

NMR Laboratory

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Designing the Magnetic Core of Paramagnetic Contrast Agents for MRI: Influence of the Backbone Substitution on the Water Exchange Rate of Gd-DTPA Derivatives

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INTRODUCTION: So as to improve the efficiency of paramagnetic contrast agents for IRM, several ways have been envisaged : to couple, covalently or not, paramagnetic entities to a macromolecule (and thus to increase some the rotational correlation time, τ_R) and/or to accelerate the coordinated water exchange rate (therefore optimise its residence time τ_M and avoid all limitation by τ_M of the efficiency of the complex). Recent works have shown that among factors that influence the coordinated water exchange rate, the steric congestion near the lanthanide notably by substitution in position C₄ of the Gd-DTPA would be favorable[1]. So as to confirm this observation, different Gd-DTPA complexes diversely crowded at position C₄ (figure 1) have been prepared and characterized.

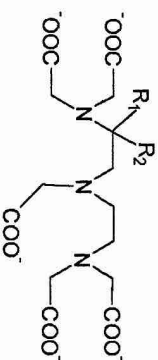


Figure 1 : Structure of Gd-(S)-C₄-Me-DTPA **1**: R₁=CH₃, R₂=H ; Gd-(S)-C₄-iBut-DTPA **2**: R₁=CH₂CH(CH₃)₂, R₂=H ; Gd-(S)-C₄-iProp-DTPA **3**: R₁=CH(CH₃)₂, R₂=H ; Gd-C₄-diMe-DTPA **4**: R₁=R₂=CH₃, Gd-DTPA **5**: R₁=R₂=H

MATERIAL AND METHODS The ligands 1-4 have been synthesized according to the protocol described by Brechbiel and al.[2] from commercial aminoacids. The C₄-DiMe-DTPA is synthesized from the 2- aminoisobutyric acid. The diethylenetriamine intermediate has not been able to be obtained directly by reduction of 2 -3-oxodiethylenetriamine because its little solubility in aprotic solvents. So as to improve its solubility in apolar media, we have therefore added two butoxycarbonyl groups (BOC) to the structure. This modification has allowed to reduce the compound oxodiethylenetriamine and after cleavage of BOC group, to obtain the precursor of the C₄-DiMe-DTPA. The ligands are complexed to the gadolinium and their structure is verified by ESI (Q-2, Micromass, Manchester, UK). The coordinated water residence time has been obtained by theoretical adjustment of relaxation paramagnetic transversal rate of the oxygen-17 measurements at variable temperature on a spectrometre Bruker AMX-300 (Karlsruhe, Germany)[3]. NMRD Curve have been noticed on a machine Stellar (Mede, Italy).

RESULTS AND DISCUSSION: The figure 2 regroups NMR data of oxygen-17 of 4 substituted complexes in position 4 and the parent complex : while the summit of the curve of Gd-DTPA **1** is observed to a close temperature to 310K, the maximum of complex curves C - substituted is significantly displaced to more lower temperatures indicating a diminution of the time of residence (25 to 37% inferior to the value of the Gd-DTPA) confirmed by the theoretical adjustment. Times of residence of the Gd-(S)-C₄-Me-DTPA **1**, Gd-(S)-C₄-iBut-DTPA **2** and Gd-(S)-C₄-iProp-DTPA **3** are similar and

comparable to values obtained for others derived substituted C_4 (table 1). The volume of substituting it seems therefore to have few influences on the speed of exchange. On the other hand, the speed of exchange accelerates clearly for Gd- C_4 -DiMe-DTPA 4 ($\tau_m^{310} = 57$ ns). These results confirm that analogous manner to bisamide complexes in order that the congestion near the group is favorable to the exchange, an increase of steric constraint in position 4 of the skeleton induces equally an acceleration of the exchange. The disubstitution in position 4 would translate into a constraint of the skeleton that would be responsible a more efficient expulsion of the coordinated water.

