

## 아미드기를 가진 소수성 비고리 폴리에테르의 합성

金鍾昇\* · 오끼 아키라† · 曹文煥‡ · 柳一龍 · 李相哲§ · 李鍾海§ · 趙南淑‡

건양대학교 자연과학연구소 화학과

† 가코시마대학교 응용공학부

‡ 강원대학교 자연과학대학 화학과

§ 한국표준과학연구원 무기분석부

‡ 충남대학교 자연과학대학 화학과

(1996. 9. 2 접수)

## Syntheses of Lipophilic Acyclic Polyethers Bearing Amide End-Groups

Jong Seung Kim\*, Akira Ohki†, Moon Hwan Cho‡, Ill Yong Yu, Sang Chul Lee‡,

Joung Hae Lee§, and Nam Sook Cho‡

Department of Chemistry, Konyang University, Nonsan 320-800, Korea

† Department of Applied Chemistry & Chemical Engineering, Faculty of Engineering,  
Kagoshima University, Kagoshima 890, Japan

‡ Department of Chemistry, Kangwon National University, Chuncheon 200-701, Korea

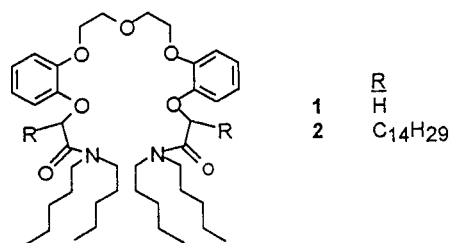
§ Korea Research Institute of Standards and Science, Taejon 305-606, Korea

‡ Department of Chemistry, Chungnam National University, Taejon 305-764, Korea

(Received September 2, 1996)

Recently, much attention has been paid to the selective separation of alkali metal, alkaline earth metal, and heavy metal ions from industrial waste.<sup>1,2</sup> Especially, investigations of metal ion complexation with potential neutral chelating functions in the side arms have been well studied.<sup>3</sup> Many natural ionophores such as valinomycin for potassium ion,<sup>4</sup> monensin for sodium ion,<sup>5</sup> nonactin for ammonium ion<sup>6</sup> and calcimycin for calcium ion<sup>7</sup> have been well known. Potentiometric selectivities of solvent polymeric membrane electrodes containing structural derivatives of dibenzo-16-crown-5-oxyacetamides for sodium ion have been determined.<sup>8</sup>

Previously, we prepared lipophilic acyclic polyether bearing amide end-groups (**1** and **2**) and reported that complexation abilities of the ligand by ISE (Ion Selective Electrode) system are found to show an excellent selectivity for  $Pb^{2+}$  over  $Cu^{2+}$ .<sup>9</sup> Especially, the value of  $\log K_{Pb,Cu}^{Pb}$  for compound **1**



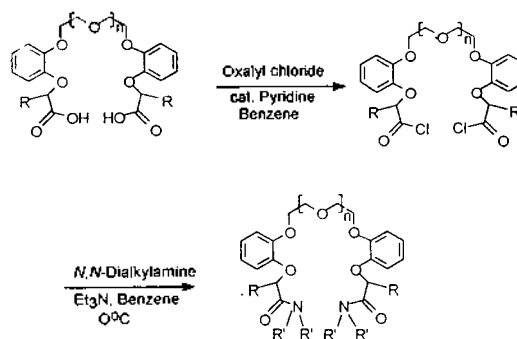
was  $-4.0$  which is the best value so far reported with respect to the potentiometric selectivity of  $Pb^{2+}$  over  $Cu^{2+}$ .<sup>9</sup> To further probe the selectivity of  $Pb$  ion complexation selectivity and efficiency over other heavy metal ions based upon the structural variations such as alkyl chain length, the length of ethereal linkage and lipophilic chains of  $N,N$ -dialkyl group, syntheses of new ionophores **5**~**18** have been proposed. In these viewpoints, now, we report that synthetic procedures for a series of novel fourteen lipophilic acyclic polyether

diamides such as 1,2-bis[2-(2'-*N,N*-dialkylcarbamoylmethoxy)phenoxy]ethane **5**~**8**, 1,2-bis[2-(2'-*N,N*-dialkylcarbamoylpentadecyloxy)phenoxy]ethane **9**~**12**, 1,5-bis[2-(2'-*N,N*-dialkylcarbamoylmethoxy)phenoxy]-3-oxapentane **13**~**15**, 1,5-bis[2-(2'-*N,N*-dialkylcarbamoylpentadecyloxy)phenoxy]-3-oxapentane **16**~**18**.

