SYNTHESIS OF NEW ARMED CYCLOPOLYAMINES AND THEIR SELECTIVE EXTRACTION PROPERTIES FOR METAL IONS

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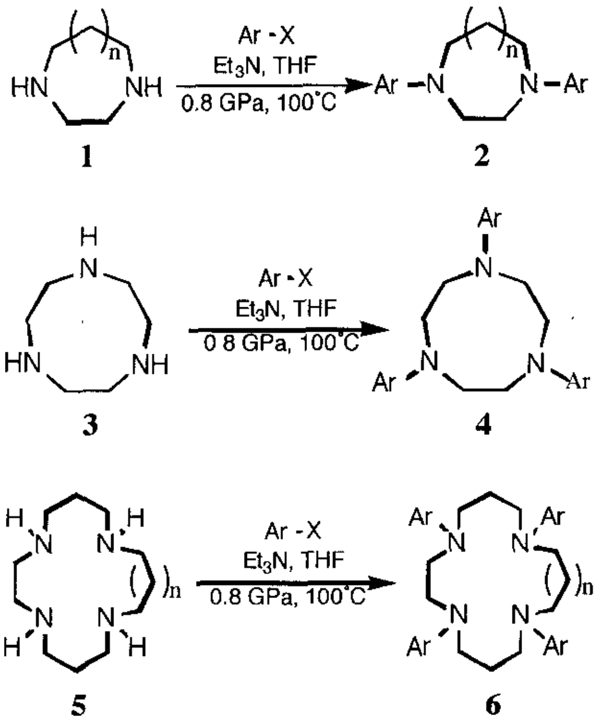
Abstract-A variety of new armed cyclopolyamines were prepared by high pressure S_NAr reactions (0.8 GPa, 100°C) of cyclopolyamines with heteroaromatic halides. Certain of these agents show selective extraction properties for Hg^{2+} and Ag^{+} ions.

Functionalized macrocyclic polyethers and polyamines are of the current interests arising from their applications in, for example, analysis, transport processes, reaction catalysis, artificial enzyme mimicry.[1] In our preceding papers, we reported the novel cation binding properties of monoaza-[2b] and diaza-crown ethers whose nitrogen atoms were directly connected to aromatic heterocycles.[2a,c] To develop their selectivities for heavy metal ions and establish a recovery system for individual metal ions, we designed new cyclopolyamines that are directly connected to aromatic heterocycles (Scheme I). It is postulated that electron densities of nitrogen atoms in cyclopolyamines are thereby reduced by connecting them directly aromatic heterocycles, so that selectivities for metal ions will be increased.

As a second stage of our project on armed oligocycles as well as armed macrocycles that are directly connected to aromatic heterocycles, the high pressure S_NAr reaction[3] was applied to the cycloamines (**1**, **3**,[4] and **5**). In a



Scheme I

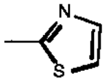
typical experiment, a mixture of 1,4,8,12-tetrazacyclopentadecane (**5**, n=1, 2 mmol), halogenoheterocycle (Ar-X, 10 mmol), and triethylamine (10 mmol) was diluted with tetrahydrofuran in an 8ml capacity of poly-tetrafluorotethylene capsule that was compressed to 0.8 GPa and heated to 100°C for the stated time in Tables 1.

In order to examine binding properties of functionalized cyclopolyamines for metal ions, particularly for heavy metal ions, liquid-liquid extraction experiments were performed as has been described previously.[3] The extraction property was estimated on the basis of partition of the metal perchlorate between dichloromethane and aqueous solution (2 h). The results were summarized in Table 2.

No clear relationships emerge between the sizes of the cavity and ion selectivities nor relationships between the types of the ligands and ion selectivities. It is interesting to note, however, that even the piperazine and homopiperazine derivatives extract Ag^+ ion rather selectively. In general, the present polyamines shows selective extraction properties for Ag^+ ions. Specifically, **6e** possessing benzoxazole groups exhibits highly selective extraction properties for Ag^+ ion, whereas **6a~6d** also extracted Hg^{2+} ion.

