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Macroring Opening in Crown Ethers. Transformation of (4'-Formylbenzo)thiacrown Ethers into Podands by the Action of Methylamine

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Abstract—A procedure has been developed for the synthesis of thiaaza podands from (4'-formylbenzo)thiacrown ethers via nucleophilic regioselective opening of the macroring by the action of methylamine and methylamine hydrochloride on heating.

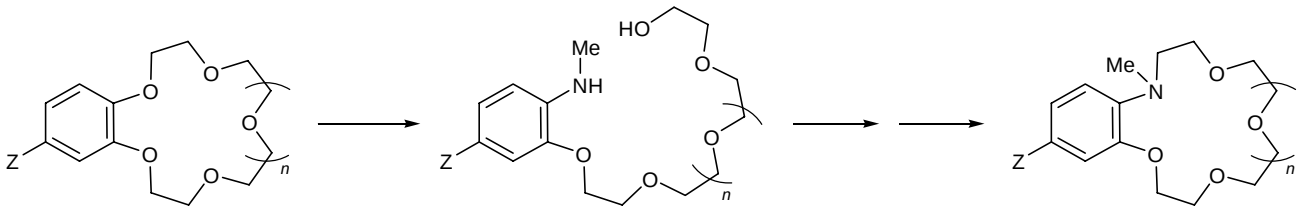
Crown ethers are capable of selectively binding metal ions, organic cations, and neutral molecules. This property underlies applications of crown compounds as selective ligands for metal cations [1–2] (including fluorescent and photochromic ligands [3–8]), for extraction and separation of metal cations [9, 10], in ion transport through membranes, in ion-selective electrodes [11], etc. Extensive search for new types of crown compounds capable of forming complexes in various media with high efficiency and selectivity is now in progress. Interest in crown compounds containing various combinations of heteroatoms (O, N, and S) in the macroring [12] also continuously increases, for such derivatives possess a strong complexing power with respect to transition and heavy metal ions. The main synthetic approach to macroheterocyclic compounds is based on 1+1 condensation of two acyclic fragments. Other methods for building up macroheterocycles have been explored to a considerably lesser extent.

We previously showed that formyl and nitro derivatives of benzocrown ethers undergo nucleophilic cleavage of the macroring by the action of amines to give open-chain analogs of crown ethers (podands) [13–16]. The latter were used to obtain benzoazacrown ethers containing a nitrogen atom attached to the benzene ring [17–21] (Scheme 1). This new synthetic approach to functionalized azacrown ether derivatives from nitrogen-containing podands formed by nucleophilic cleavage of the macroring in accessible crown ethers by the action of amines seems to be a promising alternative to the existing methods of preparation of 1-aza-2,3-benzocrown ethers [22].

In the present work we synthesized a series of thiaaza podands from (4-formylbenzo)thiacrown ethers with various combinations of oxygen and sulfur atoms in the macroring. Preliminary data on the macroring opening in some benzothiacrown ethers by the action of methylamine were reported previously [14]. Initial formyl-substituted benzothia- and benzodithiacrown ethers **Ia**–**Ie** were prepared by the procedures described in [14, 23, 24].

By heating formylbenzothiacrown ethers **Ia**–**Ie** in an ethanolic solution of $MeNH_2$ and $MeNH_3^+Cl^-$ and subsequent hydrolysis of the reaction mixture with dilute hydrobromic acid we obtained podands **IIa**–**IIe**

Scheme 1.



Z = NO_2, CHO; *n* = 0–2.

