SYNTHESIS OF CROWN ETHERS CONTAINING A SULFIDE GROUP INSIDE THE RING AND HIGH Ag^+ SELECTIVITY IN SOLVENT EXTRACTION

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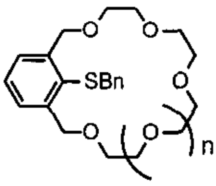
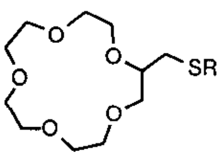
Abstract - Crown ethers bearing a sulfide, a sulfoxide, or a sulfone group inside the ring have been prepared and the sulfide derivatives exhibit a significantly high Ag^+ selectivity in solvent extraction.

Substitution of oxygens in a crown ring for sulfur notably enhances affinity to heavy metal ions due to effective coordination of sulfur lone pairs.[1,2] We have reported that remarkably high Ag^+ selectivity among heavy metals is performed by introduction of a sulfur atom near and outside a 15-crown-5 ring (thiolariat ether **2**), although **2** exhibits characteristic alkali metal affinity similar to the corresponding crown ether.[3] Here we wish to report new Ag^+ selective crown ethers (**1a~c**) with a sulfur atom not outside but inside the cavity.



1a (n=0)
b (n=1)
c (n=2)



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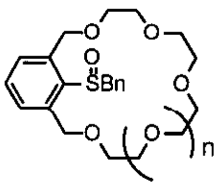
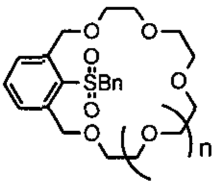


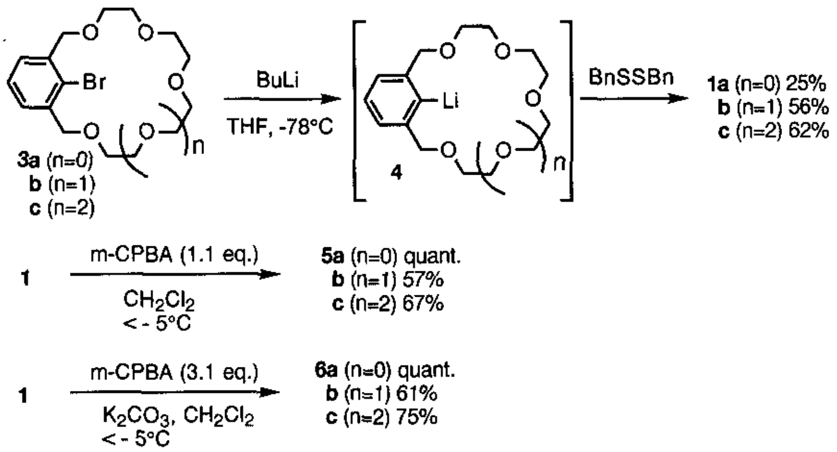
5a (n=0)
b (n=1)
c (n=2)



6a (n=0)
b (n=1)
c (n=2)

Lithio crown ethers (**4a~c**) obtained from the corresponding bromo crown ethers (**3a~c**)[4] and BuLi were treated with dibenzyl disulfide (-78°C → 5°C) in a similar procedure for preparation of sulfenyl methyl analogs reported by Reinhoudt *et al.*[4a] to give desired crown ethers (**1a~c**) in 25, 56 and 62% (based on **3a~c**), respectively, after purified by silica gel flash column chromatography. Oxidation of **1** with *m*-chloroperbenzoic acid (*m*-CPBA) yielded crown ethers with sulfoxide (**5**) and sulfone (**6**) in good yields, as shown in Scheme. The structures of **1**, **5** and **6** were confirmed by ^1H nmr, ir and high resolution ms spectroscopy.

