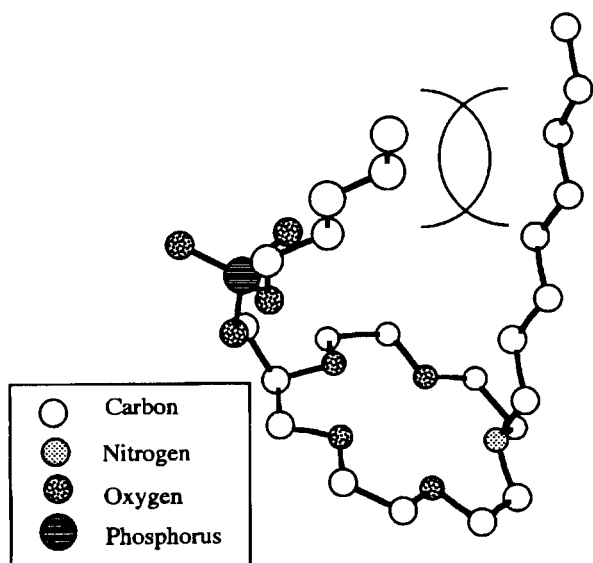


Figure 1. Postulated conformation of a partial structure of **3c**.

a steric repulsion between the dodecyl and octyl groups. In addition, several research groups reported [8a-c] that the acidic extracting reagents such as dialkyl phosphate and phosphonic acid showed lithium ion selectively in the liquid membrane transport. Therefore, it seems reasonable to assume that **3c** does not incorporate cations by the three dimensional cavity using the crown ring and the phosphoric acid site, but that the crown site and the phosphoric acid site act on the cations independently; only the crown site of **3c** significantly coordinates to the cations under the neutral source phase condition (*type A* in Figure 2), and the phosphate anion is mainly employed under the basic condition (*type B* in Figure 2).

In conclusion, we demonstrated that the dodecylphosphoric acid armed *N*-octylmonoaza-15-crown-5 is a "selectivity-controllable host compound", which can control the cation selectivities by *pH* of the aqueous phase. The changes in the cation selectivities suggested that the new armed crown compound provides new possibilities in the design of novel carrier systems.

EXPERIMENTAL

The mass spectra were recorded with a Hitachi M 80 mass spectrometer. The ^1H and ^{13}C nmr spectra were obtained on a Hitachi R-1100 (60 MHz) and Bruker AC 250 (250 MHz) spectrometers, respectively, with TMS as the internal standard. The ir spectra were recorded with a JASCO IR 810 infrared spectrometer. The concentration of the alkali metal cations were determined with a Perkin Elmer 5100 atomic absorption spectrometer. The elemental analyses were measured with a Perkin Elmer 2400 analyzer.

Materials and Reagents.

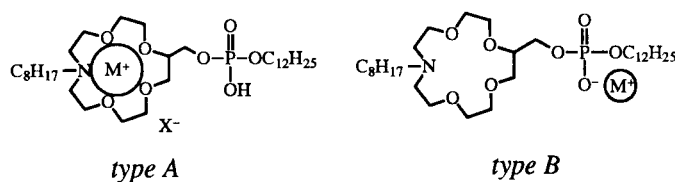


Figure 2. Cation binding fashions of **3c** under the neutral source phase (*type A*) and the basic source phase (*type B*) conditions.

The dimesylate of 7-benzyloxymethyl-3,6,9,12-tetraoxa-1,14-tetradecanediol (**1**) [4], 4-benzyloxymethyl-3,6-dioxa-1,8-octanediol (**5**), *N*-octylmonoaza-15-crown-5 (**4**) [6], and 15-crown-5 having a dodecylphosphoric acid functional group (**5**) [3d] were prepared according to the procedure described in the literature. The ditosylate of 4-benzyloxymethyl-3,6-dioxa-1,8-octanediol (**2**) was prepared in the usual manner. Reagent grade alkali metal hydroxide (lithium hydroxide, sodium hydroxide, and potassium hydroxide) and 1.00 mole/l hydrochloric acid solution were purchased from Wako Chemical Co., Inc. Other reagents and solvents were used without further purification unless otherwise specified. All aqueous solutions were prepared using deionized water.

Preparation of *N*-Octyl-8-benzyloxymethyl-4,7,10,13-tetraoxa-1-azacyclopentadecane (**3a**).

