Synthesis of formyl derivatives of benzodiazacrown ethers and benzocryptands

**O. A. Fedorova,[a]★ A. I. Vedernikov,[a] I. E. Baronova,[a] O. V. Eshcheulova,[a]
E. A. Fedorchuk,[a] K. Gloe,[b] and S. P. Gromov[a]**

[a]*Photochemistry Center, Russian Academy of Sciences,
7a ul. Novatorov, 119421 Moscow, Russian Federation.
Fax: +7 (095) 936 1255. E-mail: fedorova@photonics.ru*
[b]*Institute of Inorganic Chemistry,
D-01062 Dresden, Germany.**

A simple and convenient procedure was developed for the synthesis of formyl derivatives of benzodiazacrown ethers and benzocryptands by condensation of 3,4-bis(2-iodoethoxy)benzaldehyde with α,ω-oligooxaalkanediamines or diazacrown ethers in the presence of alkali metal carbonates under high-dilution conditions in various organic solvents and their mixtures with water. In the reactions giving rise to diazacrown ethers, alkali metal cations exhibit the negative template effect resulting in a decrease in the yield of the target product if the size of the cation matches well the size of the cavity of the crown ether formed. An *N*,*N*′-bis(carboxymethyl) derivative was prepared from the formyl derivative of benzodiaza-18-crown-6.

Key words: 3,4-bis(2-iodoethoxy)benzaldehyde, α,ω-oligooxaalkanediamines, alkali metal carbonates, template effect, formyl derivatives, diazacrown ethers, cryptands.

The incorporation of nitrogen atoms into the macrocycle of crown ethers substantially extends the range of metal cations that form complexes with such compounds.[1—3] Another useful property of nitrogen-containing crown ethers is that they provide considerable possibilities for relatively easy *N*-functionalization. Azacrown ethers thus modified are used in the synthesis of ion-selective dyes, biologically active compounds, and ionophore components of membranes.[4,5]

The aim of the present study was to develop a procedure for the synthesis of derivatives of benzodiazacrown ethers and benzocryptands containing the formyl group in the benzene ring. Formyl derivatives of crown compounds are of interest as intermediates in the synthesis of styryl and azomethine dyes[6] as well as for the preparation of crown-containing polymers.[7] The formyl group can readily be transformed into other functional groups, which can give rise to new useful derivatives of azacrown ethers.

Earlier, we have developed a procedure for the synthesis of the formyl derivative of *N*,*N*′-dimethylbenzodiaza-18-crown-6 **3c**,[8] which consists in treating the corresponding organolithium derivative with *N*,*N*-dimethylformamide. The drawbacks of this method are the necessity of using anhydrous solvents and low temperature (−100 °C) and the problems associated with isolation of the product from the reaction mixture. In the case of *N*,*N*′-dimethylbenzodiaza-15-crown-5, Li^+ ions are involved in strong coordination resulting in deactivation of its organolithium derivative in the reaction with *N*,*N*-dimethylformamide, which prevents the formation of the corresponding formyl derivative.

Recently, we have demonstrated[9—11] that formyl derivatives of benzothiacrown compounds can be synthesized in high yields by condensation of two acyclic precursors, one of which already contains the formyl group, in the presence of alkali metal carbonates in various solvents. The applicability of an analogous approach to the synthesis of formyl derivatives of benzodiazacrown ethers **3a—c** and benzocryptands **3d,e** was the subject of the present study. We examined condensation of 4-substituted 1,2-bis(2-iodoethoxy)benzenes **1a,b** with diamines **2a—c** and diazacrown ethers **2d,e** in the presence of alkali metal carbonates (Scheme 1). The influence of the nature of the solvent and the template effect of alkali metal cations were investigated and the reaction mechanism was proposed.

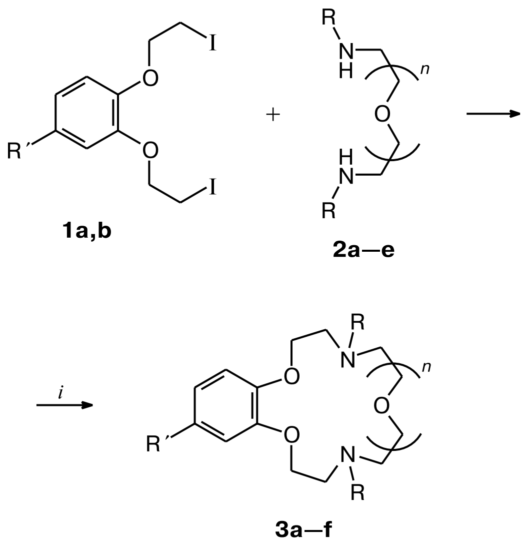
The starting 3,4-bis(2-iodoethoxy)benzaldehyde **1a** was prepared according to known procedures.[9—11] To prevent the formation of by-products (for example, the corresponding azomethines) in the condensation of aldehyde **1a** with diamines, aldehyde **1a** was transformed into

---

* TU Dresden, Institut für Anorganische Chemie, D-01062, Dresden.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 2, pp. 381—387, February, 2004.

Scheme 1



i. M_2CO_3, solvent. M = Li, Na, K, Cs.

R′ = CHO (**1a**, **3a—e**), $CH(OEt)_2$ (**1b**, **3f**)

2, 3: R = H (**a**), Me (**b, c, f**); R—R = $CH_2(CH_2OCH_2)_2CH_2$ (**d, e**); *n* = 1 (**b, d**), 2 (**a, c, e, f**)

acetal **1b** by treatment with triethyl orthoformate in the presence of catalytic amounts of NH_4Cl (Scheme 2).[9] The course of the reaction was monitored by TLC, which demonstrated that the reaction always afforded a mixture of acetal **1b** and aldehyde **1a** regardless of the reaction time. Attempts to completely shift the equilibrium toward the acetal under these conditions failed. Since it was difficult to separate diiodides **1a** and **1b**, their mixture (in the ratio ≈5 : 95 according to ^1H NMR spectroscopy) was subjected to condensation with diamines **2a,c**.

