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Macrocyclic Derivatives of Resorcinol and 1,3-Dihydroxynaphthalene. New Lithium and Sodium Selective Ionizable Chromogenic Reagents

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The synthesis of ionizable chromoionophores, derivatives of resorcinol and dihydroxynaphthalene has been described. Acid-base properties of these compounds were studied in a mixed, water containing solvent system. Complexation of metal cations was investigated. Selectivity for lithium and sodium ions for 18-membered and 21-membered crown ethers, respectively, was found.

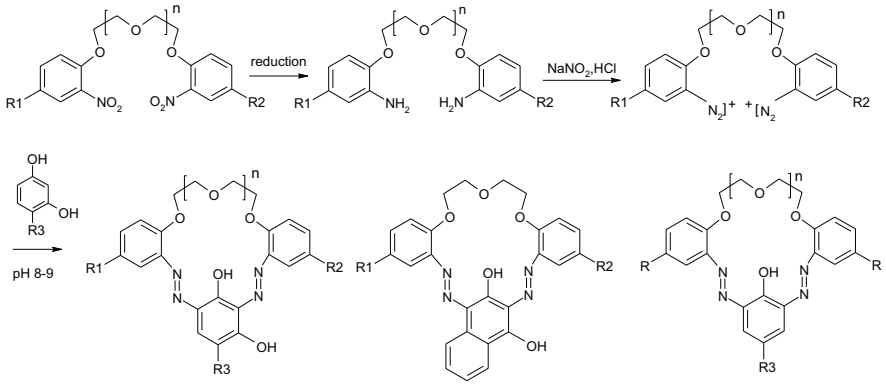
Key words: ionizable chromoionophores, azocrown ethers, resorcinol, synthesis, lithium selective reagent

Chromoionophores are compounds exhibiting interesting spectral properties [1–3]. They change color or its intensity, or fluoresce upon metal complexation [4]. The chromophore unit in the above mentioned compounds is located outside the macrocycle. Recently [5] macrocylic derivatives of *p*-alkylphenols with properties typical for ionizable [6–10] chromoionophores were synthesized. The chromophore units of these compounds, *i.e*. two azo groups compose parts of macrocycle, and the phenolic OH group is directed towards the cavity. Cation complexation inside their cavity involves direct interaction with azo groups. It was found that these crown ethers are selective for lithium ions with exceptional separation of spectral bands of the ligand and its alkali metal complexes [11–13]. Typical inconveniences, related to insufficient absorption band separation of free ligand, its anionic form and the respective alkali ion complexes [6–10], are overcome in this way.

Some years ago Sultanov and Savvin synthesized macrocyclic derivatives of resorcinol (Scheme, compound **1**) [14]. There are no much details in the article about the synthesis and spectral properties. Ability of this macrocyclic resorcinol derivative to complex metal ions was not examined. Due to structural similarity of the resorcinol macrocycles to the mentioned above *p*-alkylphenol chromoionophores **8** (Scheme), the Sultanov' type compounds are chosen for more detailed studies.

RESULTS AND DISCUSSION

The synthesis of macrocyclic derivatives of resorcinol **1–7** was carried out under conditions similar to those described for *p*-alkylphenol chromoionophores **8** [10,13] as shown in the Scheme:



1. n=1, R1= H, R2= H, R3= H

2. n=1, R1= H, R2= H, R3= NO_2

3. n=1, R1= CH_3, R2= CH_3, R3= H

4. n=1, R1= t-Bu, R2= H, R3= H

5. n=1, R1= H , R2= t-Bu , R3= H

6. n=2, R1= H, R2= H, R3= H

7. n=1, R1= H, R2= H

8. n=1 or 2, R= H or CH_3, R3= alkyl

Contrary to rather moderate yields of *p*-alkylphenol macrocycles (average 20%), the yield of compounds **1–6** obtained by this procedure is around 50% in accordance with the yield for compound **1** described in [14]. It is relatively high considering typical yield of macrocyclization reaction. For dihydroxynaphthalene derivative **7** the yield is 11%. Coupling of bis-diazonium salts with resorcinol (and its derivatives) and with 1,3-dihydroxynaphthalene was performed by high dilution technique. Any template effect during this synthesis in the presence of different metal cations was observed.