Scheme Preparation of **1**, **5**, and **6**



Solvent extraction experiment was performed to estimate affinity of the hosts toward metal ions. A 1,2-dichloroethane solution of host (3 x 10^{-4} M) was employed as the organic phase. The aqueous phase was a mixture of 3 x 10^{-5} M of metal picrate and 0.10 M of metal chloride for alkali metals, or a mixture of 3 x 10^{-5} M of picric acid and 0.01 M of metal nitrate for heavy metals. Extractability was determined spectrophotometrically by monitoring decrease of absorbance of picrate (356 nm) in the aqueous phase (Table). **1a~c** extracted Ag^+ most preferentially among Na^+, K^+, Rb^+, Cs^+, Ag^+, Cu^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+}, although the concentration of heavy metal ions in the aqueous phase (0.01 M) was lower than that of alkali metal ions (0.10 M). The structure of **1**-Ag^+ complexes is unclear, but synergistic coordination of a lone pair in a sulfur atom and a crown ring is considered to be essential for high Ag^+ selectivity in a similar fashion observed in thiolariat ethers. Ligation of lone pairs in the sulfur atom to Ag^+ is supported by considerable decrease of extractability in **5** and especially in **6**. Compared to **1b** and **1c**, extractability toward Ag^+ in **1a** having the smallest cavity decreased significantly. This difference suggests an importance of coordination of oxygen atoms in a suitable sized ring for Ag^+ binding. In addition, **1a** exhibited very low extractabilities of alkali metal ions. This result is probably rationalized by steric prohibition of the sulfur atom against coordination of the ring oxygens to alkali metal ions, judging from the space filling model inspection. In larger sized crown ethers (**1b, c**) extractabilities increased, when the size of a metal ion increased (to Na^+, K^+, Rb^+, and Cs^+; 2, 10, 14, 20% in **1b**; 3, 9, 21, 48% in **1c**), as we expected. Interestingly, **5** and **6** do not extract alkali metals efficiently. This fact clearly indicates that oxygen atoms of the sulfoxide and the sulfone group in

Table Solvent Extraction of Alkali Metal and Heavy Metal Ions

	Extractability (%)								
	Na^+	K^+	Rb^+	Cs^+	Ag^+	Cu^{2+}	Zn^{2+}	Cd^{2+}	Pb^{2+}
1a	1	2	4	3	41	2	1	1	2
1b	2	10	14	20	95	2	2	2	3
1c	3	9	21	48	82	2	4	2	2
5a	2	2	4	2	4	2	1	2	2
5b	1	4	4	4	12	2	0	1	1
5c	6	10	14	22	21	2	1	2	4
6a	3	2	3	1	3	2	1	1	3
6b	2	2	3	2	2	2	1	1	2
6c	5	6	9	14	9	1	1	3	4
none	0	0	0	0	2	1	0	1	2

org. layer : [crown] = 3×10^{-4} M

aq. layer (Alkali Metal) : [MCl] = 0.1 M, [PicM] = 3×10^{-5} M

(Heavy Metal) : [Metal Nitrate] = 0.01 M, [PicH] = 3×10^{-5} M

Extractability = $([Pic^-]_0 - [Pic^-]_{aq}) / [Pic^-]_0 \times 100$

$[Pic^-]_0$ = initial conc. of picrate in the aqueous layer

$[Pic^-]_{aq}$ = conc. of picrate in the aqueous layer at equilibrium

5 and **6** i) do not coordinate well not only to heavy metals but also to alkali metals and ii) inhibit coordination of the crown ring to the metal ions by occupying the cavity.

Synergistic coordination of a crown ring and a sulfur atom of **1** is strongly suggested for the high Ag^+ selectivity. Application of the framework reported here to recovery of waste Ag^+, photographic technology, and radioimmunotherapy may be expected.

EXPERIMENTAL SECTION

Tetrahydrofuran was distilled from sodium diphenylketyl just before use. Mps are uncorrected. Ir and uv-vis spectra were obtained on a Hitachi 270-50 and a Shimadzu UV-240 spectrophotometers, respectively. ^1H Nmr spectra were recorded on a Varian Gemini-200 (200 MHz) spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard.

