SYNTHETIC APPROACHES TO 18-TRIAZACROWN-6 ETHER AND A LEAD COMPLEX OF ITS BIPYRIDYL DERIVATIVE

Cite this: *INEOS OPEN*, **2025**, *8 (1–3)*, XX–XX
DOI: 10.32931/ioXXXXx

Received XX Month 2024,
Accepted 10 October 2024

http://ineosopen.org

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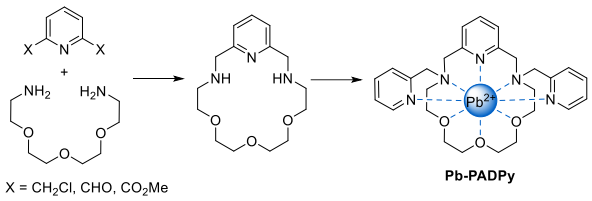
Abstract

In this study, an 18-membered triazacrown ether was prepared using three synthetic approaches to compare their efficiency. The method utilizing the macrocyclization reaction through the formation of a Schiff base turned out to be the most convenient one. The complexing features of new chelator **PADPy** bearing two pyridyl chelating groups towards Pb^{2+} ions was studied by ESI MS and ^1H NMR spectroscopy. The formation of an inclusive complex of 1:1 composition was shown.



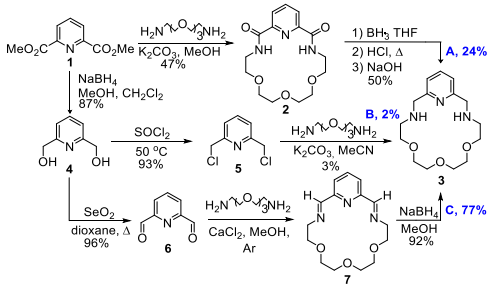
Key words: complexation, triazacrown ether, chelator, ligand, lead.

Introduction

Macrocyclic ligands based on azacrown compounds find wide application in many areas, since the selective complexation of metal ions is an important problem [1–3]. It is known that the 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]. For these crown ethers, one can expect the resistance to radiation, low dependence of complexation on the medium acidity, 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 the additional donor groups would provide its more efficient coordination in the macrocyclic cavity. In this communication, we compared the synthetic approaches to an N,O-containing 18-membered crown ether to identify the most convenient method. In addition, the chelating pyridyl groups were introduced into the triazacrown structure to yield chelator **PADPy**. The introduction of chelating groups ensures an increase in the cation-binding ability and selectivity of the ligand [9].

Results and discussion

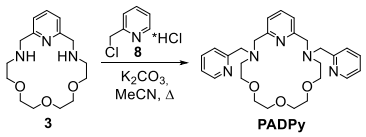
To obtain pyridine-containing triazacrown compound **3**, three methods were employed to compare their efficiency (Scheme 1). Method **A** involved three steps. The first step was the macrocyclization reaction between diester **1** and 1,11-diamino-3,6,9-trioxaundecane without using a high dilution technique. Then bis(amide) macrocycle **2** was reduced using BH_3·THF complex. However, the purification of target product **3** from the intermediate was complicated by the incomplete reduction, so the overall yield determined by NMR spectroscopy was 24%. According to methods **B** and **C**, diester **1** was reduced to 2,6-di(hydroxymethyl)pyridine **4** using $NaBH_4$. In method **B**, **4** was reacted with thionyl chloride to give 2,6-di(chloromethyl)pyridine **5**, and then the macrocyclization reaction with the diamine was accomplished in the presence of K_2CO_3. In this case, the macrocyclization process was accompanied by oligomerization, which complicated the isolation and purification of target triazacrown compound **3**. The yield of **3** according to the NMR spectroscopic analysis was 2% in three stages. Varying the solvent and the temperature of the process did not afford positive results. According to method **C**, the macrocyclization reaction using $CaCl_2$ as a template was carried out between the diamine and pyridine-2,6-dicarbaldehyde **6**, which was obtained by oxidation of **4** using SeO_2. The reduction of Shiff base **7** using $NaBH_4$ allowed us to isolate target product **3** in a total yield of 77% in four stages. To summarize, method **C** appeared to be the most optimal one. Despite a 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**.

