

Nitro Derivatives of Benzoazacrown Ethers: Synthesis, Structure, and Complexation with Metal and Ammonium Cations and Fluoride Anion

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A method was developed for the synthesis of nitrobenzoazacrown ethers by N-demethylation of N-methyl-nitrobenzoazacrown ethers on treatment with ammonium iodide, resulting in the formation of benzoazacrown ethers in 95–100 % yields. The spatial structure of nitrobenzoazacrown ethers and their complexation behaviour towards alkali and alkaline-earth metal cations, ammonium ions, and fluoride anions were investigated using X-ray diffraction and ¹H NMR spectroscopy. It was shown that the stability of host–guest type complexes of nitrobenzoazacrown ethers with metal and ammonium cations in MeCN-d₃ is lower than the stability of complexes formed by N-alkyl-substituted analogues with the same macrocycle size. It was shown that fluoride anions in DMSO-d₆ or MeCN-d₃ can bind to nitrobenzoazacrown ethers via hydrogen bonding with the NH group of the macrocycle.

Keywords: Benzoazacrown ethers, synthesis, structure, complex formation, stability constants.

Нитропроизводные бензоазакраун-эфиров: синтез, строение и комплексообразование с катионами металлов, аммония и анионом фтора

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Разработан метод синтеза нитробензоазакраун-эфиров реакцией N-деметилирования нитропроизводных N-метилбензоазакраун-эфиров под действием иодида аммония, позволяющий получать бензоазакраун-эфиры с выходами 95–100 %. Установлена пространственная структура и найдены комплексообразующие характеристики нитробензоазакраун-эфиров по отношению к катионам щелочных и щелочноземельных металлов, ионам аммония, а также аниону фтора с использованием методов РСА и спектроскопии ЯМР ¹H. Показа-

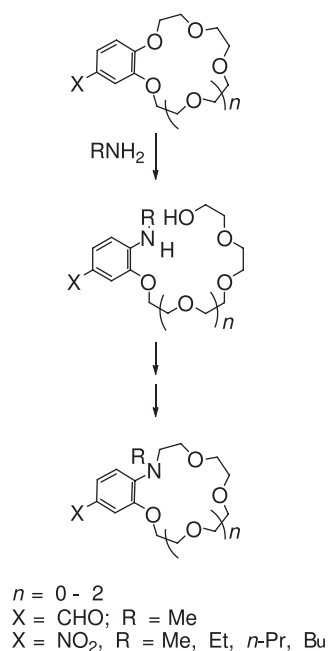
но, что устойчивость комплексов типа «гость–хозяин» нитробензоазакраун-эфиров с катионами металлов и аммония в MeCN-d_3 ниже устойчивости соответствующих комплексов *N*-алкилазамещенных аналогов с тем же размером макроцикла. Установлено, что нитробензоазакраун-эфиры способны связывать анион фтора в DMSO-d_6 и MeCN-d_3 за счет образования водородной связи с NH-фрагментом макроцикла.

Ключевые слова: Бензоазакраун-эфиры, синтез, структура, комплексообразование, константы устойчивости.

Introduction

Azacrown compounds containing nitrogen atom conjugated with chromophore are of considerable interest for the preparation of photoactive crown derivatives possessing chromogenic, fluorescent, and photochromic properties.^[1] Currently, phenylazacrown ether derivatives are used most often for these purposes; however, they suffer from a considerable drawback: their complexation constants with metal ions are modest.^[2] Benzannelated azacrown ether derivatives can have weighty advantages in this respect. For the synthesis of photoactive compounds, formyl and nitro derivatives of benzoazacrown ethers are of most interest. However, most of functional derivatives of 1-aza-2,3-benzocrown ethers proved to be inaccessible by using methods reported in the literature.^[3,4]

Previously, we developed a new strategy for the synthesis of formyl and nitro benzoazacrown ether derivatives based on the stepwise transformation of the macrocycle of accessible benzocrown ethers used as synthons (Scheme 1) and studied the spatial structure of the obtained compounds as well as their complex forming properties towards alkali and alkaline-earth metal and ammonium cations by NMR and X-ray diffraction.^[4] It was found that the obtained *N*-alkyl benzoazacrown ether derivatives, in which the nitrogen atom is linked to the benzene ring, are promising complexing agents for the above cations.

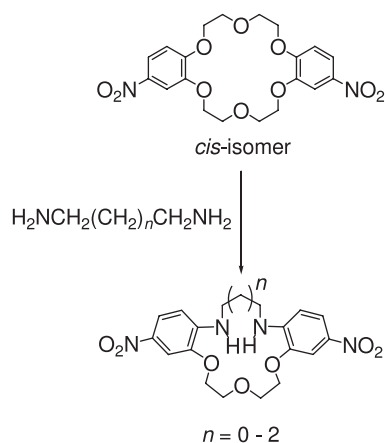


Scheme 1. Synthesis of benzoazacrown ethers by transformation of benzocrown ether macrocycle.

They exhibit a much higher binding capacity towards metal cations than *N*-phenylazacrown ethers with the same macrocycle size. In the complex forming properties, they resemble the corresponding benzocrown ethers and, in some cases, they are even superior.^[4f-h] Using formyl derivatives of benzoazacrown ethers, we synthesized a number of azacrown styryl dyes,^[5] some of which were highly efficient as optical molecular sensors for alkali and alkaline-earth metal cations.^[5a]

We also prepared dinitrodibenzodiazacrown ethers by one-step transformation of the *cis*-dinitrodibenzo-18-crown-6 ether macrocycle by treatment with aliphatic diamines (Scheme 2).^[4b,6] The structure and complexation behaviour of dibenzodiazacrown ether ($n=1$) were studied by NMR spectroscopy.

It was shown that dinitrodibenzodiaza-16-crown-5 ether does not form complexes with alkali or alkaline-earth metal cations, but can bind fluoride ions, apparently *via* hydrogen bonding with the NH groups of the macrocycle. Therefore, dibenzodiazacrown ethers of this type can be regarded as promising complexing agents for fluoride anions.

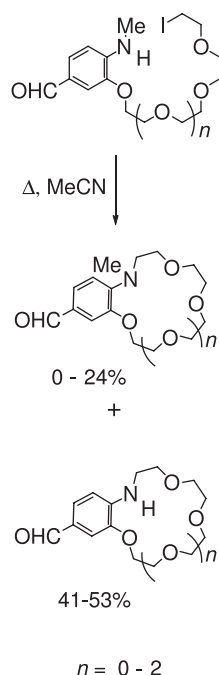


Scheme 2. Synthesis of dinitrodibenzodiazacrown ethers by transformation of the macrocycle of *cis*-dinitrodibenzo-18-crown-6 ether by treatment with aliphatic diamines.

Nitrobenzoazacrown ethers **1** containing NH group in the macrocycle (Chart 1) have been unknown until now. They could be of interest, on the one hand, as synthons for the synthesis of functional derivatives at the macrocycle nitrogen atom and, on the other hand, as complexing agents for metal and ammonium cations and fluoride anions.

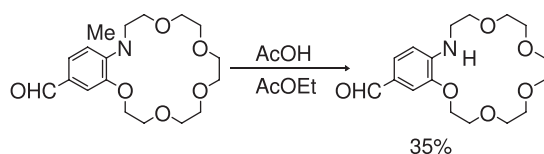
Previously we synthesized formyl derivatives of benzoazacrown ethers with N–H group in the macrocycle using two methods.^[4c] The first method comprised cyclization

of iodo-podands on heating in MeCN (Scheme 3). A drawback of this method is too long reaction time and the formation of a mixture of *N*-methylbenzoazacrown ethers and their *N*-demethylated derivatives, although the latter still considerably predominate.



Scheme 3. Synthesis of formyl benzoazacrown ether derivatives by cyclization of iodo-podands on heating in MeCN.

The second method was based on *N*-demethylation of formyl-*N*-methylbenzoaza-18-crown-6 ether, which takes place on refluxing of the *N*-methyl derivative with dilute acetic acid. The *N*-demethylated product is formed in a moderate yield (Scheme 4).



Scheme 4. Synthesis of the formylbenzoaza-18-crown-6-ether derivative by refluxing formyl-*N*-methylbenzoaza-18-crown-6 ether with AcOH.

We suggested that the use of mild acidic agent such as NH_4I in MeCN to conduct *N*-demethylation of *N*-methyl-nitrobenzoazacrown ethers could probably promote the formation of nitrobenzoazacrown ethers in high yields.

In this communication, we describe the synthesis of nitrobenzoazacrown ethers **1** from *N*-methyl-nitrobenzoazacrown ethers **2**, compare the structural features and complexation behaviours of the obtained benzoazacrown ethers **1** and starting *N*-methylbenzoazacrown ethers **2**, *N*-phenylazacrown ethers **3** with the same macrocycle size, and model compounds containing N–H group and devoid of a crown ether moiety, namely, *N*-ethyl-4-nitroaniline **4**

and *N*-ethyl-2-methoxy-4-nitroaniline **5** (Chart 1) using ^1H NMR spectroscopy and X-ray diffraction analysis.