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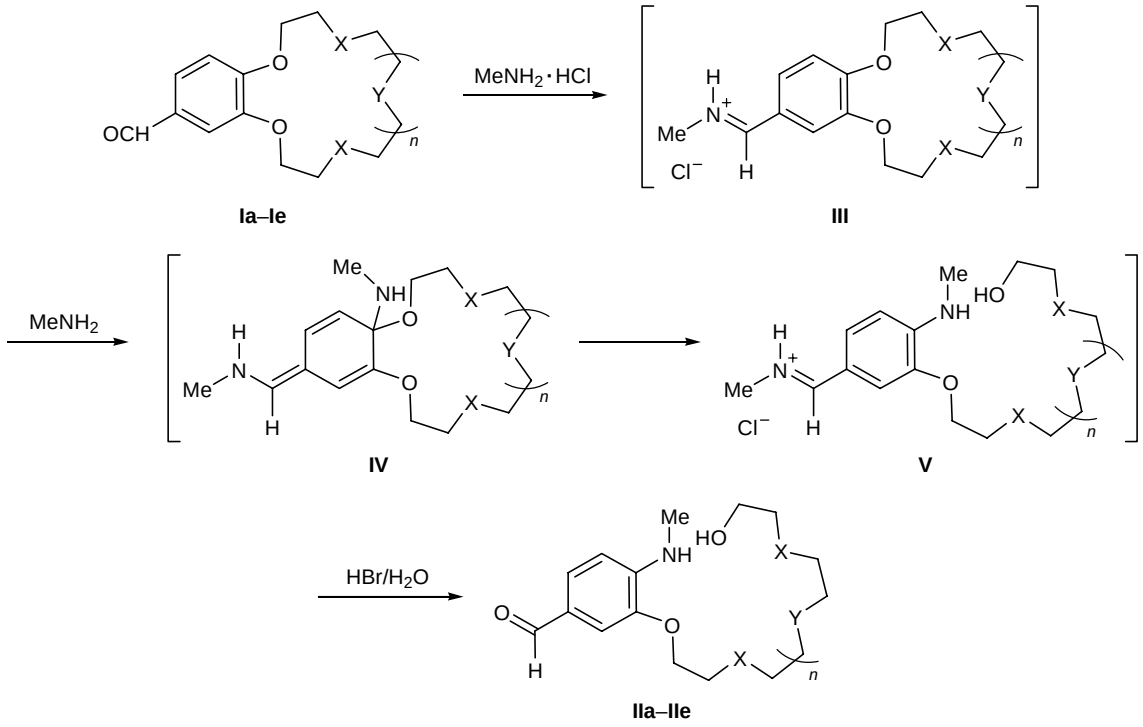
Scheme 2.



I, **II**, X = S, Y = O, *n* = 0 (**a**); X = S, Y = O, *n* = 1 (**b**); X = S, Y = O, *n* = 2 (**c**); X = S, Y = O, *n* = 3 (**d**); X = O, Y = S, *n* = 1 (**e**).

in 39–90% yield (Scheme 2). Presumably, the reaction of crown ether **I** with methylamine and methylamine hydrochloride initially gives iminium derivative **III** which is activated to nucleophilic substitution at the *para* position to a greater extent than the initial compound. In the next step, addition of methylamine to intermediate **III** leads to structure **IV** which undergoes cleavage of the macroring to afford podand **V**. Hydrolysis of the iminium fragment in the latter on treatment with dilute hydrobromic acid results in formation of target products **IIa**–**IIe**.

The yield of thiaaza podands **II** depends on the size of the macroring in initial benzothiacrown ether **I**. The maximal yields were observed for podands **IIb** and **IIe** obtained from benzothia-15-crown-5 derivatives **Ib** and **Ie**; here, no appreciable difference in the reactivity of compounds **Ib** and **Ie** was revealed. The yields of podands **IIa**, **IIc**, and **IId** from benzothiacrown ethers **Ia**, **Ic**, and **Id** with larger or smaller macroring were lower. The structure of the products was determined on the basis of their ^{1}H and ^{13}C NMR, IR, and mass spectra (including high-resolution mass spectra) and elemental analyses.