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

The possibility of forming a complex of resulting ligand **PADPy** with Pb^{2+} ions was demonstrated using ESI mass spectrometry. The formation of a single complex with a stoichiometric M:L ratio of 1:1 was observed. The structure of Pb-**PADPy** complex was studied by ^{1}H NMR spectroscopy (Fig. 1). The complex was synthesized *in situ* at room temperature by adding $Pb(ClO_4)_2$ to a solution of **PADPy** in a D_2O–CD_3CN mixture (1:1). The assignment of the signals in the ^{1}H NMR spectra was carried out using homonuclear 2D correlation methods ^{1}H–^{1}H COSY and ^{1}H–^{1}H ROESY. It was noted that the number of signals in the aliphatic region of the spectrum of complex Pb-**PADPy** doubled compared to those in the spectrum of free ligand **PADPy**. At the same time, the number of signals in the aromatic region did not change. This indicated the formation of C_2-symmetric Pb-**PADPy** complex in solution, where the geminal protons are not magnetically equivalent due to the rigid fixation of the ligand molecule by the Pb^{2+} ion. In addition, all signals in the ^{1}H NMR spectrum of the complex appeared to be shifted downfield, which is explained by the polarizing effect of Pb^{2+} ions on the protons located close to the donor centers of the ligand. Therefore, it can be concluded that all eight heteroatoms of the ligand **PADPy** participate in the binding with the Pb^{2+} ion, *i.e.*, resulting Pb-**PADPy** complex has a coordination number of eight. 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 Pb^{2+} ion (r = 1.35 Å with a coordination number of 8) [13]. Thus, it is most likely that the interaction of the Pb^{2+} ion with **PADPy** in solution leads to the formation of an inclusive complex with the pyridyl groups which completely encapsulate Pb^{2+}, coordinating with it from the opposite sides of the macrocycle. These results are consistent with those obtained by mass spectrometry (Figs. 1 and S6 in the Electronic supplementary information (ESI)). Such a structure of Pb-**PADPy** complex can provide high resistance to transchelation of the Pb^{2+} ion in biological environments.



Scheme 2. Synthesis of ligand **PADPy**.

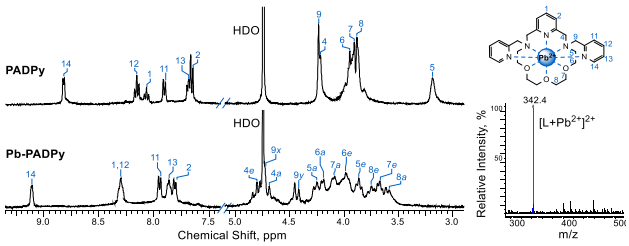


Figure 1. ^{1}H NMR spectra and ESI MS of free ligand **PADPy** and its complex **Pb-PADPy** in D_2O–CD_3CN.

Conclusions

Three approaches to the synthesis of the 18-membered N,O-containing crown ether were studied. It was found that the most suitable one is method **C** including the formation of a Schiff base. Bipyridyl chelator **PADPy** based on the 18-triazacrown-6 ether was obtained and its complexation with Pb^{2+} was studied. It was shown that mononuclear complex Pb-**PADPy** is inclusive, which can ensure the stability of the complex in biological environments, making the chelator promising for further research.

Acknowledgements

This work was supported by the Russian Science Foundation (project no. 23-73-01270). The NMR and ESI MS studies were performed using the equipment of the Center for Molecular Composition Studies of INEOS RAS.

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Electronic supplementary information

Electronic supplementary information (ESI) available online: the experimental section, the synthesis and the NMR spectra of the compounds obtained. For ESI, see DOI: 10.32931/ioXXXXx.

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