The high yield of macrocyclization could be attributed to the formation of two intramolecular hydrogen bonds between OH groups of resorcinol and both adjacent azo groups uniquely stabilizing the macrocyclic products. The presence of strong hydrogen bonds is observed in ^{1}H NMR spectra. For example, chemical shifts of OH protons for compound **3** are about 15 and 16 ppm (Figure 1).

Compounds **1–7** were studied by UV-vis spectrophotometry. Dioxane–water (1:1; v/v) mixture was used as solvent. Table 1 collects parameters of the absorption bands. The compounds comprise weak acidic OH and weak basic –N=N– centers. To investigate acid-base properties of compounds **1–7** a series of spectra were recorded in water–dioxane (1:1) system at different pH(s). In acidic medium (from hydrochloric acid) neither color nor spectral changes were observed. It indicates that azo groups engaged in hydrogen bond are not susceptible to bind additional protons under applied conditions. In basic solutions the color and spectral changes are observed at extremely high pH(s) (1 M Me_4NOH). It means an acidity decrease of OH groups by strong hydrogen bonds (*c.f.*, ^{1}H NMR spectra). Only for 4-nitroresorcinol derivative (compound **2)** the color and spectral changes are observed at somewhat lower pH(s)

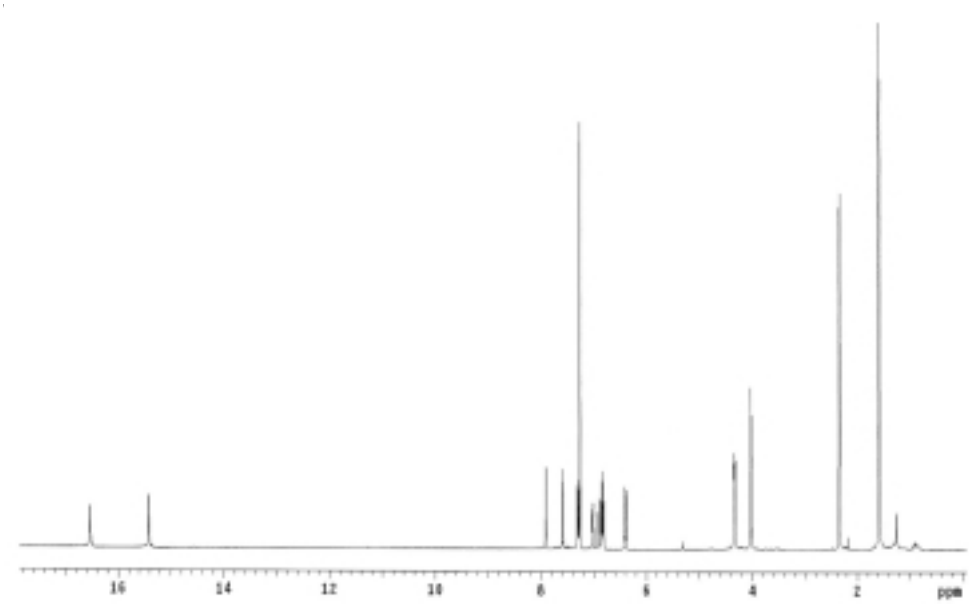


Figure 1. ^{1}H NMR spectrum of compound **3** ($CDCl_3$).

(about 9). For compound **2** the calculated pK_a is 12.9 (water–dioxane system). The limiting spectrum was found at pH(s) 13.4.

Studies of cation complexation by compounds **1** and **3–7** was performed by spectroscopy in the same mixed water–dioxane (1:1) system. Compounds **1, 3–7** form complexes with alkali metal ions in strongly basic solutions (pH(s) ≈ 12). Complexation of compound **2** was studied at pH(s) ≈ 9. For compounds, where n = 1, the most noticeable changes in absorption spectra were found in the presence of lithium salts (Figure 2).