Thus we have developed a procedure for the synthesis of thiaaza podands via nucleophilic regioselective cleavage of the macroring in accessible benzothia- and benzodithiacrown derivatives by the action of methylamine. The resulting podands may be promising for the synthesis of formyl-substituted benzothiazacrown ethers in which the nitrogen atom is linked to the benzene ring.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were measured at 30°C on a Bruker DRX-500 spectrometer from solutions in acetone-d_6 or $CDCl_3$ using the solvent as internal reference. The proton and carbon signals were assigned using ^{1}H–^{1}H homonuclear and ^{1}H–^{13}C heteronuclear correlation techniques (COSY). The chemical shifts and coupling constants were measured with an accuracy of 0.01 ppm and 0.1 Hz, respectively. The IR spectra were recorded on a Bruker spectrometer. The mass spectra were obtained on Varian MAT-311A and Finnigan MAT-8430 instruments, and the high-resolution mass spectra were run on a Finnigan MAT-8430 spectrometer using perfluorokerosene and reference (energy of ionizing electrons 70 eV; direct sample admission into the ion source). Kieselgel 60 (0.063–0.100 mm, Merck) was used for column chromatography. The progress of reactions was monitored by TLC on DC-Alufolien Kieselgel 60_{254} plates (Merck).

Thiaaza podands IIa–IIe). A mixture of 1 mmol of benzothiacrown **Ia**–**Ie**, 10 mmol of methylamine hydrochloride, and 10 ml of a 35% solution of methylamine in anhydrous ethanol was heated for 120 h at 160°C on an oil bath (in a sealed ampule). The ampule was cooled and opened, the mixture was evaporated under reduced pressure to dryness, 35 ml of 1.5% hydrobromic acid was added to the residue, and the mixture was left to stand for 1 h, made alkaline (pH 12) by adding 5% aqueous potassium hydroxide, and extracted with ethyl acetate. The extract was evaporated under reduced pressure, and the product was isolated by column chromatography on silica gel using benzene–ethyl acetate (5:1) (**IIa**), benzene–ethanol (20:1) (**IIb**, **IIe**), or ethyl acetate (**IIc**, **IId**) as eluent.

3-(8-Hydroxy-3,6-dithiaoctyloxy)-4-methylaminobenzaldehyde (IIa). Yield 39%. mp 91–93°C, R_f 0.46 (benzene–ethyl acetate, 1:1). IR spectrum (KBr), ν, cm^{-1}: 3494, 3335 (NH, OH); 1655 (CH=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.66 br.s (1H, OH), 2.74 t (2H, CH_2S, J = 6.1 Hz), 2.79 m (4H, CH_2S), 2.93 br.s (3H, MeN), 2.95 t (2H, CH_2S, J = 6.7 Hz), 3.74 t (2H, CH_2O, J = 6.1 Hz), 4.22 t (2H, C**H**$_2$OAr, J = 6.7 Hz), 5.10 br.s (1H, NH), 6.56 d (1H, 5-H, J = 7.9 Hz), 7.24 d (1H, 2-H, J = 1.2 Hz), 7.38 d.d (1H, 6-H, J = 7.9, 1.2 Hz), 9.65 s (1H, CH=O). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 29.53 (MeN), 31.20 (CH_2S), 32.04 (CH_2S), 32.63 (CH_2S), 35.19 (CH_2S), 60.95 (CH_2OH), 67.76 (**C**H_2OAr), 107.22 (C^5), 107.81 (C^2), 125.33 (C^1), 129.48 (C^6), 145.11 and 145.34 (C^3, C^4), 190.26 (CH=O). Mass spectrum, m/z (I_{rel}, %): 315 (1) $[M]^+$, 165 (13), 137 (38), 109 (10), 105 (100), 103 (10), 94 (12), 87 (13), 61 (45), 59 (13), 58 (78). Found, %: C 53.22; H 6.70; N 4.21. $C_{14}H_{21}NO_3S_2$. Calculated, %: C 53.30; H 6.71; N 4.44.

