proceedings

MDPI

Proceeding

Synthesis of macrocycles with pendant arms derived from 2- (2-bromoethyl) -1,3-dioxolane †

Rodrigo Lamelas*, Alejandro Macías, Elena Labisbal, Mª Teresa Pereira, Paula Munín, Francisco Reigosa

Departamento de Química Inorgánica, Universidade de Santiago de Compostela, Avenida das Ciencia s/n 15782 Santiago de Compostela, Spain.

alejandroalberto.macias@usc.es; mariaelena.labisbal@usc.es; mteresa.pereira@usc.es; paula.munin@usc.es; francisco.reigosa@usc.es

*Correspondence: rodrigolamelas@hotmail.com

† The 21st International Electronic Conference on Synthetic Organic Chemistry. 1-30 November 2017

Academic Editor: Dr. Julio A. Seijas Vázquez
Received: date; Accepted: date; Published: date

Abstract: In this work we report the synthesis of an azamacrocyclic ligand with ethyldioxolane and methyl groups in trans positions and their characterization by crystallographic, NMR, IR-ATR and ESI-MS techniques and the subsequent synthesis of their complexes with the lanthanide ion series.

Keywords: MRI, Gadollinium, Macrocycle.

1. Introduction

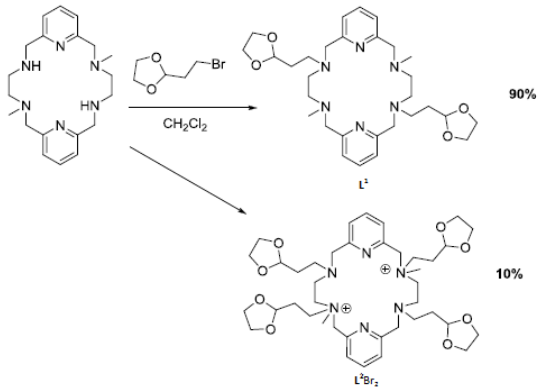
In the past, magnetic resonance imaging (MRI) has become an ever popular diagnosis method in medicine. The use of increased relaxation rates of protons in water has significantly improved the quality of the image. An example of this type of contrast agents are the compounds formed by Gd(III) with DOTA or DPTA ligands, which contain carboxyl groups, that can be prepared from ligands with dioxolane groups. These agents must have a high effective magnetic moment and for this reason Gd(III) is chosen to coordinate these ligands [1], [2].

From macrocycles with secondary amino groups in trans positions, tetra- or di- substituted compounds were obtained by direct reaction with dioxolane groups [3], which can be separated by recrystallization for further study as lanthanide ion receptors.

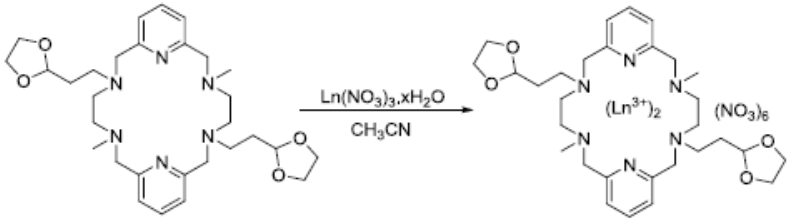
2. Section (Heading 1)

A solution of 2-(2-bromoethyl)-1,3-dioxolane in dry dichloromethane was added over a solution of the precursor ligand[4] in the same solvent. The mixture was refluxed for 24h, under N_2 atmosphere, after which it was concentrated and the residue was extracted with a CH_2Cl_2/H_2O mixture. The organic phase was dried and concentrated, thereby obtaining the ligand with pendants-arms ethyldioxolane (Scheme1).

To obtain the metal complexes, a solution of $Ln(NO_3)_3{\cdot}xH_2O$ in acetonitrile was added over a solution of the receptor ligand in acetonitrile. The mixture was stirred for 4h at room temperature, after which ethyl ether was added and a solid was separated which was characterized as the corresponding metal complex (Scheme2).



Scheme 1: Synthesis of the macrocyclic ligands with pendant-arms ethyldioxane.



Scheme 2: Synthesis of the metallic complexes

3. Results

Two new macrocyclic ligands, characterized by ESI-MS, NMR techniques or x-ray diffraction were obtained. Recrystallization of the ligand gave crystals that are valid for the resolution of its structure by X-ray diffraction (Figure 1). This structure corresponds to that of compound $\mathbf{L^2Br_2}$.

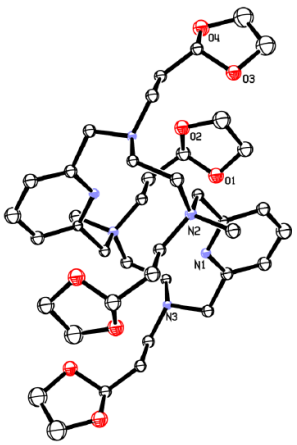


Figure 1: Crystalline structure of compound $\mathbf{L^2Br_2}$.