Scheme 2

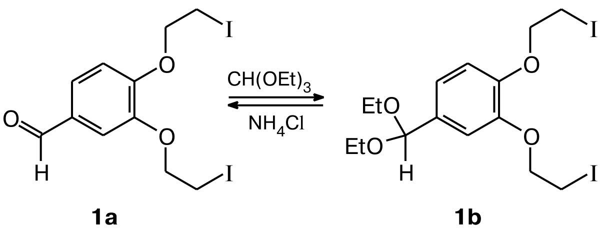


Table 1. Yields of benzodiazacrown ethers **3a—c,f** and benzocryptands **3d,e** in the reactions of diiodides **1a,b** with diamines **2a—e** in the presence of M_2CO_3 (MeCN, refluxing, 20 h)

Starting diiodide	M	Yield (%)				
		3a	3b	3c + 3f	3d	3e
1a	Na	18[a]	62	91[a] + 0	53[b]	46[c]
1a	K	26[a]	88	57[a] + 0	<10[a]	<10[a]
1b + **1a**	K	47	—	14 + 58	—	—

[a] The yield was determined from ^1H NMR spectroscopic data.

[b] The yield of the complex of cryptand **3d** with Na_2CO_3; ~20 °C, 120 h.

[c] The yield of dihydroiodide of cryptand **3e**.

Condensation of diiodides **1a,b** with diamines **2a—c** and diazacrown ethers **2d,e** was carried out in dry MeCN in the presence of alkali metal carbonates. The yields of products **3a—e** are given in Table 1. Due to the presence of the protective group in diiodide **1b**, diethyl acetal **3f** was prepared in a rather high yield. However, the yield of aldehyde **3c** after removal of the protective group appeared to be substantially lower (14% in two steps) than that in the case of the one-pot synthesis from **1a**. For this reason, the syntheses of benzodiazacrown compounds **3b—e** containing tertiary nitrogen atoms were carried out without pre-protection of the formyl group. The lowest yield (~18%) was observed for compound **3a**. A substantial increase in the yield was achieved with the use of diiodides **1a,b**. Although the protection was removed in the course of formation of diazacrown ether and(or) its isolation from the reaction mixture, the yield of **3a** was increased more than twofold. It should be noted that compound **3a** is unstable on storage due, apparently, to the presence of the reactive formyl and amino groups.

The published data on the dependence of the yields of azacrown compounds on the nature of the solvent and the template effect of metal cations are scarce and often contradictory.[12,13] In the studies,[13—15] it was noted that alkali metal cations virtually do not exhibit the template effect in the synthesis of azacrown ethers. Investigation of the formation of diaza-18-crown-6 from the corresponding diamine and diiodide in MeOH, dioxane, 1,2-dimethoxyethane, and MeCN demonstrated that the highest yield in MeCN was obtained in the presence of Na_2CO_3, whereas the highest yields in other solvents were attained in the presence of K_2CO_3.[16] In DMF, the yield of tetra(*N*-tosylaza)-18-crown-6 in the presence of K_2CO_3 was four times higher than that in the presence of Na_2CO_3.[17] An increase in the yield of mono- and diazacrown ethers was observed[18,19] under the conditions of phase transfer catalysis in the presence of alkali metal cations, whose size matches well the size of the cavity of the crown ether synthesized.

The synthesis of [2.2.2]-cryptand from 1,8-diiodo-3,6-dioxaoctane and diaza-18-crown-6 called for a search for the appropriate solvent and alkali metal carbonate.[20—22] For example, the synthesis of [2.2.2]-cryptand in MeCN proceeds most successfully in the presence of Na_2CO_3, whereas the use of potassium, cesium, or lithium carbonates leads to a substantial decrease in the yield of the product.[20] The reactions with the use of the corresponding ditosylate instead of diiodide in the presence of so-

Table 2. Yields of **3c** prepared by condensation of diiodide **1a** with diamine **2c** in the presence of Na_2CO_3 in different solvents at 64—85 °C (50 h) according to ^{1}H NMR spectroscopic data

Solvent	Yield (%)	Solvent	Yield (%)
EtOH	0	EtOH—water (1 : 1)	26
MeCN	89	MeCN—water (1 : 1)	0
THF	5	THF —water (1 : 1)	84
DMF	3	DMF—water (1 : 1)	0
Dioxane	6	Dioxane—water (1 : 1)	20

Table 3. Influence of alkali metal cations on the yields of **3b,c** prepared by condensation of **1a** with **2b,c** in the presence of M_2CO_3 (MeCN, 80 °C, 20 h) according to ^{1}H NMR spectroscopic data

Diazacrown ether	Yield (%)			
	Li	Na	K	Cs
3b	38	62	88	37
3c	55	91	57	46

dium or potassium cations afforded [2.2.2]-cryptand in virtually equal yields.[21—23] It was also demonstrated[24] that alkali metal cations influence substantially the side processes in the synthesis of cryptands.

The published data provide evidence that the reactions giving rise to diazacrown ethers and cryptands are sensitive to the nature of the solvent, conditions of condensation, and the base used. Therefore, the synthesis of new nitrogen-containing crown ethers calls for an in-depth examination of all these factors.

Using the synthesis of compound **3c** as an example, we studied the influence of the nature of the solvent on the yield of the target product (Table 2). The use of anhydrous MeCN or aqueous THF in the presence of Na_2CO_3 allowed us to prepare **3c** in high yield. In other solvents, the reaction afforded the target product in low yield, if at all. Apparently, these results are indicative of the influence of a number of factors, such as solubility of M_2CO_3, polarity of the solvent, its ability to form hydrogen bonds with the nitrogen atoms in **2a—e** and podand **5**, resistance of the solvent to aqueous alkali, *etc*.

It can be suggested that the reaction giving rise to diazacrown compounds **3a—e** involves several steps (Scheme 3). *N*-Alkylation of diamines **2a—e** with diiodide **1a** produces cation **4**, whose deprotonation affords aza podand **5**. Metal cations can promote the final step of condensation through the intermediate formation of template complex **6**. This effect has been observed earlier in the synthesis of crown and thiacrown ethers.[9]

We studied the influence of alkali metal cations on the formation of benzodiazacrown ethers **3b,c** (Table 3). The highest yield of **3b** was achieved in the presence of K^+ ions, whereas the highest yield of **3c** was obtained in the presence of Na^+ ions, although it is known[25] that the sizes of the sodium and potassium cations are most suitable for the cavities of 15-crown-5 and 18-crown-6, respectively.

