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New Chromogenic Azothiacrown Ethers – Synthesis and Properties

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Abstract

New chromogenic azocrown ethers possessing sulfur atoms and two azo- groups in the macrocycle are described. The synthesized macrocycles have been applied as ion carriers in ion-selective membrane electrodes. Their selectivity and sensitivity were studied towards alkali and transition metal cations. Complexation of the compounds was studied by UV-vis spectrophotometry in water-dioxane (1:1; v/v) solvent system. Stability constants of copper and silver complexes were determined. Contrary to oxygen analogues, the azothiacrowns do not form complexes with alkali or alkaline earth metal cations.

Introduction

During last years the development of proton dissociable crown ether chromogenic reagents for determination of metal ions have been noticed. Chromoionophores are compounds changing color or its intensity upon interaction with metal ions. Molecular structure of such compounds is a combination of two parts: crown ether residue as an ionophore unit and a chromophore that converts the chemical information about ion-ionophore interaction into optical signal. Previously described ionizable chromogenic azocrown ethers [1] posses two azo- groups as a part of macrocycle and phenolic –OH group directed inside crown ether cavity as a proton-releasing residue. This phenolic proton can be easily replaced for metal ions. Such chromogenic reagents exhibit great ability to form complexes with Li^+, K^+ and Na^+ in dioxane-water-TEA solution with the most pronounced spectral changes for lithium cation. “Neutral” azocrowns with oxygen(s) atom(s) replaced by

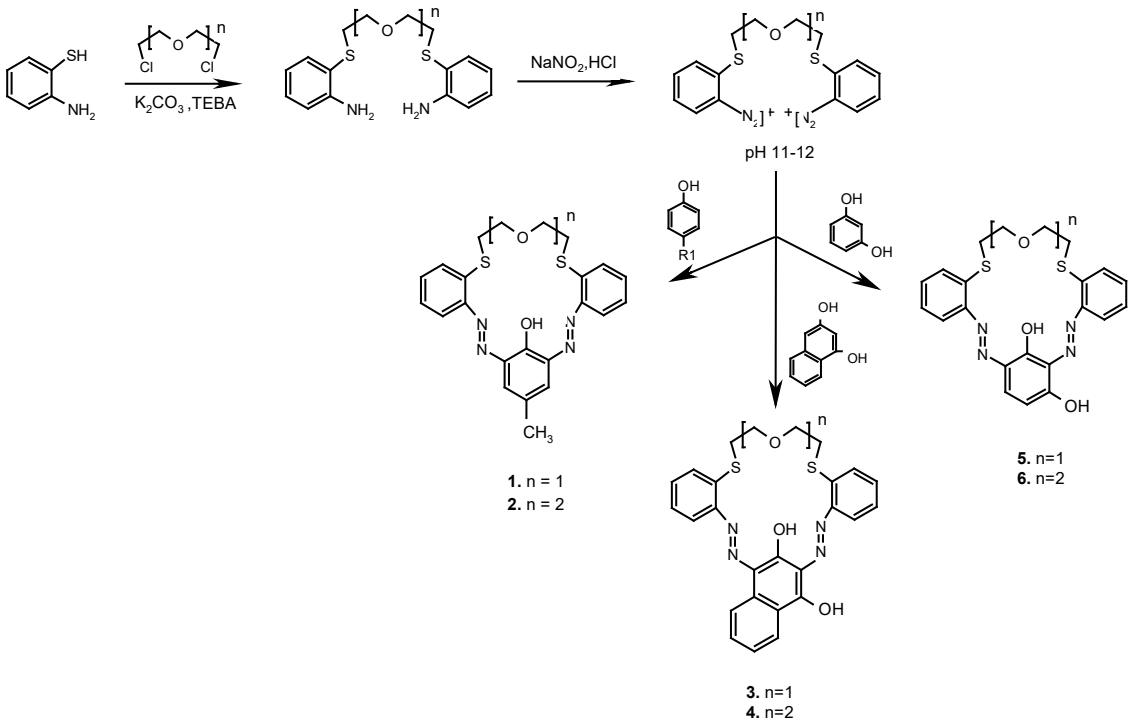
sulfur in the ether chain were described in another publication [3], and it proves that the new macrocycles posses higher susceptibility towards heavy metal cations with simultaneous decrease of affinity to form complexes with transition metal ions. The aim of this paper is synthesis and studies of a new type of chromogenic crown ethers, which contain sulfur atoms in the ether chain, two azo groups and phenolic residue. Such kind of macrocyclic derivatives was mentioned in Sultanov's and Savvin's paper. They synthesized analogous macrocyclic thiaderivatives of resorcinol and *p*-cresol [2], however experimental details were not shown. More, these compounds were not studied as chromoionophores. One could expect increased affinity of new macrocyclic chromoionophores towards "soft" metal cations. Therefore this type of compounds was chosen for more detailed studies.