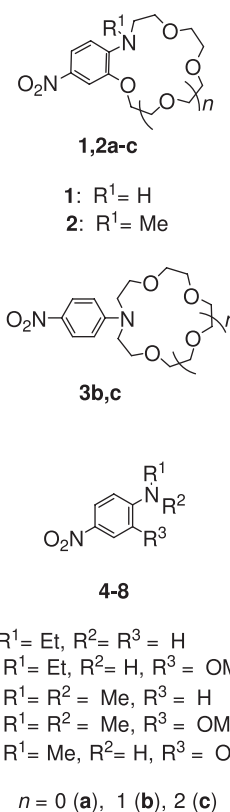


Chart 1. Structure of compounds **1–8**.

The stability constants of complexes formed by azacrown ethers **1a–c** with alkali and alkaline-earth metal and ammonium cations and fluoride anions were determined by ^1H NMR titration.

Experimental

^1H NMR spectra were recorded on a Bruker DRX500 spectrometer (operating at 500.13 MHz) in $\text{DMSO}-d_6$ and $\text{MeCN}-d_3$ at 25 °C with the solvent functioning as an internal standard (δ_{H} 2.50 and 1.96 ppm, respectively). ^{13}C NMR spectra were recorded on a Bruker DRX500 spectrometer (operating at 125.76 MHz) in $\text{DMSO}-d_6$, CDCl_3 , or $\text{MeCN}-d_3$ at 25 °C with the solvent functioning as an internal standard (δ_{C} 39.43, 77.00, and 118.10 ppm, respectively). The chemical shifts were measured to an accuracy of 0.01 ppm and spin-spin coupling constants were determined to an accuracy of 0.1 Hz. The proton and carbon signals were assigned using 2D ^1H – ^1H homonuclear COSY and NOESY spectra and ^1H – ^{13}C heteronuclear COSY spectra (HSQC and HMBC).

IR spectra were measured on a Bruker IFS-113V spectrophotometer in KBr pellets. Mass spectra were run on Finnigan MAT-212 and Finnigan MAT 95 XL instruments (with perfluorokerosene as the standard) with ionization energy of 60 or 70 eV and direct sample injection.

Elemental analysis was carried out in the Laboratory of Microanalysis, A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences. Melting points were measured on a MEL-Temp II apparatus in a capillary.

Column chromatography was carried out using SiO_2 (Kieselgel 60, 0.063–0.100 mm, Merck) and Al_2O_3 (Aluminium oxide

150 basic, type T, 0.063–0.200 mm, Merck). The reactions were monitored by TLC on DC-Alufolien Kieselgel 60 F₂₅₄ (Merck) and DC-Alufolien Aluminium oxide 60 F₂₅₄ neutral (Merck) plates.

The salts NH₄ClO₄, NaClO₄, KClO₄, Ca(ClO₄)₂, and Ba(ClO₄)₂ (Aldrich) were dried *in vacuo* (at 60 °C for NH₄ClO₄ and at 200 °C for other salts). EtNH₃ClO₄ was prepared by neutralization of 70 % aqueous solution of ethylamine with a 70 % aqueous solution of HClO₄ (Aldrich) and dried *in vacuo* at 60 °C. Tetrabutylammonium fluoride (Bu₄NF·3H₂O, Aldrich) was stored in a desiccator over a drying agent.

2-Methoxy-*N,N*-dimethyl-4-nitroaniline (**7**) was synthesized by a reported procedure.^[7]

N-Ethyl-4-nitroaniline (**4**), *N,N*-dimethyl-4-nitroaniline (**6**), and 2-methoxy-4-nitroaniline (**10**) were purchased from abcr GmbH Germany.

Synthesis

Synthesis of benzoazacrown ethers 1a–c (general procedure). *Method A.* A mixture of *N*-methylbenzoazacrown ether **2a–c** (0.3 mmol), NH₄I (0.44 g, 3.0 mmol), and dry MeCN (15 mL) was stirred at reflux for 100 h. After cooling, the reaction mixture was evaporated *in vacuo*, diluted with water (30 mL), extracted with C₆H₆ (3×25 mL), and the combined extracts were evaporated *in vacuo*. The residue was purified by column chromatography on SiO₂. The elution was carried out, first, with an AcOH–EtOAc mixture (1:1) for **2a,b** or a C₆H₆–AcOH–EtOAc mixture (1:1:2) for **2c** to wash out compounds **1a–c**, and then with EtOAc to wash out unreacted starting **2a–c**. After evaporation of fractions containing compounds **1a–c**, a 5 % aqueous solution of Na₂CO₃ (to pH 10) was added to the residues, and the products were extracted with C₆H₆ (3×30 mL). The extracts were washed with water and evaporated. Compounds **1a–c** were formed as yellow powders. The yields of compounds **1a–c** and data on recovered compounds **2a–c** are summarized in Table 1. *Method B.* A mixture of *N*-methylbenzoazacrown ether **2a–c** (0.15 mmol), NH₄I (0.22 g, 1.5 mmol), and dry MeCN (7 mL) was heated for 55 h (**2a**), 100 h (**2b,c**), or 255 h (**2c**) (see Table 1) in a sealed tube at 130 °C (oil bath). The reaction mixtures were worked-up and the residues were purified as described above in *method A* in the case of **2a,b**; EtOAc was used as the eluent in the case of **2c**. Compounds **1a–c** were formed as yellow powders. The yields of compounds **1a–c** and data on recovered compounds **2a–c** are summarized in Table 1.

13-Nitro-2,3,5,6,9,10-hexahydro-8H-1,4,7,10-benzotrioxazacyclododecine (4-nitrobenzoaza-12-crown-4 ether) (1a) was obtained from **2a** as described above. M.p. 150–152 °C. Found: C 52.54, H 5.95, N 10.01 %. C₁₂H₁₆N₂O₅·0.3H₂O requires C 52.66, H 6.11, N 10.24 %. *m/z* (%) 268 (100) [M⁺], 211 (33), 193 (64), 180 (16), 167 (71), 165 (50), 150 (20), 134 (28), 119 (17), 78 (16). IR (KBr) ν_{\max} cm^{−1}: 3354 (NH), 1490 and 1323 (NO₂). ¹H NMR (DMSO-*d*₆) δ_{H} ppm: 3.38 (2H, m, NCH₂CH₂O), 3.52 (2H, m, CH₂O), 3.56 (2H, m, CH₂CH₂OAr), 3.59 (2H, m, CH₂O), 3.67 (2H, t, *J*=4.9 Hz, NCH₂CH₂O), 4.20 (2H, m, CH₂OAr), 6.65 (1H, t, *J*=4.8 Hz, NH), 6.78 (1H, d, *J*=9.2 Hz, 11-H), 7.86 (1H, d, *J*=2.4 Hz, 14-H), 7.91 (1H, dd, *J*=9.2, 2.4 Hz, 12-H). ¹³C NMR (MeCN-*d*₃) δ_{C} ppm: 43.20 (NCH₂CH₂O), 68.66 (NCH₂CH₂O), 69.37 (CH₂CH₂OAr), 69.94 (CH₂O), 70.10 (CH₂O), 74.21 (CH₂OAr), 109.38 (11-C), 116.86 (14-C), 123.09 (12-C), 137.13 (13-C), 145.28 (14a-C), 149.54 (10a-C).

16-Nitro-2,3,5,6,8,9,12,13-octahydro-11H-1,4,7,10,13-benzotetraoxazacyclopentadecine (nitrobenzoaza-15-crown-5 ether) (1b) was obtained from **2b** as described above. M.p. 93–95 °C. Found: C 53.83, H 6.64, N 8.79 %. C₁₄H₂₀N₂O₆ requires C 53.84, H 6.45, N 8.97 %. *m/z* (%) 312 (100) [M⁺], 255 (18), 211 (13), 193 (34), 167 (45), 166 (9), 165 (21), 149 (10), 147 (12), 73 (14). IR (KBr) ν_{\max} cm^{−1}: 3391 (NH), 1498 and 1322 (NO₂). ¹H NMR (DMSO-*d*₆) δ_{H} ppm: 3.33 (2H, m, NCH₂CH₂O), 3.55 (4H, m, 2CH₂O), 3.60 (4H, m, 2CH₂O), 3.69 (2H, t, *J*=4.8 Hz, NCH₂CH₂O), 3.76 (2H, m, CH₂CH₂OAr), 4.19 (2H, m, CH₂OAr), 5.92 (1H, t, *J*=4.8 Hz,

NH), 6.66 (1H, d, *J*=8.9 Hz, 14-H), 7.61 (1H, d, *J*=2.3 Hz, 17-H), 7.86 (1H, dd, *J*=8.9, 2.3 Hz, 15-H). ¹³C NMR (CDCl₃) δ_{C} ppm: 42.29 (NCH₂CH₂O), 68.05 (NCH₂CH₂O), 68.18 (CH₂OAr), 68.74 (CH₂CH₂OAr), 69.75 (CH₂O), 69.85 (CH₂O), 69.97 (CH₂O), 70.16 (CH₂O), 106.50 (17-C), 106.68 (14-C), 120.37 (15-C), 136.75 (16-C), 144.47 (17a-C), 145.23 (13a-C).

