



UNIVERSITA' DEGLI STUDI DEL PIEMONTE
ORIENTALE "A. AVOGADRO"

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*CHARLES UNIVERSITY IN PRAGUE
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PhD Thesis

« Pyridine-N-oxide analogue of DOTA as a building block for MRI contrast agents »

Candidate: Mr. Miloslav Polášek

The aim of the research subject of the present thesis has been very well defined and clearly described by the candidate:

- a) the preparation and characterization of a bifunctional derivative (DO3A-py^{NO-C}) of a ligand (DO3A-py^{NO}), synthesized by the candidate during his master thesis, that features a pyridine-N-oxide moiety in place of a carboxylate group in the basic structure of DOTA ;
- b) the investigation of the structural properties of the Ln(III) complexes of DO3A-py^{NO}, both in solution and at the solid state, in order to be able to interpret in greater detail the relaxometric data of the corresponding Gd(III) complex, with particular emphasis on the water exchange dynamics;
- c) the synthesis and characterization of GdDO3A-py^{NO-C}-appended macromolecular systems.

This work represents a significant and interesting piece of research with a solid scientific basis.

- The work has been carefully planned after a clear definition of the problem and the appropriate choice of the experimental procedures. The thesis contains an adequate account of the synthetic work, purification strategy and relative steps and a careful explanation of the procedures of characterization of the products.
- The results are presented in good detail and following a rationale scheme. The discussion of the data is satisfactory and evidences rigor in the analysis and interpretation of the results. The conclusions reported are based on detailed and convincing analyses of the various spectroscopic data and theoretical fitting/simulations

Originality – A new octadentate macrocyclic ligand based on DOTA and the corresponding lanthanide complexes have been prepared and completely characterized with a variety of techniques. In this new chelator a carboxylic group has been replaced by a modified pyridine-N-oxide moiety which has been introduced in order to provide the metal complexes with some favourable properties in view of the use as MRI probes:

- a) electro neutrality of the complexes and then significant increase of their tolerability and possibly internalization into cells;
- b) fast rate of exchange of the bound water molecule;
- c) ease of coupling to other substrates through the modified pyridine-N-oxide group.

Most of the available Gd-based MRI probes do not fulfil the above requisites and therefore the research project discussed in the doctoral thesis of Miloslav Polášek is timely and innovative.

Quality – As clearly demonstrated by the publications based on these results and included in the thesis, the overall quality of the work is very good. The synthetic

procedure is based on clear and rational basis: the bifunctional complex has been designed in order to rigorously satisfy some precise requisites. The level of detail in the characterization of the Ln-complexes is excellent. Several experimental techniques have been used in order to provide a complete and convincing characterization of the systems in solution and at the solid state. The analysis of the experimental data has been performed with accuracy, demonstrating a good knowledge of the methodologies and of the relevant literature. The results appears carefully discussed and, whenever possible, compared with the appropriate published data.

In summary, I think this is a work of high quality that contributes new knowledge to the lanthanide coordination chemistry.

Presentation – The quality of the presentation is excellent, characterized by precision and clarity. The thesis includes satisfactory abstract, references, figures and lay-out. The tables are well organized, useful and help the reading. The discussion at the end of each chapter and the general conclusions are particularly remarkable.

In conclusion, I recommend the acceptance of this doctoral thesis without reservation.

Prof. Mauro Botta

Alessandria, January 14, 2009

Questions and remarks

- 1) Pag. 7. What about the faster rate of exchange associated with an octacoordinate ground-state and an associatively-activated mechanism of exchange? For example all the Gd(III) complexes of the HOPO family or the Gd aquoion itself. Please discuss also this point
- 2) Pag. 10, lines 10-11 from the bottom. "...should have one molecule..." Why? The relaxivity increases with q and then complexes with $q>1$ are preferable for high efficacy. However, formation of ternary complexes should not take place. Please briefly discuss this point with some relevant examples.
- 3) Pag. 22, lines 14-16. It has been found a strict correlation of the dipolar shift with the nature and polarizability of the axial ligand in DOTA-like complexes (p.e. *Dalton Trans.*, **2003**, 1264). Thus, the assignment of the axial peaks to SA or TSA isomers is not always trivial and depends whether the structures are capped ($CN=9$) or not ($CN=8$). You should perhaps comment on this.
- 4) Pag. 22, lines 16-18. What is the relative importance of distance and angle in determining the dipolar shift?
- 5) Pag 23, lines 13-16. At pag. 2731/32 in the paper "*Inorg. Chem.* **1996**, 35, 2726" there is a discussion about isomerisation processes that could be related to what you comment. Can you get any information from or note anything unusual in the temperature-dependence of the chemical shifts of the proton spectra?
- 6) Pag. 35, lines 12-14. Retention times do not depend just on size but also on shape. To confirm your statement would light-scattering data be more appropriate?
- 7) Pag.39, Table 1. Do you have any explanation why there is more than 10% increase in relaxivity on passing from GdDO3A-py^{NO} to GdDO3A-py^{NO-C}? The two complexes have nearly identical mass and size and therefore their rotational dynamics should be nearly identical.
- 8) The LnDO3A-py^{NO} complexes are neutral whereas the corresponding LnDO3A-py^{NO-C} derivatives are anionic. Do you think the different charge could influence the structural and/or relaxometric properties of the complexes?