RESULTS AND DISCUSSION

It was reported that reaction of *sym*-(hydroxy)(propyl)dibenzo-16-crown-5 with potassium hydride in tetrahydrofuran then with *N,N*-dipentyl-2-chloroacetamide as an alkylating agent gave a *sym*-(propyl)dibenzo-16-crown-5-oxacetamide with a quantitative yield.<sup>10</sup> However, a number of attempts for syntheses of acyclic polyether diamides by reported procedures<sup>10</sup> including the synthetic procedures for reaction of 1,5-bis(2-hydroxyphenoxy)-3-oxapentane with *N,N*-dipentyl-2-chloroacetamide as a direct coupling method<sup>9</sup> were found to be unsuccessful. Also, several attempts by modified procedures for synthesis of compound **5** in which ethylene glycol ethereal group connects two benzene rings- reaction of 1,2-(2-hydroxyphenoxy)ethane with *N,N*-dialkyl-2-chloroacetamide in the presence of potassium hydride as a base- are found to be unsuccessful. On the other hand, we have found that a chlorination of dicarboxylic acid **3** with oxalyl chloride in the presence of catalytic amount of pyridine followed by treatment with diethylamine provided the non-ionizable polyether diamide **5** with a quantitative yield.

For structural variation focused on the length of ethereal linkage as well as on the lipophilicity of alkyl chains on the nitrogen atoms, reactions of acyclic polyether dicarboxylic acids with oxalyl chloride in the presence of catalytic amount of pyridine were found to give a quantitative yield as depicted in *Scheme 1*. No reaction undergoes without catalytic amount of pyridine and with other base such as triethylamine. Without any further purification, reaction of acid chlorides with *N,N*-diethyl, *N,N*-dipropyl, *N,N*-dibutyl, *N,N*-dipentyl amine in the presence of triethylamine as a base followed by filtration through column chromatog-



Compound	n	R	R'
<b>5</b>	0	H	Ethyl
<b>6</b>	0	H	Propyl
<b>7</b>	0	H	Butyl
<b>8</b>	0	H	Pentyl
<b>9</b>	0	C <sub>14</sub> H <sub>29</sub>	Ethyl
<b>10</b>	0	C <sub>14</sub> H <sub>29</sub>	Propyl
<b>11</b>	0	C <sub>14</sub> H <sub>29</sub>	Butyl
<b>12</b>	0	C <sub>14</sub> H <sub>29</sub>	Pentyl
<b>13</b>	1	H	Ethyl
<b>14</b>	1	H	Propyl
<b>15</b>	1	H	Butyl
<b>16</b>	1	C <sub>14</sub> H <sub>29</sub>	Ethyl
<b>17</b>	1	C <sub>14</sub> H <sub>29</sub>	Propyl
<b>18</b>	1	C <sub>14</sub> H <sub>29</sub>	Butyl

Scheme 1.

raphy provided the desired products with excellent yields (see *Table 1*).

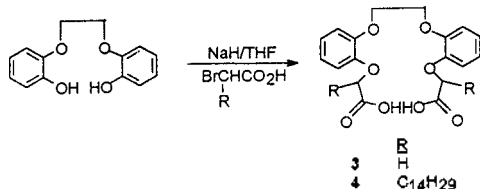
Synthetic route for precursors **3** and **4** is described in *Scheme 2*. The starting material, 1,2-(2-hydroxyphenoxy)ethane, was synthesized by three steps from catechol.<sup>11</sup> Subsequently, coupling reactions of 1,2-(2-hydroxyphenoxy)ethane with bromoacetic acid or 2-bromohexadecanoic acid in the presence of sodium hydride as a base gave a white solid with a quantitative yield in both cases (compound **3** and **4**). In similar manner to reported procedures,<sup>12</sup> when 1,2-(2-hydroxyphenoxy)ethane reacts with bromoacetic acid to make compound **3**, the reaction mixture stirred for 10 hours at room temperature. However, for compound **4**, no reaction underwent without heating at reflux temperature. It is probably attributed to a steric hindrance when phenoxide ion as a nucleophile attacks the secondary carbon at which bulky tetradecyl group is substituted.