Complexing properties of the synthesized azothiacrown ethers with *p*-cresol, resorcinol and 1,3-dihydroxynaphthalene residues were investigated spectrophotometrically in water/dioxane solution (1:1 v/v). Compounds were also used as ionophores in ion-selective membrane electrodes.

Results and discussion

Synthesis

The synthesis of thiachromoionophores **1-6** shown in Scheme 1 involve: alkylation of 2-aminothiophenol with the respective dichloroethyl ether [4] to form diaminodithioethers, diazotization of the diamines, and one step coupling of the bis-diazonium salts under high dilution conditions with *p*-cresol, resorcinol or 1,3-dihydroxynaphthalene to obtain macrocyclic compounds with phenolic group and two azo groups.



The yield of macrocyclization products is small for *p*-cresol derivatives (8%), and it is growing for resorcinol (average 15%) and 1,3-dihydroxynaphtalene (about 30%). Larger yield for resorcinol and dihydroxynaphthalene derivatives can be attributed to the formation of two intramolecular hydrogen bonds between -OH groups of resorcinol or 1,3-dihydroksynaphthalene with the adjacent azo groups stabilizing the macrocyclic products. Hydrogen bonds are observed in ^{1}H NMR spectra, where -OH group signal appears around 15-16 ppm for macrocyclic products. It suggests rather strong bonding contrary to acyclic compounds, for which such signal is observed at about 12-14 ppm responsible for weaker bond [5].

Compounds **1-6** were studied by UV-vis spectrophotometry in water-dioxane (1:1; v/v) system as a solvent. Data on absorption bands are collected in Table 1. Studies of cation complexation by compounds **1-6** were recorded in neutral water-dioxane system.

Contrary to oxygen analogues, these thiacompounds do not form complexes with alkali or alkaline earth metal cations. Even at very high concentration of organic base (pH about 12) no significant changes were observed. On the other hand, all studied compounds give changes in absorption spectra in the presence of copper salts without addition of organic base. Examples of such spectra are shown in Figure 1. The investigated 18- and 21-membered azothiacrown ethers (compound **1** and **2**) in water-dioxane solution show a characteristic color change when copper salt is added. The color changed dramatically from orange to pink and

new absorption bands appear at λ_{max}=550 nm (logK=4.70) and λ_{max}=555 nm (logK=5.48), respectively. The most interesting spectral properties are found for naphthothiacrown ether **3** and **4**. These thiacrown ethers are selective reagents for copper ions. The spectral bands appear at λ_{1max}= 418 nm and λ_{2max}=526 nm for free chromoionophore **3** and at λ_{1max}= 414 nm and λ_{2max}=528 nm for compound **4**. The bands for copper complexes for these compounds are found in UV-vis spectrum at λ_{1max}= 540 nm and λ_{2max}=534 nm with stability constants logK=2.93 and 2.69, respectively. Compound **1** was also investigated by UV-vis spectrophotometry in the case of Ag^+ complexation. The new, weak spectral maximum for silver complex of compound **1** appeared at λ_{max}=570 nm, stability constant logK=3.0 with isosbestic point at 500 nm. No significant spectral changes are observed for all investigated macrocyclic compounds in the presence of Pb^{2+} and Cd^{2+} ions under applied conditions.

Table 1. Absorption bands for compounds **1-7** in water-dioxane (1:1; v/v) solvent system and stability constants for copper complexes.

