

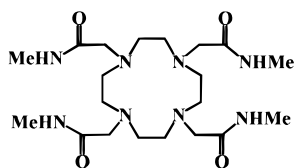
Prototropic vs Whole Water Exchange Contributions to the Solvent Relaxation Enhancement in the Aqueous Solution of a Cationic Gd³⁺ Macrocyclic Complex

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The ability shown by Gd³⁺ complexes to enhance the nuclear relaxation rate of solvent water protons is the result of the efficient dipolar magnetic coupling between the unpaired electrons of the metal ion and the nuclear spins which is believed to occur through three processes:¹ (i) diffusion of water molecules in the proximity of the paramagnetic complex (*outer-sphere* term); (ii) exchange of the water molecules from the coordination sites to the bulk (*inner-sphere* term); (iii) prototropic exchange involving mobile protons of the complex and/or of the coordinated water itself. In these systems, the latter contribution is extremely difficult to evaluate because the exchange rate of the coordinated water molecules is usually much faster than the rate of prototropic exchange.^{2,3} Recently, it has been shown that Gd³⁺ complexes with a single coordinated water molecule (hydration number $q = 1$) may display rather large values of the exchange lifetime τ_M .⁴ Moreover τ_M increases approximately by 1 order of magnitude on passing from the negatively charged [Gd(DTPA)]²⁻ (DTPA = diethylenetriaminepentaacetate) to the neutral [Gd(DTPA-BMA)] (DTPA-BMA = 1,7-bis[(*N*-methylcarbamoyl)methyl]-1,4,7-triazaheptane-1,4,7-triacetate) complex.⁵ We thought then that a possible route to assess the contribution of the prototropic exchange to the overall water exchange may be possible in complexes characterized by an even slower water exchange rate. Thus, the observation that τ_M increases as the negative residual charge decreases prompted us to consider the triflate salt of the tripositively charged [Gd(DTMA)]³⁺ complex [DTMA = DOTA tetrakis(methylamide)].^{6,7}



DTMA (**1**) acts as a neutral octadentate ligand toward lanthanide(III) ions, thus forming cationic complexes capable of further coordinating one water molecule. The solution ¹H and ¹³C NMR spectra of [Eu(DTMA)]³⁺ in aqueous solution are consistent with the presence of one main, largely dominant isomer possessing a high degree of stereochemical rigidity.

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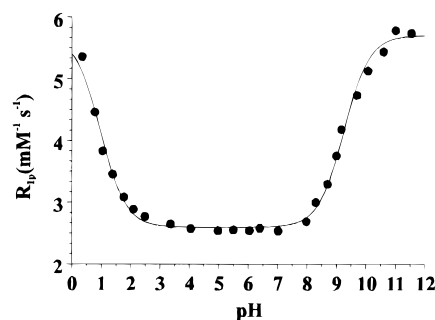


Figure 1. pH dependence of the solvent longitudinal relaxivity for an aqueous solution of [Gd(DTMA)](CF₃SO₃)₃ at 298 K and 20 MHz. The solid curve is calculated from a best fitting procedure of the data to eq 1 (pH 7–12) and its analogous form for the acid limb (pH 0.5–7).

Importantly, no change in the spectral pattern was observed over the pH range 0.5–11.5. Luminescence measurements of the excited-state lifetime of [Eu(DTMA)H₂O]³⁺ measured in H₂O and D₂O in the pH(D) range 2–8, gave a constant q value of 1.0, after allowing for the additional effect of the proximate exchangeable amide NH oscillators.⁸ The bound water molecule was relatively acidic, and potentiometric titration analysis (298 K, $I = 0.1$ NMe₄NO₃) gave pK_a value of 7.03 (01) for [Eu(DTMA)H₂O]³⁺ and 7.90 (01) for the corresponding Gd³⁺ complex.

At 20 MHz and 298 K the water proton relaxation enhancement shown by [Gd(DTMA)](CF₃SO₃)₃ was found to be markedly and unusually dependent upon the pH of the solution (Figure 1). The low relaxivity values observed in the pH range 2–8 are consistent with the occurrence of an outer-sphere contribution only.⁹ On the other hand, the relaxivity measured at pH = 10 ($R_{1p} = 5.17$ mM⁻¹ s⁻¹) is rather similar to that of the analogous tetraacetate complex [Gd(DOTA)]⁻ ($R_{1p} = 4.70$ mM⁻¹ s⁻¹). Thus, in basic media the relaxivity of [Gd(DTMA)]³⁺ may be accounted for in terms of structural and dynamic relaxation parameters (reorientational correlation time of the complex, Gd–H distance of the coordinated water molecule and its residence lifetime, electronic relaxation time of the metal ion, etc.) which are strictly similar to those found for [Gd(DOTA)]⁻. This has been further checked by comparing the corresponding 1/T₁ NMRD (*nuclear magnetic relaxation dispersion*) profiles measured on a field-cycling spectrometer over an extended range of observation frequencies (0.01–50 MHz).^{1b}

