



NEW PYRIDINE-CONTAINING AZACROWN CHELATORS PATPy AND PAPPy FOR Pb²⁺ IONS

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

Received XX Month 20XX
Accepted 15 October 2024

<http://ineosopen.org>

O. V. Tarasenko,^{*a,b} A. A. Shchukina,^a A. D. Zubenko,^a and Yu. V. Fedorov^a

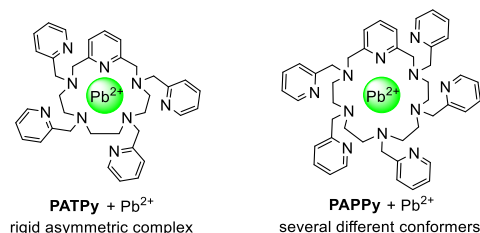
^a Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences,
ul. Vavilova 28, str. 1, Moscow, 119334 Russia

^b Mendelev University of Chemical Technology of Russia,
Miusskaya pl. 9, Moscow, 125047 Russia

Abstract

New macrocyclic chelators with four and five pendant pyridine groups, **PATPy** and **PAPPy**, are synthesized and characterized. Their ability to coordinate with Pb²⁺ ions was studied using NMR spectroscopy and mass spectrometry. It was shown that both chelators form Pb²⁺ 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 Pb²⁺ ions [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 ²⁰³Pb (*t*_{1/2} = 51.9 h) and ²¹²Pb (*t*_{1/2} = 10.6 h) [2]. ²⁰³Pb has γ -emission at 279 keV which is ideal for single-photon emission computed tomography (SPECT) [3–5]. ²¹²Pb decays via β^- particle emission to form the α -emitting daughter radionuclide ²¹²Bi (*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 Pb²⁺ ions. The complexing features of these ligands towards Pb²⁺ ions 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: BH₃·THF, BH₃·DMS, and BH₃·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 BH₃·THF. However, compound **2** requires a larger excess of the borane complex (60 equiv.) than compound **1** (20 equiv.).

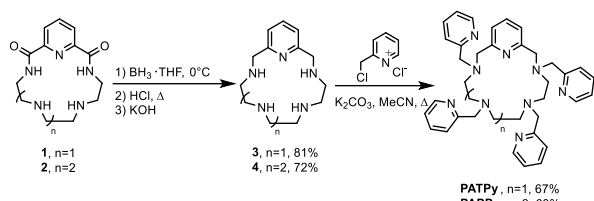
Table 1. Optimization of the reduction step using borane complexes

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

The introduction of chelating groups was accomplished by the alkylation of azacrown ethers **3** and **4** with 2-(chloromethyl)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 Pb²⁺ ions 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 Pb²⁺ ions 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 units. 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 ions, as well as the lability of the resulting complex.



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

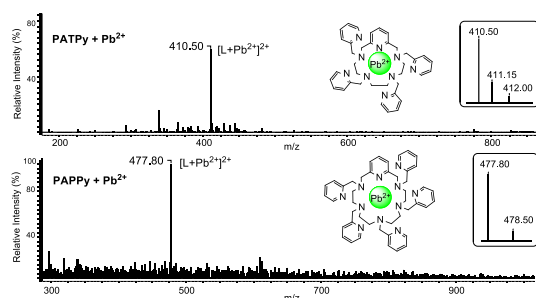


Figure 1. ESI MS of complexes **Pb-PATPy** and **Pb-PAPPy**.

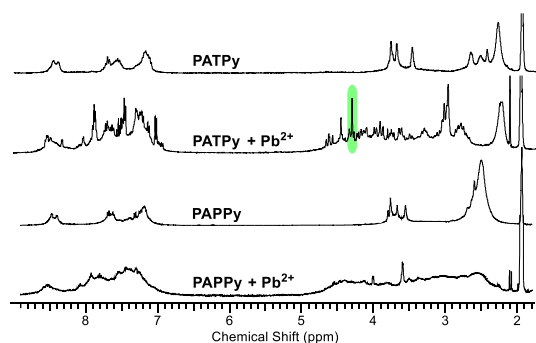


Figure 2. ^1H NMR spectra of free ligands **PATPy** and **PAPPy** and their Pb^{2+} complexes in CD_3CN .

