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Synthesis and Alkali Cation Extraction Ability of New Mono and Bis(benzocrown ether)s with Terminal Alkenyl Groups

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Abstract

A series of mono and bis(benzo-15-crown-5 and 18-crown-6)ethers comprising terminal alkenyl functions were synthesized and their alkali cation complexing abilities were evaluated by picrate extraction method. These ionophores provide the possibility of binding covalently to polymer matrices.

Introduction

During the past decades several mono and bis(crown ethers) have been synthesized and used as potential active sites in ion selective electrodes (ISEs). Some of them exhibited excellent selectivity toward different ions in plasticized PVC membrane electrodes [1]. The typical composition of these PVC membranes is 66 w% plasticizer, 33% PVC, 1 w% ionophore and a small amount of lipophilic additive. The analytical properties of the ISEs (life-time, response-stability, selectivity, etc.) are highly influenced by the possible leaching of the different membrane components (plasticizer, ionophore, lipophilic additive) [2]. The rate of leaching is dependent on several factors and can be more pronounced in case of less lipophilic membrane additives, biological samples (such as blood, urine, etc.) [3], or in flow analysis.

However, the problems related to leaching arise most frequently from the ionophore and the plasticizer loss [4] that should be avoided in cases such as *in vivo* measurements (possible toxicity), ultra-miniaturized sensors (extremely low ionophore content), solid state minidevices, etc.

Beside the introduction of highly lipophilic groups into the ionophore molecules, several other ways can be used for the ionophore immobilization. Among the different approaches, the covalent immobilization is one of the favorable methods [5, 6].

During the past years several researchers have tried to prepare chemical sensors based on plasticizer-free polymers, such as polyurethanes [7], silicone rubber [8], polyacrylates [9], etc. Of the different polymer types methacrylic/acrylic or methacrylic/methacrylic copolymers with different mechanical properties can be easily prepared by simply varying the monomer types and ratios or the method of polymerization. Thus, "self plasticized" acrylate or methacrylate polymers are accessible by applying long alkyl chains in the ester moieties which behave as "internal plasticizers" [10–12].

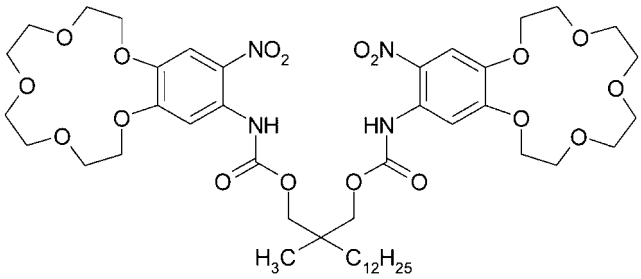

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Figure 1. Structure of the BME 44 (Fluka Potassium Ionophore III.)

Further on successful attempts have been made to prepare these self-plasticized polymers with covalently bound ionophore. Malinowska and coworkers synthesized methyl methacrylate/isodecyl acrylate copolymer based self-plasticized polymeric membranes where a calix[4]arene type Na^+ selective ionophore was covalently attached to the polymer backbone [13].

Potassium ISE's have been frequently used in the medical practice for the determination of K^+ concentration in biological fluids, especially in blood. For this purpose valinomycin based ISE's have been applied for a long time, however, efforts have been made to substitute it by synthetic ionophores (mainly crown or calixarene-type) to overcome some shortcomings of valinomycin (low lipophilicity, toxicity etc.). In this field one of the most successful molecules is biscrown **1** (BME 44, FLUKA 60397, Potassium Ionophore III.) synthesized in our laboratory [14] (Figure 1).

Ionophore **1** is highly selective over Na^+ (log $K^{\text{pot}}_{K^+/Na^+} = -3.2$) and insensitive to the stirring of the sample. These important characteristics can be attributed to

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the nitrourethane subunits and to the high lipophilicity. The former is beneficial in the preorganisation of an appropriate ion trap via internal H-bonds for a sandwich complex of potassium. In addition, the electron withdrawing nitro groups decrease the binding stability of sodium ions by the separate 15-crown-5 rings thus providing an enhanced selectivity towards K^+. The excellent electroanalytical performances of K^+ sensor made of **1** has been utilized for years in the clinical ion analyzer of HORIBA Ltd. (Japan).