Crown Ethers with a Sulfide Moiety (1). To a solution of bromide (**3c**) (1.01 g, 2.40 mmol) in dry tetrahydrofuran (40 ml) was slowly added 1.66 ml of n-BuLi (1.59 mol/l) at -78°C. After stirring the mixture at -78°C for 2.5 h, dibenzyl disulfide (1.78 g, 7.20 mmol) was added. The temperature was maintained for additional 1 h, and then warmed gradually up to 5°C, followed by the addition of 3 N HCl to acidify the reaction mixture. The solvent was evaporated in vacuo. The residue thus obtained was dissolved in CH_2Cl_2 (100 ml), washed with 3 N HCl (80 ml), water (80 ml x 2) and brine (100 ml), and dried over $MgSO_4$. The organic layer was concentrated in vacuo to give crude product, which was purified by silica gel flash column chromatography (ethyl acetate-n-hexane = 1 : 1), affording **1c** in 62% yield as a colorless solid. Crown ethers (**1a** and **1b**) were prepared in a similar way to **1c**. Crude **1a** and **1b** were purified by flash column chromatography on silica gel using CH_2Cl_2-ethyl acetate-n-hexane (2 : 1 : 2) to give **1a** and **1b** as a colorless solid in 25 and 56% yields, respectively. **1a**: mp 89-90 °C; ^{1}H nmr ($CDCl_3$, 200 MHz): δ 3.1-3.3 (m, 2H), 3.3-3.8 (m, 10H), 3.86 (s, 2H, SCH_2Ar), 4.13 (d, J = 12.4 Hz, 2H, ArCH), 5.12 (d, J = 12.4 Hz, 2H, ArCH), 7.0-7.1 (m, 2H), 7.1-7.3 (m, 3H), 7.3-7.4 (m, 3H); HRms (FAB) Found: 397.14603. Calcd for $C_{21}H_{26}O_4NaS$ ($[M+Na]^+$): 397.14498. **1b**: mp 81-82 °C; ^{1}H nmr ($CDCl_3$, 200 MHz): δ 3.2-3.8 (m, 16H), 4.21 (s, 2H, SCH_2Ar), 4.24 (d, J = 11 Hz, 2H, ArCH), 5.35 (d, J = 11 Hz, 2H, ArCH), 7.1-7.5 (m, 8H); HRms (FAB) Found: 419.19064. Calcd for $C_{23}H_{31}O_5S$ ($[M+H]^+$): 419.18922. **1c**: mp 77-78 °C; ^{1}H nmr ($CDCl_3$, 200 MHz): δ 3.3-3.8 (m, 20H), 4.02 (s, 2H, SCH_2Ar), 4.75 (s, 4H, $ArCH_2$), 7.2-7.5 (m, 8H); HRms (FAB) Found: 485.19513. Calcd for $C_{25}H_{34}O_6NaS$ ($[M+Na]^+$): 485.19741.

Crown Ethers with a Sulfoxide Moiety (5). To a solution of **1a** (130 mg, 0.347 mmol) in CH_2Cl_2 (30 ml) on an ice-salt bath (-5 ~ -10°C) was added *m*-CPBA (68 mg, 0.39 mmol). After completion of the reaction monitored by tlc, ammonia gas was bubbled into the reaction mixture. After removal of the precipitates by filtration, the filtrate was concentrated in vacuo, and the residue was purified by silica gel flash column chromatography (ethyl acetate-n-hexane-ethanol = 5 : 4 : 1) to give **5a** quantitatively as a colorless solid. **5b** and **5c** were obtained in a similar way. Eluent of chromatography was CH_2Cl_2-ethyl acetate (1 : 1) to yield **5b** and **5c** in 57 and 67% yields as a colorless solid, respectively. **5a**: mp 179 °C; ^{1}H nmr ($CDCl_3$, 200 MHz): δ 3.0-3.1 (m, 2H), 3.2-3.4 (m, 4H), 3.4-3.8 (m, 6H), 4.13 (d, J = 13 Hz, 1H, ArCH), 4.29 (d, J = 13 Hz, 1H, ArCH), 4.93 (d, J = 14 Hz, 1H, ArCH), 5.23 (d, J = 14 Hz, 1H, ArCH), 5.39 (d, J = 13 Hz, 1H, ArCH), 6.30 (d, J = 13 Hz, 1H, ArCH), 7.2-7.5 (m, 6H), 7.6-7.6 (m, 2H); ir (KBr): 1084, 1028, 1014 cm^{-1}; HRms(FAB) Found: 391.15720. Calcd for $C_{21}H_{27}O_5S$ ([M+H]$^+$): 391.15792. **5b**: mp 160-161 °C; ^{1}H nmr (CDCl$_3$, 200 MHz): δ 2.7-3.0 (m, 2H), 3.0-3.9 (m, 14H), 4.18 (d, J = 12 Hz, 1H, ArCH), 4.31 (d, J = 10 Hz, 1H, ArCH), 4.95 (d, J = 13.5 Hz, 1H, ArCH), 5.32 (d, J = 13.5 Hz, 1H, ArCH), 5.38 (d, J = 12 Hz, 1H, ArCH), 6.24 (d, J = 10 Hz, 1H, ArCH), 7.2-7.5 (m, 6H), 7.6-7.7 (m, 2H); ir (KBr): 1114, 1030 (SO) cm^{-1}; HRms (FAB) Found: 435.18582. Calcd for $C_{23}H_{31}O_6S$ ([M+H]$^+$): 435.18414. **5c**: mp 138-140 °C; ^{1}H nmr (CDCl$_3$, 200 MHz): δ 3.05-3.4 (m, 8H), 3.5-3.9 (m, 12H), 4.55 (d, J = 13H, 2H, ArCH), 4.6-5.0 (br. m, 2H, ArCH$_2$), 5.10 (d, J = 13H, 2H, ArCH), 7.3-7.5 (m, 6H), 7.6-7.7 (m, 2H); ir (KBr): 1102, 1040 (SO) cm^{-1}; HRms (FAB) Found: 479.21283. Calcd for $C_{25}H_{35}O_7S$ ([M+H]$^+$): 479.21035.