In conclusion, syntheses of a series of novel acyclic polyethers bearing amide end-groups were

Table 1. Yields, spectral data and combustion analysis data for acyclic polyether diamides 5~18<sup>a</sup>

Compound	Yield (%) <sup>b</sup>	<sup>1</sup> H NMR Spectra (CDCl <sub>3</sub> ), ppm	IR Spectra, cm <sup>-1</sup>	Molecular formula	Combustion analysis Cald./Found	
					C	H
5	88	0.91 (t, 12 H), 3.37 (q, 8 H), 4.40 (s, 4 H), 4.72 (s, 4 H), 6.91~7.10 (m, 8 H)	1648 (C=O), 1497, 1451, 1254, 1204, 1061, 1107 (C-O)	C <sub>24</sub> H <sub>36</sub> N <sub>2</sub> O <sub>6</sub> ·CH <sub>2</sub> Cl <sub>2</sub>	58.16 58.10	6.82 6.74
6	92	0.86 (t, 12 H), 1.10~1.50 (m, 8 H), 3.31 (t, 8 H), 4.38 (s, 4 H), 4.71 (s, 4 H), 6.91~7.11 (m, 8 H)	1651 (C=O), 1497, 1455, 1262, 1057, 1108 (C-O)	C <sub>19</sub> H <sub>24</sub> N <sub>2</sub> O <sub>6</sub>	68.18 68.10	8.33 8.30
7	95	0.85 (t, 12 H), 1.12~1.81 (m, 16 H), 3.29 (t, 8 H), 4.40 (s, 4 H), 4.70 (s, 4 H), 6.91~7.12 (m, 8 H)	1650 (C=O), 1495, 1455, 1214, 1260, 1060, 1118 (C-O)	C <sub>24</sub> H <sub>32</sub> N <sub>2</sub> O <sub>6</sub>	69.86 69.74	8.90 8.81
8	92	0.86 (t, 12 H), 1.13~1.80 (m, 24 H), 3.30 (t, 8 H), 4.39 (s, 4 H), 4.72 (s, 4 H), 6.91~7.10 (m, 8 H)	1651 (C=O), 1497, 1450, 1210, 1258, 1060, 1107 (C-O)	C <sub>28</sub> H <sub>40</sub> N <sub>2</sub> O <sub>6</sub> ·H <sub>2</sub> O	69.30 69.21	9.42 9.38
9	88	0.70~1.67 (m, 70 H), 1.72~2.20 (m, 4 H), 3.37 (q, 8 H), 4.36 (s, 4 H), 4.78 (t, 2 H), 6.86~7.72 (m, 8 H)	1651 (C=O), 1497, 1455, 1215, 1262, 1061, 1119 (C-O)	C <sub>21</sub> H <sub>26</sub> N <sub>2</sub> O <sub>6</sub>	74.95 74.75	10.74 10.71
10	93	0.78~1.09 (m, 18 H), 1.10~1.73 (br s, 60 H), 1.71~2.20 (m, 4 H), 3.17~3.48 (m, 8 H), 4.36 (s, 4 H), 4.77 (t, 2 H), 6.80~7.71 (m, 8 H)	1641 (C=O), 1497, 1455, 1215, 1260, 1058, 1118 (C-O)	C <sub>28</sub> H <sub>40</sub> N <sub>2</sub> O <sub>6</sub> ·0.5H <sub>2</sub> O	74.91 74.88	10.87 10.64
11	87	0.80~1.11 (m, 18 H), 1.12~1.71 (br s, 68 H), 1.72~2.24 (m, 4 H), 3.17~3.48 (m, 8 H), 4.35 (s, 4 H), 4.78 (t, 2 H), 6.88~7.23 (m, 8 H)	1647 (C=O), 1497, 1455, 1215, 1268, 1060, 1121 (C-O)	C <sub>62</sub> H <sub>104</sub> N <sub>2</sub> O <sub>6</sub>	76.18 76.08	11.14 11.22