19-Nitro-2,3,5,6,8,9,11,12,15,16-decahydro-14H-1,4,7,10,13,16-benzopentaoxazacyclooctadecine (nitrobenzoaza-18-crown-6 ether) (1c) was obtained from **2c** as described above. M.p. 81–83 °C. Found: C 54.11, H 6.78, N 7.49 %. C₁₆H₂₄N₂O₇ requires C 53.92, H 6.79, N 7.86 %. *m/z* (%) 356 (100) [M⁺], 227 (44), 201 (26), 199 (57), 193 (53), 167 (80), 165 (30), 89 (21), 87 (26), 73 (34). IR (KBr) ν_{\max} cm^{−1}: 3414 (NH), 1494 and 1321 (NO₂). ¹H NMR (DMSO-*d*₆) δ_{H} ppm: 3.42 (2H, m, NCH₂CH₂O), 3.53 (4H, m, 2CH₂O), 3.56 (6H, m, 3CH₂O), 3.60 (2H, m, CH₂O), 3.63 (2H, t, *J*=4.9 Hz, NCH₂CH₂O), 3.78 (2H, m, CH₂CH₂OAr), 4.23 (2H, m, CH₂OAr), 5.82 (1H, t, *J*=5.5 Hz, NH), 6.70 (1H, d, *J*=9.2 Hz, 17-H), 7.60 (1H, d, *J*=2.4 Hz, 20-H), 7.85 (1H, dd, *J*=9.2, 2.4 Hz, 18-H). ¹³C NMR (MeCN-*d*₃) δ_{C} ppm: 43.31 (NCH₂CH₂O), 69.07 (CH₂OAr), 69.37 (NCH₂CH₂O), 69.45 (CH₂CH₂OAr), 70.73 (CH₂O), 70.86 (2CH₂O), 70.96 (2CH₂O), 71.03 (CH₂O), 106.13 (20-C), 107.48 (17-C), 120.52 (18-C), 137.39 (19-C), 145.15 (20a-C), 145.34 (16a-C).

***N*-Demethylation of 2-methoxy-*N,N*-dimethyl-4-nitroaniline (7).** A mixture of nitroaniline **7** (59 mg, 0.3 mmol), NH₄I (437 mg, 3.0 mmol), and dry MeCN (15 mL) was stirred at reflux for 100 h. After cooling, the reaction mixture was evaporated *in vacuo*, diluted with water (30 mL), extracted with C₆H₆ (3×25 mL), and the combined extracts were evaporated *in vacuo*. The residue was purified by column chromatography on Al₂O₃. The elution was carried out first with a C₆H₆–hexane mixture (1:1) and then with C₆H₆. This gave 39 mg of compound **8** (71 % conversion and 98 % yield based on reacted **7**) and 16 mg of starting compound **7** (27 % recovery) as yellow powders.

2-Methoxy-*N*-methyl-4-nitroaniline (8). M.p. 99–100 °C (cf. lit.^[7] m.p. 103 °C). ¹H NMR (DMSO-*d*₆) δ_{H} ppm: 2.83 (3H, d, *J*=4.9 Hz, MeN), 3.89 (3H, s, MeO), 6.54 (1H, d, *J*=9.2 Hz, 6-H), 6.70 (1H, br q, *J*=4.9 Hz, NH), 7.55 (1H, d, *J*=2.4 Hz, 3-H), 7.85 (1H, dd, *J*=9.2, 2.4 Hz, 5-H).

2-Methoxy-*N,N*-dimethyl-4-nitroaniline (7). M.p. 96–97 °C (cf. lit.^[7] m.p. 97 °C). ¹H NMR (DMSO-*d*₆) δ_{H} ppm: 2.95 (6H, s, Me₂N), 3.89 (3H, s, MeO), 6.88 (1H, d, *J*=9.2 Hz, 6-H), 7.65 (1H, d, *J*=2.4 Hz, 3-H), 7.81 (1H, dd, *J*=9.2, 2.4 Hz, 5-H).

Methylation of benzoazacrown ethers 1a–c (general procedure). A mixture of benzoazacrown ether **1a–c** (0.03 mmol), NaH (60 % in wax) (24 mg, 0.6 mmol), MeI (19 μ L, 0.3 mmol), and dry THF (3 mL) was stirred at reflux for 40 min. Then the reaction mixture was diluted with water (15 mL) and extracted with C₆H₆ (3×10 mL). The benzene extracts were evaporated and the residue was passed through a thin Al₂O₃ layer (basic) using a C₆H₆–EtOAc mixture (5:1) as the eluent.

10-Methyl-13-nitro-2,3,5,6,9,10-hexahydro-8H-1,4,7,10-benzotrioxazacyclododecine (*N*-methylnitrobenzoaza-12-crown-4 ether) (2a) was prepared as described above as a yellow powder. Yield 95 %. M.p. 108–109 °C (cf. lit.^[4d] m.p. 108–109 °C). ¹H NMR (DMSO-*d*₆) δ_{H} ppm: 2.91 (3H, s, MeN), 3.58 (2H, t, *J*=7.2 Hz, NCH₂CH₂O), 3.60 (2H, m, CH₂O), 3.66 (2H, m, CH₂O), 3.82 (2H, t, *J*=7.2 Hz, NCH₂CH₂O), 3.84 (2H, m, CH₂CH₂OAr), 4.21 (2H, m, CH₂OAr), 6.85 (1H, d, *J*=9.1 Hz, 11-H), 7.64 (1H, d, *J*=2.5 Hz, 14-H), 7.79 (1H, dd, *J*=9.1, 2.5 Hz, 12-H).

13-Methyl-16-nitro-2,3,5,6,8,9,12,13-octahydro-11H-1,4,7,10,13-benzotetraoxazacyclopentadecine (*N*-methylnitrobenzoaza-15-crown-5 ether) (2b) was prepared as described above as a yellow powder. Yield 96 %. M.p. 93–95 °C (cf. lit.^[4d] m.p. 93–95 °C). ¹H NMR (DMSO-*d*₆) δ_{H} ppm: 2.93 (3H, s, MeN), 3.41 (2H, t, *J*=7.0 Hz, NCH₂CH₂O), 3.57 (4H, s, 2CH₂O), 3.60 (4H, m, 2CH₂O), 3.83 (2H, m, CH₂CH₂OAr), 3.86 (2H, t, *J*=7.0 Hz, NCH₂CH₂O), 4.20 (2H, m, CH₂OAr), 6.88 (1H, d, *J*=8.9 Hz, 14-H), 7.63 (1H, d, *J*=2.5 Hz, 17-H), 7.79 (1H, dd, *J*=9.1, 2.5 Hz, 15-H).

16-Methyl-19-nitro-2,3,5,6,8,9,11,12,15,16-decahydro-14H-1,4,7,10,13,16-benzopentaoxazacyclooctadecine (N-methyl-nitrobenzoaza-18-crown-6 ether (2c)) was prepared as described above as a yellow oil. Yield 96 %. (cf. lit.: oil,^[4d] m.p. 43–45 °C^[4b]). ¹H NMR (DMSO-*d*₆) δ_H ppm: 3.01 (3H, s, MeN), 3.51 (4H, m, 2CH₂O), 3.53 (4H, m, 2CH₂O), 3.59 (6H, m, NCH₂CH₂O, 2CH₂O), 3.73 (2H, t, *J*=5.4 Hz, NCH₂CH₂O), 3.79 (2H, m, CH₂CH₂OAr), 4.18 (2H, m, CH₂OAr), 6.84 (1H, d, *J*=9.1 Hz, 17-H), 7.62 (1H, d, *J*=2.5 Hz, 20-H), 7.79 (1H, dd, *J*=9.1, 2.5 Hz, 18-H).