Several attempts are recorded in the literature on the fabrication of plasticizer free K^+ ISE membranes [10–12] and on the covalent immobilization of crown ether ionophores on polymer matrices [5, 6, 15], but only poor K^+/Na^+ selectivities were achieved due to the low selectivities of ionophores used and entrapped or covalently bound in the polymer.

Since our BME 44 ionophore has excellent K^+/Na^+ selectivity, primarily we aimed at synthesizing analogous biscrown **10** by introducing allyl group in the connecting chain which is expected to copolymerize with acrylates (Scheme 1). In addition, biscrown **7** was also planned to prepare but failed to obtain sufficient quantity for extraction experiments beside the dominant monoester-crown **8**. Compound **7** was expected to exhibit poorer extractabilities comparing with **10** since here the beneficial nitrourethane moieties are omitted.

To study how the binding properties are influenced by coordination sphere and the number and flexibility of the alkenyl chain, several monobenzo(15-crown-5) **8**, **12**, **14**- and (18-crown-6) **17**, **19** with one or two alkenyl groups of different length in the urethane moiety were also prepared (Scheme 2).

Before polymerization experiments the alkali cation extractability of ligands were assessed by picrate extraction method.

Experimental

Melting points are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ at 250 MHz on a Bruker AC 250 instrument using TMS as internal standard. IR spectra were obtained with a Perkin Elmer 1600 FTIR spectrometer. Precoated silica gel plates (Merck 60 F_{254}) were used for analytical TLC. All chemicals were reagent grade and used without further purification.

4′-Acetyl(benzo-15-crown-5) (**3**) [16], 4′-carboxy(benzo-15-crown-5) (**4**) [17], 4′-isocyanato-5′-nitro(benzo-15-crown-5) (**9**) [18] and 4′-isocyanato-5′-nitro(benzo-18-crown-6) (**15**) [19] were prepared as described in the literature.

2-Allyloxymethyl-2-ethyl-propane-1,3-diol (**6**), 2,2-bis(allyloxymethyl)-butan-1-ol (**18**), 5-hexene-1-ol (**16**), 9-decen-1-ol (**13**) were obtained from ALDRICH, 4-penten-1-ol (**11**) was prepared as described in the literature [20].

Synthesis

Preparation of crown ethers **7** *and* **8**

$SOCl_2$ (3.57 g, 30 mmol) was added to the stirred solution of 6.24 g (20 mmol) of **4** in 50 mL CH_2Cl_2 containing DMF (0.1 mL) catalyst and the mixture was refluxed for 2 h. After cooling the solvent was removed under reduced pressure to afford crude acid chloride **5** which was used in the next step without isolation. Thus compound **5** and 1.74 g (10 mmol) of **6** in 50 mL CH_2Cl_2 was allowed to react in the presence of 3.03 g (30 mmol) of triethylamine at ambient temperature overnight. Then the reaction mixture was washed with water. The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure to give dominantly **8** and a small amount of **7**. The latter was separated by column chromatography (Brockmann II. neutral Al_2O_3, EtOAc eluent) followed by a subsequent TLC (silica-plate, acetone/EtOH: 9/1 eluent) to remove the traces of **8**.

Compound **7**: colorless oil, IR (neat): ν = 1716 cm^{-1} (CO).

^{1}H-NMR: 0.82–0.98 (t, 3H); 1.38–1.57 (q, 2H); 3.35-3.37 (d, 2H); 3.46 (s, 2H); 3.72–3.80 (s, 16H); 3.85–3.97 (m, 8H); 4.13–4.20 (m, 8H); 4.23–4.30 (s, 4H); 5.09–5.27 (m, 2H); 5.73–5.94 (m, 1H); 6.77–6.87 (d, 2H); 7.55 (d, 2H); 7.55–7.65 (m, 2H). Anal. calcd. for $C_{39}H_{54}O_{15}$ (762.86); C 61.41; H 7.14; found C 61.32; H 7.08.

Compound **8**: colorless oil, (3.34 g, 35.6%); IR (neat): ν = 3480 cm^{-1} (OH), 1712 cm^{-1} (CO).