To elucidate the question of whether cyclization proceeds through the intermediate formation of complex **6** and reveal its influence on the final step of cyclization, we studied mixtures of diazacrown ethers **3b,c** with alkali metal perchlorates by ^{1}H NMR spectroscopy. It is known that NMR spectroscopy is extensively used for gaining insight into the structures and stability of complexes of crown-containing compounds.[6,27] The changes in the ^{1}H NMR spectra observed after the addition of an excess of $MClO_4$ to solutions of **3b,c** in CD_3CN are presented in Table 4.

It should be noted that no changes in the positions of the signals for the protons of benzodiazacrown ethers **3b,c** were observed upon the addition of the same excess of Et_4NClO_4, which cannot form guest—host complexes with macrocyclic compounds, to solutions of **3b,c**. Consequently, the changes in δ_H presented in Table 4 are associated primarily with the complex formation (Scheme 4).

Scheme 3

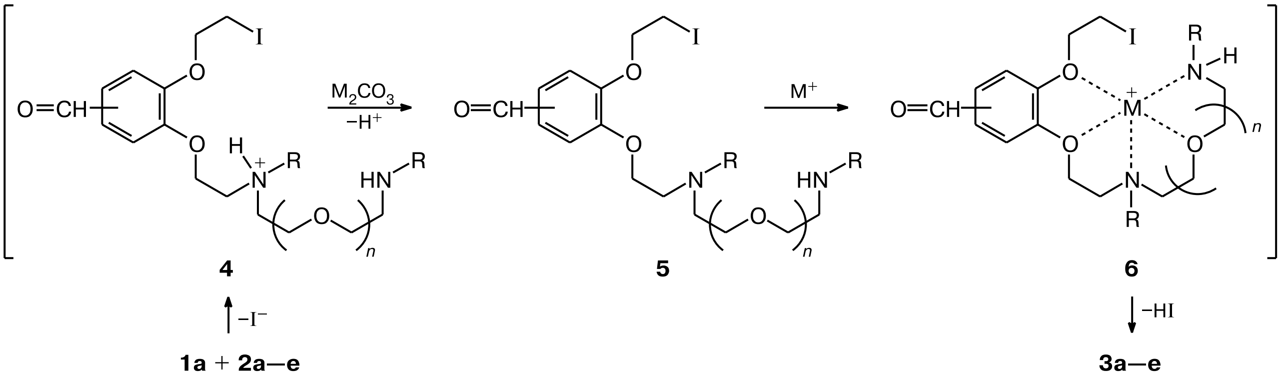
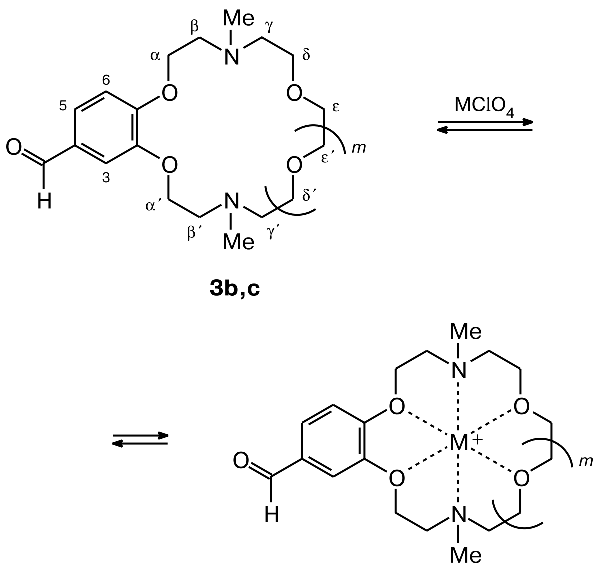


Table 4. Changes in the chemical shifts ($\Delta\delta_H$) of the signals for the protons of crown ethers **3b,c** upon the addition of $MClO_4$

Complex	$\Delta\delta_H$										
	α-CH_2O	α′-CH_2O	β,β′-CH_2N	γ,γ′-CH_2N	δ,δ′-CH_2O	ε,ε′-CH_2O	H(3)	H(5)	H(6)	CH=O	Me
(**3b** • Li)$^+$	0.20	0.21	0.11, 0.09	−0.06	0.00	—	0.12	0.13	0.13	0.05	0.04
(**3b** • Na)$^+$	0.09	0.11	−0.15, −0.17	0.01	−0.04	—	0.08	0.09	0.08	0.04	0.04
(**3b** • K)$^+$	0.07	0.09	−0.09, −0.11	−0.03	−0.06	—	0.05	0.07	0.06	0.03	0.02
(**3b** • Cs)$^+$	0.04	0.04	−0.06, −0.08	−0.04	−0.07	—	0.04	0.04	0.04	0.02	−0.03
(**3c** • Li)$^+$	0.15	0.11	−0.15, −0.07	−0.09, −0.02	0.01, 0.10	0.14, 0.17	0.27	0.22	0.21	0.07	0.14
(**3c** • Na)$^+$	0.09	0.10	−0.09, −0.10	−0.11	0.02	0.06	0.10	0.09	0.09	0.04	−0.02
(**3c** • K)$^+$	0.11	0.13	−0.08, −0.10	−0.13	0.00	0.05	0.12	0.08	0.12	0.04	−0.10
(**3c** • Cs)$^+$	0.08	0.09	−0.14, −0.16	−0.13	−0.02	0.04	0.10	0.06	0.10	0.04	−0.11

Note. $\Delta\delta_H = \delta_{complex} - \delta_{ligand}$. Conditions: CD_3CN, 25 °C; $C_L = 1 \cdot 10^{-3}$ mol L^{-1}; ligand : metal = 1 : 5; M = Li, Na, K, or Cs.

Scheme 4



3b,c

(3b,c • M)$^+$

M = Li, Na, K, Cs; *m* = 0, 1.

The complex formation of diazacrown ethers **3b,c** with metal cations differs substantially from the complex formation with all-oxygen crown ethers. The inclusion of a cation into the cavity of the crown-ether fragment of the latter compounds causes downfield shifts of δ_H for all types of protons. By contrast, there is no single direction for $\Delta\delta_H$ for the protons of the CH_2O and CH_2N groups of **3b,c**. This difference may be associated with a substantial conformational rearrangement of the macroheterocycle of the diazacrown ethers in the course of complex formation.