Synthesis of N-ethyl-2-methoxy-4-nitroaniline (5). A mixture of 2-methoxy-4-nitroaniline (**10**) (0.84 g, 50 mmol), triethyl orthoformate (1.1 mL, 75 mmol), and a drop of concentrated H₂SO₄ was stirred for 4 h in a flask equipped with a reflux condenser at 115–120 °C (oil bath). Then the temperature was raised to 175 °C during 1 h. The reaction mixture was cooled, 10 % aqueous HCl (2 mL) was added, and the mixture was heated for 1 h at 100 °C (oil bath). After cooling, 10 % aqueous NaOH (2 mL) was added to the reaction mixture, and the mixture was extracted with C₆H₆ (3×10 mL). The benzene extracts were evaporated, and the residue was purified by column chromatography on SiO₂ with C₆H₆ as the eluent. This gave 0.60 g of the starting compound **10** (71 % recovery) and 0.125 g of compound **5** (13 % conversion, 45 % yield based on reacted **10**) as yellow needles. M.p. 74–75 °C. Found: C 54.90, H 6.04, N 14.26 %. C₉H₁₂N₂O₅ requires C 55.09, H 6.16, N 14.28 %. *m/z* (%) 196 (61) [M⁺], 182 (10), 181 (100), 166 (10), 149 (6), 135 (35), 107 (6), 79 (6), 78 (13), 51 (6). IR (KBr) ν_{max} cm⁻¹: 3386 (NH), 1479 and 1317 (NO₂). ¹H NMR (DMSO-*d*₆) δ_H ppm: 1.16 (3H, t, *J*=7.2 Hz, MeCH₂), 3.26 (2H, m, CH₂), 3.89 (3H, s, MeO), 6.53 (1H, t, *J*=5.0 Hz, NH), 6.61 (1H, d, *J*=9.1 Hz, 6-H), 7.55 (1H, d, *J*=2.5 Hz, 3-H), 7.83 (1H, dd, *J*=9.1, 2.5 Hz, 5-H). ¹³C NMR (DMSO-*d*₆) δ_C ppm: 13.90 (MeCH₂), 36.69 (CH₂), 55.72 (MeO), 104.34 (3-C), 106.26 (6-C), 119.99 (5-C), 134.98 (4-C), 144.68 (1-C), 144.80 (2-C).

¹H NMR Titration

The solvents used included MeCN-*d*₃ and DMSO-*d*₆ (both <0.05 % water, Federal State Unitary Enterprise, Russian Research Center “Applied Chemistry”, St.-Petersburg). The composition and stability constants of complexes of benzoazacrown ethers **1a–c** with the salts M^{m+}(ClO₄)_m and *n*-Bu₄NF were determined by analyzing the variation of the positions of proton signals of the ligand (LH) as functions of the concentration of salt added. The total LH concentration was invariable and amounted to ~2.5·10⁻³ M, while the salt concentration was varied starting from zero. The highest M^{m+}/LH ratio was ~3. When **1b** was titrated with singly charged cations, the salt concentration was brought to the M^{m+}/LH ratio of ~6. In the case of titration with NH₄ClO₄ and KClO₄, the total concentration of LH was maintained at ~1·10⁻³ M due to limited solubility of the salts. In the titration with *n*-Bu₄NF, the *n*-Bu₄NF/LH ratio was brought to ~8.

The Δδ_H values were measured to an accuracy of 0.001 ppm. The stability constants of complexes were calculated using the HYPNMR program.^[8]

X-Ray Diffraction Study, Crystal Data

The crystals of benzoazacrown ethers **1a,c**, **2a** and model anilines **4**, **5**, and **7** were prepared by slow evaporation of their solutions in a CH₂Cl₂–hexane mixture at room temperature. The crystalline complex of benzoazacrown ether **2c** with barium perchlorate was obtained by slow saturation of a MeCN solution of an equimolar mixture of the ligand with Ba(ClO₄)₂ with C₆H₆ vapour.

A single crystal of each of the compounds was mounted on a CCD SMART diffractometer under a stream of cooled nitrogen where crystallographic parameters and reflection intensities were measured. A reduction of the data was performed using the SAINT program.^[9] Using Olex2,^[10] the structure was solved

with the SHELXL-2014^[11] structure solution program using Direct Methods and refined with the XH^[12] refinement package using Least Squares minimization.

It should be noted that structure **1a** was studied with a rather big errors caused by low quality and small size of the crystals. However, its discussion is important for the comparison of the structural features in the series of investigated compounds.

1a. Crystal data for C₁₂H₁₆N₂O₅ (*M*=268.27 g·mol⁻¹): monoclinic, space group *P*2₁ (no. 4), *a*=4.5282(3) Å, *b*=11.8234(8) Å, *c*=11.5477(7) Å, β=101.067(4)°, *V*=606.75(7) Å³, *Z*=2, *T*=123 K, μ(CuKα)=0.974⁻¹, *D*_{calc}=1.468 g·cm⁻³, 3513 reflections measured (7.80°≤2θ≤149.16°), 1901 unique (*R*_{int}=0.0588, *R*_σ=0.0826) which were used in all calculations. The final *R*₁ was 0.1513 (*I*>2σ(*I*)) and *wR*₂ was 0.4250 (all data) (CCCD 1864860).

2a. Crystal data for C₁₃H₁₈N₂O₅ (*M*=281.94 g·mol⁻¹): triclinic, space group *P*1̄ (no. 2), *a*=4.5563(3) Å, *b*=12.1237(8) Å, *c*=12.1879(9) Å, α=85.789(6)°, β=89.004(5)°, γ=79.999(5)°, *V*=661.22(8) Å³, *Z*=2, *T*=123 K, μ(MoKα)=0.110 mm⁻¹, *D*_{calc}=1.416 g·cm⁻³, 8238 reflections measured (6.70°≤2θ≤55.00°), 2597 unique (*R*_{int}=0.0791, *R*_σ=0.1072) which were used in all calculations. The final *R*₁ was 0.0626 (*I*>2σ(*I*)) and *wR*₂ was 0.1424 (all data) (CCCD 1864859).

1c·H₂O. Crystal data for C₁₆H₂₆N₂O₈ (*M*=374.39 g·mol⁻¹): orthorhombic, space group *Pca*2₁ (no. 29), *a*=17.519(3) Å, *b*=12.356(2) Å, *c*=8.3866(15) Å, *V*=1815.4(5) Å³, *Z*=4, *T*=123 K, μ(MoKα)=0.110 mm⁻¹, *D*_{calc}=1.370 g·cm⁻³, 14717 reflections measured (3.30°≤2θ≤58.00°), 4664 unique (*R*_{int}=0.2965, *R*_σ=0.3425) which were used in all calculations. The final *R*₁ was 0.0848 (*I*>2σ(*I*)) and *wR*₂ was 0.1429 (all data) (CCCD 1864855).

4. Crystal data for C₈H₁₀N₂O₂ (*M*=166.18 g·mol⁻¹): monoclinic, space group *P*2₁/*n* (no. 14), *a*=7.611(2) Å, *b*=7.979(3) Å, *c*=13.196(4) Å, β=91.657(9)°, *V*=801.1(4) Å³, *Z*=4, *T*=123 K, μ(MoKα)=0.101 mm⁻¹, *D*_{calc}=1.378 g·cm⁻³, 9275 reflections measured (5.96°≤2θ≤57.00°), 2034 unique (*R*_{int}=0.1224, *R*_σ=0.1026) which were used in all calculations. The final *R*₁ was 0.0784 (*I*>2σ(*I*)) and *wR*₂ was 0.1890 (all data) (CCCD 1864864).

5. Crystal data for C₉H₁₂N₂O₃ (*M*=196.21 g·mol⁻¹): monoclinic, space group *P*2₁/*c* (no. 14), *a*=7.8779(3) Å, *b*=15.9215(5) Å, *c*=7.5549(2) Å, β=96.650(2)°, *V*=941.22(5) Å³, *Z*=4, *T*=123 K, μ(CuKα)=0.882 mm⁻¹, *D*_{calc}=1.385 g·cm⁻³, 6173 reflections measured (11.12°≤2θ≤148.84°), 1809 unique (*R*_{int}=0.0670, *R*_σ=0.0661) which were used in all calculations. The final *R*₁ was 0.0711 (*I*>2σ(*I*)) and *wR*₂ was 0.1844 (all data) (CCCD 1864867).

7. Crystal data for C₉H₁₂N₂O₃ (*M*=196.21 g·mol⁻¹): orthorhombic, space group *Pna*2₁ (no. 33), *a*=14.269(5) Å, *b*=16.787(6) Å, *c*=3.8590(14) Å, *V*=924.3(6) Å³, *Z*=4, *T*=123 K, μ(MoKα)=0.107 mm⁻¹, *D*_{calc}=1.410 g·cm⁻³, 8285 reflections measured (3.74°≤2θ≤57.98°), 2451 unique (*R*_{int}=0.2277, *R*_σ=0.1864) which were used in all calculations. The final *R*₁ was 0.0692 (*I*>2σ(*I*)) and *wR*₂ was 0.1415 (all data) (CCCD 1864865).

