Evaluation of the PhD thesis
"From Monomeric to Dendrimeric MRI contrast agents" by Jakub Rudovský

Jakub Rudovský has in his dissertation "From Monomeric to Dendrimeric MRI contrast agents" made an important contribution to the field MRI contrast agents. A thorough and systematic study was made of the design and synthesis of MRI contrast agents based on a mono-methylphosphonate analogue of DOTA. The Gd(III) chelate of this ligand is characterized by an exchange rate between the Gd(III) bound water and bulk water that is in the optimal range for application as MRI contrast agent, particularly after binding to a high molecular weight carrier. Several of these systems were designed and physico-chemically characterized. The work is well done and the thesis is written very well. The candidate has shown to have great skills in a variety of disciplines including organic synthesis, several NMR techniques, and X-ray crystallography. The results are well presented and discussed, also with regard to relevant prior art. The developed systems show very promising properties and this work may be the basis of a novel generation of contrast agents for molecular imaging by means of MRI.

In conclusion, I find that the dissertation is worthy of being defended and that its quality fulfils the criteria for obtaining the PhD degree by the candidate.

I have the following questions for the candidate, which may be addressed during the defense of this thesis:

1. On p. 28-29, you seem to reconsider the interpretation of experimental NMR data presented in the paper included as appendix 2. On p. 28-29, the resonances of the two species are assigned on the basis of a comparison with chemical shifts reported in the literature for Yb(DOTA), whereas in appendix 2, the NMR pH titrations are used as a basis for these assignments. As a result there is a discrepancy between Fig. 3.3b (p. 29) and Fig. 7 (p. 72). The reassignment has also consequences for Fig 6 (p. 72), and finally may even lead to the conclusion that $q < 1$ for Gd(do3aP). Could you please clarify this?

2. On p. 49, you mention that the rotational correlation times, $^{298}\tau_R$ for Gd(do3aP^{aBn}) and Gd(do3aP^{NBn}) are 88 and 163 ps (Table 3.2 on p.35: 88 and 137 ps), respectively. This is

a rather large difference considering the relatively small difference in molecular volumes of the two complexes concerned. Do you have an explanation for this?

3. In Fig. 7 on p. 96, you propose a structure for the $[GdY(CS(DO3A\text{-}P^{NBn})_2(H_2O)]^{2-}$ complex. The distance between Gd and Y is 6.25 Å. I assume that the corresponding Gd_2-complex has a similar structure. This means that the water protons in each of the two Gd(III) bound water molecules in this complex is in close proximity of the other Gd(III) ion. Did you take this into account during your simulations? Can you exclude a structure with a back-to-back arrangement of the two DO3AP units?

4. An amino group on a phenyl is electron donating, whereas a nitro group is strongly electron withdrawing. Could these effects have significant influences on the charge densities on the phosphinate functions in $DO3AP^{ABn}$ and $DO3AP^{NBn}$ and therefore on the water structure around these groups?

5. On p. 50, you give some plans for future in vivo tests on the compounds that you have developed. What are your expectations regarding efficacy, biodistribution etc. and how do you think that these properties compare with those of compounds based on other Gd(III) complexes with "optimal" τ_M values, including Gd-HOPO, Gd-AAZTA, Gd-DO3A-pyNox, Gd-TRITA?

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