Characterization of relaxational properties of new Bis-hydrazide-Gd-DTPA-complexes as contrast agents for molecular MRI

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Introduction

The development of new paracest agents (paramagnetic contrast agents) containing Gadolinium and ligands aiming for specific molecular sites has attracted increasing interest recently. In this abstract the synthesis of a new class of functionalized Bis-hydrazido-Gd-DTPA complexes obtained by coupling the appropriate hydrazines to DTPA has been studied. It is shown that their relaxivities are quite similar compared to Bis-Amido-DTPA-complexes. The relaxometric properties of the isolated complexes are characterized by inversion recovery NMR.

Methods

Synthesis: DTPA-Bis-anhydride and the twofold excess of substituted hydrazines react in DMF at 60º C for 2h. After removal of the solvents in high vacuum the ligands were obtained as amorph solids, washed with chloroform and dried for 6h. The complexation was performed with equimolar amounts of ligand and $GdCl_3$ in aqueuos solution by titration with sodiumhydroxide to pH=7. The reaction mixture was desalted using QMA-catrigdes for ionchromatographyand lyophilized to obtain amorph solids of light yellow color.
The chemical structure of all described compounds were confirmed and characterized by Elektrospray Ionisation-Massspectrometry and NMR. Fig.1 shows the molecular structures of the new isolated paracest agents.
Relaxometric Measurements: T_1-measurements were performed at three different magnetic field strengths corresponding to (200 MHz, 360 MHz, 600 MHz) at 20ºC by using an inversion recovery sequences. The T_1 times were determined for aqueous solutions of 1mmol/L Gd-complexes.
Magnetic Resonance Imaging: Visualization of the paramagnetic properties of these Gd-complexes was realized by T_1 weighted MRI experiments of a phantom with concentration series (microtiter plate with 96 wells) recorded with a Biospec 4,7/40 MR scanner (200MHz).

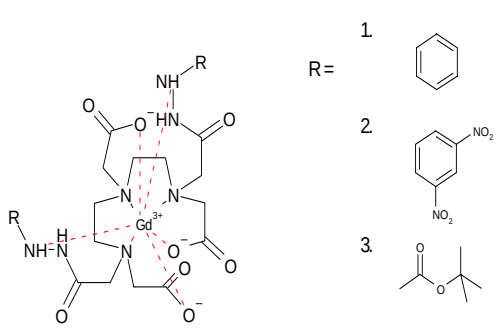
Results and Discussion

The Bis-Dinitrophenylhydrazido-Gd-DTPA has the shortest T_1-relaxation time out of three presented complexes (Fig. 2) due to the wide spread charge delocalization induced by the two polar electron withdrawing nitro groups. This also increases the dimension of the dlocalized paramagnetic center. Allthough the solubility of the nitro-Gd-complex is somewhat lower compared to the other synthesized bis-hydrazido-complexes, but this is more then compensated ba the stronger relaxivity..
The two other subtituents have primarily electron donor properties and focus the paramagnetic gadolinium center. Their recovery curves are very similar except the slightly smaller relaxivity of the tert-butyl ester compound in comparison to the phenyl substituted complex in (Tab. 1). The influence of the magnetic field to T_1-times was very little. it is also described the relaxational behaviour of water at 600MHz.

Tabl. 1: Molar T_1-times and relaxivity of Bis-hydrazido-Gd-DTPA-complexes in water at different magnetic field strength

B_0	14,1T		8,46T		4,7T	
	T_1 [mmol s]	r_1 [$mmol^{-1}$ s^{-1}]	T_1 [mmol s]	r_1 [$mmol^{-1}$ s^{-1}]	T_1 [mmol s]	r_1 [$mmol^{-1}$ s^{-1}]
Bis-Phenylhydrazide-Gd-DTPA	0,317	3,15	0,296	3,38	0,195	5,13
Bis-Tertbutylcarbamoyl-hydrazide-Gd-DTPA	0,353	2,83	0,339	2,95	0,31	3,23
Bis-Dinitrophenylhydrazide-Gd-DTPA	0,085	11,76	0,069	14,50	0,068	14,71
Pure Water	3,03 s	-	2,879 s	-	2,272 s	-

*Gd-DTPA-BMA at B_0=0,47T, T_1=0,244 [mmol s], r_1=4,1 [$mmol^{-1}$ s^{-1}][4]



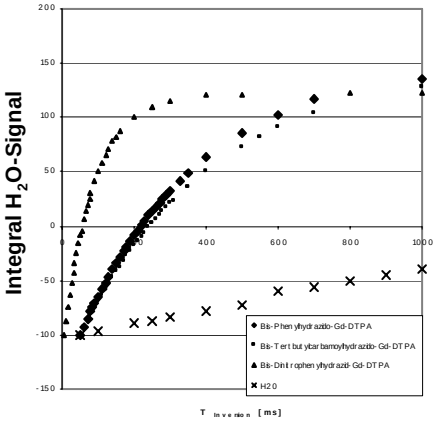


Fig.1 Structures of new Bis-hydrazide-Gd-DTPA-Complexes

Fig.2 Inversion Recovery at 600 MHz

Conclusion

Gd-DTPA-hydrazides are a new alternative ligand family for contrast enhancement in MRI. Electronical and sterical proerties of the substituents coupled to the hydrazinemoiety allow to develop variable relaxivities. The stability carbonic acid hydrazides against hydrolysis of is very similar for bis-amides .

References:[1] Feng J (et al.) Bioorg. Med. Chem 2003;15:3359 [2] Tang HA (et al.) Synth. Comm. 2003; 33, 16:2811 [3] Scozzafava A (et al.) J. Med. Chem. 2002; 45, 7:1466 [4] Fossheim S (et al.) JMRI 1997, 7:251