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13-Membered crown ethers with azo or azoxy unit in the macrocycle - synthesis, membrane electrodes, voltammetry and Langmuir monolayers

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A facile way to obtain substituted azo- and azoxycrown ethers has been developed. Applicability of these crown ethers in sodium-sensitive membrane electrodes has been studied. Voltammetric behavior of the crown ethers bearing azo- and azoxy- subunits in the macrocyclic system has been characterized. Formation of Langmuir-Blodgett monolayers of amphiphilic azocrown ethers on aqueous subphase has been investigated.

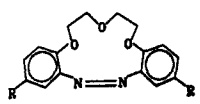
INTRODUCTION

Renewed interest in azobenzene derivatives can be related to their application in functional devices such as molecular switches and optical memories.[1,2,3] The azo unit may be inserted as part of a macrocycle in crown ethers. This suggests their extended applicability to similar purposes due to *cis-trans* isomerization of the azo unit followed by spectral changes, changes in susceptibility to form complexes, and changes of the redox potentials of the azo unit. Recently we have described the structure, electrochemical and ion-selective membrane electrode properties of 13-membered crown ethers containing an azo group in the macrocycle (compound **1**) as an electroactive unit[4].

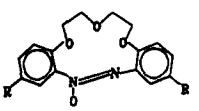
The previous successful synthesis of analogues of crown ethers bearing an azo- **1**[2,4,5] or azoxygroup **6**[6] in the macrocycle and their interesting properties inspired us to synthesize the respective derivatives.

The X-ray structures of the parent compounds have been determined[4,6] and thus the geometry of the -N=N- and -N(O)=N- residues has been fully described.

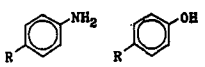
13-Membered azocrown ether **1** forms a complex with sodium iodide of 2:1 (ligand to sodium cation) stoichiometry[7]. Chemical modifications, especially changes of lipophilicity of the parent compound should lead to changes in selectivity of complex formation and, when applied in membrane electrodes, to changes in their selective response due to differences in stoichiometry of complexes formed with analyte and interfering cations[8]. The selectivity of calcium electrode response has been found to be directly dependent on partition of the cation complexes between aqueous and organic phase[9]. This



1. R = H
2. R = *tert*-butyl
3. R = 1,1,3,3-tetramethylbutyl
4. R = dodecyl
5. R = lauroyl

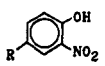


6. R = H
7. R = *tert*-butyl
8. R = 1,1,3,3-tetramethylbutyl
9. R = dodecyl
10. R = lauroyl

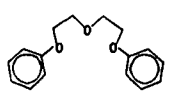


15.

16. R = *tert*-butyl
17. R = 1,1,3,3-tetramethylbutyl
18. R = dodecyl



19. R = *tert*-butyl
20. R = 1,1,3,3-tetramethylbutyl
21. R = dodecyl



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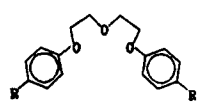
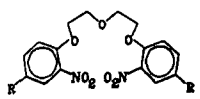


23. R = lauroyl



11. R = *tert*-butyl
12. R = 1,1,3,3-tetramethylbutyl
13. R = dodecyl
14. R = lauroyl

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stimulated us to synthesize more lipophilic derivatives, preferentially alkyl derivatives. Moreover, high lipophilicity of ionophores in membrane electrodes increases their lifetime[10].

EXPERIMENTAL

GENERAL

Synthesis

All materials and solvents used for synthesis were of analytical reagent grade. Silica gel (5/40μm) containing 13% gypsum (Chemapol, Czechoslovakia) was used for column chromatography.

^{1}H NMR spectra, all in $CDCl_3$, of chromatographically homogenous compounds were carried out with a Varian 60 MHz instrument for intermediates and a 200 MHz instrument for crown ethers. Their purity and identity was established by mass spectra carried out on a Varian MATT 711 spectrometer using field desorption technique, or with a AMD-604 apparatus. The m.p. are uncorrected.

Membrane electrodes and potentiometric measurements

High molecular poly(vinyl chloride) (POLANVIL S-70) and *o*-nitrophenyl octyl ether either synthetized in our own laboratory[11] or commercial (Fluka) were used for membranes preparation. Potassium tetrakis(4-chlorophenyl)borate (Fluka) was used as lipophilic salt. All measurements were performed at 25 ± 1°C using a 654 pH-meter (Metrohm) allowing readings with an accuracy of ±0.1mV. Lithium acetate (1 mol·dm^{-3}) was used as external electrolyte in the double-junction reference electrode (RADELKIS OP-08020P Ag/AgCl electrode).

Voltammetry and Langmuir-Blodgett monolayers

Voltammetric experiments were performed in dry DMF and DMF solutions with water added purposely. DMF (Aldrich) was distilled and dried over 3 Å molecular sieve. Tetraethylammonium perchlorate (TEAP, Fluka) was recrystallized from water and used to prepare the supporting electrolyte solution. All electrochemical experiments were done at 25°C in deoxygenated solutions and argon blanket was kept over the solution during the experiments. Distilled water used as the subphase for the Langmuir monolayer experiments was passed through Milli-Q water purification system. Chloroform (Aldrich) was used as the spreading solvent.

Voltammetric experiments were carried out in a three-electrode arrangement with a saturated calomel reference electrode, platinum foil counter electrode and static mercury drop electrode, SMDE 1 (Laboratorni Pristroje) of 0.015 cm^2 drop area, used in the hanging mode. Voltammograms were recorded with BAS-100 Electrochemical Analyzer (Bioanalytical Systems Inc.) and a HIPLOT DMP-40 Plotter (Houston Instrument).

Surface pressure vs. mean molecular area isotherms were recorded using the KSV-Minitrough with Wilhelmy plate type microbalance. The instrument was controlled by a PC AT computer. Software version KSV 5000 was used to control the experiment. The experimental system was enclosed in a plexiglass box. The procedures of cleaning the trough and monolayer spreading have been described earlier[12].

SYNTHESES

4-Dodecylphenol 18

A mixture of conc. sulfuric acid (1.5 mL), water (5.5 mL) and 4-dodecylaniline[13] hydrochloride (2 g; 6.97 mmol) was stirred to obtain fine suspension. The mixture was stirred and cooled to 0° and ice cooled solution of sodium nitrite (0.48 g) in 1.5 mL water was added for 30 min. Stirring was continued for 1 h at 5° and then the mixture was added dropwise to 8 mL of boiling 20% sulfuric acid and kept on boiling to complete decomposition of the diazonium salt.