12	67	0.80~1.07 (m, 18 H), 1.10~1.71 (br s, 76 H), 1.72~2.22 (m, 4 H), 3.17~3.50 (m, 8 H), 4.35 (s, 4 H), 4.78 (t, 2 H), 6.85~7.71 (m, 8 H)	1651 (C=O), 1497, 1455, 1215, 1262, 1061, 1119 (C-O)	C <sub>46</sub> H <sub>104</sub> N <sub>2</sub> O <sub>6</sub> ·CH <sub>2</sub> Cl <sub>2</sub>	71.44 71.30	10.47 10.43
13	88	1.10~1.35 (2t, 12 H), 3.43 (q, 8 H), 3.90~3.97 (m, 4 H), 4.15~4.23 (m, 4 H), 4.69 (s, 4 H), 6.92 (s, 8 H)	1651 (C=O), 1497, 1450, 1230, 1061, 1120 (C-O)	C <sub>28</sub> H <sub>40</sub> N <sub>2</sub> O <sub>6</sub> ·0.5CH <sub>2</sub> Cl <sub>2</sub>	59.49 59.31	7.67 7.66
14	89	0.79~0.90 (2t, 12 H), 1.20~1.80 (m, 24 H), 3.25 (t, 8 H), 3.88~4.20 (m, 4 H), 4.15~4.25 (m, 4 H), 4.71 (s, 4 H), 6.91 (s, 8 H)	1647 (C=O), 1497, 1455, 1262, 1061, 1111 (C-O)	C <sub>60</sub> H <sub>88</sub> N <sub>2</sub> O <sub>7</sub>	67.10 67.19	8.45 8.44
15	90	0.79~1.10 (2t, 12 H), 1.11~1.80 (m, 32 H), 3.22 (t, 8 H), 3.88~3.97 (m, 4 H), 4.15~4.23 (m, 4 H), 4.70 (s, 4 H), 6.92 (s, 8 H)	1650 (C=O), 1497, 1453, 1211, 1257, 1060, 1118 (C-O)	C <sub>26</sub> H <sub>36</sub> N <sub>2</sub> O <sub>7</sub>	68.76 68.61	8.98 8.74
16	94	0.87~1.91 (2t, 18 H), 1.18~1.70 (br s, 52 H), 1.69~2.03 (m, 4 H), 3.19~3.27 (m, 8 H), 3.77 (t, 4 H), 4.73 (t, 4 H), 4.78 (t, 2 H), 6.89~7.27 (m, 8 H)	1644 (C=O), 1488, 1453, 1215, 1260, 1060, 1120 (C-O)	C <sub>26</sub> H <sub>36</sub> N <sub>2</sub> O <sub>7</sub>	73.80 73.50	10.84 10.65
17	93	0.81~0.90 (m, 18 H), 1.16~1.67 (br s, 60 H), 1.68~2.00 (m, 4 H), 3.19~3.37 (m, 8 H), 3.88 (t, 4 H), 4.10 (t, 4 H), 4.78 (t, 2 H), 6.88~7.26 (m, 8 H)	1650 (C=O), 1496, 1455, 1214, 1262, 1061, 1119 (C-O)	C <sub>46</sub> H <sub>104</sub> N <sub>2</sub> O <sub>6</sub> ·0.5CH <sub>2</sub> Cl <sub>2</sub>	71.92 71.85	10.59 10.50
18	89	0.80~0.88 (m, 18 H), 1.16~1.67 (br s, 68 H), 1.73~2.08 (m, 4 H), 3.20~3.40 (m, 8 H), 3.91 (t, 4 H), 4.16 (t, 4 H), 4.78 (t, 2 H), 6.85~7.24 (m, 8 H)	1651 (C=O), 1497, 1455, 1215, 1262, 1060, 1118 (C-O)	C <sub>64</sub> H <sub>114</sub> N <sub>2</sub> O <sub>7</sub>	75.11 75.08	11.23 11.21

<sup>a</sup>All compounds were isolated as oils. In some cases the oil crystallized after long standing. <sup>b</sup>Total percent yields from starting material, dicarboxylic acid to final product. <sup>c</sup>Deposited from methylene chloride.