Conclusions

Two novel chelators for Pb^{2+} ions 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+} ions 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+} ions seems to be very promising.

Acknowledgements

This work was supported by the Russian Science Foundation (project no. 23-13-00424). The NMR and ESI/MS studies were performed using the equipment of the Center for Molecular Composition Studies of INEOS RAS.

Corresponding author

* E-mail: taraseoksana@yandex.ru (O. V. Tarasenko).

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/ioXXXXx.

References

1. F. Cuenot, M. Meyer, E. Espinosa, A. Bucaille, R. Burgat, R. Guillard, C. Marichal-Westrich, *Eur. J. Inorg. Chem.*, **2008**, 267–283. DOI: 10.1002/ejic.200700819
2. A. Ingham, T. Kostelnik, B. McNeil, B. Patrick, N. Choudhary, M. Jaraquemada-Peláez, C. Orvig, *Dalton Trans.*, **2021**, 50, 11579–11595. DOI: 10.1039/d1dt01653a
3. L. Chappell, E. Dadachova, D. Milenic, K. Garmestani, C. Wu, M. Brechbiel, *Nucl. Med. Biol.*, **2000**, 27, 93–100. DOI: 10.1016/s0969-8051(99)00086-4
4. D. Milenic, M. Roselli, M. Brechbiel, C. Pippin, T. McMurray, J. Carrasquillo, D. Colcher, R. Lambrecht, O. A. Gansow, J. Schlom, *Eur. J. Nucl. Med.*, **1998**, 25, 471–480. DOI: 10.1007/s002590050246
5. S. Banerjee, I. Minn, V. Kumar, A. Josefsson, A. Lisok, M. Brummet, J. Chen, A. P. Kiess, K. Baidoo, C. Brayton, R. C. Mease, M. Brechbiel, G. Sgouros, R. F. Hobbs, M. G. Pomper, *J. Nucl. Med.*, **2020**, 61, 80–88. DOI: 10.2967/jnumed.119.229393
6. J. Li, T. Huang, J. Hua, Q. Wang, Y. Su, P. Chen, S. Bidlingmaier, A. Li, Z. Xie, A. P. Bidkar, S. Shen, W. Shi, Y. Seo, R. R. Flavell, D. Gioeli, R. Dreicer, H. Li, B. Liu, J. He, *J. Exp. Clin. Cancer Res.*, **2023**, 42, 61. DOI: 10.1186/s13046-023-02636-x
7. B. Bartoś, K. Lyczko, A. Kasperek, S. Krajewski, A. Bilewicz, *J. Radioanal. Nucl. Chem.*, **2013**, 295, 205–209. DOI: 10.1007/s10967-012-2238-4
8. M. Fernández-Fernández, R. Bastida, A. Macías, L. Valencia, P. Pérez-Lourido, *Polyhedron*, **2006**, 25, 783–792. DOI: 10.1016/j.poly.2005.07.045
9. B. McNeil, K. Kadassery, A. McDonagh, W. Zhou, P. Schaffer, J. Wilson, C. Ramogida, *Inorg. Chem.*, **2022**, 61, 9638–9649. DOI: 10.1021/acs.inorgchem.2c01114
10. C. Harriswangler, B. McNeil, I. Brandariz-Lendoiro, F. Lucio-Martínez, L. Valencia, D. Esteban-Gómez, C. Ramogida, C. Platas-Iglesias, *Inorg. Chem. Front.*, **2024**, 11, 1070–1086. DOI: 10.1039/d3qi02354k
11. Y. Fedorov, O. Fedorova, A. Peregudov, S. Kalmykov, B. Egorova, D. Arkhipov, A. Zubenko, M. Oshchepkov, *J. Phys. Org. Chem.*, **2016**, 29, 244–250. DOI: 10.1002/poc.3526

This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