The cooled reaction mixture was extracted with chloroform and 4-dodecylphenol **18** was isolated by column chromatography with methylene chloride as an eluent. The solvent was evaporated under reduced pressure and the residue crystallized from heptane to give 0.54 g (30 %) of a white compound melting at 61-62°.

^{1}H NMR (δ, ppm.): 0.63-1.77 m, 23 H; 2.51 t (J = 7 Hz) 2H; 4.60 (broad) 1H; 6.71 d (J = 8.5 Hz) 2H; 7.02 d (J = 8.5 Hz) 2H.

4-*tert*-Butyl-2-nitrophenol 19

A solution of fuming nitric acid (1.1 mL; 30 mmol) in acetic acid (5 mL) was gradually added to an ice cooled solution of 4-*tert*-butylphenol **16** (4.53 g; 30 mmol) in acetic acid (10 mL) with stirring. The reaction mixture was left to stand for 1 h in an ice bath and for 1 h more at room temperature; it was then diluted with water (20 mL) and extracted with methylene chloride. The organic layer was washed with water, saturated potassium carbonate solution and dried. After solvent evaporation the product was isolated by column chromatography on silica gel with hexane as an eluent. The slightly yellowish fraction yielded on evaporation 4.6 g (76%) of an oily, pale yellow product.

^{1}H NMR (δ, ppm): 1.35 s, 9H; 7.1 d (J = 9 Hz) 1H; 7.7 dd (J = 9 Hz, J = 3 Hz) 1H; 8.05 d (J = 3 Hz) 1H; 10.5 s 1H.

4-(1,1,3,3-Tetramethylbutyl)-2-nitrophenol 20

This compound was prepared in a way similar to the *tert*-butyl derivative starting from 4-(1,1,3,3-tetramethylbutyl)phenol **17** (8.24 g; 40 mmol) dissolved in 30 mL acetic acid and a solution of fuming nitric acid (1.46 mL) in acetic acid (6 mL). The reaction mixture was diluted with water and the product extracted with hexane. The organic solution was washed with water and with saturated solution of potassium carbonate. The aqueous layer was separated and the organic layer was filtered to remove the precipitated picric acid (420 mg; 4.6%). The residual solution was chromatographed on silica gel with hexane as an eluent. The pale yellow fraction, after solvent evaporation under reduced pressure, afforded 7 g (70%) of oily product **20**.

^{1}H NMR (200 MHz; δ, ppm.): 0.73 s, 9H; 1.37 s, 6H; 1.73 s, 2H; 7.09 d (J = 8.8 Hz) 1H; 7.63 dd (J = 2.5 Hz, J = 8.8 Hz) 1H; 8.05 d (J = 8.8 Hz) 1H; 10.48 s, 1H.

4-Dodecyl-2-nitrophenol 21

To a solution of 4-dodecylphenol **18** (2.62 g; 10 mmol) in a mixture of acetic acid (20 mL) and chloroform (40 mL) was gradually added a solution of concentrated nitric acid (1.15 mL) in acetic acid (20 mL). The reaction mixture was stirred for 2 h at room temperature. Then 20 mL water and sodium carbonate was added to neutralize the mixture. The organic layer was separated, and the aqueous solution was extracted twice with chloroform. The combined organic solutions were evaporated and the residue was chromatographed on silica gel column using heptane as an eluent. The yellowish fraction was separated, the solvent evaporated and the residue crystallized from ethanol-water. Yield: 2.6 g (85%) of yellowish nitroderivative **21** melting at 49-50.5°.

^{1}H NMR (δ, ppm): 0.70-1.70 m, 23H; 2.57 t (J = 7.5 Hz) 2H; 7.03 d (J = 9 Hz) 1H; 7.42 dd (J = 9 Hz, J = 2 Hz) 1H; 7.89 d (J = 2 Hz) 1H.

1,5-Bis(4-lauroylphenoxy)-3-oxapentane 23

A mixture of 1,5-diphenoxy-3-oxapentane[14] (0.260 g; 1 mmol), Eaton reagent[15] (3 mL) and lauric acid (0.5 g; 2.5 mmol) was stirred and heated to 50° for 18 h. The mixture was cooled in an ice bath and diluted with ice cooled water. The crystalline product was collected and recrystallized from ethanol. Yield 0.46 g (74%) of product **23** melting at 74-76°.

^{1}H NMR (δ, ppm): 0.60-2.00 m, 42H; 2.85 t (J = 7 Hz) 4H; 3.82-4.37 m, 8H; 6.97 d (J = 9 Hz) 4H; 7.97 d (J = 9 Hz) 4H.

1,5-Bis(4-*tert*-butyl-2-nitrophenoxy)-3-oxapentane 11

A mixture of 4-*tert*-butyl-2-nitrophenol **19** (3.92 g; 20 mmol), 2,2'-dichlorodiethyl ether (1.23 mL; 10 mmol), anhydrous potassium carbonate (3.9 g) and dimethylformamide (8 mL) was refluxed for 7 h, and then diluted with water. The product was extracted with methylene chloride, the organic layer washed with water and the solvent was evaporated. After dissolving in a small amount of carbon tetrachloride, the residue was applied on a short silica gel column and a compound of interest was eluted with carbon tetrachloride and methylene chloride. Yield: 3.56-4.28 g (77.5-93%) of pale yellow oil **11**.

^{1}H NMR (δ, ppm.): 1.4 s, 18H; 4.0-4.25 m, 4H; 4.3-4.6 m, 4H; 7.18 d (J = 10 Hz) 2H; 7.65 dd (J = 2 Hz, J = 9 Hz) 2H; 7.9 d (J = 2 Hz) 2H.

1,5-Bis[4-(1,1,3,3-tetramethylbutyl)-2-nitrophenoxy]-3-oxapentane 12

This compound was obtained analogously to the *tert*-butyl derivative starting from compound **20** (3.5 g; 14 mmol) and stoichiometric amounts of the other reaction components. The desired oily product **12** was obtained (3.6 g; 90%).

^{1}H NMR (δ, ppm.): 0.73 s, 18H; 1.36 s, 12H; 1.73 s, 4H; 4.01 t (J = 4.5 Hz) 4H; 4.27 t (J = 4.5 Hz) 4H; 7.04 d (J = 9 Hz) 2H; 7.53 dd (J = 2.5 Hz, J = 9 Hz) 2H; 7.83 d (J = 2.5 Hz) 2H.

1,5-Bis(4-dodecyl-2-nitrophenoxy)-3-oxapentane 13

Compound **13** was prepared analogously to compound **12** starting from 2.6 g of compound **21**, but the reaction mixture was boiled for 30 h. The product was extracted with chloroform and purified by column chromatography with the carbon tetrachloride-chloroform (1:1) mixture as an eluent. Yield was 1.7 g (58%) of compound **13**. The starting dodecylnitrophenol (320 mg) was recovered.