^{1}H-NMR: 0.82–0.98 (t, 3H); 1.38–1.57 (q, 2H); 2.55 (s, 2H) 3.4–3.5 (d, 2H); 3.66–3.79 (s, 8H); 3.85–3.94 (m, 4H); 3.95–3.99 (d, 2H); 4.13–4.19 (m, 4H), 4.30 (s, 2H); 5.13–5.29 (m, 2H); 5.75–5.95 (m, 1H); 6.78–6.87 (d, 1H); 7.5 (s, 1H); 7.55-7.65 (d, 1H). Anal. calcd. for $C_{24}H_{36}O_9$ (468.55); C 61.52; H 7.74; found C 61.41; H 7.68

General procedure for the preparation of crown nitrourethanes **10**, **12**, **14**, **17**, **19**

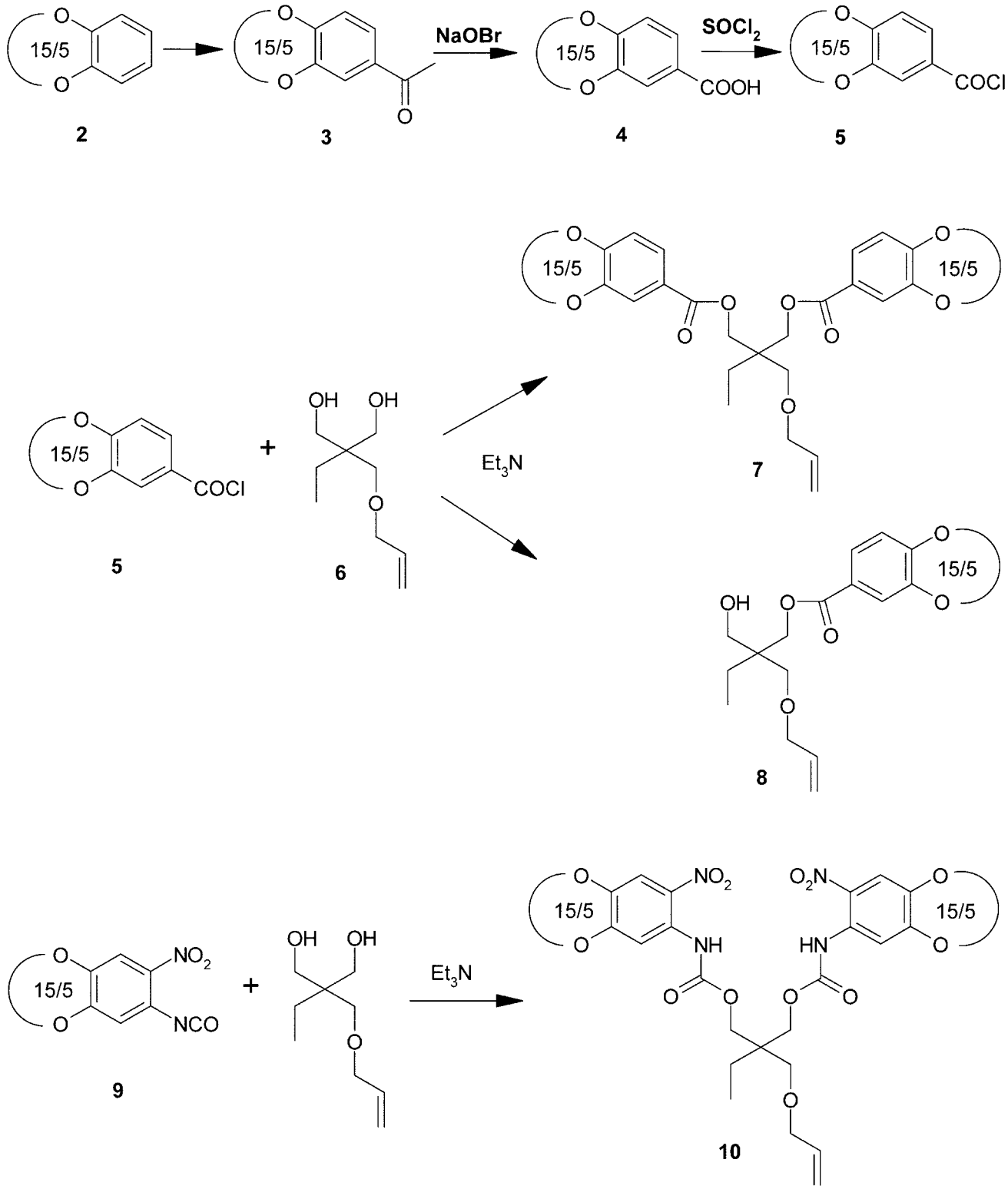
Nitroisocyanate **9** or **15** (10.5 mmol), diol **6** (0.87 g, 5 mmol) or alcohol **11**, **13**, **16**, **18** (10 mmol) in 50 mL CH_2Cl_2 were allowed to react in the presence of 0.5 mL triethylamine catalyst at ambient temperature overnight. The reaction mixture was subsequently washed with 3% aqueous HCl and water. The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure.