Table 1. Preparation of new cyclopolyamines (**2a** - **6e**) at 0.8 GPa and 100°C

	Halogenoheterocycles			Reaction	mp	yield
Product	Ar	X	n	time (d)	(°C)	(%)
2a	**7**	Br	0	4	244-245	94
2b	**7**	Br	1	4	66-67	92
2c	**8**	F	0	4	126-127	87
2d	**8**	F	1	4	67-68	100
2e	**9**	Cl	0	4	138-139	51
2f	**9**	Cl	1	4	207-208	69
4a	**7**	Br	-	4	121-124	35
4b	**9**	Cl	-	4	257-259	18
6a	**7**	Br	0	4	273-275	50
6b	**7**	Br	1	5	155-156	23
6c	**8**	F	0	7	203-207	22
6d	**8**	F	1	7	208-210	79
6e	**9**	Cl	1	6	281-282	70



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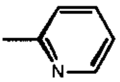

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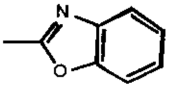

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Remarkably, the compound (**6c**) having pyridyl groups shows both effective extraction and high selectivity for Hg^{2+}, though it also extracts Ag^{+}, Pb^{2+}, and Cd^{2+} ions, but to a much lesser extent.[5] Although it has been reported both the parent 1,4,8,11-tetraazacyclotetradecane (**10**) and 1,4,8,12-tetraazacyclopentadecane (**11**) bind with Hg^{2+} ion, based upon the polarographic method,[6] neither the parent 1,4,8,11-tetraazacyclotetradecane (**10**) nor 1,4,8,12-tetraazacyclopentadecane (**11**) extract Hg^{2+} ion in our hands; this is probably partly because of the differences of the experimental conditions and partly because turbidity appeared at the boundary surface of the organic and aqueous phases in the present extraction experiment.

Further investigations on transport properties and metal complexes of these cyclopolyamines are currently under way.

Table 2. Single cation extraction with armed cyclopolyamines[a]

	Extraction percentage (%)				
Carrier	Cu^{2+}	Cd^{2+}	Pb^{2+}	Ag^{+}	Hg^{2+}
2a	0	6	1	30[d]	6
2b	0	6	7	20	4[d]
2c	0	7	2	17	0
2d	0	6	0	18[d]	0
2e	0	4	0	23	1[d]
2f	4	0	0	24[d]	7
4a	0	0	0	24[d]	8[d]
4b	0	0	0	26	5
6a	0	0	0	38[d]	14[d]
6b	0	1	0	36[d]	6[d]
6c	4	0	0	42	53[c,d]
6d	2	2	0	26	19[d]
6e	0	0	0	48[d]	0
10[b]	7	3	0	21[d]	0[e]
11[b]	3	11	3	26[d]	0[e]

a Conditions : 0.01 M-M $(ClO_4)_2$ or $MClO_4$ (2 ml) // 0.01 M-polyamines in CH_2Cl_2 (2 ml), stirred for 2 h.

b **10** : 1,4,8, 11-tetraazacyclotetradecane (**5**, n=0)
11 : 1,4,8,12-tetraazacyclopentadecane (**5**, n=1)

c Under vigorously stirring.

d Precipitate appeared.

e Turbidity appeared at the boundary surface of the two phases.

EXPERIMENTAL

General

Melting points were taken on a Yanagimoto micro melting point apparatus and were uncorrected. The ^{1}H nmr spectra were measured either on a Hitachi R40 (90 MHz) or on a JEOL JNM-EX270 (270MHz) instrument. ^{13}C nmr spectra were recorded either on a JEOL JNM- FX90Q or JNM-EX270 or JNM-ALPHA500 spectrometer operating at 22.49 MHz, 67.80 Hz, and 125.65 Hz, respectively. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Preparative medium-pressure liquid chromatography was carried out using a column (25 x 310 mm) prepacked with silica gel (Lobar, LiChroprep Si60, Merck).

