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Synthesis of benzoaza-15(18)-crown-5(6) ethers and study of their complexes with lead(II)

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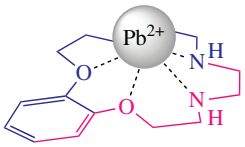
Two methods for obtaining of benzoaza-15(18)-crown-5(6) ethers from 1,2-bis(2-iodoethoxy)benzene or diethyl 1,2-phenylenebis(oxy)diacetate have been reported. The ability of the crown ethers to coordinate lead(II) ions has been estimated by potentiometric and NMR methods.



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Over the past decade, much of the research interest has been driven into the rapidly growing field of heavy metal complexes.[1,2] Heavy metal ions such as Pb^{2+} are commonly encountered toxic substances in the environment and pose significant health hazards when they are present in drinking water even in ppm concentrations.[3,4] Despite the negative effect of lead(II) related to pollution and health, lead-containing materials are increasingly used in batteries, nonlinear optical materials, ferroelectric compositions and semiconductors.[5–8] There is a continuous search for rapid, selective and sensitive techniques for the infield screening of Pb^{2+} ions in the environment.[9] Current treatments of lead intoxication involve various chelating agents, but they are usually nonspecific and relatively toxic.[10,11] Furthermore, Pb^{2+} cation possesses useful properties for application in nuclear medicine and is therefore of particular interest in the field of targeted and pretargeted radioimmunotherapy.[12]

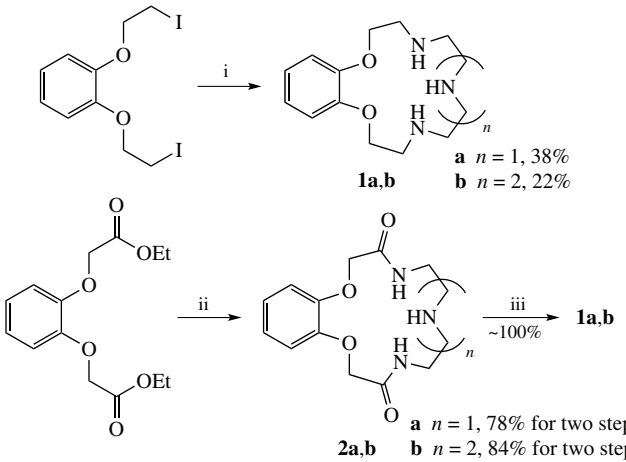
Lead(II) cation has a large ionic radius, variable coordination numbers (from 2 to 10), special coordination geometries (hemidirected or holodirected ones)[13,14] and is capable of binding to both hard and soft donor atoms. These properties make lead(II) an interesting metal to study, which forms as it often does the complexes with various types of ligands.[15] Therefore, the proper ligand that could bind lead(II) ions more strongly and efficiently is still sought for.[16,17] The Pb^{2+} ions have a high affinity to ligands containing O, N or both the donor atoms. The macrocyclic frameworks seem to be appropriate to prepare due to the high thermodynamic stability and kinetic inertness of such bindings.

In this research, benzoaza-15(18)-crown-5(6) ethers were chosen as ligands for Pb^{2+} ions. The combination of oxygen and nitrogen atoms in the crown ether ligand should provide strong affinity for lead(II). Besides, benzene ring was introduced to increase macrocyclic rigidity and thus to increase the rate of the complex formation and its stability.[18,19]

Two approaches have been tested for the synthesis of benzoazacrown compounds **1a** and **1b** (Scheme 1). The first method is based on a macrocyclization reaction between a dihalide and amines. The second approach is a two-stage one and consists of macrocyclization between a diester and amines, followed by reduction of the amide groups. The starting dihalide and diester were obtained according to the known methods.[20,21]

The synthesis of azacrown compounds **1a**,**b** by the first method was carried out for 3–4 days at room temperature in acetonitrile without using the high dilution technique and in the presence of potassium carbonate, which acted as a base and in the meantime its cation could exhibit a template effect to properly coordinate both the reactants. Macrocycle **1a** was thus prepared with a yield of 38% and compound **1b** with a one of 22%.[22] The moderate yields may be due to alkylation of reactive secondary amino groups presented in the initial polyamines.