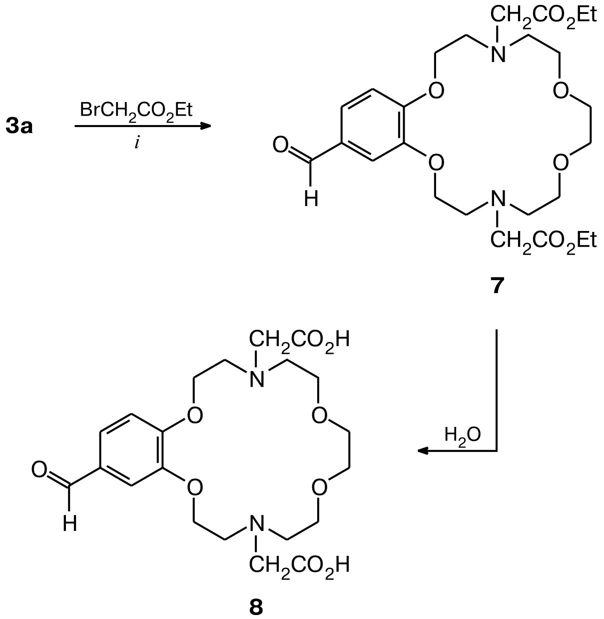
As can be seen from Table 4, the majority of the most downfield or least upfield changes in δ_H in the NMR spectra of **3b,c** in the series of Na^+, K^+, and Cs^+ are observed for crown ether **3b** in the presence of Na^+ ions, whereas the corresponding changes for **3c** are observed in the presence of K^+ or Na^+ ions. Although the heteroatoms of the macrocycles are involved in coordination to the metal cations in a different mode, the correlation between the sizes of the cavity of benzodiazacrown ether and the metal cation is, on the whole, confirmed. This is indirect evidence for the possible existence of intermediate template complex **6** in the course of formation of **3b,c**. In this complex, the lone electron pairs of the amino groups are involved in formation of coordination bonds with the metal cation (see Scheme 3). However, too strong coordination of the metal cation by the nitrogen atom of the terminal amino group in complex **6** should hinder the final step of formation of **3b,c**, *viz.*, *N*-alkylation of this amino group, which was observed in experiments. Hence, the NMR spectroscopic study confirmed that metal cations can exhibit the negative template effect resulting in a decrease in the yield of the target product where the size of the metal cations involved in the reaction matches well the size of the cavity of the diazacrown ether formed.

It is known[28] that Li^+ ions in an aprotic medium inhibit the formation of benzo-18-crown-6 due to strong coordination by the *ortho*-phenylenedioxy fragment of the molecule of the corresponding podand. Of all the metal alkali complexes under study, the largest shifts of the signals for the aromatic protons and the protons of the $C\underline{H}_2OAr$ groups were observed for lithium complexes **3b,c**, which is, apparently, evidence in favor of this type of coordination. However, in the present case, this coordination should not lead to a substantial decrease in the template effect of the lithium cation and, correspondingly, to a decrease in the yield of the target product due to a large distance from the reaction center. This conclusion was confirmed experimentally (see Table 3). The complex formation of diazacrown ethers **3b,c** with $CsClO_4$ results predominantly in small downfield and substantial upfield shifts $\Delta\delta_H$ in the series of the metals studied. Apparently, the low charge density of the Cs^+ ion due to its large size decreases the efficiency of pre-organization of the aza podand in complex **6**, which has an adverse effect on the yield of macroheterocycles.

Examination of the possibility of the synthesis of cryptands **3d,e** demonstrated that this process depends even more substantially on the nature of the metal cation. In MeCN, compounds **3d,e** were formed only in the presence of Na_2CO_3. The use of other alkali metal carbonates gave rise to substantial amounts (>90%) of polymeric products. This result is consistent with the data obtained in the study aimed at developing a procedure for the synthesis of [2.2.2]-cryptand.[20—22] Cryptand **3d** was isolated as a complex with sodium carbonate, which indicates that the size of the Na^+ cation matches well the size of the cavity of **3d**. Cryptand **3e** possessing a larger cavity was isolated as dihydroiodide monohydrate. Apparently, **3e** is an inclusion compound in which two hydrogen cations within the cavity of the cryptand are bound correspondingly to two nitrogen atoms.

Using crown ether **3a** as an example, it was demonstrated that diazacrown ethers containing secondary nitrogen atoms in the macrocycle can be subjected to further *N*-functionalization. For example, bis(ethoxycarbonylmethyl) derivative **7** was prepared by alkylation of **3a** with ethyl bromoacetate in refluxing acetonitrile or THF at ≈20 °C. Subsequent hydrolysis of the ester groups in **7** afforded new promising ligand **8**, *viz*., a macrocyclic analog of ethylenediaminediacetic acid (Scheme 5).

Scheme 5



i. Na_2CO_3, MeCN, 80 °C or Et_3N, THF, 20 °C.

To summarize, condensation of 3,4-bis(2-iodoethoxy)benzaldehyde **1a** with diamines **2a—c** and diazacrown ethers **2d,e** in the presence of alkali metal carbonates under high dilution conditions in MeCN or aqueous THF afforded formyl derivatives of benzodiazacrown ethers and benzocryptands in good yields. It was found that the metal cations have the dual template effect on the course of the reaction. On the one hand, the pre-organization of an intermediate podand giving rise to a pseudomacrocyclic complex in the presence of metal cations facilitates the formation of the final product. On the other hand, coordination of the nitrogen atoms to the metal cation in the intermediate complex hinders cyclization involving the terminal amino group and decreases the yield of the product. Consequently, the yields of compounds **3a—e** reflect the influence of all the above factors. It was demonstrated that the benzoazacrown ethers synthesized can be subjected to further *N*-functionalization. In the present study, simple and convenient procedures were developed for the synthesis of benzodiazacrown ethers containing various functional groups both in the benzene ring and at the nitrogen atoms of the macroheterocycle.

