UNIVERSIDADE DE COIMBRA
FACULDADE DE CIÊNCIAS E TECNOLOGIA
DEPARTAMENTO DE BIOQUÍMICA
TELEF.: 239- 853 600 – FAX: 239- 853 607
e - mail dp bioquc @ cygnus . ci.uc pt
APARTADO 3126
3001 - 401 COIMBRA – PORTUGAL

Report on the Ph. D. Thesis of Miloslav Polášek

Mr. **Miloslav Polášek** has submitted a Ph.D. Thesis, with the title "Pyridine-N-oxide analogue of DOTA as a building block for MRI contrast agents", to the Department of Inorganic Chemistry, Faculty of Science, Charles University of Prague, under the supervision of Professor Dr. Ivan Lukeš. As a member of the Jury, officially nominated by the Dean of the faculty, I was asked to present a report on the quality of the Thesis.

The Thesis contains six basic sections, and complementary sections on references, acknowledgements and appendixes. Section 1 gives a background of the field of MRI contrast agents and section 2 details the aims of the work the The original contribution, with the description of the results, in Sections 3, 4 and 5 and in Section 6 with the Conclusions.

Section 3 is concerned with the monomeric ligands DO3Apy^{NO} and DO3Apy^{NO-C}, with a detailed description in Appendixes 1-3. These two new macrocyclic ligands were synthesized, containing a modified pyridine-N-oxide arm. The characterization of their Ln(III) complexes sowed that they are thermodynamically and kinetically stable. The Gd(III) complex, with one inner-sphere water molecule, has a almost optimal water exchange rate with the bulk, giving good relaxivities. The parameters controlling the relaxivity were studied by ^{17}O NMR and ^{1}H NMRD techniques. The solution and solid state structures were studied by NMR and X-ray diffraction, respectively, revealing that the chelates are present in solution as only one of the two possible isomers, making their derivatives interesting as paramagnetic NMR protein tags.

Section 4 describes the synthesis and studies based on polyamidoamine (PAMAM) dendrimers of various sizes (G0, G1, G2, G4) conjugated to DO3Apy^{NO-C} ligands. The electroneutral Gd(III) conjugates had relaxivities lower than expected from their sizes due to significant internal flexibility (Appendix 4).

Section 5 describes some preliminary studies of Gd(III)-DO3Apy^{NO-C} conjugated to per-amino derivative of β-cyclodextrin, which gave higher relaxivity than the dendrimer derivatives.

Therefore, my general evaluation of the Thesis is that it contains a large number of original results of high scientific quality, well presented. The Thesis reads well, as the description of the results and their discussion is clear, concise and precise, and the graphical aspect of the Thesis is quite agreable. It has originated three publications in Journals of high quality and impact (*Chem. Commun*., two in press in *Inorg. Chem*.), with another one to be submitted to *Bioconj. Chem*. Thus, I propose that the Thesis is accepted for the Ph. D. defense without reservation as it stands.

Coimbra, 7th January 2009

(Carlos F.G.C. Geraldes, Prof. Doutor)

Carlos F. G. C. Geraldes, D. Phil.

Professor