Crown Ethers with a Sulfone Moiety (6). Sulfide (**1a**) (208 mg, 0.555 mmol) in CH_2Cl_2 (60 ml) was treated with *m*-CPBA (296 mg, 1.72 mmol) and K_2CO_3 (79 mg, 0.572 mmol). After a similar workup for sulfoxide derivatives (**5**), the crude product was purified by flash column chromatography (SiO$_2$, ethyl acetate-n-hexane-ethanol = 5 : 4 : 1) to give **6a** (232 mg) quantitatively as a colorless solid. In a similar fashion, **6b** and **6c** were obtained in 61 and 75% yields as a colorless solid using CH_2Cl_2-ethyl acetate (1 : 1) as eluent for chromatography. **6a**: mp 215-216 °C; ^{1}H nmr (CDCl$_3$, 200 MHz): δ 3.0-3.2 (m, 2H), 3.2-3.4 (m, 4H), 3.5-3.7 (m, 4H), 3.7-3.9 (m, 2H), 4.23 (d, J = 13.4 Hz, 2H, ArCH), 5.20 (s, 2H, SO$_2$CH$_2$Ar), 6.13 (d, J = 13.4 Hz, 2H, ArCH), 7.4-7.6 (m, 6H), 7.6-7.7 (m, 2H); ir (KBr): 1304 (SO$_2$), 1150, 1118, 1088 cm^{-1}; HRms(FAB) Found: 407.15411. Calcd for $C_{21}H_{27}O_6S$ ([M+H]$^+$): 407.15284. **6b**: mp 206-207 °C; ^{1}H nmr (CDCl$_3$, 200 MHz): δ 2.7-2.9 (m, 2H), 3.0-3.2 (m, 2H), 3.3-3.9 (m, 12H), 4.21 (d, J = 10.7 Hz, 2H, ArCH), 5.51 (s, 2H, SO$_2$CH$_2$Ar), 6.11 (d, J = 10.7 Hz, 2H, ArCH), 7.3-7.8 (m, 8H, ArH); ir (KBr): 1298 (SO$_2$), 1148, 1122, 1108, 1092 cm^{-1}; HRms (FAB) Found: 451.17880. Calcd for $C_{23}H_{31}O_7S$ ([M+H]$^+$): 451.17905. **6c**: mp 139-140 °C; ^{1}H nmr (CDCl$_3$, 200 MHz): δ 3.13 (s, 4H), 3.3-3.4 (m, 4H), 3.5-3.6 (m, 4H), 3.7-3.8 (m, 8H), 5.05 (s, 2H, SO$_2$CH$_2$Ar), 5.12 (br. s, 4H, ArCH$_2$), 7.3-7.6 (m, 6H), 7.6-7.7 (m, 2H); ir (KBr): 1306 (SO$_2$), 1114, 1104, 1046, 1034 cm^{-1}; HRms (FAB) Found: 495.20248. Calcd for $C_{25}H_{35}O_8S$ ([M+H]$^+$): 495.20527.

Solvent Extraction. In a 30 ml vial, 4 ml of an aqueous solution of metal ion containing picrate or picric acid and 4 ml of an 1,2-dichloroethane solution of a host were mixed vigorously for 2 ~ 6 h at 25°C.

Concentrations of host and metal ion employed here and definition of extractability are shown in the caption of Table. After mixing, the aqueous phase was centrifuged, and then the concentration of picrate ion in the aqueous phase was determined by uv-vis spectroscopy monitoring absorption at 356 nm to give the extractability.

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