Experimental

The melting points (uncorrected) were measured on a Mel-Temp II instrument. The ^1H NMR spectra were recorded on a Bruker DRX500 spectrometer (500.13 MHz) using $CDCl_3$, DMSO-d_6, C_6D_6, and CD_3CN as the solvents; the residual protons of the solvents were used as the internal standard (δ 7.27, 2.50, 7.15, and 1.96, respectively). The chemical shifts were measured with an accuracy of 0.01 ppm. The spin-spin coupling constants were measured with an accuracy of 0.1 Hz. The assignment of the signals for the protons was made based on the results of 2D COSY and NOESY spectroscopy. The IR spectra were recorded on Shimadzu IR-435 and Bruker ISF-113V spectrometers in Nujol mulls or in films on KBr. The mass spectra were obtained on a Varian MAT 311A instrument with direct inlet of the sample into the ionization zone; the energy of ionizing electrons was 70 eV. Elemental analyses were carried out at the Laboratory of Microanalysis of the A. N. Nesmeyanov Institute of Organoelement Compounds of the Russian Academy of Sciences (Moscow). The course of the reaction was monitored by TLC on DC-Alufolien Kieselgel 60 F_{254} and DC-Alufolien Aluminiumoxid 60 F_{254} neutral (Typ E) plates. Column chromatography was carried out on silica gel (Kieselgel 60, 0.063—0.200 mm, Merck) and Al_2O_3 (Aluminiumoxid 150 basisch, Typ E, 0.063—0.200 mm, Merck).

2,2´-(Ethylenedioxy)bisethylamine, 7,16-diaza-18-crown-6, ethyl bromoacetate, 1,2,4,5-tetrachlorobenzene, anhydrous solvents (acetonitrile, ethanol, THF, dioxane, DMF), anhydrous alkali metal carbonates (Aldrich), 1,8-bis(methylamino)-3,6-dioxaoctane, 1,5-bis(methylamino)-3-oxapentane, and 7,13-diaza-15-crown-5 (Janssen) were used without additional purification. 3,4-Bis(2-iodoethoxy)benzaldehyde **1a** was prepared according to a procedure described earlier.[9,11]

Synthesis of formyl derivatives of benzodiazacrown ethers 3a—c (general procedure). A solution (10 mL) of diiodide **1a**

(0.50 g, 1.2 mmol) and a solution (10 mL) of diamine **2a—c** (1.3 mmol) were added simultaneously with stirring to a solution (100 mL) of M_2CO_3 (M = Li, Na, K, or Cs) (5.6 mmol) at 64—85 °C for 30 min. The reaction mixture was refluxed for 20—50 h and then cooled. The precipitate that formed was filtered off and the filtrate was concentrated *in vacuo*. Pure products **3a—c** were isolated by chromatography of the residue on Al_2O_3 using a benzene—ethanol mixture (20 : 1) as the eluent. Products **3b,c** were additionally purified by extraction with refluxing hexane. The solvents used and the yields of the target products are given in Tables 1—3. The yields of **3a—c** were determined from the ^{1}H NMR spectra according to the following procedure. A mixture of weighed samples of the residue, which was obtained after concentration of the filtrate, and 1,2,4,5-tetrachlorobenzene was dissolved in $CDCl_3$ or CD_3CN. The yields were determined with an accuracy of $\pm 10\%$ by comparing the integral intensities of the signals for the aromatic protons belonging to products **3a—c** and 1,2,4,5-tetrachlorobenzene. It should be noted that the chemical shifts of the signals for H_{arom} of the products differ from those of the starting diiodide.

3,4,5,6,8,9,12,13,14,15-Decahydro-2*H*,11*H*-benzo-1,7,10,16,4,13-tetraoxadiazacyclooctadecene-18-carbaldehyde (3a), yellow oil. ^{1}H NMR (CD_3CN, 25 °C), δ: 2.85 (m, 4 H, 5- and 12-CH_2N); 3.05 (m, 4 H, 3- and 14-CH_2N); 3.57 (s, 4 H, 8- and 9-CH_2O); 3.59 (m, 4 H, 6- and 11-CH_2O); 4.19 and 4.22 (both m, 4 H, 2- and 15-CH_2O); 7.13 (d, 1 H, H(20), J = 8.3 Hz); 7.43 (d, 1 H, H(17), J = 1.9 Hz); 7.43 (dd, 1 H, H(19), J = 8.3 Hz, J = 1.9 Hz); 9.84 (s, 1 H, CH=O). IR (in film), ν/cm^{-1}: 3410 (N—H), 1686 (C=O). MS, m/z (I_{rel} (%)): 338 $[M]^+$ (0.4), 176 (43), 162 (23), 128 (100), 127 (99), 89 (23), 64 (22), 63 (41), 61 (24), 57 (29), 56 (53).

4,10-Dimethyl-3,4,5,6,9,10,11,12-octahydro-2*H*,8*H*-benzo-1,7,13,4,10-trioxadiazacyclopentadecene-15-carbaldehyde (3b), yellowish powder, m.p. 70—73 °C (heptane). Found (%): C, 57.65; H, 8.75; N, 7.86. $C_{17}H_{26}N_2O_4 \cdot 2H_2O$. Calculated (%): C, 56.97; H, 8.44; N, 7.82. ^{1}H NMR (CD_3CN, 30 °C), δ: 2.29 (s, 6 H, 2 NMe); 2.64 (t, 4 H, 5- and 9-CH_2N, J = 5.6 Hz); 2.82 (m, 4 H, 3- and 11-CH_2N); 3.62 (m, 4 H, 6- and 8-CH_2O); 4.08 (m, 2 H, 12-CH_2O); 4.11 (m, 2 H, 2-CH_2O); 7.06 (d, 1 H, H(17), J = 8.3 Hz); 7.32 (d, 1 H, H(14), J = 1.7 Hz); 7.49 (dd, 1 H, H(16), J = 8.3 Hz, J = 1.7 Hz); 9.83 (s, 1 H, CH=O). IR (in film), ν/cm^{-1}: 1682 (C=O). MS, m/z (I_{rel} (%)): 322 $[M]^+$ (0.6), 222 (25), 221 (61), 208 (33), 88 (100), 84 (28), 72 (39), 71 (31), 70 (69), 58 (44), 57 (28).