2c·Ba(ClO₄)₂·0.25H₂O. Crystal data for C₁₇H_{26.5}N₂O_{15.25}Cl₂Ba (*M*=711.14 g·mol⁻¹): monoclinic, space group *P*2₁/*c* (no. 14), *a*=13.7161(5) Å, *b*=11.7809(3) Å, *c*=15.6719(4) Å, β=94.546(3)°, *V*=2524.44(13) Å³, *Z*=4, *T*=123 K, μ(MoKα)=1.862 mm⁻¹, *D*_{calc}=1.871 g·cm⁻³, 20007 reflections measured (5.14°≤2θ≤58.00°), 6717 unique (*R*_{int}=0.0547, *R*_σ=0.0665) which were used in all calculations. The final *R*₁ was 0.0390 (*I*>2σ(*I*)) and *wR*₂ was 0.0844 (all data) (CCCD 1864866).

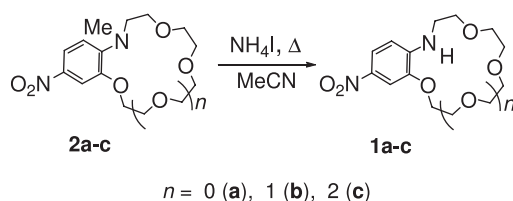
Results and Discussion

Synthesis of Nitrobenzoazacrown Ethers

We studied the efficiency of *N*-demethylation of *N*-methylnitrobenzoazacrown ethers **2** with different

macrocycle size on treatment with ammonium iodide with heating in anhydrous MeCN (Scheme 5). The starting *N*-methylbenzoazacrown ethers **2** were prepared by reported procedures.^[4d]

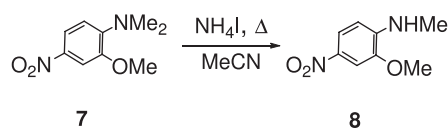
It was shown that the degrees of conversion of *N*-methylnitrobenzoaza-12(15,18)-crown-4(5,6) ethers **2** to demethylated products **1** depend on the macrocycle size (Table 1). The reaction proceeds most readily for *N*-methylbenzoazacrown ether **2a** with a 12-membered macrocycle. Indeed, the reactions conducted under identical conditions in boiling MeCN over a period of 100 h yielded benzoaza-12(15,18)-crown-4(5,6) ethers **1a–c** with degrees of conversion of 95 %, 62 %, and 19 %, respectively. The yields of products **1a–c** (based on reacted starting compounds **2a–c**) depend little on the macrocycle size and amount to 86–95 %. By increasing the reaction temperature to 130 °C, we attained complete conversion of *N*-methylnitrobenzoaza-12(15,18)-crown-4(5,6) ethers **2** to demethylated products **1**, which were formed in 95–100 % yields (see Table 1).



Scheme 5. Synthesis of nitrobenzoazacrown ethers **1a–c** by demethylation of *N*-methylbenzoazacrown ethers **2a–c** by treatment with NH_4I with heating in MeCN.

In the case of *N,N*-dimethyl-4-nitroaniline **6**, elimination of *N*-methyl group does not take place under analogous conditions (refluxing at 130 °C). The reaction of 2-methoxy-*N,N*-dimethyl-4-nitroaniline **7** carried out in refluxing MeCN for 100 h gave compound **8** (Scheme 6) in 98 % yield based on reacted **7** (27 % recovery of starting **7**, see Experimental section).

In the case of *N*-methylbenzoaza-12-crown-4 ether **2a**, the reaction did not proceed without ammonium iodide (at 130 °C). For compound **2c**, no reaction was observed in the presence of *n*- Bu_4NI , instead of NH_4I , under similar conditions. It was also shown that refluxing of **2a** in MeCN in the presence of NH_4Cl , instead of NH_4I , does not lead



Scheme 6. Demethylation of 2-methoxy-*N,N*-dimethyl-4-nitroaniline **7** by treatment with NH_4I with heating in MeCN.

to elimination of the *N*-methyl group. On refluxing of **2a** and **2c** with dilute acetic acid in EtOAc or MeCN (100 h), the degrees of conversion of **2a,c** to **1a,c** were low (5–20 %); in addition, products of macrocycle destruction were formed in minor amounts, with the recovery of initial compounds **2a,c** being 70–86 %.

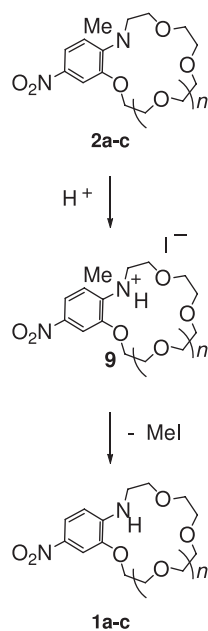
The obtained results suggest the following mechanism of formation of demethylated products **1** from compounds **2**. Since the reaction takes place in the presence of a mild acidic agent (NH_4I) over a long period of time, compounds **1** are apparently formed *via* the intermediate formation of macrocyclic ammonium salt **9**, which then eliminates a methyl group under the action of nucleophile (I^-) (Scheme 7). The reaction for model compound **7** follows a similar pathway. The reaction does not proceed without the electron-donating MeO group in the *ortho*-position relative to NMe_2 group in the benzene ring, which creates steric hindrance (compound **6**). Another suggestion is that the formation of host–guest complexes of **2** with ammonium ions may prevent *N*-demethylation, as indicated by different degrees of conversion of **2a–c** to **1a–c** for different macrocycle sizes for incomplete reaction (refluxing in MeCN, 100 h). For example, in the case of **2c** with a 18-membered macrocycle, which forms the most stable complex with the ammonium ion,^[4h] the degree of conversion is the lowest and complete conversion of **2c** to **1c** requires the longest time. Compounds **2a** and **7** do not form stable complexes with the ammonium ion and, therefore, they are easily demethylated. Probably, the rate of demethylation of **2** is also affected by the degree of steric hindrance in the vicinity of macrocycle nitrogen. This can account for the fact that **2a** reacts much faster than **7**.

The nitrobenzoazacrown ethers **1a–c** thus obtained can be readily methylated at the macrocycle nitrogen atom to give **2a–c** by the reaction with methyl iodide induced by sodium hydride with heating in anhydrous THF (Scheme 8). This reaction for compounds **1a–c** is fast and gives products in nearly quantitative yields. This demonstrates the possibil-

Table 1. Conditions of demethylation of *N*-methylbenzoazacrown ethers **2a–c** by treatment with NH_4I in anhydrous MeCN and yields of benzoazacrown ethers **1a–c**.

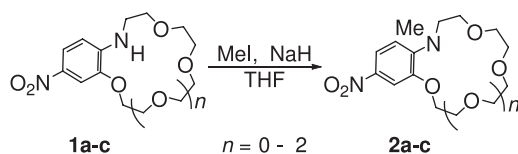
Starting compound	Temperature, °C	Time, h	Recovery of starting 2 , %	Degree of conversion 2 , %	Yield of 1 , ^a %
2a	82	100	0	95	95
	130	55	0	95	95
2b	82	100	30	62	88
	130	100	0	100	100
2c	82	100	78	19	86
	130	100	57	41	96
	130	255	0	98	98
	130	255	0	98	98

^aBased on reacted compound **2**.



Scheme 7. Presumptive mechanism of demethylation of **2a-c** on treatment with NH_4I with heating in MeCN.

ity of converting compounds **1** to *N*-substituted functional derivatives.



Scheme 8. Synthesis of *N*-methylbenzoazacrown ethers **2a-c** by methylation of **1a-c** with MeI induced by NaH.

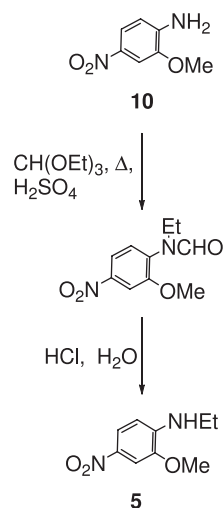
Model *N*-ethyl-2-methoxy-4-nitroaniline **5** was prepared in 45 % yield (based on reacted compound **10**) by a modification of the procedure reported for the synthesis of *N*-ethyl-*p*-chloroaniline,^[13] using the reaction of 2-methoxy-4-nitroaniline (**10**) with triethyl orthoformate catalyzed by sulfuric acid followed by hydrolysis of the reaction mixture with hydrochloric acid (Scheme 9).

The structures of the products were determined by ^1H and ^{13}C NMR spectroscopy, IR spectroscopy, and mass spectrometry and confirmed by elemental analysis.

NMR Spectroscopic Studies

1D and 2D NMR spectroscopy in $\text{MeCN-}d_3$ and $\text{DMSO-}d_6$ solutions was employed to study the structure, complex formation properties, and conformational behaviour of the macrocyclic moiety both in free compound **1** and in complexes of **1** with alkali and alkaline-earth metal cations, ammonium ions, and fluoride anions.