Compound	λ_{max}	ε_{max}	λ_{max} for copper complex	$logK_{Cu}$ (isosbestic point [nm])
1	331	$4.68\cdot10^3$	550	4.70 (490)
	422	$2.65\cdot10^3$		
2	555	$1.87\cdot10^4$	555	5.48
		$9.14\cdot10^3$		
3	418	$1.87\cdot10^3$	540	2.93 (496)
	526	$7.19\cdot10^2$		
4	414	$1.94\cdot10^4$	534	2.69 (492)
	528	$8.50\cdot10^3$		
5	414	$7.89\cdot10^3$	541	4.13 (548)
	510	$3.42\cdot10^3$		
6	301	$4.36\cdot10^3$	584	4.11
	412	$5.72\cdot10^3$		
	517(slope)	$2.61\cdot10^3$		

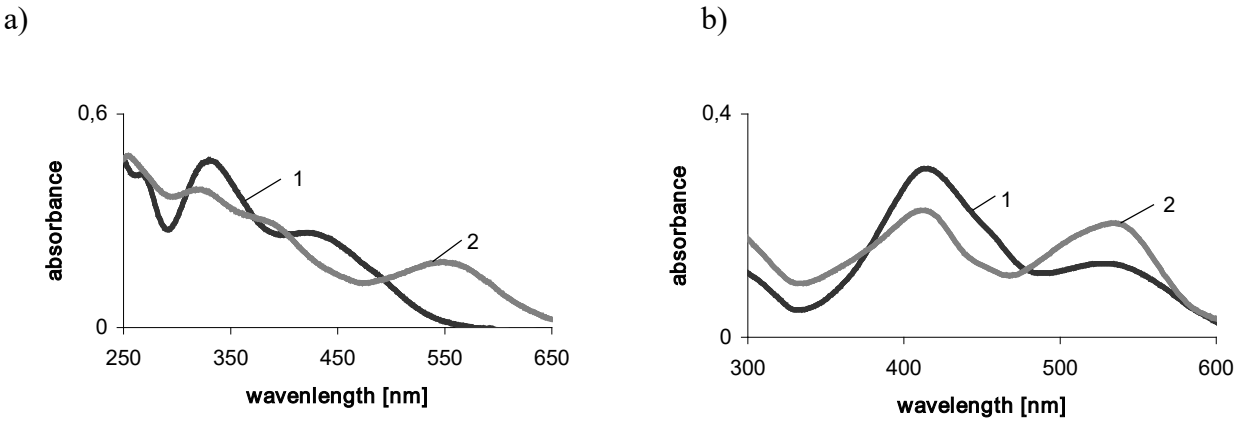


Figure 1. Absorption spectra of: a) compound **1,** 1- "free" ligand (c=1.53 $\cdot 10^{-5}$ mol/dm^3), 2- spectrum in the presence of $CuCl_2$ (c=4.52 $\cdot 10^{-4}$ mol/dm^3); b) compound **4**, 1- "free" ligand (c=1.55 $\cdot 10^{-5}$ mol/dm^3), 2- spectrum in the presence of $Cu(ClO_4)_2$ (c=1,93 $\cdot 10^{-2}$ mol/dm^3).

Membrane electrodes

The properties of ion-selective membrane electrodes doped with thiacrown ethers are presented in Table 2. The alkali and alkaline earth metal ions belong to the group of most discriminated cations. According to Pearson's Hard-Soft Acid-Base theory [7], as expected, replacing oxygen's for sulfur atoms in macroring of crown ethers increases their susceptibility to bind heavy metal cations. The examined electrodes responded to cations in the 10^{-4}-10^{-1}mol·dm^{-3} concentration range. The slopes for divalent Mg^{2+}, Cu^{2+}, Pb^{2+}, Hg^{2+}cations appear around 28.6-34.91 mV/dec but for monovalent as Na^+, K^+ about 52.8-60.22 mV/dec. The best selectivity coefficients are found for "soft" metal ions, such as Hg^{2+}, Cu^{2+} and Pb^{2+}. It was found that membrane doped with azocompound **2** showed higher affinity towards heavy metal ions than compounds **1** and **4**. Chromoionophore **3** showed unexpected worse selectivity coefficients for these metal ions. Selectivity coefficients for silver cation are not included in Table 2 because of difficulties with determination of stable responses, although in the presence of Ag^+ the spectral changes are observed for these compounds.

