

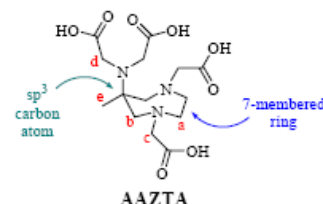
Equilibrium and Kinetic Properties of Gd(III)AAZTA complex a highly efficient MRI contrast agent

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Introduction

Highly stable complexes are needed for in vivo applications to avoid problems associated to the release of toxic metal ions. Recent reports outlined the development of a Gd(III) related pathology (dubbed NSF/NFD *i.e.*: Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy) in patients with renal failure as a result of the slow dissociation of some acyclic Gd containing MRI contrast agents. Clearly these findings pointed out the need for the design of more stable complexes also improving their efficiency in order to reduce the exposure to Gd(III) ion. Recently our group proposed a new heptadentate ligand AAZTA which can wrap around the Gd(III) ion yielding a system containing two coordinated water molecules in fast exchange with the “bulk water” solvent. This endows Gd(AAZTA)⁻ with a relaxivity which is almost twice than that of the clinically used agents. More importantly, when Gd(AAZTA)⁻ is bound to a slowly moving substrate, thanks to the short lifetime of the coordinated water molecules, very high relaxivities can be attained.



Scheme 1. The ligand AAZTA

Materials and Methods

Intravenously administered metal complexes enter a number of equilibria with large variety of species present in the body fluids, including several metal ions and ligands. For such equilibrium calculations it is necessary to know the protonation constants of the ligand, the composition, protonation and stability constants of the complexes participating in the equilibria. The protonation and the stability constants of some metal complexes formed with AAZTA ligand were determined by pH-potentiometric titration. The titrations were made in the pH range 1.7- 11.7. The kinetic stability of the Gd(AAZTA)⁻ was characterized by the rates of the exchange reactions taking place between the Gd(AAZTA)⁻ and Eu(III) or Cu(II). These experiments were carried out under pseudo-first-order conditions.

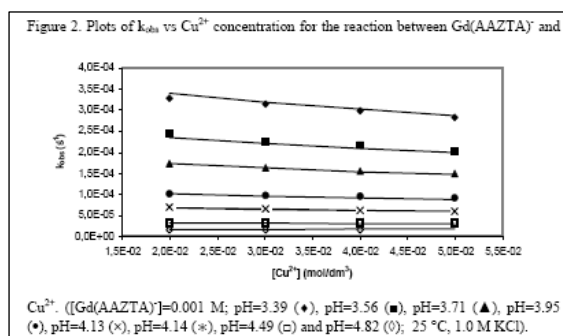
Results and discussion

The stability constants of the metal complexes formed with AAZTA are generally about 1–2 orders of magnitude lower than those of the corresponding complexes of DTPA. The complexes formed with AAZTA, similarly to those of DTPA, can be protonated at lower pH values and the protonation constants have been determined by pH-potentiometry.

The kinetic stabilities of complexes are characterized either by the rates of their dissociation measured in 0.1M HCl or by the rates of transmetallation reaction, occurring in solutions with Zn(II) and Cu(II) or Eu(III). The rates of the transmetallation reactions were studied by spectrophotometry using Cu(II) and Eu(III) as exchanging metal ions. The rates of the transmetallation reactions have been studied at

Protonation and stability constants of metal complexes of ligands H₄AAZTA and H₄DTPA (25°C).

Ionic strength	H ₄ AAZTA 0.1 M KCl			H ₄ DTPA ⁻ 0.1 M KCl	
	logK _{M.L.}	logK _{M.H.}	logK _{M.H.}	logK _{M.H.}	logK _{M.L.}
Cu ²⁺	20.51 (0.03)	4.00 (0.01)	2.72 (0.01)	10.81 (0.01)	21.5
Zn ²⁺	18.01 (0.02)	3.87 (0.01)	2.36 (0.02)	11.25 (0.03)	18.6
Eu ³⁺	19.93 (0.01)	1.91 (0.01)	–	–	22.39
Gd ³⁺	20.24 (0.01)	1.89 (0.01)	–	–	22.46



different concentrations of the exchanging ions in the pH range 3.3 – 5.3. An example of obtained rate constants k_{obs} is presented in Figure 2 as a function of the concentration of the exchanging ions and pH.

The rate constants characterizing the proton assisted dissociation of the Gd(AAZTA)⁻ resulted to be higher than that measured for Gd(DTPA)²⁻. However, the reactions between Gd(DTPA)²⁻ and Cu(II) and Eu(III) proceed much faster than in the case of GdAAZTA⁻. The half-times of dissociation of Gd(AAZTA)⁻ and Gd(DTPA)²⁻ near to physiological conditions, calculated with the kinetic data obtained by in vitro experiments, are 4337 h and 127 h respectively, indicating a remarkable higher kinetic stability of Gd(AAZTA)⁻.

Conclusion

The high thermodynamic stability shown by Gd(AAZTA)⁻ promotes the system into the group of Gd(III) chelates for in vivo applications in spite of its lower denticity. The rate of the proton assisted dissociation of Gd(AAZTA)⁻ is somewhat higher than that of Gd(DTPA)²⁻, but it is of low importance at physiological pH. Gd(AAZTA)⁻ shows a much higher resistance against the attack of metal ions, so the rates of its transmetallation reaction with Cu(II) and presumably with other endogenous metal ions are significantly lower than that of Gd(DTPA)²⁻.