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Review report

Ph.D. thesis by **Miloslav Polášek**

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

Ph.D. thesis comprises 48 text pages, one published paper, two articles in press, and one manuscript in preparation. The thesis consists of six main chapters supplemented by 39 references. Role of the referee is somewhat facilitated since the major part of the thesis has been accepted for publication in journals *Chem. Commun*. and *Inorg. Chem.*

General description:

Clearly written Chapter 1 "Introduction" incorporates theoretical background of the topic ranging from a very brief general description of MRI to structural design of contrast agents. Short Chapter 2 "Aims of this work" straightforwardly outlines objectives of the project. The objectives, methods, implementations, and results are subsequently elaborated in Chapters 3-5. Achievements are summarized in Chapter 6 "Conclusions". There are some expressions and phrases in the thesis that would need language revision, however, the text is generally written in logic and readable style.

Some specific questions, comments, and remarks:

1. Page 6, paragraph 1 . . . . . *is dependent on reorientation of the Gd-H vector* . . . . . is quite general and needs some deeper explanation and discussion. What is the physical background of this observation? Please, comment on this.
2. Page 7. paragraph 2,

   There are two basic strategies to shorten the values of τ_M*. The first one is to introduce a six-membered chelate ring into the structure of the Gd(III) complex. This can be achieved either by prolonging the chain of the ligand in its backbone or in the pendant arm.*

   This paragraph requires some structural explanation. Could you demonstrate this on any example?

3. Page 7

   However, in most of Gd(III) complexes of DOTA-like ligands the TSA isomer in solution constitutes only minor part of the contrast agent.

   I am puzzled by this sentence. Could you say . . . . . TSA represents only minor component of the mixture of isomers in solution?

4. What kind of information extracted from EXSY (Figure 7) supports conclusion . . .

   *This experiment (Figure 7) showed that there undoubtedly **is** an exchange between the enantiomers.*

5. Description of VT NMR and conclusions drawn from it are unclear to me. Could you summarize conclusions made from the VT ^{1}H NMR measurements and comment on the signal assignment and the structural relations? What is observed in EXSY spectra at low temperatures (e.g., 238 K)? Could you estimate rate constants for the SA ↔ TSA and *syn*-SA ↔ *anti*-SA processes?

6. Pg 29, *syn* x *anti* exchange is estimated from the ^{1}H NMR spectra in solution:

   As the existence of syn-SA and anti-SA structures originates from flexibility of the six-membered chelate ring, these isomers should be also in a dynamic exchange in solution. This exchange has been indeed confirmed by ^{1}H NMR spectroscopy at very low temperatures (below –41 °C).

   However, no supporting materials describing the observations and the signal assignments are provided. I would like to see any explanation.

7. Cyclodextrine proved to be suitable substrate (rigidity of the frame) for binding the chelate. Have other types of macromolecular carriers (e.g., polyalkynes, polystaffanes differing in τ_g) been considered for attaching the Gd(III) complex?

In conclusion, several facts should be highlighted. Author proved his creative skills essential for the scientific research. His thesis contains some new and interesting results as supported by four scientific articles. The thesis is written in a clear and logic way and fulfills the formal and content requirements specified for Ph.D. degree. I **approve** thesis of Miloslav Polášek for further evaluation **and recommend** it for the final defense leading to academic degree **Ph.D**.

Doc. RNDr. Radek Marek, Ph.D.