4,13-Dimethyl-3,4,5,6,8,9,12,13,14,15-decahydro-2*H*,11*H*-benzo-1,7,10,16,4,13-tetraoxadiazacyclooctadecene-18-carbaldehyde (3c), yellow oil.[8] ^{1}H NMR (CD_3CN, 25 °C), δ: 2.30 and 2.31 (both s, 6 H, 2 NMe); 2.72 (t, 4 H, 5- and 12-CH_2N, J = 5.7 Hz); 2.92 (m, 4 H, 3- and 14-CH_2N); 3.55 (s, 4 H, 8- and 9-CH_2O); 3.59 (m, 4 H, 6- and 11-CH_2O); 4.14 (t, 2 H, 15-CH_2O, J = 5.6 Hz); 4.17 (t, 2 H, 2-CH_2O, J = 5.7 Hz); 7.11 (d, 1 H, H(20), J = 8.3 Hz); 7.42 (d, 1 H, H(17), J = 1.9 Hz); 7.51 (dd, 1 H, H(19), J = 8.3 Hz, J = 1.9 Hz); 9.84 (s, 1 H, CH=O).

Complex of 4,11,17,20,25-pentaoxa-1,14-diazatricyclo[12.8.5.0^{5,10}]heptacosa-5,7,9-triene-7-carbaldehyde with Na_2CO_3 (3d·Na_2CO_3). A mixture of diiodide **1a** (100 mg, 0.22 mmol), diazacrown ether **2d** (54 mg, 0.25 mmol), Na_2CO_3 (131 mg, 1.24 mmol), and anhydrous MeCN (3 mL) was stirred at ≈20 °C for 120 h. The precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was washed with benzene (3×10 mL) and recrystallized from an acetonitrile—benzene mixture to prepare the complex **3d**·Na_2CO_3 in a yield of 62 mg (53%) as yellow crystals, m.p. 255—257 °C (with decomp.). Found (%): C, 49.93; H, 6.13. $C_{21}H_{32}N_2O_6 \cdot Na_2CO_3 \cdot H_2O$. Calculated (%): C, 49.62; H, 6.44. ^{1}H NMR (DMSO-d_6, 30 °C), δ: 2.34 and 2.98 (both m, 4 H each, 2 CH_2N); 3.15 and 3.28 (both m, 2 H each, CH_2N); 3.42 (m, 4 H, 2 CH_2O); 3.55 (s, 4 H, 2 CH_2O); 3.68 (m, 4 H, 2 CH_2O); 4.18 (m, 4 H, 2 $C\underline{H}_2OAr$); 7.24 (d, 1 H, H(9), J = 8.3 Hz); 7.45 (d, 1 H, H(6), J = 1.7 Hz); 7.62 (dd, 1 H, H(8), J = 8.3 Hz, J = 1.7 Hz); 9.88 (s, 1 H, CH=O). IR (Nujol mulls), ν/cm^{-1}: 1682 (C=O).

4,11,17,20,25,28-Hexaoxa-1,14-diazatricyclo[12.8.8.0^{5,10}]triaconta-5,7,9-triene-7-carbaldehyde dihydroiodide (3e·2HI). A solution of diiodide **1a** (0.50 g, 1.12 mmol) in anhydrous MeCN (10 mL) and a solution of diazacrown ether **2e** (0.23 g, 0.86 mmol) in anhydrous MeCN (10 mL) were simultaneously added with stirring and refluxing to a suspension of Na_2CO_3 (0.59 g 5.6 mmol) in anhydrous MeCN (70 mL) for 1 h. The reaction mixture was refluxed for 20 h and then cooled. The precipitate that formed was filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ and the solution was washed with water and concentrated *in vacuo*. The residue was transferred to a thin silica gel layer (h = 7 cm). Elution with a benzene—ethyl acetate mixture (20 : 1) afforded the starting compound **1a** in a yield of 0.20 g. Subsequent elution with a gradient benzene—ethanol mixture (to 33%) gave **3e**·2HI in a yield of 0.29 g (46%) as a yellow powder, m.p. 134—138 °C (MeOH—Et_2O). Found (%): C, 38.15; H, 5.09. $C_{23}H_{36}N_2O_7 \cdot 2HI \cdot H_2O$. Calculated (%): C, 38.03; H, 5.55. ^{1}H NMR (DMSO-d_6, 25 °C), δ: 2.55—2.70 (m, 8 H, 4 CH_2N); 2.76 (m, 4 H, 2 CH_2N); 3.49 (m, 8 H, 4 CH_2O); 3.57 (s, 8 H, 4 CH_2O); 4.26 and 4.30 (both m, 2 H each, $C\underline{H}_2OAr$); 7.32 (d, 1 H, H(9), J = 7.9 Hz); 7.51 (s, 1 H, H(6)); 7.60 (d, 1 H, H(8), J = 7.9 Hz); 9.87 (s, 1 H, CH=O). IR (in film), ν/cm^{-1}: 1685 (C=O). MS, m/z (I_{rel} (%)): 452 $[M - 2 HI]^+$ (2), 315 (48), 144 (67), 114 (92), 100 (90), 84 (49), 71 (48), 70 (80), 57 (59), 56 (100), 55 (46).

Synthesis of benzodiazacrown ethers 3a,c using diiodide containing an acetal protective group. A mixture of diiodide **1a** (1.00 g, 2.24 mmol), triethyl orthoformate (0.56 mL, 3.00 mmol), NH_4Cl (10 mg, 0.2 mmol), and anhydrous EtOH (2 mL) was refluxed for 3 h, concentrated, and dried *in vacuo*. The residue, which contained (according to the ^{1}H NMR spectroscopic data) a mixture of **1a** and its acetal **1b** in a ratio of ≈5 : 95, was used in condensation with diamines **2a,c**.

A solution of a mixture of **1a** and **1b** (≈5 : 95) in anhydrous MeCN (10 mL) and a solution of diamine **2a,c** (2.6 mmol) in anhydrous MeCN (10 mL) were simultaneously added with stirring and refluxing to a suspension of K_2CO_3 (1.55 g, 11.2 mmol) in anhydrous MeCN (100 mL) for 30 min. The reaction mixture was refluxed for 20 h and then cooled. The precipitate was filtered off, the filtrate was concentrated *in vacuo*, and the residue was chromatographed on Al_2O_3 using a benzene—ethanol mixture (20 : 1) as the eluent. The reaction of diamine **2a** afforded diazacrown ether **3a** in a yield of 0.36 g (47%). The reaction of diamine **2c** gave rise to acetal **3f** and aldehyde **3c** in yields of 0.57 g (58%) and 0.11 g (14%), respectively.