The resorcinol crown ethers **1–5** are selective reagents for lithium ions with spectral band separation of about 20 nm for the ligand and its complex. Interesting are spectral properties of naphthocrown **7.** This crown has four bands in UV-vis spectrum (Table 1). In this case the complexation process is easier to observe, because absorption at 550 nm (Figure 2) extensively decreases and absorption at about 500 nm increases upon addition of lithium salts. Well-pronounced isosbestic point for the system is at about 530 nm, indicating two absorbing species in equilibrium. In the presence of sodium ions negligible spectral changes are observed for 18-membered resorcinol derivatives **1–5** and **7**.

For 21-membered crown ether (compound **6**) the most noticeable spectral changes were observed in the presence of sodium cations. Neither for 18-membered nor 21-membered crown ethers spectral changes for potassium cation are seen. Thus, the crown ether size is crucial for cation recognition. A quite similar example of cation discrimination with except of lithium by chromogenic cryptand was described [15]. Table 1 collects the stability constants determined.

Table 1. Absorption bands for compounds **1–7** in water–dioxane (1:1) solvent system and stability constants for their lithium and sodium complexes.

Compound	λ_{max} [nm]	ε_{max}	log K_{Li} (isosbestic point [nm])
1	434	3.02×10^4	3.79 (516)
2	356	1.03×10^5	3.52 (449)
3	441	1.12×10^4	3.96 (525)
4	438	2.95×10^4	–
5	436	3.84×10^4	–
7	237	7.60×10^3	3.36 (530)
	264	1.66×10^4	
	434	1.74×10^4	
	550	7.40×10^3	
			log K_{Na} (isosbestic point [nm])
6	421	3.78×10^4	3.28 (505)

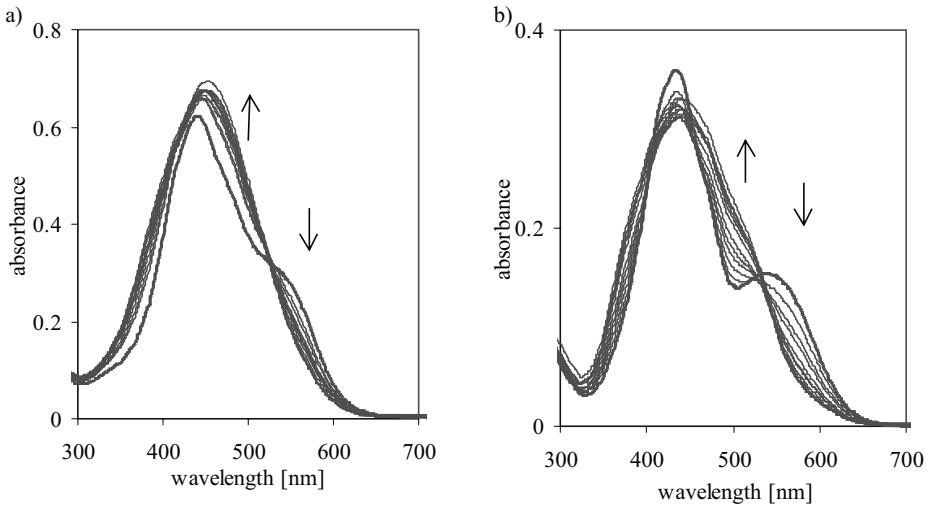


Figure 2. Absorption spectra of: a) compound **3** (concentration 6.70×10^{-5} mol·dm^{-3}), and spectra in the presence of $LiClO_4$ ($0 - 2.62 \times 10^{-3}$ mol·dm^{-3}); b) compound **7** (1.7×10^{-5} mol·dm^{-3}) and spectra in the presence of $LiClO_4$ ($0 - 6.68 \times 10^{-3}$ mol·dm^{-3}) in water-dioxane (1:1) solvent system, pH(s) ≈ 12.

