

DOTASA Revisited: ^1H 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 - tetraazacyclodecane -1-(*R,S*)-succinic acid -4, 7, 10 -triacetic acid) ¹ is a DOTA-like macrocyclic ligand (DOTA = 1, 4, 7, 10 - tetraazacyclododecane -1, 4, 7, 10 -tetraacetic acid) showing a carboxymethyl -CH₂COOH substituent moiety at a C_α carbon of one of the four acetate pendant arms, present as a racemic mixture of *R* and *S* configurations.

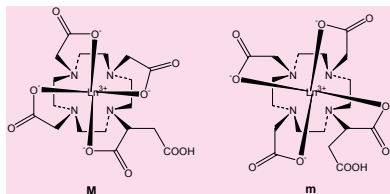


Fig. 1 - Schematic representation of the two diastereoisomers of $[\text{Gd}(\text{DOTASA})(\text{H}_2\text{O})]^{2-}$ complexes, endowed with the same square [3333] conformation of the tetraaza ring, but with a different layout of the acetate groups: **M** isomer (square antiprismatic) and **m** isomer (twisted antiprismatic). The H₂O molecule (in the apical position above the plane of the four oxygen atoms has been omitted for clarity).

log <i>K</i> _i	DOTASA		DOTA		
	0.1 M Me ₂ NCl	0.5 M Me ₂ NNO ₃	0.1 M Me ₂ NCl [15]	0.1 M Me ₂ NNO ₃ [14]	0.1 M Me ₂ NNO ₃ [13]
log <i>K</i> ₁	10.99 (0.02)	11.17	11.74	11.73	12.09
log <i>K</i> ₂	9.18 (0.02)	9.38	9.76	9.40	9.68
log <i>K</i> ₃	5.35 (0.02)	5.25	4.68	4.50	4.55
log <i>K</i> ₄	4.40 (0.02)	4.21	4.11	4.19	4.13
log <i>K</i> ₅	3.75 (0.02)	3.28	2.37	-	-
log <i>K</i> ₆	2.93 (0.02)	-	-	-	-
log <i>K</i> ₇	1.8 (0.04)	-	-	-	-
log <i>K</i> ₈	1.2 (0.06)	-	-	-	-

Table 1 - Protonation constants (log *K*) of DOTASA and DOTA at 25 °C obtained by potentiometry.

Results and discussion

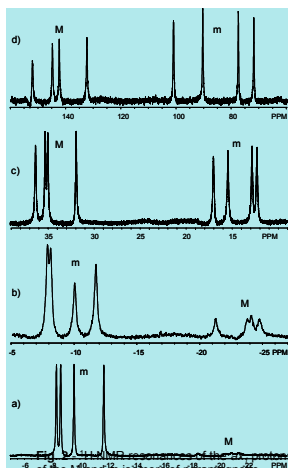
A) Protonation constants of the ligand

- i) Potentiometry gave values close to DOTA except for the extra p*K*₃ value of 5.35 assigned to protonation of the extra carboxylate group in the succinyl arm (Table 1).
- ii) ^1H 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 carboxylate groups, excluding the C_α substituent, are protonated.

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

Potentiometry gave log *K*_{ML} = 27.2 (0.2), which is higher than that of $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^{2-}$.

C) NMR studies of the $[\text{Ln}(\text{DOTASA})(\text{H}_2\text{O})]^{2-}$ complexes



of the **M** and **m** isomers of paramagnetic $[\text{Ln}(\text{DOTASA})(\text{H}_2\text{O})]^{2-}$ (D₂O, pH 8.0, 298 K):
a) Ln = Ce; b) Ln = Eu; c) Ln = Yb.

Ln	m isomer	M isomer	M / m
Ce	-8.31, -8.62, -9.58, -11.73	-18.52, -20.48, -20.94, -21.43	1:11.5
Pr	-23.53, -23.99, -27.65, -30.39	-40.35, -46.05, -46.17, -46.30	1:6.7
Nd	-7.80, -8.05, -9.97, -11.67	-21.18, -23.65, -23.99, -24.63	1:3.3
Sm	not assigned	-2.47, -2.96, -2.96, -3.60	-
Eu	17.93, 16.36, 13.76, 13.22	37.28, 36.23, 35.94, 32.85	1:0.9
Yb	101.01, 90.44, 77.56, 71.92	152.22, 145.05, 142.52, 132.49	1:1.2

Table 2 - NMR shifts (δ - ppm) of the ax, protons of the paramagnetic $[\text{Ln}(\text{DOTASA})(\text{H}_2\text{O})]^{2-}$ chelates in the M and m isomeric forms.

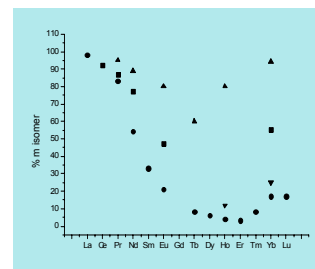


Fig. 3 - Molar fractions of the isomer **m** for Ln-tetraazamacrocycles in aqueous solution, pH 7, 298 K, as a function of the complexed metal ion obtained from ^1H NMR:
 (■) $[\text{Ln}(\text{DOTASA})]^{2-}$ (this work);
 (●) $[\text{Ln}(\text{DOTA})(\text{H}_2\text{O})]^{2-}$ [11,25];
 (▲) $[\text{Ln}(\text{RRRR})-(\text{TCE-DOTA})(\text{H}_2\text{O})]^{2-}$ [31];
 (▼) $[\text{Ln}(\text{DOTA-pNP})(\text{H}_2\text{O})]^{2-}$ [32].

Conclusions

The present studies illustrate the multiple effects that derivatisation 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 p*K* 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 $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^{2-}$. The number of isomers in solution of the Ln(III) chelates of DOTASA also doubles, combining the M and S structures of the framework of the complexes with the *R* and *S* configurations of the substituted pendant arm C_α 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_α effect of the more sterically bulky para-nitrophenyl group, like in the Gd(III)-DOTA-pNP chelate [32], where the % 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 RRRR tetrasubstitution of DOTA [31], and can thus be considered a good strategy of connecting a Gd(III)-tetraazamacrocycle to a carrier while increasing its water exchange rate, and thus its relaxivity.