^{1}H NMR (200 MHz; δ, ppm.): 0.79-0.86 m, 6H; 1.21 s, 36H; 1.45-1.60 m, 4H; 2.53 t (J = 7.7 Hz) 4H; 3.94 t (J = 4.5 Hz) 4H; 4.20 t (J = 4.5 Hz) 4H; 6.97 d (J = 8.8 Hz) 2H; 7.26 dd (J = 2.2 Hz, J = 8.8 Hz) 2H; 7.58 d (J = 2.2 Hz) 2H.

1,5-Bis(4-lauroyl-2-nitrophenoxy)-3-oxapentane 14

To a stirred ice cooled solution of acylderivative **23** (2.6 g; 4.18 mmol) in acetic anhydride (22 mL), concentrated nitric acid (3 mL) was added dropwise. The temperature was maintained below 30°. The mixture was stirred at room temperature for 6 h and then diluted with water. The precipitated product was collected and dried. After purification on silica gel column with the hexane-methylene chloride (1:1) eluent the crude product was crystallized from hexane-methylene chloride (3:1). The yield of compound **14** was 1.75 g (58%), m.p. 74-77°.

^{1}H NMR (δ, ppm): 0.57-1.93 m, 42H; 2.87 t (J = 7.5 Hz) 4H; 3.82-4.50 m, 8H; 7.13 d (J = 9 Hz) 2H; 8.10 dd (J = 9 Hz, J = 2 Hz) 2H; 8.33 d (J = 2 Hz) 2H.

Macrocyclic azo and azoxy compounds

1,2-Azo-3,4,12,13-bis(4-*tert*-butylbenzo)-5,8,11-trioxacyclotridecane 2 and azoxy compound 7

A mixture of 1,5-bis(4-*tert*-butyl-2-nitrophenoxy)-3-oxapentane **11** (4.3 g; 9.35 mmol), anhydrous stannous chloride (7.62 g), sodium hydroxide (12.2 g), acetone (35 mL) and water (30 mL) was stirred vigorously and heated to gentle boiling for 4 h[4]. To the cooled reaction mixture toluene (30 mL) was added, and the precipitated sodium chloride was removed by filtration. The solid was washed with toluene and the filtrates were combined. The organic layer was separated, washed with water and the solvent was evaporated under reduced pressure to constant weight. Yield: 3.4 g of a crude product. The mixture was chromatographed on a short silica gel column using methylene chloride to remove polymers. The red fraction (1.5 g) was rechromatographed on silica gel using chloroform as an eluent. The first yellowish fraction, after removal of the solvent and crystallization from methanol, afforded 670 mg (17%) azoxycrown ether **7**; the second red fraction afforded 240 mg (6%) of azocrown ether **2** after crystallization from heptane.

Azoxycrown ether **7** m.p. 152-153°; for $C_{24}H_{32}N_2O_4$ (412) found M/z = 412.

^{1}H NMR (δ, ppm.): 1.35 s, 18H; 3.86-3.97 m, 4H; 4.29-4.39 m, 4H; 7.00 d (J = 8.5 Hz) 1H; 7.02 d (J = 8.5 Hz) 1H; 7.31 dd (J = 2.5 Hz, J = 8.5 Hz) 1H; 7.43 dd (J = 2.5 Hz; J = 8.5 Hz) 1H; 7.71 d (J = 2.5 Hz) 1H; 7.72 d (J = 2.5 Hz) 1H.

Azocrown ether **2** m.p. 111-113°; for $C_{24}H_{32}N_2O_3$ (396) found M/z = 396. ^{1}H NMR (δ, ppm.): 1.26 s, 18H; 3.73-3.95 m, 4H; 4.05-4.30 m, 4H; 6.92 d (J = 9 Hz) 2H; 7.25 dd (J = 2 Hz, J = 9 Hz) 2H; 7.57 d (J = 2 Hz) 2H.

1,2-Azo-3,4,12,13-bis(4-tetramethylbutylbenzo)-5,8,11-trioxacyclotridecane 3 and azoxy compound 8

These compounds were obtained similarly to the di-*tert*-butyl crown ethers starting from 1,5-bis(4-tetramethylbutyl-2-nitrophenoxy)-3-oxapentane **12** (2,86 g; 5 mmol), stannous chloride dihydrate (4.95 g), sodium hydroxide (6.5 g), acetone (25 mL) and water (20 mL). The product (2.6 g) was dissolved in a small amount of methylene chloride and chromatographed on a silica gel column with methylene chloride as an eluent.

The first yellowish fraction was evaporated and the residue was crystallized from 2-propanol-heptane. Yield: 400 mg (15%) of creamy azoxycrown ether **8** melting at 134-135°.

For $C_{32}H_{48}N_2O_4$ (524) found M/z = 524.

^{1}H NMR (δ, ppm.): 0.77 s, 9H; 0.78 s, 9H; 1.40 s, 12H; 1.75 s, 2H; 1.77 s, 2H; 3.89-3.99 m, 4H; 4.19-4.29 m, 4H; 6.98 d (J = 9 Hz) 2H; 7.30 dd (J = 2 Hz, J = 9 Hz) 1H; 7.41 dd (J = 2 Hz, J = 9 Hz) 1H; 7.71 d (J = 2 Hz) 1H; 7.72 d (J = 2 Hz) 1H.

The second red fraction after evaporation and crystallization from methanol, afforded 600 mg (24%) of red azocrown ether **3** melting at 100-102°.

For $C_{32}H_{48}N_2O_3$ (508) found M/z = 508. ^{1}H NMR (δ, ppm.): 0.77 s, 18H; 1.44 s, 12H; 1.79 s, 4H; 3.92 t (J = 4 Hz) 4H; 4.25 t (J = 4 Hz) 4H; 7.03 d (J = 8.5 Hz) 2H; 7.37 dd (J = 2.5 Hz, J = 8.5 Hz) 2H; 7.80 d (J = 2.5 Hz) 2H.

1,2-Azo-3,4,12,13-bis(4-dodecylbenzo)-5,6,11-trioxacyclotridecane 4 and azoxy compound 9

These crown ethers were prepared analogously starting from 1,5-bis(4-dodecyl-2-nitrophenoxy)-3-oxapentane **13** (1.7 g; 2.5 mmol), stannous chloride dihydrate (2.5 g), sodium hydroxide (3.25 g), acetone (10 mL) and water (10 mL). The crude product was chromatographed on silica gel using methylene chloride as an eluent. The first yellowish fraction, after removal of the solvent and crystallization from methanol, afforded 270 mg of slightly yellowish azoxycrown ether **9** (17%) melting at 50-52°.