Typical procedure.

1,4,8,12-Tetrakis-(2-pyridyl)-1,4,8,12-tetraazacyclopentadecane (6d) A mixture of 1,4,8,12-tetraazacyclopentadecane (11, 0.43 g, 2 mmol), 2-fluoropyridine (0.97 g, 10 mmol), triethylamine (1.01 g, 10 mmol), and tetrahydrofuran (4 ml) in polytetrafluoroethylene tube (8 ml) was placed in a stainless vessel and compressed to 0.8 GPa, and heated to 100°C for 7 days. A mixture was diluted with dichloromethane (*ca.* 100 ml), and washed with water. The organic layer was dried over anhydrous Na_2SO_4. After evaporation of solvent, the residue was either chromatographed on silica gel using benzene/ethyl acetate as eluent or recrystallized from dichloromethane-hexane giving **6d** (0.82 g, 79%).

Colorless crystals; mp 208.0-210.0°C (from CH_2Cl_2-hexane) ; ^1H nmr($CDCl_3$; 270 MHz) δ 1.98-2.13 (m, 4H), 2.13-2.30 (m, 2H), 3.53-3.62 (m, 8H), 3.62 (s, 4H) 3.72 (t, 4H, J = 6.3 Hz), 6.48-6.59 (m, 4H), 6.64 (d, 2H, J = 8.9 Hz), 7.07 (d, 2H, J = 12.7 Hz), 7.41-7.52 (m, 4H), 8.14-8.22 (m, 4H); ^{13}C nmr ($CDCl_3$) δ 27.9, 29.2, 46.6, 46.9, 47.1, 47.3, 106.2, 106.3, 111.7, 137.3, 137.5, 147.8, 158.1. Anal. Calcd for $C_{31}H_{38}N_8$: C, 71.23; H, 7.33; N, 21.44. Found: C, 70.98; H, 7.24; N, 21.15.

1,4-Bis-(2-thiazolyl)-1,4-diazacyclohexane (2a)

Colorless crystals; mp 244.0-245.0°C (from ethyl acetate-hexane) (33%); ^1H nmr ($CDCl_3$) δ 3.61 (s, 8H), 6.53 (d, 2H, J = 3.5 Hz), 7.14 (d, 2H, J = 3.5 Hz); ^{13}C nmr ($CDCl_3$) δ 48.0, 108.0, 139.7, 171.8; Anal. Calcd for $C_{10}H_{12}S_2N_4$: C, 47.59; H, 4.79; N, 22.20. Found: C, 47.70; H, 4.70; N, 22.10.

1,4-Bis-(2-thiazolyl)-1,4-diazacycloheptane (2b)

Colorless crystals; mp 66.0-67.0°C (from CH_2Cl_2-hexane) (92%); ^1H nmr ($CDCl_3$) δ 2.16 (quintet, 2H, J = 5.9 Hz), 3.60 (t, 4H, J = 5.9 Hz), 3.83 (s, 4H), 6.40 (d, 2H, J = 3.5 Hz), 7.06 (d, 2H, J = 3.5 Hz); ^{13}C nmr ($CDCl_3$), δ 24.8, 49.8, 51.1, 106.4, 139.8, 169.9; Anal. Calcd for $C_{11}H_{14}N_4S_2$: C, 49.60; H, 5.30; N, 21.03. Found: C, 49.68; H, 5.29; N, 20.85.

1,4-Bis-(2-pyridyl)-1,4-diazacyclohexane (2c)

Colorless crystals; mp 108.0-109.0°C (from CH_2Cl_2-hexane) (76%); ^1H nmr ($CDCl_3$) δ 3.64 (s, 8H), 6.44-6.69 (m, 4H), 7.24-7.51 (m, 2H), 8.10 (d, 2H, J = 5.9 Hz); ^{13}C nmr ($CDCl_3$) δ 45.0, 107.1, 113.5, 137.5, 148.0, 159.5; Anal. Calcd for $C_{14}H_{16}N_4$: C, 69.98; H, 6.71; N, 23.31. Found: C, 70.14; H, 6.63; N, 23.28.