After solvent evaporation compound **10** was triturated with ether to give a solid. The crude product was recrystallized from EtOAc.

In case of compounds **12** and **14** after solvent evaporation the resulted dense yellow oil was dissolved in chloroform and purified by column chromatography (Brockmann II. neutral Al_2O_3, EtOAc/Hexane: 1/2 eluent) to afford **12**, **14** as thick oils that solidified after some days.

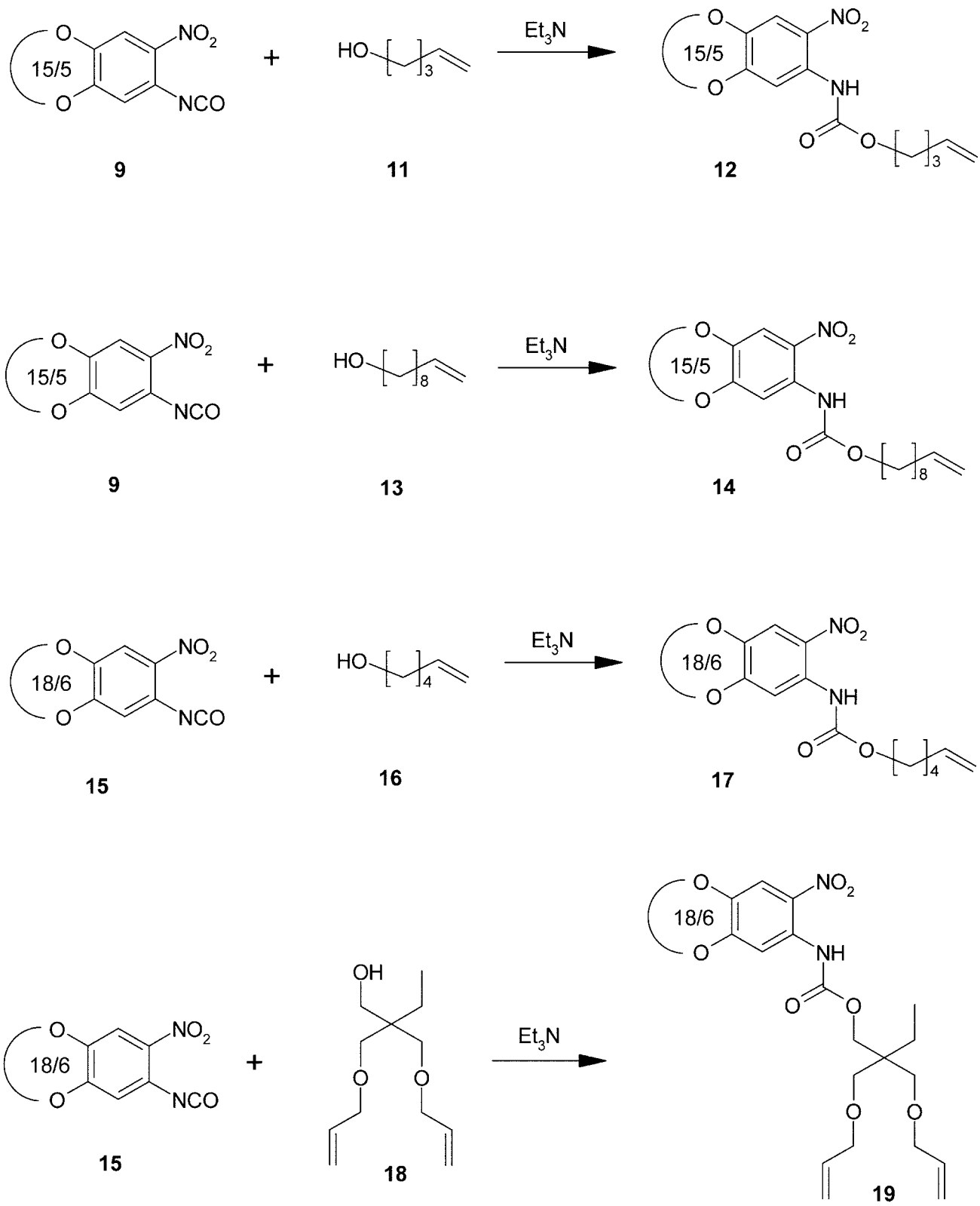
In case of compound **17** the resulted oil was purified by column chromatography in two steps (Brockmann II. neutral Al_2O_3, acetone/hexane: 1/2 eluent) to afford **17** as thick oil that solidified after some days.