Quantitative evaluation of the stability of complexes formed by nitrobenzoazacrown ethers **1** and model compounds **4**, **5** with metal and (ethyl)ammonium cations and fluoride anions was performed by ^1H NMR titration.



Scheme 9. Synthesis of *N*-ethyl-2-methoxy-4-nitroaniline **5**.

The NOESY spectra of free benzoazacrown ethers **1a-c** exhibited intense cross-peaks between the α -protons of the NCH_2 group and the benzene 3-H proton located in the *ortho*-position to macrocycle nitrogen (see Figure 1; for convenience, the benzoazacrown atom numbering differs from the IUPAC rules), which attests to their spatial proximity, and no cross-peaks between the NH proton and the 3-H proton. In the case of **1c**, a weak cross-peak is also present between the β - CH_2O protons and the 3-H proton. Furthermore, for all compounds **1a-c**, we observed less intense cross-peaks between the NH proton and the NCH_2 -group α -protons and weak cross-peaks between the NH proton and the β - CH_2O protons. Weak cross-peaks were present between NH and α' - CH_2O protons and β' - CH_2O protons for compound **1a** and between NH and γ (or γ')- CH_2O protons for compound **1b**. These results indicate that hydrogen at the nitrogen atom in compounds **1** points inside the macrocycle and, perhaps, is hydrogen bonded to some of the crown ether oxygen atoms. The nitrogen atom configuration probably corresponds to sp^2 hybridization (planar geometry) and the nitrogen lone pair of electrons (LP) is efficiently conjugated with the benzene ring.^[4c,f]

Thus, the spatial structure of benzoazacrown ethers **1** is unfavourable for complex formation due to conjugation of the LP of the NH nitrogen with the benzene ring and the orientation of the hydrogen atom inside the macroheterocycle, which generates steric hindrance for cations entering the crown ether cavity. Therefore, the stability constants of complexes **1** are expected to be lower than those of their *N*-alkyl-substituted analogues, which are characterized by a pyramidal geometry of the macrocycle nitrogen atom.^[4e,g,h]

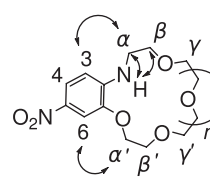
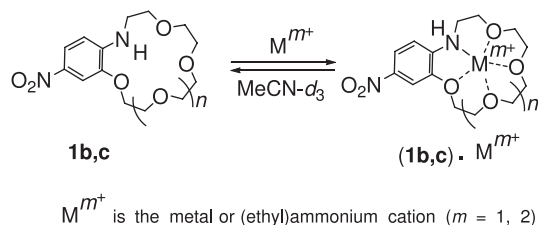


Figure 1. Schematic view of NOESY interactions in compounds **1a-c**, $\text{MeCN-}d_3$.

The addition of excess alkali or alkaline-earth metal or (ethyl)ammonium perchlorate to benzoazacrown ether **1c** in MeCN- d_3 , or the addition of excess alkaline-earth metal perchlorate to **1b** in MeCN- d_3 induces downfield shifts ($\Delta\delta_H$) of most ^1H NMR signals of these ligands. This behaviour is typical of host–guest inclusion complexes (Scheme 10). The most pronounced downfield shifts ($\Delta\delta_H$ up to 0.47 ppm for compound **1c** with doubly charged cations) are observed for signals of the benzene 3-H protons located in the *ortho*-position to the macrocycle nitrogen atoms, which evidently reflects switching of their LPs from conjugation with the benzene rings to cation coordination. The greatest downfield shift of the CH_2O proton signals is 0.34 ppm. The signals of the NH protons (and NCH_2 protons in the case of calcium and barium salts) provide an exception, as they shift upfield upon the addition of salts. In all cases, the greatest $\Delta\delta_H$ values upon the complex formation of **1b,c** were inherent in the signals of the NH protons, being up to -1.0 ppm for the addition of alkaline-earth metal perchlorates to compound **1c**, which is apparently due to both the change in the nitrogen atom geometry (transition from the sp^2 -hybridized (planar) state to the sp^3 -hybridized (pyramidal) state) and a conformational transition of macrocycle **1b,c** upon cation binding. As a result of reorientation of the LPs of all heteroatoms towards the centre of macrocycle cavity accommodating the metal or (ethyl)ammonium, the conjugation of the macrocycle nitrogen LP with the benzene ring is substantially weakened, and the NH hydrogen atom and, in some cases, also the NCH_2 methylene group, apparently markedly deviate from the benzene ring plane with respect to their positions in free ligands (Scheme 10).



Scheme 10. Complex formation of benzoazacrown ethers **1b,c** with metal and (ethyl)ammonium cations; MeCN- d_3 .

The addition of excess alkali metal or ethylammonium perchlorate to a solution of benzoazacrown ether **1b**, or the addition of excess calcium perchlorate to a solution of **1a** induces slight changes in the positions of all ^1H NMR signals of the ligand (the greatest observed $\Delta\delta_H$ is up to -0.01 ppm and belongs to the NH proton of **1b**), which is indicative of the formation of low-stability complexes.

Analysis of the NOESY spectra of benzoazacrown ethers **1b,c** in the presence of excess calcium or barium perchlorate demonstrated that the conformation of the macrocycle near the nitrogen atom changes upon complexation with respect to the free ligand conformation. A cross-peak appears between the NH proton and the 3-H benzene proton located in the *ortho*-position relative to the macrocycle nitrogen (Figure 2), which attests to their spatial proximity. In the case of **1b**, this cross-peak is very intense (only slightly less intense than the cross-peak between the α -protons of the NCH_2

group and the 3-H proton (Figure 2)), while in the case of **1c**, the peak intensity is moderate. This attests to more significant conformational changes upon complexation of compound **1b** containing a 15-membered macrocycle with M^{2+} ions compared with the 18-membered **1c**.

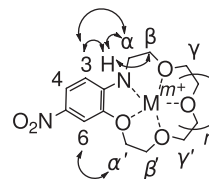
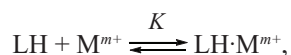


Figure 2. Schematic view of NOESY interactions in compounds **1b,c** in the presence of excess $\text{Ca}(\text{ClO}_4)_2$ or $\text{Ba}(\text{ClO}_4)_2$; MeCN- d_3 .

Quantitative evaluation of the stability of the complexes formed by nitrobenzoazacrown ether **1b,c** with metal and (ethyl)ammonium perchlorates was performed by ^1H NMR titration. The stability constants of the complexes were calculated from the dependences of proton chemical shifts of the ligand on the amount of the added salt using the HYPNMR program;^[8] the results were in good agreement with the scheme of formation of $1(\text{LH}) : 1(\text{M}^{m+})$ complexes:



where LH is the azacrown ether, M^{m+} is the metal or (ethyl)ammonium cation ($m=1, 2$), K/M^{-1} is the stability constant of the complex. The results are summarized in Table 2. For comparison, Table 2 gives the stability constants of complexes of the same salts with close structural analogues of nitrobenzoazacrown ethers **1**, *N*-methylbenzoazacrown ethers **2** and *N*-phenylazacrown ethers **3** with the same macrocycle size, which were prepared in our previous study.^[4g,h]

The stability constants of complexes **1b,c** with doubly charged cations are much higher than those for singly charged cations, which is caused by higher charge density on the alkaline-earth metal cations. The stability constants of complexes of **1b** with singly charged cations are below the level detectable by ^1H NMR titration. We also found that the stability constant of complex of **1a** with calcium perchlorate is below the level detectable by ^1H NMR titration ($\log K < 1$). The stability constants of complexes of **1c** with 18-membered macrocycle are higher than those for similar complexes formed by 15-membered **1b**.

In all cases, complexes of benzoazacrown ethers **1b,c** are markedly less stable than the complexes of *N*-methylbenzoazacrown ethers **2b,c** and *N*-alkyl-substituted analogues in general.^[4g,h] The complex-forming properties of **1c** are similar to those of *N*-phenylaza-18-crown-6 ether **3c** with the same macrocycle size, while **1b** is much inferior to *N*-phenylaza-15-crown-5 ether **3b**. This means that the hydrogen atom at nitrogen, which points inside the macrocycle, hampers the complexation to a much higher extent in **1b** than in **1c**, possibly, because of formation of stronger intramolecular $\text{NH} \cdots \text{OCH}_2$ hydrogen bonds in the case of **1b**.

We also used ^1H NMR titration to study the ability of benzoazacrown ethers **1a-c** and model anilines **4** and **5** to bind fluoride anions *via* hydrogen bonding with the mac-

Table 2. Stability constants of complexes of azacrown ethers **1–3** with (ethyl)ammonium and metal perchlorates^a.

