Gadoxane – A Novel Degradable Silsesquioxane Based Macromolecular MRI Contrast Agent

J. Engelmann[1], J. Henig[2], S. Gottschalk[1], and H. A. Mayer[2]
[1]High Field MR Center, Max Planck Institute for Biological Cybernetics, Tuebingen, Germany, [2]Institute for Inorganic Chemistry, University of Tuebingen, Tuebingen, Germany

Introduction Since their discovery polyhedral oligosilsesquioxanes (POSS) have found an ever increasing number of applications in material science, catalysis, as building blocks for dendrimers and only recently biomedical use (e.g. as drug carrier systems) were reported as well. In the last two years studies of silsesquioxane based contrast agents (CA) for MRI were published [1,2] in which the silsesquioxane acts as a core dendrimer for MRI reporters like gadolinium chelates. The resulting compact globular macromolecular contrast agents show significantly enhanced relaxivities due to their increased size. Although it is known that POSS can be hydrolysed in aqueous media no studies on the stability of the core structure under physiological conditions are reported so far. Here we are presenting a new silsesquioxane based macromolecular CA (Gadoxane, Fig. 1). Its stability towards hydrolysis was studied by nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry and relaxivity measurements.

Methods Gadoxane was synthesized and fully characterized. The stability of the compound was tested under various conditions (25°C, pH 7.0 for up to 14 days + additional 8 days at 75°C; 37°C, pH 7.0 for up to 144h; 37°C, in typical serum containing cell culture medium buffered with HEPES, pH 7.4-7.6, or without, pH 8.1-8.6). While the gadolinium complex was used for relaxivity measurements and electrospray ionisation mass spectrometry (ESI-MS), NMR spectroscopy was performed with the diamagnetic yttrium complex.

Results and Discussion Gadoxane consists of eight $[Gd(DOTAGA)(H_2O)]^-$ chelates (DOTAGA = 1,4,7,10-tetraazacyclododecane-1-glutaric-4,7,10-triacetic acid) attached to a symmetric octa(3-aminopropyl)silsesquioxane core (Fig. 1). DOTAGA was used as it permits the coupling of the well-established DOTA unit (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetracetic acid) to molecules without decreasing stability or water exchange rate of the complex.
Aqueous solutions of Gadoxane could be stored at -28°C for at least 10 months without any detectable decomposition (data not shown). However, already at 25°C and pH 7.0 a slow hydrolysis of the silsesquioxane core could be observed. Under physiological conditions, the decay was significantly faster (half-life of about 18 h) as indicated by the time-dependent decrease in the longitudinal relaxivity r_1 in serum containing cell culture medium (Fig. 2). These results indicated that the silsesquioxane core was relative stable only in the first 4 h (insert Fig. 2) and was almost completely hydrolysed after about 125 h whereas no release of gadolinium from the chelate could be detected. Thus, in the context of biomedical applications functionalised silsesquioxanes can no longer be considered as stable. For the toxicity of such compounds this can be crucial especially in case of gadolinium containing silsesquioxane based MRI CAs. If the stability of the gadolinium complex depends on the intactness of the silsesquioxane, the risk of gadolinium related diseases increases. However, with appropriate stable gadolinium chelators, like DOTAGA as in the case of Gadoxane, the decomposition of the silsesquioxane core has no influence on the stability of the gadolinium complex. This will allow the development of even larger and still well defined macromolecular CAs for MRI, whose fragments are then readily excreted *via* the kidneys. These CAs would have the advantages of macromolecular CAs without their drawbacks.

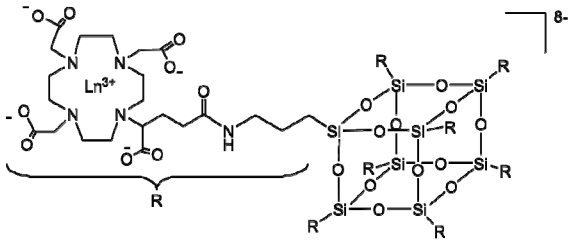

Figure 1: Structure of Gadoxane

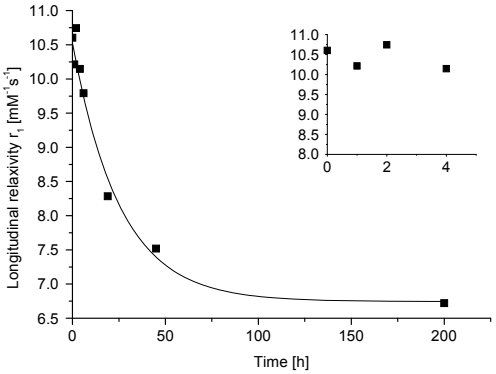

Figure 2: Longitudinal relaxivity r_1 during the degradation of Gadoxane in HEPES buffered serum containing culture medium, ph 7.4-7.6

References (1) Kaneshiro TL. *et al.*, *Biomacromolecules.* 2008, *9*, 2742.
(2) Tanaka K. *et al.*, *Polym J* 2009, *41*, 287.