Hydrolysis of diethyl acetal **3f** was carried out by keeping a solution of acetal (362 mg) in 5% HCl (10 mL) at ≈20 °C for one day. Then a 5% NaOH solution was added to pH 10. The reaction mixture was extracted with $CHCl_3$ (3×20 mL), the chloroform extracts were concentrated *in vacuo*, and the residue was purified as described in the synthesis of **3c** from **1a**. Crown ether **3c** was isolated in a yield of 72 mg (24%) as a yellow oil.

4-Diethoxymethyl-1,2-bis(2-iodoethoxy)benzene (1b). ^{1}H NMR (C_6D_6 30 °C), δ: 1.15 (t, 6 H, 2 Me, J = 7.1 Hz); 2.90 (t, 2 H, CH_2I, J = 6.6 Hz); 2.91 (t, 2 H, CH_2I, J = 6.7 Hz); 3.42 (dq, 2 H, 2 $C\underline{H}_aH_bMe$, J = 9.6 Hz, J = 7.1 Hz); 3.56 (dq, 2 H, 2 $CH_a\underline{H}_bMe$, J = 9.6 Hz, J = 7.1 Hz); 3.79 (t, 2 H, $C\underline{H}_2OAr$, J = 6.7 Hz); 3.80 (t, 2 H, $C\underline{H}_2OAr$, J = 6.6 Hz); 5.45 (s, 1 H, $C\underline{H}Ar$); 6.62 (d, 1 H, H(6), J = 8.2 Hz); 7.14 (dd, 1 H, H(5), J = 8.2 Hz, J = 1.9 Hz); 7.16 (d, 1 H, H(3), J = 1.9 Hz).

18-Diethoxymethyl-4,13-dimethyl-3,4,5,6,8,9,12,13,14,15-decahydro-2*H*,11*H*-benzo-1,7,10,16,4,13-tetraoxadiazacyclooctadecene (3f), yellow oil. ^{1}H NMR ($CDCl_3$—CCl_4 (1 : 1) 25 °C), δ: 1.23 (t, 6 H, 2 $\underline{Me}CH_2$); 2.38 and 2.39 (both s, 6 H, 2 MeN); 2.83 (m, 4 H, 5- and 12-CH_2N); 3.00 (t, 4 H, 3- and 14-CH_2N, J = 5.5 Hz); 3.44—3.62 (m, 8 H, 2 $C\underline{H}_2Me$, 8- and 9-CH_2O); 3.65 (t, 4 H, 6- and 11-CH_2O, J = 5.6 Hz); 4.08 (m, 4 H, 2- and 15-CH_2O); 5.41 (s, 1 H, $C\underline{H}Ar$); 6.80 (d, 1 H, H(20), J = 8.2 Hz); 6.94 (dd, 1 H, H(19), J = 8.2 Hz, J = 1.5 Hz); 6.97 (d, 1 H, H(17), J = 1.5 Hz). MS, m/z (I_{rel} (%)): 440 $[M]^+$ (1), 282 (90), 229 (92), 146 (88), 132 (90), 100 (91), 72 (94), 71 (93), 70 (100), 58 (96), 57 (95).

4,13-Bis(ethoxycarbonylmethyl)-3,4,5,6,8,9,12,13,14,15-decahydro-2*H*,11*H*-benzo-1,7,10,16,4,13-tetraoxadiazacyclooctadecene-18-carbaldehyde (7). *A*. A solution of diazacrown ether **3a** (64 mg, 0.19 mmol), ethyl bromoacetate (53 μL, 0.47 mmol), and dry triethylamine (66 μL, 0.47 mmol) in anhydrous THF (5 mL) was kept at ≈20 °C for one week. Then the solvent was evaporated *in vacuo* and the residue was chromatographed on Al_2O_3 using successively a benzene—ethyl acetate mixture (20 : 1) and a benzene—ethanol mixture (20 : 1) as the eluent. Diester **7** was prepared in a yield of 52 mg (54%) as a viscous yellow oil. ^{1}H NMR ($CDCl_3$, 25 °C), δ: 1.26 and 1.27 (both t, 6 H, 2 $\underline{Me}CH_2$, J = 7.2 Hz, J = 7.0 Hz); 3.07 (m, 4 H, 5- and 12-CH_2N); 3.27 (m, 4 H, 3- and 14-CH_2N); 3.55 and 3.56 (both s, 4 H, 2 CH_2CO_2); 3.57 (s, 4 H, 8- and 9-CH_2O); 3.64 (m, 4 H, 6- and 11-CH_2O); 4.12—4.22 (m, 8 H, 2 $C\underline{H}_2Me$, 2- and 15-CH_2O); 6.96 (d, 1 H, H(17), J = 8.1 Hz); 7.39 (d, 1 H, H(20), J = 1.9 Hz); 7.43 (dd, 1 H, H(18), J = 8.1 Hz, J = 1.9 Hz); 9.84 (s, 1 H, CH=O). IR (in film), ν/cm^{-1}: 1732 (C=O), 1681 (C=O). MS, m/z (I_{rel} (%)): 510 $[M]^+$ (5), 438 (29), 437 (100), 280 (29), 144 (37), 142 (28), 130 (54), 114 (62), 100 (55), 70 (33), 56 (89).

B. A mixture of diazacrown ether **3a** (90 mg, 0.27 mmol), ethyl bromoacetate (60 μL, 0.54 mmol), and Na_2CO_3 (140 mg, 1.35 mmol) in anhydrous MeCN (10 mL) was refluxed with stirring for 35 h. The precipitate was filtered off, the filtrate was concentrated *in vacuo*, and the residue was extracted with benzene (3×50 mL). The benzene extracts were washed with water (3×30 mL) and the solvent was distilled off *in vacuo*. The residue, which contained (according to the TLC data) product **7**, was used without additional purification in the synthesis of acid **8**.