For $C_{40}H_{64}N_2O_4$ (636) found M/z = 636. ^{1}H NMR (δ, ppm.): 0.83-2.74 m, 46H; 2.61 t (J = 7 Hz) 4H; 3.87-3.99 m, 4H; 4.18-4.28 m, 4H; 6.98 d (J = 8.5 Hz) 2H; 7.07 dd (J = 2 Hz, J = 9 Hz) 1H; 7.21 dd (J = 2 Hz, J = 9 Hz) 1H; 7.52 d (J = 2 Hz) 1H; 7.55 d (J = 2 Hz) 1H.

The second red fraction was evaporated and the residue was crystallized from acetone-methanol to give 300 mg (19%) of azocrown ether **4**, m.p. 47-48.5°. For $C_{40}H_{64}N_2O_3$ (620) found M/z = 620. ^{1}H NMR (δ, ppm.): 0.83-2.75 m, 46H; 2.64 t (J = 7 Hz) 4H; 3.91 t (J = 4 Hz) 4H; 4.25 t (J = 4 Hz) 4H; 7.02 d (J = 8 Hz) 2H; 7.17 dd (J = 2 Hz, J = 8 Hz) 2H; 7.59 d (J = 2 Hz) 2H.

1,2-Azo-3,4,12,13-bis(4-dodecanoylbenzo)-5,8,11-trioxacyclotridecane 5 and azoxy compound 10

To a vigorously stirred mixture of nitroderivative **14** (1.80 g; 2.5 mmol), sodium hydroxide (3.46 g), acetone (13 mL) and water (13 mL) was added. The mixture was stirred and boiled for 2 h. The cooled reaction mixture was filtered and the solid was washed with 20 mL toluene. The combined organic layers were washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. The product was chromatographed three times on a silica gel column with methylene chloride as an eluent. The product (0.56 g) consists of a mixture of azoxycrown **10** (90%) and azocrown ether **5** (10%). Both compounds were separated by crystallization from ethyl acetate, followed by crystallization from methanol. First crystallized azoxy compound **10** (0.40 g; 24%), m.p. 73-76°. Azocrown ether **5** was obtained from the mother liquor using methanol for crystallization. Yield 20 mg (1.3%), m.p. 94-96°.

Compound **10**: For $C_{40}H_{60}N_2O_6$ (664) found M/z = 664.

^{1}H NMR (δ, ppm): 0.80-1.86 m, 42H; 2.97 t (J = 7 Hz) 4H; 3.90-4.04 m, 4H; 4.26-4.38 m, 4H; 7.09 d (J = 9 Hz)

1H; 7.18 d (J = 9 Hz) 1H; 7.98 dd (J = 2 Hz, J = 9 Hz) 1H; 8.09 dd (J = 2 Hz, J = 9 Hz) 1H; 8.23 d (J = 2 Hz) 1H; 8.32 d (J = 2 Hz) 1H.
Compound **5**: For $C_{40}H_{60}N_2O_5$ (648) found M/z = 648.
^{1}H NMR (δ, ppm): 0.80-1.85 m, 42H; 3.03 t (J = 7 Hz) 4H; 3.96 t (J = 4 Hz) 4H; 4.35 t (J = 4 Hz) 4H; 7.19 d (J = 8.5 Hz) 2H; 8.06 dd (J = 2 Hz, J = 8.5 Hz) 2H; 8.41 d (J = 2 Hz) 2H.

EMF MEASUREMENTS

Poly(vinyl chloride) membranes for ion-selective electrodes were prepared in a conventional[8,16] way. A typical composition (w/w) of a membrane was as follows: 6% of the respective ionophore, 31% of poly(vinyl chloride), 62.5% of *o*-nitrophenyl octyl ether and 0.5% potassium tetrakis(4-chlorophenyl) borate. All the components were dissolved in a freshly distilled tetrahydrofuran, the solution was poured into a glass ring located on a glass plate and left to evaporate. The discs were incorporated into Ag/AgCl electrode bodies, with 10^{-2} M NaCl as the internal electrolyte. The average thickness of the obtained membranes was 0.28 mm. The electrode was conditioned for 1 day in 10^{-2} M NaCl solution before measurements. The slopes and the detection limits of the electrodes were determined according to IUPAC[17] recomendations. The selectivity coefficients $\log K^{pot}_{Na,M}$ were determined by separate solution method (SSM) recommended by IUPAC at a 10^{-2} mol·dm^{-3} concentration level of the corresponding metal chlorides. The fixed (10^{-2} mol·dm^{-3} KCl) interference method (FIM)[10] was employed to determine the $\log K^{pot}_{Na,K}$.

RESULTS AND DISCUSSION

Syntheses

The unsubstituted azo- and azoxycrown ethers **1** and **6** were obtained by the one-pot reducing of 1,5-bis(4-nitrophenoxy)-3-oxapentane with simultaneous macrocyclization[4,6]. This facile and efficient method may be applied to synthesize substituted crown ethers, providing that the respective substituted diphenoxyoxapentanes are available. To obtain the *tert*-alkyl derivatives, the commercially available 4-*tert*-butylphenol **16** and 4-tetramethylbutylphenol **17** were used as starting materials. Compounds **16** and **17** easily release tertiary alkyl groups on treatment with nitric acid to form picric acid[18], hence they were nitrated under mild conditions using a slight excess of nitric acid diluted with acetic acid at low temperature. The yields for the nitrophenols **19** and **20** were 76 and 70%, respectively.

Dodecylderivative **18** with unbranched alkyl chain was obtained from dodecylaniline **15** (prepared according to[13]) by diazotization followed by decomposition of the diazonium salt to afford dodecylphenol **18**, which was nitrated at ambient temperature to give compound **21**.

The alkylnitrophenols (**19-21**) were alkylated with dichloroethyl ether to form diphenoxyoxapentane derivatives **11-13** under standardized conditions in boiling dimethylformamide in presence of an excess of anhydrous potassium carbonate. All the products were isolated from the reaction mixtures by column chromatography on silica gel and identified by NMR. The yield was in the range of 93-65%.

Bis(lauroylnitrophenoxy)oxapentane **14** was obtained from diphenoxyoxapentane **22** by acylation with lauric acid in the Eaton[15] reagent to form compound **23** which, in turn, was selectively nitrated under strictly selected conditions.

