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NEW PYRIDINE-CONTAINING AZACROWN CHELATORS PATPy AND PAPPy FOR Pb^{2+} ION

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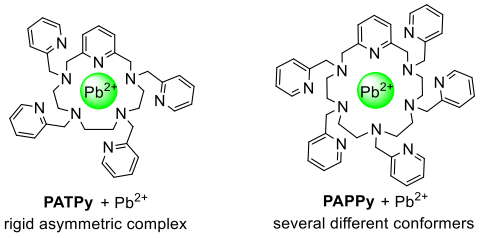
Abstract

New macrocyclic chelators with four and five pendant pyridine groups, **PATPy** and **PAPPy**, are synthesized and characterized. Their ability to coordinate with Pb^{2+} ion was studied using NMR spectroscopy and mass spectrometry. It was shown that both chelators form Pb^{2+} complexes of M:L = 1:1 composition. The NMR spectroscopic studies revealed the formation of a rigid asymmetric complex **Pb·PATPy** and rapid dynamic transitions between several different conformers of **Pb·PAPPy** in solution.



Key words: azacrown ether, chelator, ligand, metal complex, lead.

Introduction

In recent years, many investigations have been focused on finding the ligands capable of strong binding with Pb^{2+} ion [1–3]. This is not only due to its high toxicity, which requires the development of effective lead extracting agents [1], but also due to the radiochemical properties of some lead isotopes [2–7]. Two prominent radioisotopes of lead are ^{203}Pb ($t_{1/2}$ = 51.9 h) and ^{212}Pb ($t_{1/2}$ = 10.6 h) [2]. ^{203}Pb has γ-emission at 279 keV which is ideal for single-photon emission computed tomography (SPECT) [3–5]. ^{212}Pb decays via β^- particle emission to form the α-emitting daughter radionuclide ^{212}Bi ($t_{1/2}$ = 60.6 min), which makes this isotope attractive for the therapy of oncological diseases [2–7].

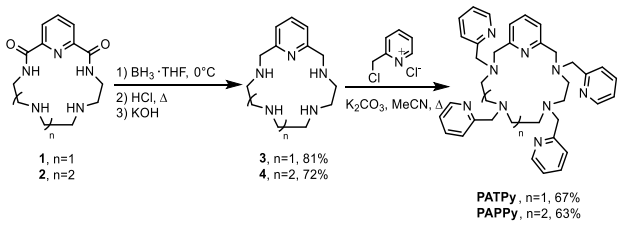
According to Pearson's HSAB theory, lead(II) is considered to be a moderate Lewis acid. For the formation of stable complexes with this ion, a ligand should have pyridine and amide donor units, which are moderate bases [1, 8–10]. Macrocyclic chelators are more attractive than acyclic as they have a pre-organized cavity for binding metal cations, resulting in thermodynamically stable and kinetically inert complexes [9, 10]. In addition, incorporating rigid spacers such as a pyridine moiety into the ligand backbone may result in lower kinetic lability [10].

Herein, we report the synthesis of new macrocyclic ligands, **PATPy** and **PAPPy**, which are 15- and 18-membered pyridine-azacrown ethers with pyridyl chelating groups for binding Pb^{2+} ion. The complexing features of these ligands towards Pb^{2+} ion were studied by NMR spectroscopy and mass spectrometry.

Results and discussion

The synthesis of the target ligands is shown in Scheme 1. Bisamide macrocycles **1** and **2**, synthesized according to the method reported by us earlier [11], were reduced to obtain pyridine-azacrown ethers **3** and **4**. To identify the most optimal reducing agent, three different borane complexes were used: BH_3·THF, BH_3·DMS, and BH_3·pyridine (Table 1). The amount of the reducing agent was also varied to achieve a maximum conversion of the initial macrocycle. The conversions were determined by analyzing the ^1H NMR spectra of the reaction mixtures. It was found that the most effective reducing agent for both of the macrocycles was BH_3·THF. However, compound **2** requires a larger excess of the borane complex (60 equiv.) than compound **1** (20 equiv.).