Because of low acidity of the crown ethers, generation of anionic form is far from quantitative, even at high pH(s). Since the coloration of the reagents proceeded upon adding metal cation, it may be presumed that color changes are caused by proton exchange for metal ion and that this process is facilitated by high pH(s), *cf.* [13,16]. Numerous other cations like beryllium, aluminium, lanthanum, zinc and copper(II) do not change the resorcinol chromoionophores spectra under applied conditions.

EXPERIMENTAL

All materials and solvents were of analytical reagent grade. 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 instruments. Mass spectra were taken on AMD-604 apparatus. UV-vis spectra were recorded on a Unicam UV-330 Spectrophotometer, IR spectra (film) on a Carl Zeiss Jena M80 Specord and Genesis II (Mattson) instruments. The mp [°C] are uncorrected.

Determination of protonation constants: A series of solutions (water–dioxane 1:1) of constant concentration of crown ether and different pH(s) (Me_4NOH) were prepared. The spectra of such prepared solutions were measured until limited spectra were obtained. Equation $\lg K = [(A_I - A)/(A - A_M)] + pH$, where A_M = absorbance of free ligand, A_I = absorbance of ionic form, was used for calculations.

Determination of stability constants: Series of solutions (water–dioxane) of constant concentration of crown ether and different concentrations of alkali metal salts were prepared and adjusted to pH(s) ≈ 12 with quaternary ammonium hydroxide (Me_4NOH). The spectra were recorded up to high excess of cation to crown ether and finally the limiting spectra were obtained. From these spectra the equilibrium constants were calculated. The formation constants were calculated using modified Benesi-Hildebrand method [17].

Syntheses

Synthesis of 1-(2-nitrophenoxy)-5-(2-nitro-4-*t*-butylphenoxy)-3-oxapentane: A mixture of 4-*t*-butyl-2-nitrophenol (2 g; 10 mmol) [18], 2-chloro-2′-(2-nitrophenoxy)ethyl ether (2.46 g; 10 mmol), anhydrous potassium carbonate (1.4 g; 12 mmol) in 6 ml dimethylformamide was heated at 110° for 18 h. To the cooled reaction mixture water was added and the organic material was extracted three times with chloroform. The product was purified by means of column chromatography in polarity gradient using hexane (beginning) and methylene chloride (end) as eluents. Yield 2.6 g (66%) of an oily product. ^{1}H NMR; δ_H (200 MHz): 7.79–7.86 (2H, m); 7.47–7.58 (2H, m); 6.98–7.16 (3H, m); 4.23–4.32 (4H, m); 3.97–4.05 (4H, m); 1.32 (9H, s).

Synthesis of 1-(2-aminophenoxy)-5-(2-amino-4-*t*-butylphenoxy)-3-oxapentane: The amine was obtained by reduction of 1-(2-nitrophenoxy)-5-(2-nitro-4-*t*-butylphenoxy)-3-oxapentane with hydrogen on Pd/C catalyst. The reaction was carried out for 12 h at room temperature in ethanol as a solvent. Yield 100%; m.p. 65–66°C. ^{1}H NMR; δ_H (200 MHz) 6.9–6.7 (7H, m); 4.23–4.14 (4H, m); 3.97–3.88 (4H, m); 3.74 (4H, s); 1.29 (9H, s).

General procedure for the synthesis of crown ethers 1–7: The syntheses were performed using high dilution technique. First, two solutions were prepared: *Solution A*: A suspension of bis-amine (2 mmol) [19,20] in 40 mL water was cooled on ice-bath and acidified with conc. hydrochloric acid (1 mL). The clear solution was diazotized with sodium nitrite (0.28 g; 4.1 mmol) dissolved in 2 mL cold water. *Solution B*: 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 water (pH about 7–8). The temperature of aqueous medium was kept at 10°. Stirring at 10° was continued for 1 h and then for 18 h at 25°. The mixture was cooled to 0–5° and pH was adjusted to 6–7 with acetic acid to precipitate crude products.

