DOTASA Revisited: $^1$H NMR and Potentiometric Studies of a Highly Asymmetrical Ligand and its Lanthanide(III) Complexes

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Introduction

Most magnetic resonance imaging (MRI) contrast agents are gadolinium(III) chelates of polyaminopolycarboxylate-like ligands. The tetraazacyclododecane polycarboxylic acid ligands proved to be suitable chelating agents in regard of the thermodynamic and kinetic stability of their Gd(III) chelates. DOTASA ($1, 4, 7, 10$ -tetraazacyclododecane - $1, 4, 7, 10$-tetracetic acid - $4, 7, 10$-triacetic acid) is a DOTA-like macroyclic ligand ($\text{DOTA} = 1, 4, 7, 10$ -tetraazacyclododecane - $1, 4, 7, 10$-tetraacetic acid) showing a carboxymethyl -CH$_2$COOH substituent moiety at a C$_\alpha$ carbon of one of the four acetate pendant arms, present as a racemic mixture of R and S configurations.

Results and discussion

A) Protonation constants of the ligand

i) Potentiometry gave values close to DOTA except for the extra pK$_i$ value of 5.35 assigned to protonation of the extra carboxylate group in the succinyl arm (Table 1).

ii) $^1$H NMR spectra of DOTASA at different pH values are too complex to allow the full determination of its microscopic protonation scheme, due to the presence of multiple isomeric structures in solution. The first two protonations are distributed among the three N-atoms bound to the acetate arms thus excluding the N-atom bound to the succinate arm. Only at pH values lower than 8,95 the carboxylic acid groups, excluding the C$_\alpha$ substituent, are protonated.

B) Thermodynamic stability constant of $\text{[Gd(DOTASA)(H}_2\text{O)}\]^{2-}$

Potentiometry gave log K$_{\text{Cu}}$ = 27.2 (0,2), which is higher than that of $\text{[Gd(DOTA)(H}_2\text{O)}\]^{2-}$.

Conclusions

The present studies illustrate the multiple effects that derivatization of the DOTA ligand has on the properties of the corresponding Gd(III) chelate, with consequences on its potential application as an MRI contrast agent. While the protonation constants of DOTASA are not much changed relative to DOTA except for an extra pK$_i$ value due to protonation of the extra carboxylate group in the succinyl arm, the stability constant of its Gd(III) chelate is significantly increased relative to $\text{[Gd(DOTA)(H}_2\text{O)}\]^{2-}$.

The number of isomers and the complexity of the frameworks of the complexes with the R and S configurations of the substituted pendant arm C$_\alpha$ atom. More importantly, the m isomer population of the Gd(III) complex with DOTASA is 3-4 times increased relative to Gd(III)-DOTA. This is in contrast with the C$_\alpha$ effect of the more sterically bulky para-nitrophenyl group, like in the Gd(III)-DOTA-pNP chelate [32], where the m % m increase is much smaller. The effect of the flexible carboxymethyl group in Gd(III)-DOTASA on the % m increase is almost as high as that resulting from water exchange rate, and thus its relativity.