The final step, i.e., the reduction of bisnitrophenoxy derivatives **11-14** associated with macroring closure was performed similarly to that described for the parent unsubstituted 13-membered azo-[4] and azoxycrown[6] ethers yielding azocompounds **2-5** and azoxycrown ethers **7-10**.

The arrangement of phenyl residues around the -N=N- group in the crystalline 13-membered azocrown ether **1** is *cis*[4], and *trans*[6] around the -N(O)=N- group for the azoxycrown ether **6**; it was assumed that the obtained crystalline crown ether derivatives possess analogous geometry, cf.[19]. However, it was observed with TLC, that the crystalline azocrown ethers isomerize to some extent when dissolved. Light induced conversion of *cis*-azocrown **3** to *trans* isomer and fast *trans* --> *cis* interchange in a dark was observed in a monolayer[20].

Membrane electrodes

It has been found that the unsubstituted azocrown ether **1** extracts preferentially sodium over potassium[5a] and does not extract lithium. However in acetonitrile the same compound forms relatively stable complexes with lithium, whereas the stability constants with sodium and potassium iodides are so small that meaningful values of K_{ML} were not obtained[5b]. Nevertheless, the ion-selective electrodes based on compounds **1-4** are sodium sensitive and highly selective. The selectivities for compound **5** are lower, probably because of the strong electron withdrawing effect of the carbonyl group, which decrease the overall electron density inside the macrocycle. The Na,K selectivities are the best for *tert*-butylazocrown ether **2** and for dodecylazocrown ether **4**. The $\log K^{pot}_{Na,K}$ values (Figure 1) equal -2.03 and -2.00, respectively. These values allow the respective electrodes to be applied to determine sodium in blood and urea[21]. The detection limits ($\log L_{DNa}$) range from -5.00 to -5.25 while slopes from 57 to 60mV. The membrane electrode based on compound 2 conditioned for 1.5 months in 10^{-2} sodium chlo-

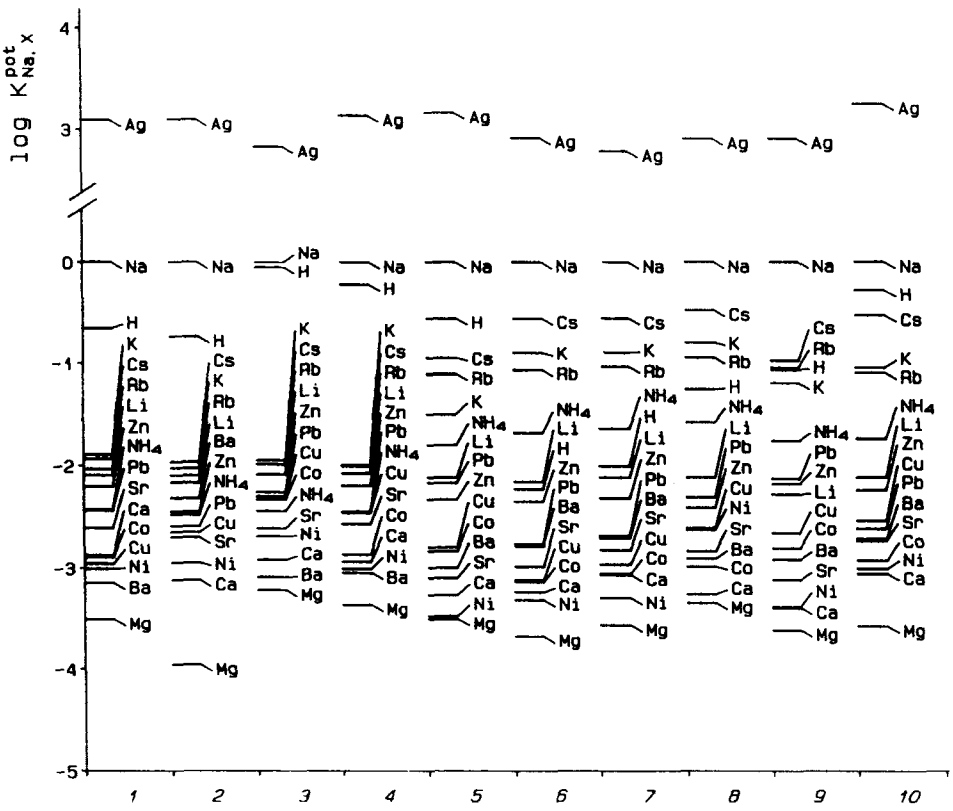

Figure 1 Diagram of $\log K^{pot}_{Na,M}$ values of ion-selective membrane electrodes based on compounds **1-10**.

ride solution maintained the above mentioned properties. The Na,Ca; Na,Mg and Na,H selectivities for crown ethers **2** and **4** are also high enough to fulfill all conditions required for sodium selective electrodes for clinical analysis[21].

The azoxycrown ethers **6-10** differ from the azocompounds **1-5** by arrangement of the aromatic residues around the -N=N- group and by the presence of an additional oxygen atom. Contrary to the azocrown ethers the azoxycompounds are less susceptible to form complexes with alkali metal cations, as shown by their separation on salt impregnated silica gel[6b]. These are the reasons which probably control the lower Na,K selectivity of the azoxycrown ether based membrane electrodes.

All the electrodes listed in Figure 1 have high sensitivity to silver as compared to other cations. However, as a rule, silver is not present in physiological fluids.

VOLTAMMETRIC PROPERTIES

Crown ethers with azo unit in the macrocycle

Cyclic voltammetry

Figure 2 presents the cyclic voltammograms of the azocrown ethers recorded in DMF solutions.

Similarly to azobenzene[22,23], the unsubstituted azocrown **1** is reduced in two steps with the formation of azo anion radical and azo dianion, respectively:

$$[-N=N-] + e \text{ ----> } [-N=N-]^{\cdot -}$$

$$[-N=N-]^{\cdot -} + e \text{ ----> } [-N=N-]^{2-}$$

The reduction peaks for the unsubstituted azocrown appear at potentials -1.49 and -2.02V, hence at more negative potentials than observed for simple azobenzene[4]. This has been explained in our previous paper[4] in terms of increased charge density on the azo group due to electron-donating properties of the oxygen atoms. Alkyl substituents enhance this effect as seen by a further shift of the reduction peaks towards negative potentials. The azocrown radicals are more susceptible than those of azobenzene for the residual proton donors present in the solution. This is exhibited by the decreased anodic (a_1) to cathodic (c_1) peak currents ratio as well as by the decrease of peak c_2 corresponding to further reduction of the radical. Decrease of scan rate, hence longer time scale of the experiment enhances the effects due to chemical reactions of the radical (Figures 2 and 3).