Crown ethers were isolated from the collected solid material using column chromatography. As an eluent consecutively chloroform and mixture of chloroform-acetone 10:1 (compounds **1–6**), and chloroform-acetone 10:1 and 4:1 (compound **7**) were used. Additionaly preparative thin layer chromatography for separation of isomeric compounds **4** and **5** was applied **(**mobile phase methylene chloride-acetone 10:1).

Compound 1: Properties of compound **1** are in good agreement with those described by Sultanov [14]. Yield 52%; m.p. > 300°C IR υ_{max} (film): 2928; 2496; 2320; 2064; 1632; 1504; 1408; 1324; 1260; 864; 816; 736 cm^{-1}. ^{1}H NMR; δ_H (500 MHz): 16.50 (0.8H, s, OH); 15.4 (0.8H, s, OH); 8.08 (1H,d, *J* 8.1 Hz, ArH); 7.76 (1H, d, *J* 8.1 Hz, ArH); 7.38–7.20 (2H, m, ArH); 7.16–7.02 (3H, m, ArH); 6.98–6.90 (2H, m, ArH); 6.40 (1H, d, *J* 9.2 Hz, ArH); 4.45–4.30 (4H, m, $ArOCH_2$); 4.10–4.00 (4H, m, CH_2OCH_2).

Compound 2: Yield 54%; m.p. > 300°C. IR υ_{max} (film): 3424; 2369; 2264; 1652; 1296; 1252; 900; 752; 720 cm^{-1}. ^{1}H NMR; δ_H (500 MHz): 16.56 (0.8H, s, OH); 16.1 (0.8H, s, OH); 8.27 (1H, s, ArH); 8.1 (1H, d, *J* 8.1 Hz, ArH); 7.84 (1H, d, *J* 7.7 Hz, ArH); 7.13 (2H, t, *J* 8.1 Hz, ArH); 7.12 (2H, t, *J* 7.7 Hz,

ArH); 6.8 (2H, t, *J* 7.3 Hz, ArH); 4.45–4.30 (4H, m, ArOCH$_2$); 4.10–4.00 (4H, m, CH$_2$OCH$_2$). MS (ESI): $[M+H]^+$ 446.1; $[M+Na]^+$ 488.1; $[2M+Na]^+$ 953.2; for M^+ = 488.1177; $C_{22}H_{19}N_5O_7Na$ requires 488.1188.

Compound 3: Yield 48%; m.p. > 300°C. IR υ_{max} (film): 3392; 2304; 1632; 1548; 1408; 1264; 1168 cm^{-1}. ^{1}H NMR; δ_H (500 MHz): 16.52 (1H, s, OH); 15.42 (1H, s, OH); 7.9 (1H, s, ArH); 7.58 (1H, s, ArH); 7.53 (1H, d, *J* 10.3 Hz, ArH); 7.02 (1H, d, *J* 8.4Hz, ArH); 6.9 (1H, d, *J* 8.4 Hz, ArH); 6.78–6.86 (2H, m, ArH); 6.4 (1H, d, *J* 9.9 Hz, ArH); 4.35 (4H, m, ArOCH$_2$); 4.0 (4H, m, CH$_2$OCH$_2$); 2.35 (3H, s, CH$_3$); 2.34 (3H, s, CH$_3$). HRMS (EI): found 448.175323; $C_{24}H_{24}N_4O_5$ requires 448. 17467.

Compounds 4 and 5: Coupling of bisdiazonium salt, obtained from 1-(2-aminophenoxy)-5-(2-amino-4-*t*-butylphenoxy)-3-oxapentane, with resorcinol produces two isomeric compounds **4** and **5**.

