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| D:\Rinat\Rinat\доки\журнал\статьи\logo.jpg | **Synthetic approaches to 18-triazacrown-6 ether and LEAD complex OF ITS ВIPYRIDYL DERIVATIVE** | | |
| Cite this: *INEOS OPEN*,  **20XX**, *X (X)*, XX–XX  DOI: 10.32931/ioXXXXx  *Received XX Month 20XX,*  *Accepted XX Month 20XX*  http://ineosopen.org | | A. A. Shchukina\*,a O. V. Tarasenko,a,b and A. D. Zubenkoa | |
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| Abstract  In this study, 18-membered triazacrown ether was prepared. We used three synthetic approaches to compare their efficiency. It was shown that the method using the macrocyclization reaction through the formation of a Schiff base turned out to be the most convenient. Coordination chemistry of new chelator **PADPy** bearing two pyridyl chelating groups with Pb2+ ion was investigated using ESI MS and 1H NMR spectroscopy. The formation of an inclusive complex of 1:1 M:L composition was shown. | | |  |

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| **Key words:** complexation, triazacrown-ether, chelator, ligand, lead. |

**Introduction**

Macrocyclic ligands based on azacrown compounds have found wide application in many areas, since selective complexation of metal ions is an important problem [1–3]. It is known that components of radiopharmaceuticals are macrocyclic ligands based on crown compounds and both nitrogen- and oxygen-containing crown ethers are developed [4–6]. Crown ethers containing only oxygen heteroatoms are used as extractants for radioactive cations in the reprocessing of spent nuclear fuel which is explained by the high resistance of crown ethers to radiation [7]. An attractive idea is the development of crown compounds combining N, O - heteroatoms in their composition [8]. In such crown ethers, one can expect resistance to radiation, a low dependence of complexation on the acidity of the medium, as well as the possibility of introducing additional chelating groups. An interesting type of ligands are double-armed crown ethers. In this class of compounds, the metal ion can be wrapped in such a way that additional donor groups provide its more efficient coordination in the macrocyclic cavity. In this article, we compared approaches to the synthesis of N, O - containing 18-membered crown ether to identify the most convenient synthesis method. In addition, chelating pyridyl groups were introduced into the triazacrown structure to yield the chelator **PADPy**. Introduction of chelating groups makes it possible to increase the cation-binding ability and selectivity of the ligand [9].

Results and discussion

To obtain the pyridine-containing triazacrown compound **3**, three methods were carried out to compare their efficiency (Scheme 1). Method A involved three steps. The first step was a macrocyclization reaction between diester **1** and 1,11-diamino-3,6,9-trioxaundecane without using high dilution technique. Then, bisamide macrocycle **2** was reduced using BH3‧THF complex. However, purification of target product **3** from the intermediate was complicated by incomplete reduction reaction, so the overall yield determined by NMR according to Method A was 24%. According to methods B and C, diester **1** was reduced to 2,6-di(hydroxymethyl)pyridine **4** using NaBH4. In method B, **4** reacted with thionyl chloride to give 2,6-di(chloromethyl)pyridine **5**, and then a macrocyclization reaction was performed with diamine in the presence of K2CO3. In this case, the macrocyclization process was accompanied by a side reaction of oligomerization, which complicated the isolation and purification of the target triazacrown compound **3**. The yield of **3** by NMRwas 2% in three stages. Varying the solvent and the temperature of the process did not give positive results. According to method C, the macrocyclization reaction using CaCl2 as a template was carried out between the diamine and pyridine-2,6-dicarbaldehyde **6**, which was obtained by oxidation of **4** using SeO2. Reduction of Shiff base **7** using NaBH4 allowed us to isolate the target product **3** with a total yield of 77% in four stages. To summarize, method C turned out the most optimal. Despite the greater number of stages, it leads to the highest total yield of triazacrown compound **3** and does not require complex and time-consuming purification methods.



Scheme 1. Methods for the synthesis of crown-compound 3.

In the next step, pyridyl chelating groups were introduced into the structure of macrocycle **3** (Scheme 2). The introduction of additional donor centers into the molecule's structure provides selectivity for corresponding metal ions and increases denticity. Pyridyl groups are intermediate in accordance with Pearson's HSAB theory [10,11], which allows them to effectively bind soft and intermediate metal cations.



Scheme 2. Synthesis of the ligand PADPy.

The possibility of forming a complex of the obtained **PADPy** ligand with the Pb2+ ion was demonstrated using ESI mass spectrometry. The results showed the formation of a single complex with a stoichiometric M:L ratio of 1:1. The structure of the Pb-**PADPy** complex was studied by 1H NMR spectroscopy (Fig. 1). The complex was synthesized *in situ* at room temperature by adding Pb(ClO4)2 salt to a solution of the ligand **PADPy** in a mixture of D2O and CD3CN (1:1). The assignment of signals in the 1H NMR spectra was carried out using homonuclear two-dimensional correlation methods 1H-1H COSY and 1H-1H ROESY. It can be noted that the number of signals in the aliphatic region of the spectrum of the complex Pb-**PADPy** doubles compared to those in the spectrum of the free ligand **PADPy**. At the same time, the number of signals in the aromatic region does not change. This indicates the formation of a *C2*-symmetric Pb-**PADPy** complex in solution, where the geminal protons are not magnetically equivalent due to the rigid fixation of the ligand molecule to the Pb2+ ion. In addition, all signals in the 1H NMR spectrum of the complex are shifted downfield, which is explained by the polarizing effect of the Pb2+ ion on the protons located close to the donor centers of the ligand. In this regard, it can be concluded that all eight heteroatoms of the ligand **PADPy** participate in the binding of the Pb2+ ion, i.e. the resulting Pb-**PADPy** complex has a coordination number of 8. It is known that the size of the macrocyclic cavity of 18-crown-6 ether (r = 1.3-1.6 Å) [12] corresponds well to the size of the Pb2+ ion (r = 1.35 Å with a coordination number of 8) [13]. Thus, it is most likely that the interaction of the Pb2+ ion with the ligand **PADPy** in solution leads to the formation of an inclusive complex with the pyridyl groups that completely encapsulate Pb2+, coordinating it from opposite sides of the macrocycle. These results are consistent with those obtained by mass spectrometry (Figs. 1, S6). Such a structure of the Pb-**PADPy** complex can provide high resistance to transchelation of the Pb2+ ion in biological environments.



**Figure 1.** 1H NMR spectra and ESI MS of free ligand **PADPy** and its complex **Pb-PADPy** in D2O/CD3CN.

**Conclusions**

We studied three approaches to the synthesis of 18-membered N, O - containing crown ether. It was found that the most suitable was method C via the formation of a Schiff base. The bipyridyl chelator **PADPy** based on the 18-triazacrown-6 ether was obtained and its complexation with Pb2+ was studied. It was shown that the mononuclear complex Pb-**PADPy** is inclusive, which can ensure the stability of the complex in biological environments, making the chelator promising for further research.

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Electronic supplementary information

The experimental section, the synthesis and the NMR spectra for the compounds obtained.

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