In case of the dodecyl substituted azocrown, peak c_2 disappears at lower scan rates (Figure 3-curve 4). This means that the anion radical formed in the first step of reduction is fully transformed into its protonated form.

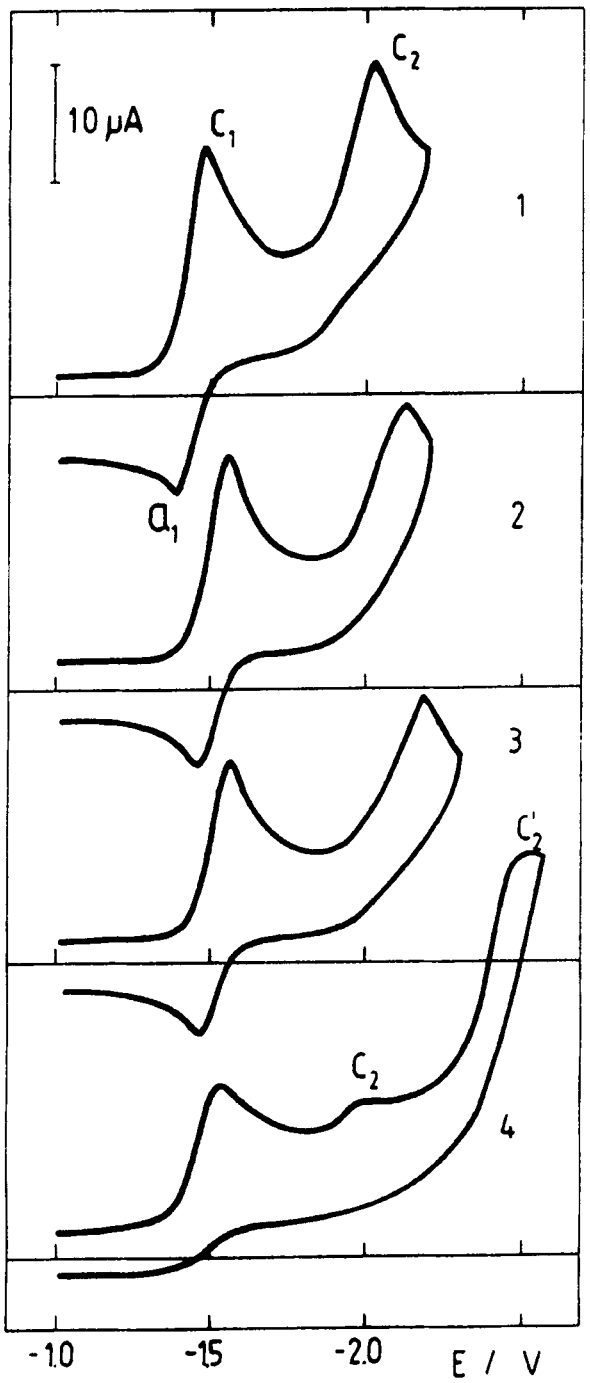

Figure 2 Cyclic voltammograms for the reduction of: 1) $6 \cdot 10^{-4}$ M azocrowns: 1) compound **1**, 2) compound **2**, 3) compound **3**, 4) compound **4** in 0.1 M TEAP/DMF. Scan rate: 10 V/s.

The protonated radical is reduced at more negative potentials with the formation of peak c_2'. The negative potential of peak c_2' (-2.37V at scan rate 100mV/s) together with large separation of peaks c_1 and c_2' proves large stabilization of the protonated radical in the hydrophobic environment formed by the long alkyl substituents in the macrocycle.

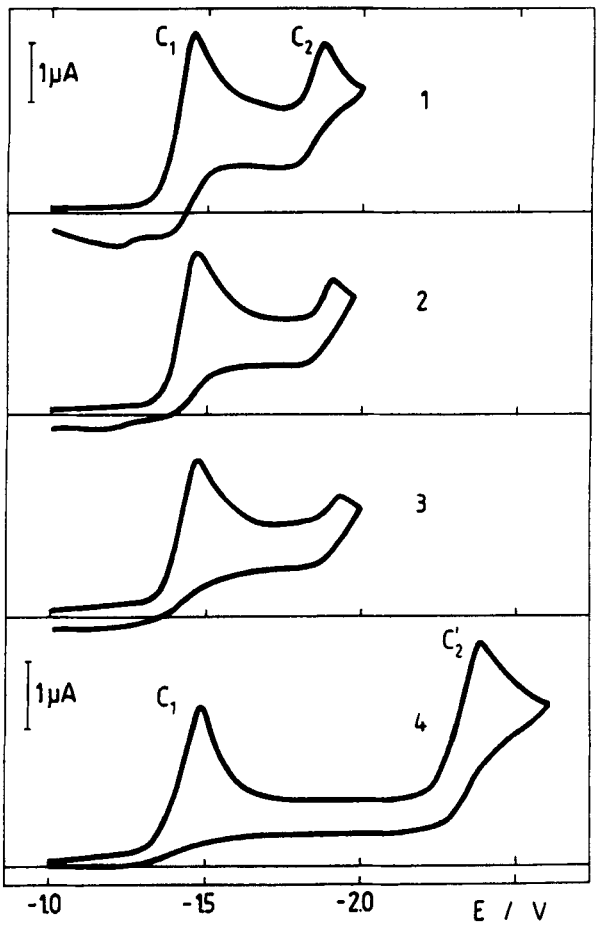

Figure 3 Cyclic voltammograms for the reduction of: 1) $6 \cdot 10^{-4}$ M azocrowns: 1) compound **1**, 2) compound **2**, 3) compound **3**, 4) compound **4** in 0.1 M TEAP/DMF. Scan rate: 100mV/s.

When proton donors are purposely added to the solution azobenzene radicals undergo protonation reactions as well[22]. However, the reduction of protonated azobenzene radical proceeds more easily than that of the parent compound, therefore increase of the c_1 peak is seen instead of the appearance of peak c_2'. For all the azocompounds including azobenzene[4,22] in DMF the c_2 and c_2' peaks do not have their anodic counterparts. This indicates that the second step of reduction corresponding to the formation of dianion is again followed by fast proton addition. The final products detected in the process are therefore the appropriate hydrazocompounds.

Normal pulse voltammetry

Normal pulse voltammetry can be applied conveniently on time scales of milliseconds[24,25] and thus in some cases presents the possibility of studying the primary electron transfer process uncomplicated by following chemical reactions[26]. The normal pulse voltammograms for the azocrowns studied are shown in Figure 4.