Table 2. Estimated selectivity coefficients of membrane electrodes doped with chromoionophores **1, 2, 3** and **4** *versus* potassium response (SSM).

Cation	Selectivity coefficients log $K^{pot}_{K/M}$ and slopes (S[mv/decade]) for			
	1	**2**	**3**	**4**
Na^+	-1.51 (56.8)	-0.62 (52.9)	-1.64 (54.9)	-1.19 (56.6)
K^+	0 (58.9)	0 (56.6)	0 (52.8)	0 (60.22)
Mg^{2+}	-0.98 (30.2)	0.08 (29.4)	-1.04 (30.8)	-0.95 (28.9)
Cu^{2+}	3.87 (30.8)	3.28 (28.2)	-0.78 (34.91)	2.66 (33.8)
Pb^{2+}	2.68 (31.2)	6.45 (29.0)	-0.285 (28.6)	1.39 (29.5)
Hg^{2+}	4.38 (28.3)	6.61 (29.2)	3.76 (28.8)	4.98 (29.6)

The slopes are determined in the 10^{-1} to 10^{-4} mol·dm^{-3} concentration range.

Experimental

General

All materials and solvents were of analytical reagent grade. Silica gel (0.035-0.070 mm, Fluka) was used for column chromatography. Preparative TLC glass plates covered with Silica gel 60 F_{254} (Merck) were used in some cases for final separation and purification of crown ethers. ^{1}H NMR spectra, all in $CDCl_3$, were recorded on Varian (500 MHz) instrument. Mass spectra were taken on AMD-604 apparatus. UV-vis spectra were recorded on a Unicam UV-330 Spectrophotometer, IR spectra on a Carl Zeiss Jena M80 Specord and Genesis II (Mattson) instruments. The m.p. °C are uncorrected.

Membrane electrodes and potentiometric measurements

Typical composition of membranes for ion-selective electrodes is: ionophore 5 mg, potassium tetrakis(*p*-chlorophenyl)borate 0.5 mg, poly(vinyl chloride) 50 mg and *o*-nitrophenyl octyl ether 0.1 ml. Internal electrolyte was 1 mol·dm^{-3} NaCl solution. Before measurements the electrodes were soaked in 10^{-2} mol·dm^{-3} $NaNO_3$ solution. The selectivity coefficients were determined using the separate solution method (SSM) [6] at 10^{-2} mol·dm^{-3} activities of metal cation.

Determination of stability constants:

Series of solutions (water-dioxane 1:1 v/v) of constant concentration of crown ether and different concentrations of metal salts were prepared. The spectra were recorded up to high excess of cation to crown ether and finally the limiting spectra were obtained. The formation constants were calculated using modified Benesi-Hildebrand method [7] or using procedure described in [8].

There were no spectral changes observed in case of alkali or alkaline earth metal complexes with examined chromotiacrown ethers in neutral or basic (adjusted to pH=12 with quaternary ammonium hydroxide (Me_4NOH) water-dioxane solution.

Syntheses of podands:

These compounds were obtained according to procedure described by Kumar [4].

A solution of 1,5-dichloro-3-oxapentane (2.35 ml; 20 mmol) or 1,8-dichloro-3,6-dioxaoctane (3.3 ml; 20 mmol), respectively, in dimethylformamide (40 ml) containing 2-aminothiophenol (5 g; 40 mmol), potassium carbonate (5.52 g; 40 mmol) as a base and TEBA (Cl) as a catalyst was stirred at room temperature for about four hours. After completion of the reaction, the solid was removed and the filtrate was evaporated under vacuum. The residue was chromatographed on silica gel to isolate products.