Ligand	logK						
	NH ₄ ⁺	EtNH ₃ ⁺	Li ⁺	Na ⁺	K ⁺	Ca ²⁺	Ba ²⁺
1b	—	— ^b	— ^b	— ^b	—	1.7	0.9
2b ^[4g]	1.7	1.4	—	2.7	1.9	3.8	4.2
3b ^[4g]	1.8	1.2	—	2.6	0.7	2.3	1.4
1c	2.5	1.9	1.7	3.0	2.6	4.4	> 5
2c ^[4h]	3.8	3.6	2.5	3.6	4.2	> 5	> 5
3c ^[4h]	2.3	1.5	1.7	3.2	2.1	4.2	4.6

^a ¹H NMR titration, MeCN-*d*₃, 25±1 °C; $K/M^{-1} = [LH \cdot M^{m+}] / ([LH] \cdot [M^{m+}])$; errors for the determination of *K* values are within ± 30 %.

^b NMR titration is inapplicable due to very low (logK < 1) value of stability constant.

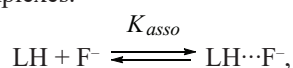
rocycle NH group or the amino group upon the addition of excess *n*-Bu₄NF in DMSO-*d*₆ or MeCN-*d*₃ to a solution of the ligand.

We found that binding of F[−] ions induces downfield shifts of the NH proton signals in all compounds and upfield shifts of signals for the aromatic protons (except for the 2-H and 6-H signals of compound **4** in MeCN-*d*₃). Most of the shifts are moderate. In addition, the NH proton signal is substantially broadened in most cases, and for model compounds it sometimes completely disappears.

The most pronounced downfield shifts were observed for NH proton signals of the macrocycles of benzoazacrown ethers (Δδ_H up to 0.04 ppm in DMSO-*d*₆ and 0.26 ppm in MeCN-*d*₃ for compound **1c**) and aniline amino groups (up to 1.7 ppm in MeCN-*d*₃ for compound **4**).

The greatest observed shifts of aromatic proton signals for benzoazacrown ethers **1a–c** in DMSO-*d*₆ and MeCN-*d*₃ do not exceed 0.01 ppm, while for model compounds they are up to 0.3 ppm for compound **5** in DMSO-*d*₆ and up to 0.03 ppm for compound **4** in MeCN-*d*₃.

Quantitative evaluation of the stability constants for the complexes formed by nitrobenzoazacrown ethers **1** and nitroanilines **4** and **5** with the tetrabutylammonium fluoride was performed by ¹H NMR titration. The binding constants were calculated from the dependences of proton chemical shifts of the ligand on the amount of the added salt using the HYPNMR program;^[8] the results were in agreement with the scheme of formation of 1(LH):1(F[−]) complexes:



where LH is benzoazacrown ether or model compound, K_{asso}/M^{-1} is the binding constant. The results are summarized in Table 3.

It was found that the binding constants of benzoazacrown ethers **1** with the fluoride anion are moderate (logK_{asso} is of about 2.0); they virtually do not depend on the macrocycle size and are comparable with the binding constants of nitroanilines **4** and **5** with the F[−] ion.

X-Ray Diffraction Studies

We were able to grow single crystals of nitrobenzoazacrown ethers **1a,c**, *N*-methylnitrobenzoazacrown

Table 3. Binding constants of benzoazacrown ethers **1a–c** and nitroanilines **4, 5** with *n*-Bu₄NF.^a

Ligand	logK _{asso}	
	DMSO- <i>d</i> ₆	MeCN- <i>d</i> ₃
1a	1.8	1.9
1b	1.9	2.0
1c	1.8	1.9
4	2.0	2.1
5	2.0	1.9

^a ¹H NMR titration, MeCN-*d*₃, 25±1 °C; $K_{asso}/M^{-1} = [LH \cdots F^-] / ([LH] \cdot [F^-])$; the errors for the determination of logK_{asso} values are within ± 0.2.

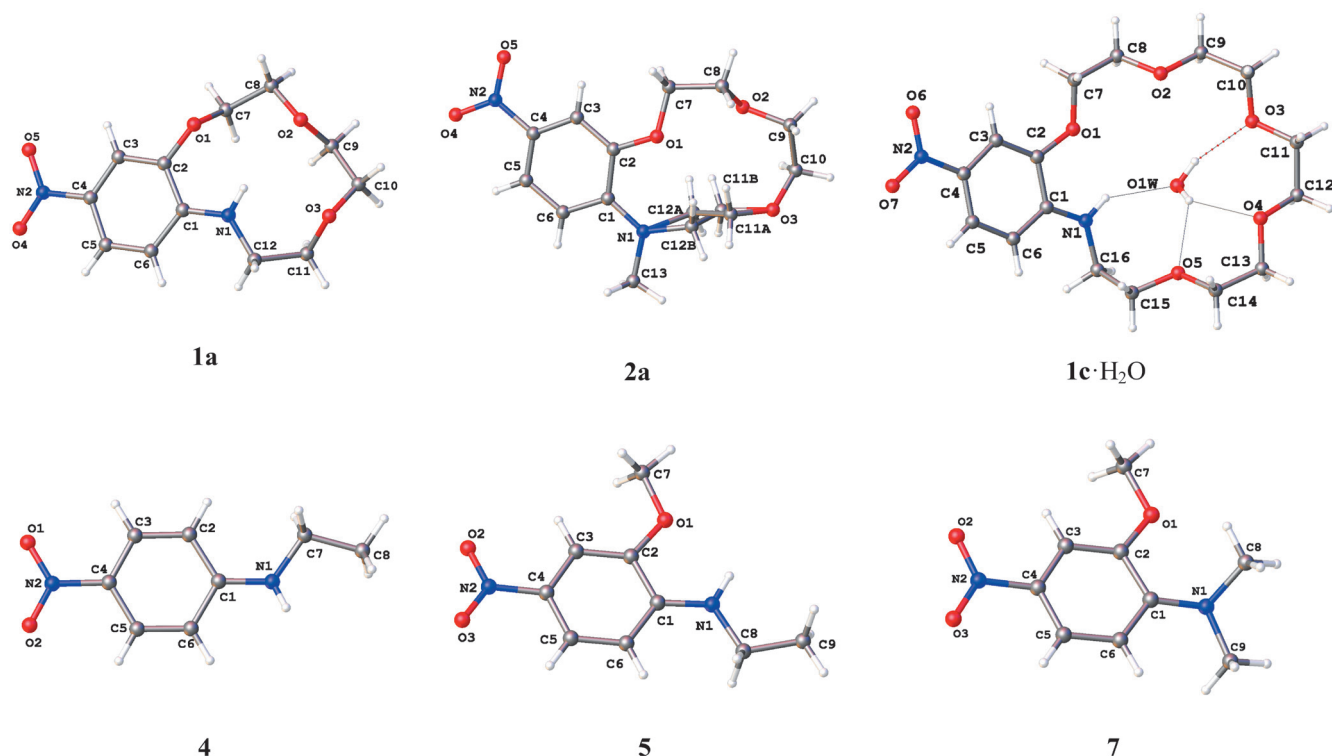
ether **2a**, model nitroanilines **4, 5**, and **7** and the complex of *N*-methyl-nitrobenzoazacrown ether **2c** with barium perchlorate. The structures of free **2b** and its complex with barium perchlorate were studied in our previous work.^[4e,g]

The X-ray diffraction structures of compounds **1a, 2a, 1c, 4, 5**, and **7** are shown in Figure 3.

In structure **2a**, one ethylene group is disordered over two positions (C11A–C12A and C11B–C12B). The crystal structure of **1c** involves one solvate water molecule. This molecule is linked by hydrogen bonds with the O3, O4, O5 and N1 atoms of the benzoazacrown ether moiety. In the N–H...O (H...O bond distance is 2.19 Å) hydrogen bond, the NH group is a proton donor. In the hydrogen bond with the oxygen atoms, water molecule is the proton donor. The water molecule forms normal O–H...O3 bond (the H...O3 distance is 2.15 Å) and a bifurcated bond with O4 and O5 atoms (distances H...O4 and H...O5 are 2.48 and 2.25 Å, respectively).

Selected geometric parameters for the structures are listed in Table 4.

Some elongation of the C1–C2 bond between two *ortho*-substituents is observed in structures **1a, 2a, 1c, 5**, and **7**. This peculiarity may be ascribed to the steric effect of the crown ether substituent. In structure **1a** where the macrocycle is rather small, this assumption is actually supported by the type of distortions of the external angles at C1 and C2; the C1–C2–O1 and C2–C1–N1 angles are smaller than the corresponding C3–C2–O1 and C6–C1–N1 angles. The greater distortion of the C–C–O angles com-

**Figure 3.** Molecular structures of compounds **1a**, **2a**, **1c·H₂O**, **4**, **5**, and **7**.**Table 4.** Selected geometric parameters (bond distances *d* in Å, bond angles ω in deg).