After the solvent evaporation compound **19** was purified by column chromatography in two steps (Brockmann II. neutral Al_2O_3, acetone/hexane/CH_2Cl_2: 1/2/1 eluent; Kies-



2 3 4 5 5 6 7 8 9 10

Scheme 1. Synthesis of different mono- and bis(benzo-15-crown-5) ethers.



Scheme 2. Synthesis of mono(benzo-15-crown-5) and (benzo-18-crown-6) ethers bearing different alkenyl-groups.

elgel, acetone/hexane: 2/1 eluent). The clear product was removed from the column with acetone as thick oil.

Compound **10**: yellow crystals, (1.90 g, 43.0%); mp.: 86-87 °C; IR (KBr): ν = 3423 cm^{-1} (NH), 1733 (CO).

^{1}H-NMR: 0.95 (t, 3H); 1.57 (q, 2H); 3.42 (s, 2H); 3.75 (s, 16H); 3.91 (d, 8H); 3.98 (d, 2H); 4.14 (m, 4H); 4.22 (m, 4H); 4.26 (m, 4H); 5.16 (d, 1H); 5.26 (d, 1H); 5.87 (m, 1H); 7.66 (s, 2H); 8.14 (s, 2H); 10.25 (s, 2H). Anal. calcd. for $C_{39}H_{54}N_4O_{19}$ (882.88); C 53.06; H 6.17; N 6.35; found C 53.15; H 6.10; N 6.41.

Compound **12**: yellow crystals, (2.00 g, 22.6%), mp.: 97-99 °C; IR: (KBr): ν = 3422 cm^{-1} (NH), 1734 (CO).

^{1}H-NMR: 1.4–1.8 (m, 4H); 3.65–3.80 (m, 8H); 3.85–3.95 (m, 4H); 4.14–4.20 (m, 4H); 4.22–4.30 (m, 2H); 4.90–5.12 (m, 2H); 5.70–5.90 (m, 1H); 7.67 (s, 1H); 8.16 (s, 1H); 10.24 (s, 1H). Anal. calcd. for $C_{20}H_{28}N_2O_9$ (440.45); C 54.54; H 6.41; N 6.36; found C 54.61; H 6.46; N 6.32.

Compound **14**: yellow crystals, (3.4 g, 66.6%), mp.: 76–78 °C; IR: (KBr): ν = 3425 cm^{-1} (NH), 1732 (CO).

^{1}H-NMR: 1.2–2.1 (m, 14H); 3.63–3.78 (m, 8H); 3.85–3.96 (m, 4H); 4.12–4.21 (m, 4H); 4.21–4.28 (m, 2H); 4.90–5.05 (m, 2H); 5.70–5.90 (m, 1H); 7.67 (s, 1H); 8.17 (s, 1H); 10.23 (s, 1H). Anal. calcd. for $C_{25}H_{38}N_2O_9$ (510.59); C 58.81; H 7.50; N 5.49; found C 58.90; H 7.42; N 5.55.