4,13-Bis(carboxymethyl)-3,4,5,6,8,9,12,13,14,15-decahydro-2*H*,11*H*-benzo-1,7,10,16,4,13-tetraoxadiazacyclooctadecene-18-carbaldehyde (8). A solution of ester **7**, which was prepared according to the procedure *B*, in water (100 mL) was refluxed with stirring for 80 h. After cooling, the reaction mixture was extracted successively with Et_2O (2×30 mL) and benzene (3×20 mL). The aqueous phase was concentrated *in vacuo*. Acid **8** was prepared in a yield of 110 mg (the total yield in two steps was 83%) as a pale-yellow powder, m.p. 60—62 °C. Found (%): C, 51.49; H, 7.18; N, 6.01. $C_{21}H_{30}N_2O_9 \cdot 2H_2O$. Calculated (%): C, 51.42; H, 6.99; N, 5.71. ^{1}H NMR (DMSO-d$_6$, 30 °C), δ: 2.86 (br.m, 4 H, 5- and 12-CH_2N); 3.06 (br.m, 4 H, 3- and 14-CH_2N); 3.37 (br.s, 4 H, 2 CH_2CO_2); 3.48 (s, 4 H, 8- and 9-CH_2O); 3.51 (m, 4 H, 6- and 11-CH_2O); 4.14 (t, 2 H, $C\underline{H}_2OAr$, J = 5.2 Hz); 4.18 (t, 2 H, $C\underline{H}_2OAr$, J = 5.3 Hz); 7.19 (d, 1 H, H(17), J = 8.4 Hz); 7.42 (d, 1 H, H(20), J = 1.7 Hz); 7.55 (dd, 1 H, H(18), J = 8.4 Hz, J = 1.7 Hz); 9.84 (s, 1 H, CH=O). IR (Nujol mulls), ν/cm^{-1}: 1738 (C=O), 1678 (C=O).

This study was financially supported by the Russian Foundation for Basic Research (Project Nos. 03-03-32178 and 03-03-32929), the Ministry of Industry, Science, and Technology of the Russian Federation, and INTAS (Grant 01-0267).

References

1. J. S. Bradshaw, K. E. Krakowiak, and R. M. Izatt, *Azacrown Macrocycles*, J. Wiley and Sons Inc., New York—Chichester—Brisbane—Toronto—Singapore, 1993.
2. J. S. Bradshaw, *J. Inclus. Phen. Mol. Recogn. Chem.*, 1997, **19**, 221.
3. N. G. Luk´yanenko, *Ukr. Khim. Zh.* [*Ukr. Chem. J.*], 1999, **65**, 17 (in Russian).
4. G. D. Zasukhina, A. D. Durnev, I. M. Vasil´eva, S. P. Gromov, O. A. Fedorova, and M. V. Alfimov, *Byul. Eksp. Biol. Med.*, 2003, **135**, 302 [*Bull. Exp. Biol. Med.,* 2003, **135** (Engl. Transl.)].
5. *Crown Compounds: Towards Future Applications*, Ed. S. R. Cooper, VCH, 1992, Ch. 10—12.
6. A. Mishra, R. K. Behera, P. K. Behera, B. K. Mishra, and G. B. Behera, *Chem. Rev.*, 2000, **100**, 1973.
7. M. Shirai, A. Ueda, and M. Tanaka, *J. Polym. Sci., Polym. Chem. Ed.*, 1987, **25**, 1811.
8. S. P. Gromov, O. A. Fedorova, A. I. Vedernikov, V. V. Samoshin, N. S. Zefirov, and M. V. Alfimov, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 121 [*Russ. Chem. Bull.*, 1995, **44**, 116 (Engl. Transl.)].
9. O. A. Fedorova, A. I. Vedernikov, O. V. Eshcheulova, P. V. Tsapenko, Yu. V. Pershina, and S. P. Gromov, *Izv. Akad. Nauk, Ser. Khim.*, 2000, 1881 [*Russ. Chem. Bull., Int. Ed.*, 2000, **49**, 1853].
10. O. A. Fedorova, A. I. Vedernikov, O. V. Yescheulova, Y. V. Pershina, P. V. Tsapenko, and S. P. Gromov, *Synth. Commun.*, 2002, **32**, 1909.
11. S. P. Gromov, O. A. Fedorova, A. I. Vedernikov, O. V. Eshcheulova, Yu. V. Fedorov, and M. V. Alfimov, Pat. RF 2176256; *BIPM Byul. Izobr.*, 2001, 33.
12. K. E. Krakowiak, J. S. Bradshaw, and D. J. Zamecka-Krakowiak, *Chem. Rev.*, 1989, **89**, 929.

13. G. W. Gokel, D. M. Dishong, R. A. Schultz, and V. J. Gotto, *Synthesis*, 1982, 1997.
14. H. K. Frensdorff, *J. Am. Chem. Soc.*, 1971, **93**, 600.
15. J. E. Richman and T. J. Atkins, *Org. Synth.*, 1978, **58**, 86.
16. S. Kulstad and L. A. Malmsten, *Tetrahedron*, 1980, **36**, 521.
17. J. F. Beirnat and E. Luboch, *Tetrahedron*, 1984, **40**, 1927.
18. N. G. Lukyanenko, S. S. Basok, and L. K. Filonova, *Synthesis*, 1988, 335.
19. N. G. Lukyanenko, S. S. Basok, and L. K. Filonova, *J. Chem. Soc., Perkin Trans. 1*, 1988, 3141.
20. S. Kulstad and L. A. Malmsten, *Tetrahedron Lett.*, 1980, **21**, 643.
21. K. E. Krakowiak, J. S. Bradshaw, and R. M. Izatt, *Synlett*, 1993, 611.
22. K. E. Krakowiak, P. A. Krakowiak, and J. S. Bradshaw, *Tetrahedron Lett.*, 1993, **34**, 777.
23. K. E. Krakowiak and J. Inclus, *Phen. Mol. Recogn. Chem.*, 1997, **29**, 283.
24. K. E. Krakowiak, J. S. Bradshaw, X. Kou, and N. K. Dalley, *Tetrahedron*, 1995, **51**, 1599.
25. *Host Guest Complex Chemistry Macrocycles. Synthesis, Structure, Applications*, Eds. F. Vögtle and E. Weber, Springer-Verlag, Berlin—Heidelberg—New York—Tokyo, 1985, 31.
26. O. A. Fedorova, S. P. Gromov, and M. V. Alfimov, *Dokl. Akad. Nauk,* 1995, **341**, 219 [*Dokl. Chem.*, 1995 (Engl. Transl.)].
27. L. A. Fedorov and A. N. Ermakov, *Spektroskopiya YaMR v neorganicheskom analize* [*NMR Spectroscopy in Inorganic Analysis*], Nauka, Moscow, 1989, Ch. 2 and 3 (in Russian).
28. G. Ercolani, L. Mandolini, and B. Masci, *J. Am. Chem. Soc.*, 1981, **103**, 2780.

Received June 3, 2003;
in revised form October 31, 2003