Compound **3a** was prepared *via* two routes as follows:

- (i) The dimesylate **1** (54.9 g, 0.106 mole) and *n*-octylamine (14.5 g, 0.119 mole) were added to a fine granulated sodium carbonate (56.2 g, 0.530 mole) suspended in 1.2 l of acetonitrile at room temperature under a nitrogen atmosphere and stirred for 48 hours at 100–110°. The reaction mixture was cooled and the solid material was removed by filtration. The filtrate was concentrated under reduced pressure. The residual solid was dissolved in water (300 ml) and extracted with dichloromethane (150 ml x 3). The organic layer was washed with water, dried over sodium sulfate and then concentrated under reduced pressure. After the separation of crude **3a** and purification by gel-permeation column chromatography (Sephadex LH-20, ethanol as eluent), pure **3a** was obtained as a pale yellow hygroscopic oil in 21% yield.
- (ii) Under a nitrogen atmosphere, Na metal (2.3 g-atoms) was dissolved in *tert*-butyl alcohol (800 ml). The ditosylate **2** (28.9 g, 0.05 mole) in dioxane (300 ml) and *N*-octyldiethanolamine (10.85 g, 0.05 mole) in dioxane (300 ml) were added dropwise to the solution with the same rate over a period of 6 hours at 40°. After the reaction was continued for 12 hours at 40°, the mixture was filtered and the precipitate was washed with dichloromethane. The filtrate was concentrated under reduced pressure and diluted with dichloromethane. The dichloromethane layer was combined and washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residual oil was chromatographed on an alumina column (hexane:ethyl acetate = 5:1 as eluent), and pure **3a** was obtained as a pale yellow hygroscopic oil in 56% yield; ms: (20 eV): *m/z* 452 ($\text{M}^+ + 1$); ^1H nmr (60 MHz; deuteriochloroform, TMS): 7.39 (s, 5H), 4.58 (s, 2H), 4.10–3.25 (m, 17H), 2.95–2.36 (m, 6H), 1.70–1.10 (m, 12H), 1.10–0.80 (m, 3H); ir (potassium bromide): ν 3035 (Ar-H) cm^{-1} .

Anal. Calcd. for $\text{C}_{26}\text{H}_{45}\text{NO}_5 \cdot 2.5\text{H}_2\text{O}$: C, 62.87; H, 10.15; N, 2.82. Found: C, 62.89; H, 9.92; N, 3.12.

Preparation of *N*-Octyl-8-hydroxymethyl-4,7,10,13-tetraoxa-1-azacyclopentadecane (**3b**).

To a stirred suspension of the benzyloxymethyl derivative **3a** (1.01 g, 2.24 mmoles) in 50 ml of liquid ammonia was added a total of 0.198 g (0.086 mole) of sodium in portionwise over 10-12 minutes. After the continuation of a characteristic deep blue color for 20 minutes was confirmed, ammonium chloride was carefully added to the reaction mixture until it became colorless and the reaction mixture was concentrated to dryness under a stream of nitrogen. Water (10 ml) was added to the reaction mixture and extracted with ether (30 ml x 3). The ether layer was washed with water, dried over sodium sulfate and then concentrated. After the residual brown oil was distilled using a Kugelrohr apparatus, pure **3b** was obtained as an extremely hygroscopic oil in 52% yield, bp: 240° (1 Torr); ms: (20 eV) *m/z* 362 ($M^{+}+1$); ^1H nmr (60 MHz; deuteriochloroform; TMS): 4.10 (broad s, 1H), 3.93-3.40 (m, 17H), 3.00-2.32 (m, 6H), 1.70-1.07 (m, 12H), 1.07-0.78 (m, 3H); ir (potassium bromide): ν 3400 (O-H) cm^{-1} .

Satisfactory elemental analysis could not be obtained due to the extremely hygroscopic character of the compound.

Preparation of *N*-Octyl(dodecyloxyhydroxyphosphoryloxy-methyl)-1,4,7,10,13-tetraoxa-1-azacyclopentadecane (**3c**).

Compound **3c** was also prepared *via* two routes.

Method 1.

Under a nitrogen atmosphere, dodecyl dichlorophosphate (0.112 g, 0.369 mmole) in dry THF (2 ml) was added to a mixture of 60% sodium hydride in mineral oil (0.0199 g, 0.498 mmole) and **3b** (0.098 g, 0.271 mmole) in dry THF (2 ml) at 0° and then the reaction mixture was stirred for 24 hours at room temperature. Water (2 ml) was added to the mixture and stirred for 24 hours at room temperature. The reaction mixture was extracted with chloroform (20 ml x 2). The organic layer was washed with water, dried over sodium sulfate and then concentrated under reduced pressure. After the separation of crude **3c** and purification by gel-permeation column chromatography (Sephadex LH-20, ethanol as eluent), pure **3c** was obtained as a pale yellow oil in 44% yield.

Method 2.