Compound **17**: yellow crystals, (2.38 g, 47.7%), mp.: 78–80 °C; IR: (KBr): ν = 3422 cm^{-1} (NH), 1734 (CO).

^{1}H-NMR: 1.3–2.1 (m, 6H); 3.60–3.80 (m, 12H); 3.86–3.97 (m, 4H); 4.14–4.22 (m, 4H); 4.23–4.30 (m, 2H); 4.90–5.10 (m, 2H); 5.70–5.90 (m, 1H); 7.66 (s, 1H); 8.18 (s, 1H); 10.22 (s, 1H). Anal. calcd. for $C_{23}H_{34}N_2O_{10}$ (498.53); C 55.41; H 6.87; N 5.62; found C 55.49; H 6.93; N 5.57.

Compound **19**: yellow oil, (2.63 g, 42.9%); IR: (neat): ν = 3425 cm^{-1} (NH), 1736 (CO).

^{1}H-NMR: 0.75–0.95 (t, 3H); 1.4–1.6 (q, 2H); 3.35 (s, 4H); 3.55–3.80 (m, 12H); 3.85–3.98 (m, 8H); 4.11–4.20 (m, 4H); 4.22–4.30 (m, 2H); 5.00–5.30 (m, 4H); 5.75–5.95 (m, 2H); 7.66 (s, 1H); 8.19 (s, 1H); 10.21 (s, 1H). Anal. calcd. for $C_{29}H_{44}N_2O_{12}$ (612.68); C 56.85; H 7.24; N 4.57; found C 56.78; H 7.29; N 4.54

Results and discussion

Synthesis

The key intermediate nitroisocyanates **9** and **15** were prepared as described in the literature [18, 19]. The synthesis of the target compounds **10**, **12**, **14**, **17** and **19** was straightforward: the reaction of **9** and **15** with the respective diols or alcohols (2-allyloxymethyl-2-ethyl-propane-1,3-diol for **10**, 4-penten-1-ol for **12**, 9-decen-1-ol for **14**, 5-hexene-1-ol for **17**, and 2,2-bis-allyloxymethyl-butan-1-ol for **19**) was carried out at room temperature in the presence of triethylamine (TEA) catalyst affording the ligands after column chromatography or precipitation and recrystallization. Compound **8** was obtained from acid chloride **5** and diol **6** in the presence of TEA base as unexpected byproduct. This reaction was ineffective for the preparation of the required biscrown **7** resulting in a small quantity for identification.

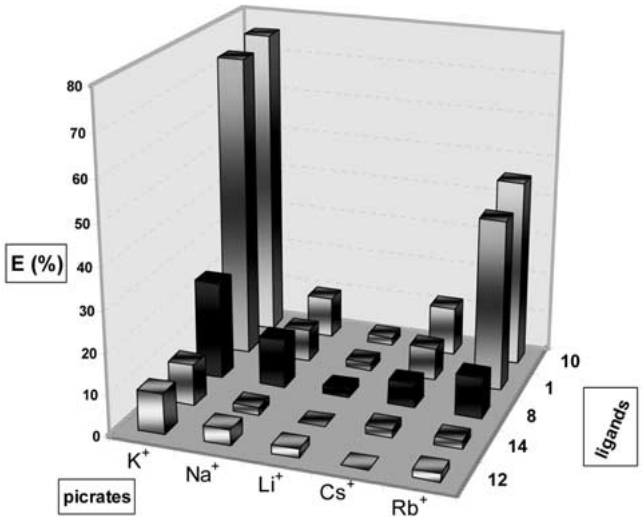


Figure 2. Extractabilities (E%) of alkali cations by 15-crown-5 ethers.

The structure of the products was proved by ^{1}H NMR spectroscopy and elemental analysis.