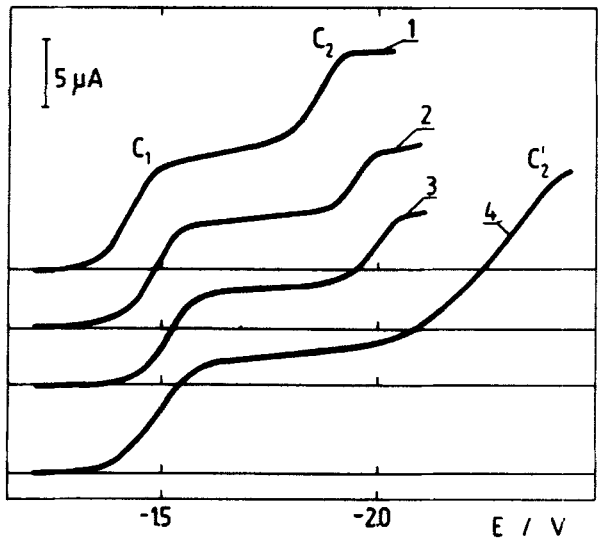

Figure 4 Normal pulse voltammograms for $6 \cdot 10^{-4}$ M azocrowns: 1) compound **1**, 2) compound **2**, 3) compound **3**, 4) compound **4** in TEAP/DMF solutions. tdrop = 2s, tp = 50ms.

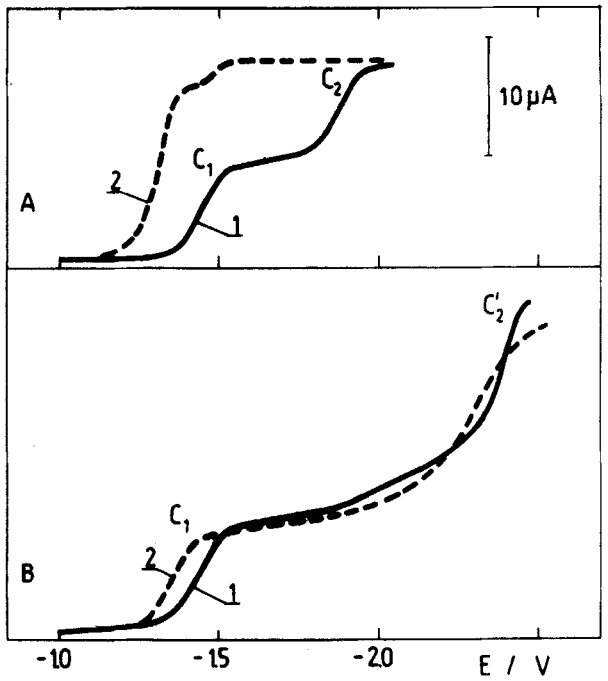

Figure 5 Normal pulse voltammograms for $6 \cdot 10^{-4}$ M azocrown **1** (A) and n-dodecylazocrown **4** (B) in TEAP/DMF solution (1) before and (2) after adding 1ml H_2O to the 20 mL sample, tp = 50ms, td = 3s.

In these experiments the initial potential at which each mercury drop is kept between pulse application is set at a value where no reduction of the compound takes place, i.e. -1.2V (Figure 4). Pulses of 50 millisecond time-scale are then applied to the drop. At sufficiently negative potentials two separate steps of reduction are seen in form of waves c_1 and c_2. The half-wave potentials of both waves are shifted to more negative potentials with larger alkyl substituents in the crown. For the unsubstituted azocrown the height of the c_2 wave is slightly smaller than that of c_1 indicating again involvement of fast protonation of the radical - primary product of reduction. As noted above this following reaction occurs most readily in case of the dodecyl derivative. This is clearly seen by the shift of wave c_1 towards positive potentials. Hence two phenomena determine the position of wave c_1: the electron donating properties of the substituent (shift to negative potentials with increasingly donating substituents) and the ease of protonation of the radical form (shift in the opposite direction with larger substituents). It seems that the latter predominates in case of the dodecyl azocrown since no radical reduction wave (c_2) is seen even at the millisecond time-scale. The protonated form undergoes reduction at potential -2.39V (Figure 4-wave c_2').

Addition of proton donors leads to the shift of all of the radical reduction waves towards positive potentials. For all of the compounds except the dodecyl derivative, increase of peak c_1 at the expense of the radical reduction wave (c_2) is also observed (Figure 5,A).

In contrast to other azocompounds, the dodecyl derivative is reduced in a stepwise process even in the presence of 5% water in DMF (Figure 5,B). It confirms the results of cyclic voltammetry revealing the unique stability of the protonated form of the radical anion in case of long chain substituted azocrowns.

Crown ethers with azoxy unit in the macrocycle

The normal pulse voltammograms for azoxybenzene and azoxycrown **6** are compared in Figure 6. In case of azoxybenzene three waves are seen in agreement with the literature data[27]. They correspond to reactions:

$$[-N{=}N-] + e \text{ ----> } [-N{=}N-]^{\cdot -}$$
$$\quad\;\; | \qquad\qquad\quad |$$
$$\quad\;\; O \qquad\qquad\quad O$$

$$-O^{2-}$$

$$[-N{=}N-]^{\cdot -} + 2e \text{ ----> } [-N{=}N-]^{\cdot -}$$
$$\quad\;\; |$$
$$\quad\;\; O$$

$$[-N{=}N-]^{\cdot -} + e \text{ ----> } [-N{=}N-]^{2-}$$

Incorporation of azoxy group into the crown ether impedes the azoxy radical formation so that the first two steps of reduction merge into one wave c_1 with the azo radical as the product of reduction. This product is further transformed into dianion in wave c_2.