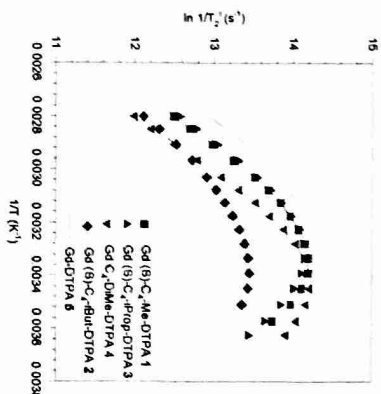


Figure 2 : Evolution of $1/T_2'$ of O-17 versus temperature ($1/T_2' = 1/T_2^0 / (55.55x [Gd-complex])$)

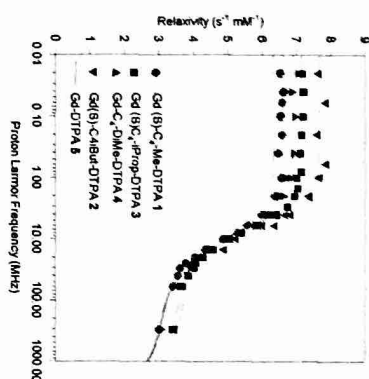


Figure 3 : NMRD Profiles of complexes

Table 1: Parameters obtained by theoretical adjustment of NMRD curves

Complexes	τ_1^{30} (μ^2 mM $^{-1}$, nH)	τ_m^{30} (ps)	τ_2^{30} (ps)	τ_{∞}^{30} (ps)	τ_q^{30} (ps)	r (Å)
Gd-DTPA 5	3.8	143 ± 25	39	82	23	3.1
Gd(S)- C_4 -Me-DTPA 1	3.8	91 ± 10	57	83	20	3.1
Gd(S)- C_4 -iPr-DTPA 3	4.2	108 ± 11	68	96	15	2.99
Gd(S)- C_4 -tBu-DTPA 2	4.3	98 ± 10	68	96	20	3.1
Gd(S)-DiMe-DTPA 4	4.1	57 ± 6	60	97	20	3.1
Gd(S)- C_4 -Bz-DTPA [1]	4.8	87 ± 25	61	81	17	2.9
Gd(S)-BOB-DTPA [4]	5.6	82 ± 21	61	63	17	2.8

At 310 K, NMRD profile (Nuclear Magnetic Dispersion Relaxation) of water protons are comparable for 4 complexes 1-4 and the longitudinal relaxivities are slightly higher than for the parent derivative Gd-DTPA 5 (figure 3). Stemming parameters of the theoretical adjustment of NMRD profiles are summarized in the table 1 (parameters fixed : $q = 1$, $d = 0.36$ nm, $D = 3.3 \cdot 10^{-9}$ m 2 /s and τ_m^{310} fixed to the value determined by 17O).

CONCLUSIONS: 4 new ligands of the DTPA have been synthesized. As compared to Gd-DTPA 5, the coordinated water exchange rate of gadolinium complexes is approximately 1.5 more rapid time for the Gd(S)- C_4 -Me-DTPA 1 and the Gd(S)- C_4 -iPr-DTPA 3. The insertion of methyl groups in position 4 increases considerably the water exchange rate of Gd- C_4 -DiMe-DTPA 4. The comparison of exchange rates of complexes 1-3 and others complexes substituted in C_4 [1, 4] and Gd- C_4 -DiMe-DTPA 4 confirms that this position of substitution allows a notable improvement of the exchange rate.

REFERENCES: [1] S. Laurent, L. Vander Elst, S. Houzé, N. Guérin, R.N. Muller, *Helv. Chim. Acta*, **83**, 394, (2000); [2] M.W. Brechbiel, O.A. Gansow, R.W. Atcher, J. Schiom, J. Esteban, D.E. Simpson, D. Colcher, *Inorg. Chem.*, **25**, 2772 (1986); [3] F. Botteman, G.M. Nicolle, L. Vander Elst, S. Laurent, A.E. Merbach, R.N. Muller, *Eur. J. Inorg. Chem.*, 2686, (2002); [4] L. Vander Elst, F. Maton, S. Laurent, F. Seghi, F. Chapelle, R.N. Muller, *Magn. Reson. Med.*, **38**, 604 (1997)

REMERCIEMENTS: This work has been supported by the ARC program of the French Community of Belgium (contrat 00/05-258) and the FNRS (Fonds National de la Recherche Scientifique)