Characterization of compounds **8**, **10**, **12**, **14**, **17** *and* **19** *by solvent extraction*

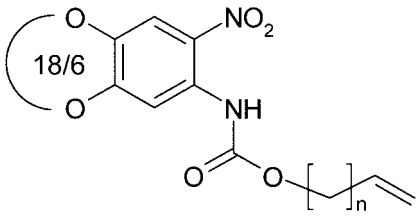
The metal ion complexing abilities of the synthesized ligands were assessed by solvent extraction experiments [21]. Dichloromethane solutions of ligands (1×10^{-2} M) were equilibrated for 8 h with aqueous Li^+, Na^+, K^+, Rb^+, Cs^+ picrate solutions (5×10^{-3} M). The ion extractabilities (E%) were calculated from the picrate concentration of the aqueous phase determined by UV spectrophotometry.

Extraction properties of benzo-15-crown-5 derivatives **8**, **10**, **12** *and* **14**

For comparison, the extraction data of compound **1** is also included in Figure 2.

The experimental results clearly show that biscrown nitrourethanes **1** and **10** are the best extractants of potassium ion exhibiting excellent to good selectivities over Li^+, Na^+, Cs^+ and medium selectivity over Rb^+. Since the overall binding site in **10** is identical with that of **1**, it is not surprising that almost the same extraction data were obtained. Thus, our main goal was achieved, compound **10** seems to be a good candidate for covalent immobilization.

Monocrown nitrourethanes **12** and **14** are proved to be equally poor extractants but the preference of K^+ towards the other cations is clearly seen. This results provide additional evidences for the nitro effect which decreases the overall binding capacity of the 15-crown-5 unit, but better towards Na^+ than K^+ which can form a more stable complex with 2:1 ligand/K^+ stoichiometry. Obviously, here the complex stabilities are inferior to those of biscrowns **1** and **10** due to the lack of preorganization of the ligands. This explanation seems to be supported by the higher extraction percentages and the lower selectivities of **8** due to the reduced electron withdrawing effect of the ester as compared to nitro group.



n=3 **20**

8 **21**

Figure 3. Structure of mono(benzo-18-crown-6) ethers with different alkenyl-chains.

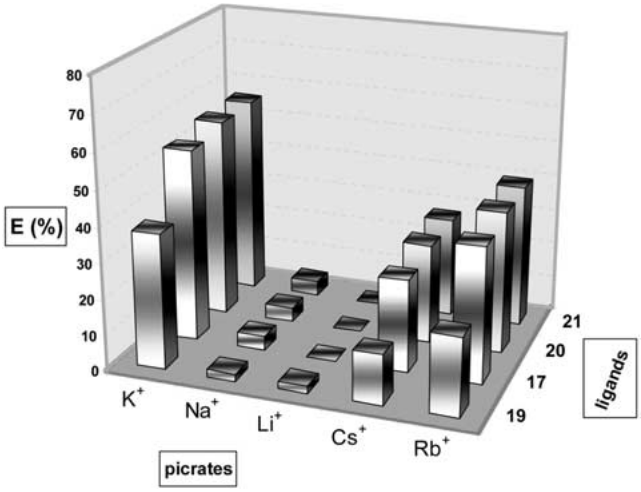


Figure 4. Extractabilities (E%) of alkali cations by benzo-18-crown-6 ethers.

Extraction properties of benzo-18-crown-6 derivatives **17** *and* **19**

For comparison, the extraction percentages of two monocrown ethers **20**, **21** (Figure 3) synthesized earlier [19] are also included in Figure 4.

The experimental results show that all ligands extract K^+, Rb^+ and Cs^+ ions with the medium preference of K^+ but each of them retards Li^+ and Na^+ ions. As was expected the chain length in compounds **17**, **20** and **21** did not cause noticeable differences in the extractabilities. On the contrary, ligand **19** is poorer extractant with similar features of selectivity presumably due to the lower lipophilicity and the steric hindrance of the side chain. The overall potassium selectivity in this series can be explained by the larger 18-crown-6 ring, while the enhanced Cs^+ extractabilities when compared to biscrown **1** and **10** can be attributed to the increased flexibility of receptors facilitating the formation of a 2:1 ligand/Cs^+ complex.

Conclusion

A series of benzo(15-crown-5 and 16-crown-6) ethers supplied with different alkenyl terminal groups capable of covalent immobilization on acrylate polymer matrices were synthesized. Based on the alkali cation extractabilities biscrown **10** was selected to copolymerize with acrylate monomers to develop potassium sensors of improved durability.

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