The introduction of chelating groups was accomplished by the alkylation of azacrown ethers **3** and **4** with 2-(chloromethyl)-



Scheme 1. Synthesis of ligands **PATPy** and **PAPPy**.

Table 1. Optimization of the reduction step using borane complexes

Macrocycle	Reducing agent	Excess (equiv.)	Conversion
1	BH_3·THF	20	**1.0**
	BH_3·DMS	20	0.9
	BH_3·pyridine	20	0.3
2	BH_3·THF	20	0.5
		40	0.7
		60	**1.0**
	BH_3·DMS	20	0.4
		40	0.9
	BH_3·pyridine	20	0.2

pyridine in MeCN in the presence of a base (Scheme 1). The target ligands were isolated after purification by column chromatography in 67 and 63% yields, respectively.

The complexation of the resulting ligands with Pb^{2+} ion was studied using ESI mass spectrometry and ^1H NMR spectroscopy. The mass spectrometry method afforded the data on the composition of the resulting species, showing that both chelators form a single complex with Pb^{2+} ion in solution with an M:L ratio of 1:1 (Fig. 1).

The structural studies of the Pb^{2+} complexes with **PATPy** and **PAPPy** were performed using NMR spectroscopy (Fig. 2). The ^1H NMR spectrum of complex **Pb·PATPy** was found to be significantly complicated compared to that of the free ligand. The presence of the well-resolved signals, their increased number and integral intensities indicated the formation of rigid asymmetric complex **Pb·PATPy** in solution. Of note is a singlet in the spectrum (highlighted in green) presumably assigned to one free pyridyl unit. In contrast to **Pb·PATPy**, the ^1H NMR spectrum of complex **Pb·PAPPy** contains broadened signals in the regions of both aliphatic and aromatic proton signals, which can be explained by the rapid dynamic transformations between different conformers. This feature indicates a discrepancy between the ligand structure and metal ion, as well as the lability of the resulting complex.

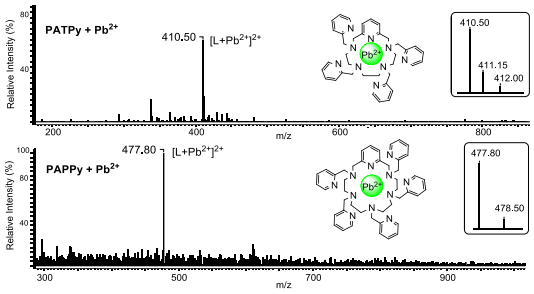


Figure 1. ESI MS of complexes **Pb·PATPy** and **Pb·PAPPy**.

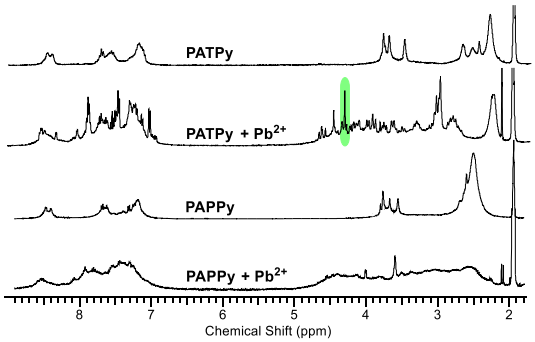


Figure 2. ^1H NMR spectra of free ligands **PATPy** and **PAPPy** and their Pb^{2+} complexes in CD_3CN.

Conclusions

Two novel chelators for Pb^{2+} ion were synthesized and fully characterized. Their metal ion chelation was studied using ESI mass spectrometry and NMR spectroscopy. It was shown that only **PATPy** forms a complex with Pb^{2+} ion featuring a rigid asymmetric structure, while complex **Pb·PAPPy** was found to be labile. Hence, further studies of **PATPy** as a chelating agent for Pb^{2+} ion seems to be very promising.

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Electronic supplementary information

Electronic supplementary information (ESI) available online: the experimental section and NMR spectra of the compounds obtained. For ESI, see DOI: 10.32931/io2504a.

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