Alkylation of the secondary amines in the precursor ligand leads to $\mathbf{L^1}$ and $\mathbf{L^2}$. The former is functionalized with two ethyldioxolane groups, however $\mathbf{L^2}$ is a quaternary ammonium salt functionalized with four pendant-arm groups. This mixture of macrocycles can be purified by recrystallization from a saturated solution in dichloromethane.

As shown in **Table1**, after the functionalization of the ligand with the pendant-arm groups, a ligand interacting with lanthanide ions was obtained in high yields.

Table 1. Complexes of lanthanide ions.

Complex	%yield

Complex	%Rto
$[La_2\mathbf{L}](NO_3)_6{\cdot}4H_2O$	68
$[Ce_2\mathbf{L}](NO_3)_6{\cdot}3H_2O$	62
$[Pr_2\mathbf{L}](NO_3)_6{\cdot}5H_2O$	45
$[Nd_2\mathbf{L}](NO_3)_6{\cdot}4H_2O$	49
$[Sm_2\mathbf{L}](NO_3)_6{\cdot}4H_2O$	89
$[Eu_2\mathbf{L}](NO_3)_6{\cdot}4H_2O$	87
$[Gd_2\mathbf{L}](NO_3)_6{\cdot}CH_3CN$	82
$[Tb_2\mathbf{L}](NO_3)_6{\cdot}CH_3CN$	71
$[Dy_2\mathbf{L}](NO_3)_6{\cdot}2CH_3CN$	63
$[Ho_2\mathbf{L}](NO_3)_6$	69
$[Er_2\mathbf{L}](NO_3)_6{\cdot}3H_2O$	81
$[Tm_2\mathbf{L}](NO_3)_6{\cdot}H_2O{\cdot}CH_3CN$	75
$[Yb_2\mathbf{L}](NO_3)_6$	89

[1] Tables may have a footer.

4. Discussion

The objective with which the ligand was synthesized was to obtain a species with dioxolane pendant-arms. These groups are used as synthetic intermediates in the preparation of compounds with carbonyl groups such as: DOTA, DPTA… The corresponding gadolinium complexes are used in MRI as contrast agents.

Characterization of the solid shows that this objective has been fulfilled. In addition to obtaining ligand **L**[1], which can be used to obtain pendant-arms carboxylate groups, the coordinating capacity of the ligand with the lanthanide ion series was studied, giving high yields.

5. Conclusions

1. A synthetic route for the production of ligands with pendant-arms ethyldioxolane in trans positions was successfully developed.
2. This route allows the production of two ligands, which can be purified by recrystallization.
3. The metal complexes of $\mathbf{L^1}$ were obtained with a series of lanthanide ions.

Acknowledgments: This work was made possible thanks to the financial support received from the Xunta de Galicia (Galicia, Spain) under the Grupos de Referencia Competitiva Programme (Project GRC2015/009). F.L.–M. thanks the Spanish Ministry of Education (grant FPU13/05014).

Author Contributions: E. L. and A. M. conceived and designed the experiments; R.L. performed the experiments and wrote the paper; M. P. T. contributed reagents/materials/analysis tools**;** P. M. and F. R. analyzed the data

Conflicts of Interest: The authors declare no conflict of interest.

Appendix data for the Ligand

IR (KBr, cm^{-1}): [ν(O-CH-O)]: 2878; [ν(C=N)Py]: 1591; [ν(C=C)Py]: 1458; [ν(C-N)]: 1111; [ν(C-O-C)]: 945. ESI (m/z): 555 $[L^1+H]^+$..

References

1. Zheng, Q.; Dai, H.; Merritt, M. E.; Malloy, C.; Pan, C. Y.; Li, W.; A New Class of Macrocyclic Lanthanide Complexes for Cell Labeling and Magnetic Resonance Imaging Applications *J. Am. Chem. Soc.*, **2005**, *127*, 16178. DOI: 10.1021/ja054593v
2. Moi, M. K.; Meares, C. F.; De Nardo, S. J.; The peptide way to macrocyclic bifunctional chelating agents: synthesis of 2-(*p*-nitrobenzyl)-1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid and study of its yttrium(III) complex; *J. Am. Chem. Soc.*, **1988**, *110*, 6266-6267. DOI: 10.1021/ja00226a063
3. Núñez, C.; Bastida, R.; Macías, A.; Aldrey, A.; Valencia, L.; Synthesis of metal complexes with a novel ethyldioxolane pendant-arm hexaazamacrocyclic ligand; *Polyhedron*, **2010**, *29*, 126-133. DOI: 10.1016/j.poly.2009.06.093
4. R. Lamelas, V. García, A. Liñares, R. Bastida, E. Labisbal, A. Fernández-Lodeiro, C. Lodeiro, C. Núñez, L. Valencia; Novel trans-disubstituted hexaaza-macrocyclic ligands containing pyridine head units: Synthesis, disubstitution and colorimetric properties; *Sensors and Actuators B*, **2015**, *225*, 481-491. DOI: 10.1016/j.snb.2015.11.090.