Macrocyclization according to the second method between the diester and amines was carried out without using the high dilution technique and template ions in ethanol at room temperature for seven days (see Scheme 1). The ethanol molecule in this macrocyclization reaction can promote self-assembly



Scheme 1 *Reagents and conditions*: i, $H_2NCH_2(CH_2NHCH_2)_nCH_2NH_2$, K_2CO_3, MeCN, room temperature, 3–4 days; ii, $H_2NCH_2(CH_2NHCH_2)_nCH_2NH_2$, EtOH, room temperature, 7 days; iii, 1 M $BH_3 \cdot THF$, 0 °C, ~18 h, then 1 M HCl, reflux, 4 h.

phenomena, which explains the high yields of the target products. This solvent effect has already been revealed.[23,24] The yields of bisamides **2a**,**b** were 78 and 84%, respectively.[25,26] Note, that this type of macrocyclization provides significantly higher yields compared with the first method, which may be attributed to insignificant contribution of the acylation of secondary amino groups. The second stage involves the reduction of macrocyclic bis-amides **2a**,**b** with complex $BH_3 \cdot THF$,[27] the yields of the target benzoazacrown compounds **1a**,**b** being nearly quantitative (see Scheme 1). Thus, the two-step protocol brings about compound **1a** with a total yield of 78% and compound **1b** with a one of 82%.[28,29]

Earlier, we found that the bisamide benzocrown compounds bearing carboxylate or picolinate substituents are able to effectively coordinate Pb^{2+}.[26] Herein, we studied the complex formation for benzoazacrown ether compounds **1a**,**b** as well as their amide precursors **2a**,**b**. ^1H NMR spectra were recorded for the free ligands at different pD values and then with the addition of lead perchlorate and adjusting pDs of the solution. The spectra in the presence and in the absence of Pb^{2+} ion were compared to assess the interaction between the ions and benzoazacrown compounds.

The analysis of the protonation of ligand **1a** shows that its proton resonances at pD = 10.1 correspond to its deprotonated form [Figure 1(*a*)]. Acidification up to pD = 6.7 results in the protonation of the amino groups of ligand **1a**, causing the most pronounced changes in the resonances of macrocyclic protons [$\Delta\delta(H^4)$ = 0.14 ppm, $\Delta\delta(H^5)$ = 0.54 ppm, $\Delta\delta(H^6)$ = 0.45 ppm, $\Delta\delta(H^7)$ = 0.25 ppm], whereas the benzene proton signals are almost unchanged [see Figure 1(*b*) and Table S1, Online Supplementary Materials]. The resulting spectrum of protonated ligand **1a** is well resolved and corresponds to a compound with C_s symmetry, the greatest shifts being observed for the signals of the H^5 and H^6 protons. Therefore, it can be assumed that diprotonated species $H_2 \cdot$**1a** are formed, and two protons are attached to the opposite amino groups of the macrocycle.

In the presence of Pb^{2+} ion, the five proton signals of free ligand **1a** transform into the twenty ones resulting from the different magnetic environment for each proton [Figure 1(*c*)]. Such a behavior is consistent with the presence of single complex Pb·**1a** with a relatively rigid structure having C_1 symmetry. In the spectrum of complex Pb·**1a**, the resonances of macrocyclic protons change under the polarization effect of the metal ion, experiencing downfield shifts, which are more pronounced for the axial protons H^5, H^6 and H^7 [$\Delta\delta(H^{5a})$ = 0.93 ppm, $\Delta\delta(H^{5'a})$ = 0.62 ppm, $\Delta\delta(H^{6a})$ = 1.30 ppm, $\Delta\delta(H^{6'a})$ = 1.18 ppm, $\Delta\delta(H^{7a})$ = 0.85 ppm, $\Delta\delta(H^{7'a})$ = 1.12 ppm]. Signals for axial protons H^4 and benzene protons are shifted much less [$\Delta\delta(H^{4a})$ = 0.23 ppm, $\Delta\delta(H^{4'a})$ = 0.14 ppm, $\Delta\delta(H^1)$ = 0.05 ppm, $\Delta\delta(H^{1'})$ = 0.24 ppm, $\Delta\delta(H^2)$ = 0.28 ppm, $\Delta\delta(H^{2'})$ = 0.11 ppm], while the equatorial protons H^4 are shifted upfield [$\Delta\delta(H^{4'e})$ = −0.34 ppm] (see Table S1). The order of the chemical shift changes for proton peaks is H^5, H^6, $H^7 > H^4 > H^1$, H^2. The largest shifts for H^5, H^6 and H^7 adjacent to N donors indicate the strong coordination affinity between soft Pb^{2+} ion and soft N donor, whereas the smaller shift for the H^4 proton nearby hard O donors indicates weak affinity. Anyway, the data obtained indicate the formation of a complex with participation of all the heteroatoms in the coordination of Pb^{2+} cation. Since the diameter of Pb^{2+} cation (2.40 Å) is larger than the size of the macrocyclic cavity in ligand **1a** (1.7–2.2 Å), it can be concluded that the cation is located above the azacrown plane and the complex Pb·**1a** has a nest-like structure [see Figure 1(*c*)].