Substitution of the azocrown with alkyl chains leads to a shift of the reduction waves towards negative potentials, hence in the same direction as for the substituted azocrowns. Introduction of alkyl chain results also in the change of the shape of voltammogram, i.e. the couple of peaks corresponding to azoxy radical formation becomes

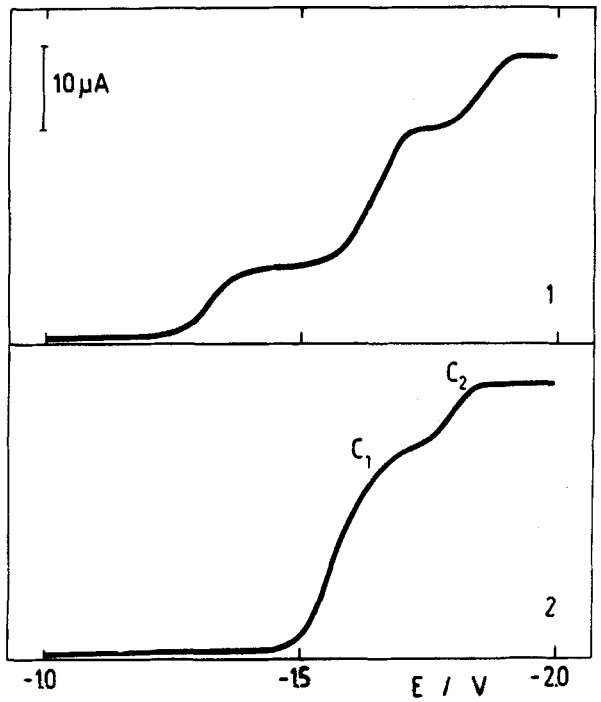

Figure 6 Normal pulse voltammograms for $6 \cdot 10^{-4}$ M azoxybenzene (1), and azoxycrown **6** (2) in TEAP/DMF solution, Ei = -1V, tp = 50ms, td = 3s.

well resolved. This is shown for tetramethylbutyl derivative in Figure 7. The process becomes similar to the reduction of azoxybenzene (Figure 6-curve 1), however the peaks corresponding to sequential electron transfers appear at more negative potentials. It suggests that modification of the crown ethers by inserting different substituents may serve as a way to separate individual electron transfers and to control the range of potentials at which the compound is electroactive.

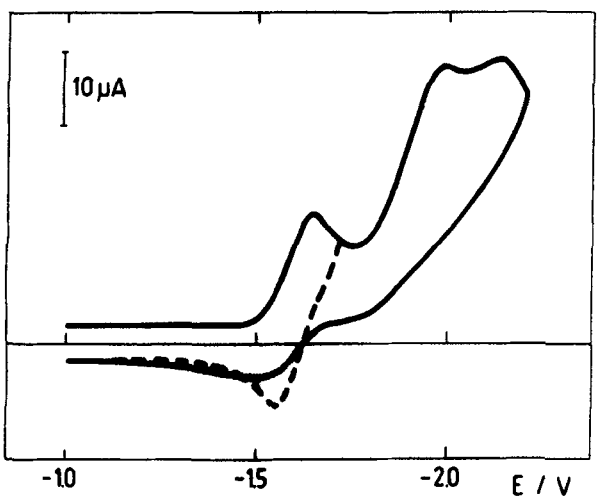

Figure 7 Cyclic voltammogram of $6 \cdot 10^{-4}$ M azoxycrown **8** in 0.1 M TEAP/DMF solution; (---) potential scan reversed at -1.7V; scan rate = 10 V/s.

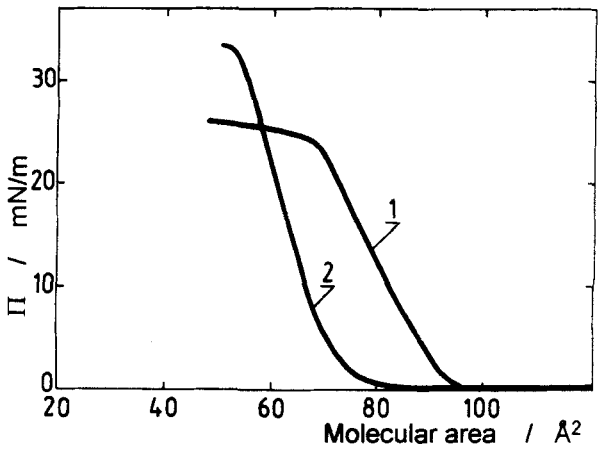

Figure 8 Isotherms of surface pressure (π) vs. mean molecular area for 1) compound **3** and 2) compound **4** on pure aqueous subphase.

Langmuir-Blodget monolayers. Behavior on the water-air interface

The experiments described above were performed in DMF solutions since all of the substituted azocrowns are water insoluble. The amphiphilic character of the compounds allowed the expectation that they might be useful reagents for the formation of well organized monolayers at the water-air interface. Indeed, the least soluble of the azocrowns, compound **3** and **4**, were found to spread at the water-air interface when diluted samples of the compounds in chloroform were syringed onto the water surface. The surface pressure - mean molecular area isotherms for these compounds are shown in Figure 8. They indicate that well-organized and stable monolayers of the amphiphilic derivatives of the azocrowns can be formed on the aqueous subphase. The area occupied by the molecule in the monolayer on water is 93 $Å^2$ and 72 $Å^2$ for tetramethylbutyl and n-dodecyl substituted crown compounds (compound **3** and **4**, respectively). The high stability of the azocrown substituted with the normal alkyl chain opens the possibility of using the Langmuir-Blodgett technique for electrode surface modification with an oriented monolayer of lipophilic azocrown compounds preorganized on the water surface. This method of azocrowns attachment to the electrode surfaces and applications of the modified electrodes in recognition studies are subject of further investigations in our laboratory.

CONCLUSIONS

The synthetic procedure presented is a convenient way to obtain substituted crown ethers bearing the azo or azoxy group in the macrocycle. Lipophilic azocrown ethers **2** and **4** when applied in ion selective membrane electrodes are highly selective towards sodium cations.

The crown ethers with azo unit in the macrocycle **1-4** are reduced in nonaqueous medium in two well resolved one-electron steps. Substituting the azocrown with alkyl side chains results in much easier protonation of the radical anion formed in the first step of the azo unit reduction process. The protons seem to incorporate into the macroring and the stability of the protonated radical is further increased by the lipophilic environment provided by the alkyl substituents. The protective function of these substituents towards the protonated radical becomes stronger with the increase of the number of carbons in the substituent. Normal long chain substituents were found to be most effective–the protonated radical is reduced at potentials more negative than -2 V and the stepwise reduction of the azocrown is observed even in presence of large amounts of proton donors, thus under conditions when azobenzene and simple azocrown **1** are reduced in one 2-electron process to the corresponding hydrazo compound.

Compared to azoxybenzene reduction of the azoxy crown compound **6** proceeds at potentials 200mV more negative and substitution of the azoxycrown with alkyl side chains makes the reduction even more difficult. The unique feature of the long-chain derivatives of the azoxycrown is that during their reduction azoxy radicals are formed and highly stabilized in the alkyl environment. They can be detected both by linear scan and normal pulse voltammetry.

The least soluble in water compounds: tetramethylbutyl- and dodecyl- crown ether derivatives bearing the azo unit **3** and **4** were found to form stable monolayer films on the water-air interface. The surface pressure vs. molecular area isotherms allowed to calculate the mean area per molecule in the monolayer of amphiphilic crown derivatives.

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