3-(11-Hydroxy-6-oxa-3,9-dithiaundecyloxy)-4-methylaminobenzaldehyde (IIb). Yield 90%. Yellow oily substance, R_f 0.55 (benzene–ethyl acetate, 5:1). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 2.68 t (2H, CH_2S, J = 7.1 Hz), 2.71 t (2H, CH_2S, J = 6.8 Hz), 2.80 t (2H, CH_2S, J = 6.5 Hz), 2.87 br.s (1H, OH), 2.94 d (3H, MeN, J = 5.1 Hz), 3.02 t (2H, CH_2S, J = 6.5 Hz), 3.62 t (2H, CH_2O, J = 6.7 Hz), 3.66 br.t (4H, CH_2O, J = 6.5 Hz), 4.27 t (2H, C**H**$_2$OAr, J = 6.6 Hz), 5.70 br.s (1H, NH), 6.64 d (1H, 5-H, J = 8.1 Hz), 7.27 d (1H, 2-H, J = 1.4 Hz), 7.43 d.d (1H, 6-H, J = 8.1, 1.4 Hz), 9.68 s (1H, CH=O) [14]. ^{13}C NMR spectrum (acetone-d_6), δ_C, ppm: 29.55 (MeN), 31.79 (CH_2S), 31.99 (CH_2S), 32.24 (CH_2S), 35.53 (CH_2S), 62.25 (CH_2OH), 69.02 (**C**H_2OAr), 71.36 (CH_2O), 71.51 (CH_2O), 107.79 (C^5), 108.98 (C^2), 126.20 (C^1), 128.90 (C^6), 146.13 and 146.23 (C^3, C^4), 189.89 (CH=O).

3-(14-Hydroxy-6,9-dioxa-3,12-dithiatetradecyloxy)-4-methylaminobenzaldehyde (IIc). Yield 61%. R_f 0.55 (benzene–ethyl acetate, 5:1). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 2.68 t (2H, CH_2S, J = 6.6 Hz), 2.69 t (2H, CH_2S, J = 6.6 Hz), 2.79 t (2H, CH_2S, J = 6.5 Hz), 2.93 d (3H, MeN, J = 5.1 Hz), 3.01 t (2H, C**H**$_2$CH$_2$OAr, J = 6.5 Hz), 3.57 m (4H, CH_2O), 3.60 t (2H, CH_2O, J = 6.7 Hz), 3.66 t (2H, CH_2O, J = 6.4 Hz), 3.67 t (2H, CH_2O, J = 6.5 Hz), 3.83 br.s (1H, OH), 4.26 t (2H, C**H**$_2$OAr, J = 6.5 Hz), 5.70 br.q (1H, NH), 6.62 d (1H, 5-H, J = 8.2 Hz), 7.27 d (1H, 2-H, J = 1.4 Hz), 7.43 d.d (1H, 6-H, J = 8.2, 1.4 Hz), 9.68 s (1H, CH=O) [14]. ^{13}C NMR spectrum (acetone-d_6), δ, ppm: 29.76 (MeN), 31.92 (CH_2S), 32.13 (CH_2S), 32.38 (CH_2S), 35.70 (CH_2S), 62.37 (CH_2OH), 69.18 (**C**H_2OAr), 70.81 (CH_2O), 70.87 (CH_2O), 71.80 (CH_2O), 72.01 (CH_2O), 107.94 (C^5), 109.11 (C^2), 126.27 (C^1), 129.12 (C^6), 146.25 and 146.35 (C^3, C^4), 190.13 (CH=O).