The acidification of the crown compound **1b** solution produces changes in the ^1H NMR spectrum similar to those observed for the protonation of ligand **1a**. The spectrum at pD = 10.2 corresponds to a fully deprotonated form of ligand **1b** (Figure S1). At pD = 6.2, compound **1b** is protonated, which causes a significant downfield shift of the signals for all aliphatic rotons with the most pronounced changes in the resonances of protons adjacent to N atoms [$\Delta\delta(H_4)$ = 0.13 ppm, $\Delta\delta(H_5)$ = 0.34 ppm, $\Delta\delta(H_6)$ = 0.36 ppm, $\Delta\delta(H_7)$ = 0.35 ppm, $\Delta\delta(H_8)$ = 0.30 ppm] (Table S2 and Figure S1). The spectrum of protonated ligand **1b** has six well-resolved signals and corresponds to a structure with C_s symmetry. It can be assumed that protons are mainly attached to two opposite nitrogen atoms or move rapidly between the nearby nitrogen atoms.

The spectrum of complex Pb·**1b** exhibits downfield shifts of all signals as well as their significant broadening (see Figure S1). Such phenomena are typical for the formation of a labile complex with non-rigid structure, in which dynamic processes of transformation between different conformations occur at an average rate. There are small downfield shifts of the signals of the protons of benzene ring and protons H^4 [$\Delta\delta(H^4)$ = 0–0.18 ppm, $\Delta\delta(H^{1,2})$ = 0.09–0.19 ppm]. This polarization effect is most likely due to the formation of coordination with the O atoms of ligand **1b** and, accordingly, the close position of Pb^{2+} ion to benzene ring, which may indicate the formation of inclusive complex Pb·**1b**. However, since the size of the metal cation is smaller than the macrocyclic cavity (2.6–3.2 Å) of compound

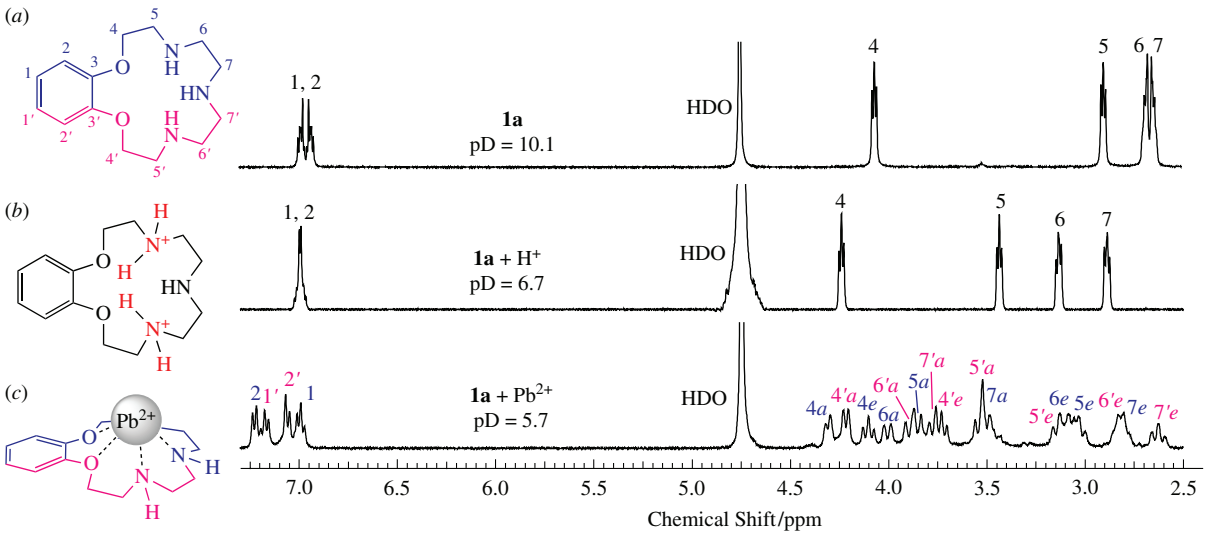


Figure 1 ^1H NMR spectra in D_2O of (*a*) free ligand **1a** (C_L = 10 mM, pD = 10.1), (*b*) ligand **1a** in the presence of H^+ (C_L = 10 mM, pD = 6.7) and (*c*) in the presence of Pb^{2+} (C_L = 10 mM, pD = 5.7).