1,4-Bis-(2-pyridyl)-1,4-diazacycloheptane (2d)

Colorless crystals; mp 67.0-68.0°C (from CH_2Cl_2-hexane) (51%); ^1H nmr ($CDCl_3$) δ 2.06 (quintet, 2H, J = 5.9 Hz), 3.52 (t, 4H, J = 5.9 Hz), 3.84 (s, 4H), 6.34-6.54 (m, 4H), 7.22-7.45 (m, 2H); ^{13}C nmr ($CDCl_3$) δ

24.1, 46.4, 48.2, 105.6, 111.6, 137.3, 148.3, 157.6; Anal. Calcd for $C_{15}H_{18}N_4$: C, 70.84; H, 7.13; N, 22.03. Found: C, 71.14; H, 7.11; N, 22.02.

1,4-Di-(2-benzoxazolyl)-1,4-diazacyclohexane (2e)

Colorless crystals; mp 138-139°C (from ethyl acetate-hexane) (51%); ^{1}H nmr ($CDCl_3$) δ 3.83 (s, 8H), 6.70-7.40 (m, 8H); ^{13}C nmr ($CDCl_3$) δ 45.2, 109.0, 116.8, 121.1, 124.2, 143.0, 149.0, 161.9; Anal. Calcd for $C_{18}H_{16}O_2N_4$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.35; H, 4.98; N, 17.41.

1,4-Di-(2-benzoxazolyl)-1,4-diazacycloheptane (2f)

Colorless crystals; mp 207.0-208.0°C (from ethyl acetate-hexane) (69%); ^{1}H nmr ($CDCl_3$) δ 2.20 (quintet, 2H, *J* = 6.1 Hz), 3.72 (t, 4H, *J* = 6.1 Hz), 3.92 (s, 4H), 6.93-7.31 (m, 8H); ^{13}C nmr ($CDCl_3$) δ 26.9, 47.4, 49.5, 108.8, 116.3, 120.6, 124.1, 143.4, 149.1, 161.7; Anal. Calcd for $C_{19}H_{18}O_2N_4$: C, 68.25; H, 5.43; N, 16.76. Found: C, 68.11; H, 5.27; N, 17.01.

1,4,7-Tris-(2-thiazolyl)-1,4,7-triazacyclononane (4a)

Brown crystals; mp 120.5-123.5°C (from ethyl acetate-hexane) (35%); ^{1}H nmr ($CDCl_3$) δ 3.80 (s, 12H), 6.50 (d, 3H, *J* = 3.5 Hz), 7.18 (d, 3H, *J* = 3.5 Hz); ^{13}C nmr ($CDCl_3$) δ 53.1, 106.9, 139.6, 170.6; Anal. Calcd for $C_{15}H_{18}N_6S_3$: C, 47.59; H, 4.79; N, 22.20. Found: C, 47.30; H, 4.74; N, 21.95.

1,4,7-Tris-(2-benzoxazolyl)-1,4,7-triazacyclononane (4b)

Colorless crystals; mp 257.0-259.0°C (from CH_2Cl_2-hexane) (18%); ^{1}H nmr ($CDCl_3$) δ 3.95 (s, 12H), 6.85 (d, 3H, *J* = 7.6 Hz), 6.93-7.02 (m, 6H), 7.12-7.20 (m, 6H), 7.35 (d, 3H, *J* = 7.6 Hz); ^{13}C nmr ($CDCl_3$) δ 50.6, 108.8, 116.4, 120.8, 124.0, 142.9, 148.8, 161.6; Anal. Calcd for $C_{27}H_{24}N_6O_3$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.27; H, 5.06; N, 17.38.