1,5-Bis[2-aminophenyl(thio)]-3-oxapentane (yield 85%), yellow oil; MS m/z 320 (M^+); δ_H (200 MHz, $CDCl_3$) 2.73 (4H, t, *J* 7Hz, SCH_2), 3.30 (4H, t, *J* 7Hz, OCH_2), 4.00 (4H, s, NH_2), 6.18-7.12(8H, m, ArH); IR ν_{max} ($CHCl_3$): 3480, 3360 (NH_2), 1105 (C-O) cm^{-1}.

1,8-Bis[2-aminophenyl(thio)]-3.6-dioxaoctane (yield 56%), brownish oil; MS m/z 364 (M^+); δ_H (200 MHz, $CDCl_3$): 2.92 (4H, t, *J* 6Hz, SCH_2), 3.37-3.69 (8H, m, OCH_2), 3.95 (4H, s, NH_2), 6.40-7.43 (8H, m, ArH); IR ν_{max} ($CHCl_3$): 3460, 3320 (NH_2), 1120 (C-O) cm^{-1}.

General procedure for the synthesis of crown ethers 1-6:

The syntheses were performed using high dilution technique [5]. First two solutions were prepared:

Solution A: A suspension of bis-amine (2 mmol) in solution of 40 ml water was ice-cooled and acidified with conc. hydrochloric acid (1 ml). The solution was diazotized with sodium nitrite (0.28 g; 4.1 mmol) dissolved in 2 ml cold water.

Solution B: *p*-Cresol, resorcinol or 1,3-dihydroxynaphthalene (2 mmol) and sodium hydroxide (0.2 g; 5 mmol) were dissolved in 40 ml water and ice-cooled. The above cold solutions *A* and *B* were dropped with the same speed during 45 min into 600 ml of vigorously stirred cooled water (pH≈7-8). Stirring was continued for 1 h at 10°C and then for 18 h at 25°C. The mixture was extracted using methylene chloride. The organic layer was separated and the solvent was removed. The crude residue was chromatographed on silica gel column using methylene chloride as an eluent for compounds **1** and **2**, and chloroform-acetone 10:1 for compounds **3-6**. In the case of compound **1** and **5** preparative TLC was applied for final purification.

Compound 1: Yield of this thiacompound in comparison with oxygen analogue [5] is dramatically lower and equals 8%. IR, ν_{max} (film) 3054, 2920,2860, 1578, 1480, 1460, 1351, 1280, 1060 cm^{-1}. ^1H NMR; δ_H (500 MHz): 2.51 (3H, s, CH_3); 3.375 (4H, t, *J* 5.8Hz, C$\underline{H_2}$S); 3.867 (4H, t, *J* 5.8 Hz, C$\underline{H_2}$O); 7.29-7.34 (2H, m, Ar$\underline{H}$); 7.39-7.43 (2H, m, Ar$\underline{H}$); 7.52-7.58 (2H, m, Ar$\underline{H}$); 7.79 (2H, dd, J_1 1.53 Hz, J_2 8.24 Hz, Ar$\underline{H}$); 7.85 (2H, s, ArH); 15.0 (1H, s, O$\underline{H}$). HRMS (EI): M^+ found 450.11846; $C_{23}H_{22}O_2N_4S_2$ requires 450.11842.

Compound 2: Yield 12%. IR, ν_{max} (film) 3056, 2920, 2861, 1579, 1482, 1284, 1069 cm^{-1}. ^1H NMR; δ_H (500 MHz): 2.50 (3H, s, CH_3); 3.24 (4H, t, *J* 5.8Hz, C$\underline{H_2}$S); 3.72 (4H, m, C$\underline{H_2}$O); 3.84 (4H, t, *J* 5.8 Hz, C$\underline{H_2}$O); 7.34-7.40 (4H, m, Ar$\underline{H}$); 7.45-7.55 (2H, m, Ar$\underline{H}$); 7.85 (2H, s, ArH); 7.92 (2H, s, Ar$\underline{H}$); 15.1 (1H, s, O$\underline{H}$). HRMS (EI): M^+ found 454.14478; $C_{25}H_{26}O_3N_4S_2$ requires 454.14463.