1b, this leads to the formation of several conformations of nonrigid complex Pb·**1b**, among which intramolecular dynamic exchange processes occur in solution.

^{1}H NMR spectra of azacrown compound **2a** in free form, protonated form and in the presence of Pb^{2+} ion are shown in Figure S2. At pD = 5.8, the H^6 and H^7 protons exhibited downfield shifts compared to the free ligand at pD = 8.2 [$\Delta\delta(H^6)$ = 0.23 ppm, $\Delta\delta(H^7)$ = 0.42 ppm] (Table S3), indicating the protonation of single amine group in the presence of acid. The positions of the signals of benzene protons H^1, H^2 and the protons H^4 do not change. In the presence of Pb^{2+} ion in a solution, the downfield shifts of the signals of protons H^6 and H^7 [$\Delta\delta(H^6)$ = 0.24 ppm, $\Delta\delta(H^7)$ = 0.44 ppm] were observed (see Table S3). However, the resulting spectrum is completely analogous to the spectrum of the protonated form of ligand **2a** at the same pD value of 5.8. Thus, it can be concluded that crown compound **2a** does not form a complex with Pb^{2+} ion, or their interaction is insignificant in an aqueous solution. The study of protonation and complexation of compound **2b** demonstrated the results similar to those for ligand **2a**, namely, the formation of monoprotonated form H·**2b** in acidic condition and no interaction with Pb^{2+} ion (Figure S3 and Table S4).

Potentiometric titration showed that the first and second protons bound ligands **1a** and **1b** through the two step process with closed stepwise constants logarithm log$K$ = 8–9. The values are typical of processes of protonation for secondary amines. For ligand **1b** the value for the third protonation constant is log$K$ ~5, which is much lower than those for the first and second protonations due to electrostatic repulsion arising between the neighboring protonated aminogroups.

The presence of amide moiety in ligands **2a**,**b** significantly decreases the overall basicity provided by amines. Thus, only one amino group is found to be protonated upon titration of compound **2a** with log$K$ = 6.7. The complete deprotonation of ligand **2a** occurs already at pH = 9, in contrast to the one for other studied ligands (Figure S4). For ligand **2b**, the protonation of both amino groups of the macrocyclic moiety were observed (see Table 1), this was in agreement with the NMR data. At pH = 6.5, >95% of ligand **2b** exists in the monoprotonated form (Figure S5).

Ligands **1a**,**b** are able to bind Pb^{2+} with small difference in the values of stability constants, which is in accordance with their close basicity. Ligands **2a**,**b** do not demonstrate formation of complexes with Pb^{2+}.

In summary, two step protocol for the preparation of benzoazacrown ether compounds **1a**,**b** through the amide benzoazacrown precursors **2a**,**b** followed by reduction provides better yields compared with direct amination of 1,2-bis(2-iodoethoxy)-benzene. Amine ligands **1a**,**b** form complexes with Pb^{2+}, in which the cation is located above or inside the macrocyclic cavity. For bisamide ligands **2a**,**b**, the binding with Pb^{2+} ion in aqueous solution does not occur. Most likely, this difference can be explained by the lower basicity of ligands **2a**,**b** compared with **1a**,**b**, the less amount of donor amino groups and the greater rigidity of macrocycle structure, which is difficult to rearrange and provide a required number of coordination sites to fill the lead coordination sphere.

Table 1 Protonation and stability constants for the complexes of ligands **1a**,**b**/**2a**,**b** (denoted as L) with Pb^{2+} in 0.1 M KNO_3 at T = 25.0 °C.

Ion	Species	**1a**	**1b**	**2a**	**2b**
H^+	[LH]	9.38±0.04	9.5±0.1	6.7±0.2	8.9±0.3
	[LH_2]	17.53±0.05	18.0±0.2	–	14.5±0.5
	[LH_3]	–	23.0±0.3	–	–
Pb^{2+}	[LPb]	9.35±0.02	10.8±0.2	–	–

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.03.016.

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