1,4,8,11-Tetrakis-(2-thiazolyl)-1,4,8,11-tetraazacyclotetradecane (6a)

Brown crystals; mp 194.0-196.0°C (from benzene) (26%); ^{1}H nmr ($CDCl_3$) δ 1.98-2.07 (m, 4H), 3.62 (t, 8H, *J* = 6.8 Hz), 3.78 (s, 8H), 6.49 (d, 4H, *J* = 3.5 Hz), 7.15 (d, 4H, *J* = 3.5 Hz); ^{13}C nmr ($CDCl_3$) δ 26.9, 51.6, 52.4, 106.8, 139.5, 171.5; Anal. Calcd for $C_{22}H_{28}N_8S_4$: C, 49.59; H, 5.30; N, 21.03. Found: C, 49.31; H, 5.27; N, 20.73.

1,4,8,12-Tetrakis-(2-thiazolyl)-1,4,8,12-tetraazacyclopentadecane (6b)

Colorless crystals; mp 163.5-167.5 °C (from benzene) (20%); ^{1}H nmr ($CDCl_3$) δ 2.05-2.24 (m, 6H), 3.61 (t, 12H, *J* = 6.6 Hz), 3.74 (s, 4H), 6.51 (dd, 4H, *J* = 3.6, 1.3 Hz), 7.16 (dd, 4H, J = 3.6, 1.3 Hz); ^{13}C nmr

($CDCl_3$) δ 27.1, 28.4, 50.2, 50.6, 50.9, 51.10, 106.5, 106.9, 139.5, 170.9, 171.2; Anal. Calcd for $C_{23}H_{22}N_8S_4$: C, 50.52, H, 5.53; N, 20.49. Found: C, 50.24; H, 5.48; N, 20.17.

1,4,8,11-Tetrakis-(2-pyridyl)-1,4,8,11-tetraazacyclotetradecane (6c)

Colorless crystals; mp 203.0-207.0°C (from benzene) (22%); ^{1}H nmr ($CDCl_3$) δ 1.98-2.07 (m, 4H), 3.67 (t, 8H, *J* = 6.5 Hz), 3.82 (s, 8H), 6.53-6.57 (m, 4H), 6.82 (d, 4H, *J* = 8.6 Hz), 7.40-7.50 (m, 4H), 8.15-8.20 (m, 4H); ^{13}C nmr ($CDCl_3$) δ 27.4, 47.1, 48.2, 106.2, 111.8, 137.3, 147.8, 158.3; Anal. Calcd for $C_{30}H_{36}N_8$: C, 70.83; H, 7.13; N, 22.03. Found: C, 70.58; H, 7.04; N, 21.92.

1,4,8,12-Tetrakis-(2-benzoxazolyl)-1,4,8,12-tetraazacyclopentadecane (6e)

Colorless crystals; mp 281.0-282.0°C (from CH_2Cl_2-hexane) (70%); ^{1}H nmr ($CDCl_3$) δ 2.10-2.30 (m, 6H), 3.76 (t, 8H, *J* = Hz), 3.78 (t, 4H, *J* = Hz) 3.92 (s, 4H), 6.97-7.42 (m, 16H); ^{13}C nmr ($CDCl_3$) δ 27.9, 28.8, 47.7, 48.8, 108.9, 116.4, 120.7, 124.1, 143.2, 148.9, 162.2, 162.5; Anal. Calcd for $C_{39}H_{38}N_8O_4$: C, 68.60; H, 5.61; N, 16.41. Found: C, 68.40; H, 5.53; N, 16.19.

Extraction Experiment

Extraction experiments were carried out by adding a methylene chloride solution of polyamine (0.015 mmol / 1.5 ml) to an aqueous solution of metal perchlorate (0.015 mmol / 1.5 ml). After the mixture had been stirred (50 rpm) for 2 h, the aqueous phase was separated. The extraction amount of each metal cation was calculated by the disappearance of perchlorate anion in the aqueous phase, which was determined by a perchlorate ion-selective electrode (Orion EA940 Autochemistry System). The extraction amount of each metal cation was also determined by atomic absorption or flame spectroscopic method (Shimadzu AA-630-12 Atomic Absorption/Flame Emission Spectrophotometer), and was nearly equal to that of the extracted anion.

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