Bond	<i>d</i> / ω , in 1a	<i>d</i> / ω , in 2a	<i>d</i> / ω , in 1c	<i>d</i> / ω , in 4	<i>d</i> / ω , in 5	<i>d</i> / ω , in 7
C1–C2	1.41(2)	1.435(4)	1.436(8)	1.416(3)	1.430(2)	1.444(5)
C2–O1	1.39(1)	1.365(3)	1.395(6)		1.3590(19)	1.365(4)
C1–N1	1.36(2)	1.376(4)	1.331(7)	1.355(3)	1.353(2)	1.381(5)
C3–C2–O1	122(1)	123.0(3)	126.7(5)		125.51(15)	124.1(3)
C1–C2–O1	116(1)	116.0(3)	111.3(5)		113.37(14)	115.0(3)
C2–C1–N1	120(1)	123.5(2)	118.7(5)	121.9(2)	118.04(14)	121.2(3)
C6–C1–N1	123(1)	120.1(3)	125.6(6)	119.7(2)	123.60(14)	121.8(3)
C2–O1–C7	113(1)	119.3(2)	115.9(4)		117.4(1)	117.2(3)
C8–O2–C9	110.4(9)	115.3(2)	110.5(4)			
C10–O3–C11	114(1)		111.8(4)			
C12–O4–C13			112.1(5)			
C14–O5–C15			115.5(4)			

pared with C–C–N is explained by the lack of conjugation between the oxygen LP and the π -system of the benzene ring and the occurrence of conjugation between the LP of the N1 atom and the benzene ring. The C3–C2–O1–C7 torsion angle ($90(1)^\circ$) rules out the conjugation, whereas the C6–C1–N1–C12 torsion angle ($-9(2)^\circ$) is favourable for the conjugation. In this structure, the hydrogen atom at N1 points towards the centre of the benzoazacrown ether macrocycle.

A different situation is observed in structure **2a** where the macrocycle has the same size. Replacement

of the hydrogen atom at N1 by a methyl group that points outside the macrocycle leads to a different type of geometrical distortions. In this structure, the C3–C2–O1–C7 torsion angle is rather small ($14.3(4)^\circ$), which implies that the O1 atom LP is conjugated with the benzene ring. Thus, the hybridization states of O1 atoms in **1a** and **2a** are different. Indeed, the bond angle at the O1 atom in structure **1a** is $113(1)^\circ$, whereas in structure **2a**, it is equal to $119.3(2)^\circ$. Unfortunately, because of the disorder, we cannot discuss the torsion angles with participation of the N1 atom in structure **2a**. It is only clear that the N1 atom has a nonplanar

bond configuration, which should somewhat suppress the conjugation of the N atom LP with the benzene ring.

Although **1c** contains a larger benzoazacrown ether macrocycle, the same type of the angular distortions is observed in this molecule. The C6–C1–N1–C16 torsion angle is $-5.4(8)^\circ$, which evidences the occurrence of the conjugation. The situation with the O1 atom is somewhat different. The C3–C2–O1–C7 torsion angle is $-18.8(8)^\circ$, while the C2–O1–C7 bond angle is $115.9(4)^\circ$. These data may attest to conjugation, although it should be somewhat suppressed. The similar geometrical parameters have been observed in other molecules with the same crown ether moiety studied earlier.^[4c]

The model structures **4**, **5**, and **7** are devoid of macrocycles. However, the angular distortions similar to those in the above structures are also observed here (see Table 4). The torsion angles, C2–C1–N1–C7 in **4** ($-4.1(4)^\circ$), C3–C2–O1–C7 ($0.3(2)^\circ$) and C6–C1–N1–C8 ($-5.8(2)^\circ$) in **5**, and C3–C2–O1–C7 ($-2.5(5)^\circ$) and C9–N1–C1–C6 in **7** ($9.6(6)^\circ$), indicate the favourable geometry for the conjugation.

Thus, the real geometry of the macrocycle is a result of a combination of two effects: the conjugation of lone pairs of electrons of the N and/or O atoms with the benzene rings and steric strains arising in closed macrocyclic systems.

The structure of the Ba complex of **2c** represents a centrosymmetric dimer (Figure 4). This structure also contains 0.25 water molecule in a lattice cavity.

Each Ba²⁺ ion is coordinated by all six heteroatoms of the benzoazacrown ether macrocycle in equatorial position. Two perchlorate anions occupy the axial positions. One ClO₄[−] anion reveals a monodentate coordination *via* the O21 oxygen atom. Another perchlorate anion reveals a bidentate coordination with respect to one Ba²⁺ ion through O11 and O12 atoms and is additionally coordinated to the centrosymmetrically related Ba²⁺ ion through the O14 atom, thus revealing a bidentate bridging function. The Ba–heteroatom distances are listed in Table 5.

The Ba²⁺ cation is somewhat displaced from the mean plane of the macrocycle heteroatoms towards the bridging system (by 0.71 Å).

The CAr–CAr–O1 and CAr–CAr–N1 bond angles are close to those in free benzoazacrown ethers studied previ-

Table 5. Bond distances Ba–heteroatom (*d*, Å).

Bond	<i>d</i>	Bond	<i>d</i>
Ba1–N1	2.977(3)	Ba1–O5	2.754(2)
Ba1–O1	2.939(2)	Ba1–O11	2.968(3)
Ba1–O2	2.874(2)	Ba1–O12	2.882(3)
Ba1–O3	2.869(2)	Ba1–O21	2.683(3)
Ba1–O4	2.778(2)	Ba1–O14	2.791(2)

ously. The C1–O1–C7 bond angle ($116.6(2)^\circ$) and the C6–C1–O1–C7 torsion angle ($1.8(5)^\circ$) suggest the *sp*² hybridization state for the O1 atom, which implies effective conjugation between the oxygen atom and the benzene ring of compound **2c**. The C3–C2–N1–CH₂ and C3–C2–N1–Me torsion angles are $-15.0(5)^\circ$ and $109.2(4)^\circ$, respectively. Thus, the CH₂ substituent at N1 lies almost in the benzene ring plane, whereas the methyl substituent deviates considerably from this plane. The sum of the C–N1–C bond angles amounts to $333.8(3)^\circ$, being indicative of a pronounced pyramidal geometry similar to that of the ideal *sp*³ hybridization state of the nitrogen atom. It should be noted that the macrocycle conformation found in structure **2c**·Ba(ClO₄)₂·0.25H₂O differs little from those observed for free ligands with the same azacrown ether moiety.^[5a] This implies a pre-organization of *N*-methylbenzoaza-18-crown-6 ether derivatives towards complex formation with metal cations.

Conclusions

Thus, we developed a method for the synthesis of nitrobenzoazacrown ethers with different macrocycle size and macrocycle nitrogen atom being linked to the benzene ring by *N*-demethylation of *N*-methyl-nitrobenzoazacrown ethers. The method affords the new benzoazacrown ethers in high yields (up to 100 %). As complexing agents towards alkali and alkaline-earth metal cations and ammonium ions, nitrobenzoazacrown ethers are inferior to the *N*-alkyl derivatives with the same macrocycle size, but they are able to bind the fluoride anions *via* hydrogen bonding with the macrocycle NH groups. The resulting nitro benzoazacrown ethers are of interest as synthons for the synthesis of functional derivatives at the macrocycle nitrogen atom.

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Supplementary Material

¹H and ¹³C NMR spectra for all obtained compounds, and ¹H NMR titration data are available.

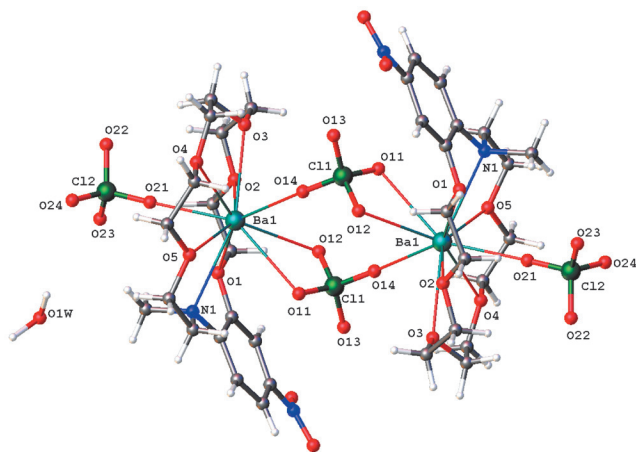


Figure 4. Structure of complex **2c**·Ba(ClO₄)₂·0.25H₂O; only heteroatoms of the crown ether system and anions are denoted.

X-Ray crystallographic data for compounds **1a**, **2a**, **1c**·H₂O, **4**, **5**, and **7** are available. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1864855, 1864859, 1864860, 1864864–1864867. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or email: deposit@ccdc.cam.ac.uk).

Supplementary data to this article can be found online at https://macroheterocycles.isuct.ru/en/system/files/mhcl81218g_supp.pdf

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