Compound 3: Yield 20%; mp. 245-250 °C. IR, ν_{max} (nujol) 1505, 1462, 1381,1260, 1117, 1189 cm^{-1}. ^1H NMR; δ_H (500 MHz): 3.20 (4H, t, *J* 5.4Hz, C$\underline{H_2}$S); 3.9 (4H, t, *J* 5.5Hz, C$\underline{H_2}$O); 7.12 (1H, t, *J* 7.32, Ar$\underline{H}$); 7.42-7.50 (3H, m, Ar$\underline{H}$); 7.60-7.68 (3H, m, Ar$\underline{H}$); 7.72 (1H, t, *J* 8.24Hz, Ar$\underline{H}$); 8.0 (1H, d, *J* 8.24Hz, Ar$\underline{H}$); 8.21 (1H, d, *J* 8.24, Ar$\underline{H}$); 8.30-8.40 (2H, m, Ar$\underline{H}$); 15,6 (1H, s, O$\underline{H}$); 16.55 (1H, s, O$\underline{H}$). HRMS (EI): M^+ found 502.11367; $C_{26}H_{22}O_3N_4S_2$ requires 502.11334.

Compound 4: Yield 25%; mp. 210-215 °C. IR, ν_{max} (nujol) 1595, 1461, 1378,1260, 1117, 1009 cm^{-1}. ^1H NMR; δ_H (500 MHz): 3.22 (4H, t, *J* 5.8Hz, C$\underline{H_2}$S); 3.74 (4H, m, C$\underline{H_2}$O); 3.86 (4H, t, *J* 5.8 Hz, C$\underline{H_2}$O);7.16 (1H, t, *J* 7.32, Ar$\underline{H}$); 7.46-7.61 (3H, m, Ar$\underline{H}$); 7.62-7.68 (3H, m, Ar$\underline{H}$); 7.74 (1H, t, *J* 8.24Hz, Ar$\underline{H}$); 8.0 (1H, d, *J* 8.24Hz, Ar$\underline{H}$); 8.21 (1H, d, *J* 8.24,

ArH); 8.34-8.42 (2H, m, ArH); 15,50 (1H, s, OH); 16.50 (1H, s, OH) HRMS (EI): M^+ found 546.13886; $C_{28}H_{26}O_4N_4S_2$ requires 546.13955.

Compound 5: Yield of this analogue in comparison with Sultanov's oxygen analogs is much lower and equals 10%. IR, ν_{max} (film) 3440, 3342, 3060, 2921, 2860, 1674, 1610, 1478, 1152, 1095 cm^{-1}. ^1H NMR; δ_H (500 MHz): 3.17 (4H, t, *J* 5.3 Hz, CH_2S); 3.84 (4H, t, *J* 5.2Hz, CH_2O); 6.57 (1H, d, *J* 10.38 Hz, ArH); 7.02-7.12 (4H, m, ArH); 7.345 (1H, dd, J_1 1.22 Hz, J_2 10.08 Hz, ArH); 7.4-7.48 (2H, m, ArH); 7.86 (1H, d, *J* 8.2 Hz. ArH); 8.2 (1H, d, *J* 8.54 Hz, ArH); 15.5 (~1H, s, OH); 16.5 (~1H, s, OH). HRMS (EI): M^+ found 452.09859; $C_{22}H_{20}O_3N_4S_2$ requires 452.09859.

Compound 6: Yield 15%. IR, ν_{max} (film) 3443, 3345, 3061, 2921, 2862, 1677, 1610, 1480, 1447, 1154, 1040 cm^{-1}. ^1H NMR; δ_H (500 MHz): 3.20 (4H, t, *J* 5.3 Hz, CH_2S); 3.78 (4H, m, CH_2O); 3.90 (4H, t, *J* 5.2Hz, CH_2O); 6.61 (1H, d, *J* 10.38 Hz, ArH); 7.1-7.15 (2H, m, ArH); 7.40-7.50 (3H, m, ArH); 7.98 (1H, d, *J* 7.97 Hz, ArH); 8.18 (1H, d, *J* 8.51 Hz, ArH); 8.30-8.38 (2H, m, ArH); 15.16 (1H, s, OH); 16.1 (1H, s, OH). HRMS (EI): M^+ found 496.12522; $C_{24}H_{24}O_4N_4S_2$ requires 496.12480.

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