Scheme 2.

successfully accomplished with quantitative yields. To further investigate the influence of number and positioning of polyether oxygen with lipophilic acyclic polyether diamides, syntheses of those in which both lipophilic alkyl chain and the number of ethylene glycol units are varied and their complexation studies with transition metal ions are in progress and the results will be reported.

## EXPERIMENTAL

Melting points were taken by the use of a Mel-Temp of Fisher-Johns melting point apparatus without any correction. IR spectra were obtained with a Perkin-Elmer 1600 Series FT-IR on potassium bromide pellet and are recorded in reciprocal centimeters.  $^1\text{H}$  NMR spectra were recorded with an AF-300 spectrometer with the chemical shifts ( $\delta$ ) reported downfield from the internal standard, tetramethylsilane. Elemental analysis was performed by Vario EL of Elemental Analyzer in Korea Basic Science Institute in Seoul, Korea.

Unless specified otherwise, reagent grade reactants and solvents were obtained from chemical suppliers and used as received. Dry solvents were prepared as follows: tetrahydrofuran was freshly distilled from sodium metal ribbon or chunks; benzene and pentane were stored over sodium ribbon, respectively; dichloromethane was freshly distilled from lithium aluminum hydride. 1,5-Bis[2-(carboxymethoxy)phenoxy]-3-oxapentane (**3**)<sup>13</sup> is known compound. The synthetic reagents 1,2-(2-hydroxyphenoxy)ethane<sup>11</sup> and 1,5-bis(2-hydroxyphenoxy)-3-oxapentane<sup>12,13</sup> were prepared by the reported methods.

**General procedure for the reaction of acyclic polyether dicarboxylic acid with oxalyl chloride followed by reaction with *N,N*-dialkylamine (Compou-**

**nds 5~18).** All of these reactions were carried out under nitrogen atmosphere. A solution of 4.90 mmole of diacid, 49.0 mmole of oxalyl chloride, and 1 drop of pyridine in 100 mL of dry benzene was refluxed for 10 hours. The solvent and excess oxalyl chloride were removed *in vacuo*. To this crude product was added 50 mL of dichloromethane and 50 mL of water. Organic layer was separated, washed with 1 N hydrochloric acid solution (2×50 mL) followed by drying over anhydrous magnesium sulfate. Removal of the solvent *in vacuo* gave corresponding acyclic polyether dicarboxylic acid chlorides in quantitative yield as a yellowish oil. With structural identification of spectroscopic evidences the obtained product was used in next reaction step without any further purification. Under nitrogen, to a turbid solution of this acid chloride and 11.3 mmole of triethylamine in 50 mL of dry benzene was added dropwise 11.3 mmole of *N,N*-dialkylamine during a period of 30 min at 10 °C. Upon the complete addition, the reaction mixture was stirred for additional 3 hours at room temperature. Stirring for 1 hour at room temperature gave a transparent brown solution. Water (100 mL) was poured and organic layer was separated. The benzene layer was dried over anhydrous magnesium sulfate followed by filtration through column chromatography of the residue on silica gel with ethyl acetate as an eluent provided *N,N*-dialkyl acyclic polyether diamides **5~18** as a colorless oil. (see detail yield, spectral data, and combustion analysis in Table 1).