3-(17-Hydroxy-6,9,12-trioxa-3,15-dithiaheptadecyloxy)-4-methylaminobenzaldehyde (IId). Yield 49%. Yellow oily substance, R_f 0.30 (ethyl acetate). IR spectrum (KBr), ν, cm^{-1}: 3391 (NH, OH); 1668 (CH=O). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 2.69 m (4H, CH_2S), 2.80 t (2H, CH_2S, J = 6.5 Hz), 2.93 d (3H, MeN, J = 5.1 Hz), 3.02 t (2H, CH_2S, J = 6.5 Hz), 3.56 m (4H, CH_2O), 3.58 s (4H, CH_2O), 3.60 t (2H, CH_2O, J = 6.8 Hz), 3.67 t (4H, CH_2O, J = 6.5 Hz), 4.27 t (2H, C**H**$_2$OAr, J = 6.5 Hz), 5.71 br.q (1H, NH), 6.63 d (1H, 5-H, J = 8.1 Hz), 7.27 br.s (1H, 2-H), 7.43 br.d (1H, 6-H, J = 8.1Hz), 9.68 s (1H, CH=O). ^{13}C NMR spectrum (acetone-d_6), δ_C, ppm: 29.94 (MeN), 32.12 (CH_2S), 32.34 (CH_2S), 32.59 (CH_2S), 35.89 (CH_2S), 62.60 (CH_2OH), 69.45 (**C**H_2OAr), 71.05 (CH_2O), 71.12 (CH_2O), 71.34 (2CH_2O), 72.06 (CH_2O), 72.26 (CH_2O), 108.15 (C^5), 109.37 (C^2), 126.53 (C^1), 129.26 (C^6), 146.50 and 146.59 (C^3, C^4), 190.29 (CH=O). Mass spectrum, m/z (I_{rel}, %): 447 (13) $[M]^+$, 297 (100), 269 (36), 193 (25), 150 (31), 105 (87), 94 (14), 89 (16), 87 (21), 61 (38), 60 (18). Found: $[M]^+$ 447.1753. $C_{20}H_{33}NO_6S_2$. Calculated: M 447.1749.

3-(11-Hydroxy-3,9-dioxa-6-thiaundecyloxy)-4-methylaminobenzaldehyde (IIe). Yield 76%. Yellow oily substance, R_f 0.41 (benzene–ethyl acetate, 5:1). IR spectrum (KBr), ν, cm^{-1}: 3373 (NH, OH); 1670 (CH=O). ^{1}H NMR spectrum (acetone-d_6), δ, ppm:

2.74 t (2H, CH_2S, J = 6.7 Hz), 2.77 t (2H, CH_2S, J = 6.6 Hz), 2.85 br.s (1H, OH), 2.93 d (3H, MeN, J = 5.1 Hz), 3.51 m (2H, CH_2O), 3.63 m (4H, CH_2O), 3.71 t (2H, CH_2O, J = 6.6Hz), 3.85 m (2H, C**H**$_2$$CH_2OAr$), 4.22 m (2H, C**H**$_2$OAr), 5.74 br.s (1H, NH), 6.64 d (1H, 5-H, J = 8.1 Hz), 7.28 d.d (1H, 2-H, J = 1.4 Hz), 7.43 d.d (1H, 6-H, J = 8.1, 1.4 Hz), 9.68 s (1H, CH=O). ^{13}C NMR spectrum (acetone-d_6), δ_C, ppm: 29.77 (MeN), 32.52 (CH_2S), 62.02 (CH_2OH), 69.15 (**C**H_2OAr), 69.85 (**C**H_2CH_2OAr), 71.90 (2**C**H_2CH_2S), 73.23 (**C**H_2CH_2OH), 108.02 (C^5), 109.60 (C^2), 126.46 (C^1), 129.16 (C^6), 146.64 (C^3), 146.68 (C^4), 190.09 (CH=O). Mass spectrum, m/z (I_{rel}, %): 343 (100) $[M]^+$, 195 (64), 194 (44), 193 (73), 151 (63), 150 (71), 149 (59), 148 (41), 87 (49), 61 (45). Found: $[M]^+$ 343.1455. $C_{16}H_{25}NO_5S$. Calculated: M 343.1453.

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