A mixture of the hydroxymethyl derivative **3b** (0.084 g, 4.3 mmoles) and dodecylphosphate (2.28 g, 8.6 mmoles) in the presence of dicyclohexylcarbodiimide (4.37 g, 21.2 mmoles) in dry pyridine (40 ml) was stirred for 24 hours at room temperature. After the pyridine was removed under reduced pressure, water (40 ml) was added to the residue and then extracted with chloroform (30 ml x 3). The combined organic extract was washed with water, dried (sodium sulfate) and then concentrated under reduced pressure. After separation and isolation were performed by silica-gel tlc (chloroform:ethylacetate:methanol=2:2:1 as eluent) followed by gel-permeation column chromatography (Sephadex LH-20, ethanol as eluent), pure **3c** was obtained as a pale yellow hygroscopic oil in 52% yield; ms: (20 eV): *m/z* 609 (M^{+}); ^1H -nmr (60 MHz, deuteriochloroform; TMS): 4.10-3.20 (m, 18H), 3.20-2.35 (m, 6H), 1.70-1.09 (m, 37H), 1.09-0.80 (m, 3H).

Anal. Calcd. for $\text{C}_{31}\text{H}_{64}\text{NO}_8\text{P}$: C, 61.06; H, 10.58; N, 2.30. Found: C, 61.14; H, 10.27; N, 2.48.

Transport Experiments.

The transport experiments were carried out using a U-tube (surface area = 3.5 cm^2) at $25 \pm 2^\circ$. Aqueous and organic phases

were stirred at 135 and 540 rpm, respectively, by synchronous motors in order to avoid stirring errors. The amounts of metal ions in the receiving phases were measured by atomic absorption spectrometry. The initial transport rate was calculated from the increase of the cation concentration in the receiving phase after a period of 9 hours. The transport rate reproducibility for alkali metal ion was confirmed to be $\pm 15\%$ or better. Conditions: [membrane phase] = 5.0 mmoles/ ℓ of crown ether in chloroform (6.0 ml). [source phase] = 0.10 mole/ ℓ lithium hydroxide, sodium hydroxide, and potassium hydroxide (3.0 ml); [receiving phase] = 1.0 mole/ ℓ hydrochloric acid (3.0 ml).

Preparation of the Samples of Lithium Hydroxide and Sodium Thiocyanate complexes of **3c** for IR Spectral Study.

A mixture of the methanol solution of **3c** (25 mmoles/ ℓ , 1.0 ml) and an aqueous solution of lithium hydroxide or sodium thiocyanate (1.0 mole/ ℓ , 25 μl) was stirred at room temperature for 12 hours and the solvent was concentrated under reduced pressure. The residual oil was dried with an Abderhalden's dryer (0.1 Torr, 100°) for 1 hour. The residual oil was used for direct ir spectral study.

^{13}C NMR Titration Experiments.

Titration experiments were carried out at 40° with the addition of 0.5 eq, 1.0 eq, and 2.0 eq, of salt solution to the crown ethers in deuterioacetonitrile/deuteriochloroform (4/1) solution. Conditions: [crown ether] = 0.05 mmole/0.5 ml, [lithium hydroxide] = [sodium thiocyanate] = 0.025 mmole/5 μl in deuterioacetonitrile/deuterium oxide (1/1). Remarkable shift changes appeared when 1.0 eq of salts were added in both cases.

Acknowledgments.

The authors wish to thank Miss Manami Ikeda for preparation of the starting materials. The present research was partially supported by the Hosono Bunka Kikin Foundation of Japan.

REFERENCES AND NOTES

- [1] Y. Inoue and G. W. Gokel, eds, *Cation Binding by Macrocycles*, MerceL Dekker, Inc, New York, 1990.
- [2] R. M. Izatt, K. Pawlak, J. S. Bradshaw, and R. L. Bruening, *Chem. Rev.*, **91**, 1721 (1991).
- [3a] Y. Habata, M. Ikeda, and S. Akabori, *Tetrahedron Letters*, **33**, 3157 (1992); [b] Y. Habata and S. Akabori, *Tetrahedron Letters*, **33**, 5815 (1992); [c] Y. Habata, M. Ikeda, and S. Akabori, *J. Chem. Soc., Perkin Trans. 1*, 2651 (1992); [d] Y. Habata, H. Ugajin, and S. Akabori, *J. Org. Chem.*, **59**, 676 (1994).
- [4] B. Son, B. P. Czech, and R. A. Bartsch, *Synthesis*, 776 (1984).
- [5] B. P. Czech, D. A. Babb, and R. A. Bartsch, *Org. Prep. Proced.*, **15**, 29 (1983).
- [6] P. -L. Kuo, M. Miki, I. Ikeda, and M. Okahara, *J. Am. Oil Chem. Soc.*, **57**, 227 (1980).
- [7] P. Clerc and S. Simon, *Table of Spectral Data for Structure Determination of Organic Compounds*, Springer-Verlag, Berlin, 1989, pp 1235.
- [8a] W. Walkowiak, P. R. Brown, J. P. Shukla, and R. A. Bartsch, *J. Membr. Sci.*, **32**, 59 (1987); [b] T. Takahashi, Y. Habata, and Y. Iri, *J. Incl. Phenom.*, **11**, 379 (1991); [c] Y. Habata, K. Uchida, Y. Sato, and S. Akabori, *J. Membr. Sci.*, **85**, 175 (1993).