**1,2-Bis[2-(2'-carboxypentadecyloxy)phenoxy]ethane (4).** After removal of the protecting mineral oil from sodium hydride (50% dispersion in mineral oil, 6.00 g, 0.34 mole) by washing with *n*-pentane under nitrogen, a solution of 1,2-(2-hydroxyphenoxy)ethane (10.0 g, 45.0 mmole) in 150 mL of dry tetrahydrofuran was added. The mixture was stirred for 2 hours at room temperature. To this reaction mixture was added dropwise 2-bromohexadecanoic acid (12.6 g, 90.0 mmole) in 20 mL of dry tetrahydrofuran at room temperature during a period of 2 hours. Upon the complete addition, the reaction mixture was refluxed for 10

hours. In the case for synthesis of compound **3** for which reaction of diphenol with bromoacetic acid is carried out, reflux was not necessary to complete the reaction. After careful addition of water to the reaction mixture in an ice bath to destroy the unreacted excess sodium hydride, which gave a homogeneous solution, tetrahydrofuran was removed *in vacuo* leaving an aqueous mixture. To this basic aqueous layer was carefully added conc. hydrochloric acid for aqueous solution to be pH 1. Crude product was extracted by use of methylene chloride (3×50 mL). The organic layer was washed with brine (3×50 mL), dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to give a crude solid. Recrystallization from 100 mL of diethyl ether provided a white solid, 28.0 g (85%), mp 108~110 °C; IR (KBr pellet): 3445 (O-H); 1703 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  0.77~1.00 (t, 6H); 1.10~2.00 (br s, 48H); 4.36 (s, 4H); 4.57 (t, 2H); 6.87~7.07 (m, 8H). Anal. calcd. for  $\text{C}_{36}\text{H}_{74}\text{O}_8$ : C, 72.88; H, 10.24. Found: C, 72.67; H, 10.21.

**Acknowledgement.** This research was fully supported by Grant for Institute-University Collaborative Project from the Korea Research Institute of Standards and Science, Taejeon, Korea.

## REFERENCES

1. Cram, D. J.; Trueblood, N. K. In *Host Guest Complex Chemistry. Macrocycles, Synthesis, Structures, and Applications*; Vötle, F.; Weber, E., Eds.; Springer-Verlag: New York, U. S. A., 1985; Chapter 3.
2. Dietrich, B.; Viout, P.; Lehn, J.-M. In *Macrocyclic Chemistry*; VCH: New York, U. S. A., 1993.
3. Vötle, F.; Weber, E. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 753.
4. Ammann, W.; Anker, P.; Metzger, E.; Oesch, U.; Simon, W. In *Ion Measurement in Physiology and Medicine*; Kessler, M.; Hoper, J.; Harrison, D. K., Eds.; Springer-Verlag: Berlin, Heidelberg, New York, Tokyo, 1988. (b) Osswald, H. F.; Asper, R.; Dimai, W.; Simon, W. *Clin. Chem.* **1976**, *35*, 39.
5. Kraig, R. P.; Nicholson, Ch. *Science* **1976**, *194*, 725.
6. (a) Thani-Wyss, U.; Morf, W. E.; Lienemann, P.; Stefanac, Z.; Mostert, I.; Döig, R.; Dohner, R. E.; and Simon, W. *Mikrochim. Acta* **1981**, *1*, 331.
7. Pressman, B. C. *Ann. Rev. Biochim.* **1976**, *45*, 501.
8. (a) Ohki, A.; Lu, J.-P.; Bartsch, R. A. *Anal. Chem.* **1994**, *66*, 651. (b) Ohki, A.; Lu, J.-P.; Huang, X.; Bartsch, R. A. *Anal. Chem.* **1994**, *66*, 4332.
9. Kim, J. S.; Ohki, A.; Cho, N. S.; Yu, I. Y.; Hayashita T.; Maeda, S. *Bull. Kor. Chem. Soc.* **1996**, *17*, 953.
10. Kasprzyk, S. P.; Bartsch, R. A. *J. Heterocyclic Chem.* **1993**, *30*, 119.
11. Hoe, G. S. In *Ph. D. Dissertation*; Department of Chemistry and Biochemistry, Texas Tech University, 1983, p 122.
12. Oepen, G. J.; Dix, P.; Vötle, F. *Liebigs Ann. Chem.* **1978**, 1592.
13. Kim, J. S.; Cho, M. H.; Lee, S. C.; Lee, Y.-I.; Sim, W.; Cho, N. S. *Microchem. J.* **1996**, *53*, in press.