Compound 4: Yield 20%; m.p. 245–247°C. IR υ_{max}: 3392; 1632; 1516;1408; 1264; 752 cm^{-1}. ^{1}H NMR; δ_H (500 MHz): 16.61 (1H, s, OH); 15.46 (1H, s, OH); 8.07 (1H, s, ArH); 7.76 (1H, d, *J* 10.1 Hz, ArH); 7.32–7.30 (1H, d, *J* 10.1 Hz, ArH); 7.29–7.24 (1H + $CDCl_3$, m, ArH); 7.15–7.11 (1H, m, ArH); 7.08–7.03 (1H, m, ArH); 6.96–6.92 (1H, m, ArH); 6.91–6.88 (1H, m, ArH); 6.48–6.42 (1H, m, ArH); 4.32–4.40 (4H, m, ArOCH$_2$); 4.0–4.1 (4H, m, CH$_2$OCH$_2$); 1.35 (9H, s, CH$_3$). HRMS (EI): found 476.20672; $C_{24}H_{24}N_4O_5$ requires 476.20597.

Compound 5: Yield 10%; m.p. 124–125°C. IR υ_{max}: 2928; 2336; 1632; 1508;1408; 1264; 752 cm^{-1}. ^{1}H NMR; δ_H (500 MHz): 16.59 (1H, s, OH); 15.54 (1H, s, OH); 8.11 (1H, d, *J* 8.1 Hz, ArH); 7.80 (1H, d, *J* 10.1 Hz, ArH); 7.40 (1H, d, *J* 10.1 Hz, ArH); 7.24–7.20 (1H, m, ArH); 7.15 (1H, dd, J_1 8.7 Hz, J_2 2.0 Hz, ArH); 7.08 (1H, t, *J* 10.1 Hz, ArH); 6.96 (1H, d, *J* 8.1 Hz, ArH); 6.87 (1H, d, *J* 8.4 Hz, ArH); 6.46 (1H, d, *J* 10.1 Hz, ArH); 4.32–4.45 (4H, m, ArOCH$_2$); 4.0–4.1 (4H, m, CH$_2$OCH$_2$); 1.35 (9H, s, CH$_3$). HRMS (EI): found 476.20458; $C_{24}H_{24}N_4O_5$ requires 476.20597.

Compound 6: Yield 48%; m.p. 199–200°C. IR υ_{max}: 2936; 1632; 1408; 1312; 1264; 1152; 1088; 1040; 832; 752 cm^{-1}. ^{1}H NMR; δ_H (500 MHz): 15.26 (1H, s, OH); 14.2 (1H, s, OH); 8.06 (1H, d, *J* 7.7 Hz, ArH); 7.78 (1H, s, ArH); 7,32 (1H, d, *J* 10.2 Hz, ArH); 7.22–7.3 (1H, m, ArH); 7.04–7.16 (3H, m, ArH); 6.05 (2H, t, *J* 8.1 Hz, ArH); 6.4 (1H, d, *J* 10.5 Hz, ArH); 4.40–4.30 (4H, m, ArOCH$_2$); 4.10–4.00 (4H, m, ArOCH$_2$CH$_2$); 3.8 (4H, s, OCH$_2$CH$_2$O). HRMS (EI): found 464.16958; $C_{24}H_{24}N_4O_6$ requires 464.16915.

Compound 7: Yield 11%; m.p. 271–275°C. IR υ_{max}: 2923; 1656; 1596; 1506; 1477; 1402; 1253; 1197; 1111; 1041; 937; 741; 694 cm^{-1}. ^{1}H NMR; υ_H (500 MHz): 16.5 (1H, s, OH); 15.4 (1H, s, OH); 8.33 (1H, d, *J* 7.6 Hz, ArH); 8.26 (1H,d, *J* 7.6 Hz, ArH); 8.10 (1H, d, *J* 7.9 Hz ArH); 7.88 (1H, t, *J* 8.9 Hz, ArH); 7.61 (1H, t, *J* 7.6 Hz, ArH); 7.40 (1H, t, *J* 7.6 Hz, ArH); 7.22 (1H, t, *J* 7.6 Hz, ArH); 7.12–7.05 (3H, m, ArH); 6.96–6.90 (2H, m, ArH); 4.45–4.30 (4H, m, ArOCH$_2$); 4.15–4.0 (4H, m, CH$_2$OCH$_2$). HRMS (EI): M^+ found 470.16149; $C_{26}H_{22}N_4O_5$ requires 470.15902.

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