To get a better understanding of the observed pH dependence of the longitudinal proton relaxivity R_{1p} , we undertook a variable-temperature study of the nuclear transverse relaxation rate of ¹⁷O nuclei (¹⁷O- R_{2p}) of the solvent, which should report on the exchange rate of the coordinated water molecule.² Both at pH = 7 and pH = 12, ¹⁷O- R_{2p} increases with the temperature in the investigated range 273–353 K. Such a behavior is typical of the occurrence of slow to intermediate exchange rates of the coordinated H₂¹⁷O molecule (i.e. $R_{2p} \propto 1/\tau_{M1} = k_1$) and allowed us to estimate the kinetic parameters of the exchange process.¹¹

(6) DTMA = 1,4,7,10-tetrakis[(*N*-methylcarbamoyl)methyl]-1,4,7,10-tetraazacyclododecane.

(7) Similar ligands have been reported: (a) Katakay, R.; Matthes, K. E.; Nicholson, P. E.; Parker, D.; Buschmann, H. J. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1425–1432. (b) Katakay, R.; Parker, D.; Teasdale, A.; Hutchinson, J. P.; Buschmann, H. J. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1347–1351. (c) Amin, S.; Morrow, J. R.; Lake, C. H.; Churchill, M. R. *Angew. Chem.* **1994**, *106*, 824; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 773–775.

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(9) Relaxivity is defined as the nuclear magnetic relaxation rate increase of water nuclei per unit concentration of the paramagnetic complex.

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The measured R_{2p} values at the two pH values are almost identical, which indicates an identical rate of coordinated water exchange. At 298K, k_1 was estimated to be $4.5 \times 10^4 \text{ s}^{-1}$, i.e. almost 2 orders of magnitude lower than the values found⁴ for $[\text{GdDTPA}]^{2-}$ and $[\text{GdDOTA}]^-$, by far the slowest water exchange rate so far reported for a Ln^{3+} complex. Thus, a very small contribution to the overall proton relaxivity is expected from the exchange of coordinated water at these pH values. Under the slow exchange condition of the coordinated water molecule, the additional contribution to $^1\text{H-}R_{1p}$ observed in basic media has been assigned to the occurrence of a prototropic exchange catalyzed by the added base. In this region τ_M is determined by $(k_1 + k_2[\text{OH}^-])^{-1}$ and the proton relaxivity can be expressed as

$$^1\text{H-}R_{1p}^{\text{H}} = \left[\frac{Nq}{55.5} \frac{1}{(T_{1M} + (k_1 + k_2[\text{OH}^-])^{-1})} \right] + R_{1p}^{\text{os}} \quad (1)$$

where N is the molar concentration of the complex, T_{1M} the longitudinal relaxation time of the coordinated water protons, and R_{1p}^{os} the contribution of the *outer-sphere* component. According to eq 1 the *inner-sphere* contribution to the observed relaxivity ($^1\text{H-}R_{1p}^{\text{is}}$) increases as τ_M decreases until when, at $\text{pH} > 10$, τ_M becomes negligibly small with respect to T_{1M} (fast exchange condition). From the fitting of the experimental R_{1p} data over the pH range from 7 to 12 we obtained a k_2 value of $1.4 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$.

Even at $\text{pH} < 3$, an increase of $^{17}\text{O-}R_{2p}$ was not detected, which means that the exchange rate of the coordinated water molecule remains constant also in this pH range. Thus, the proton relaxation enhancement observed at very acid pH values (Figure 1) cannot be accounted for in terms of a decrease of τ_M due to an increase of the exchange rate of the whole water molecule. Actually, the pH dependence of the relaxivity in this region (pH from 0.5 to 7) may be fitted through an equation analogous to 1, where τ_M is expressed by the term $(k_1 + k_3[\text{H}^+])^{-1}$. At 298 K the resulting k_3 value is $2.41 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$. It is worth noting that this complex shows a remarkable kinetic inertness toward acid-catalyzed dissociation ($t_{1/2} = 155 \text{ h}$ in HNO_3 2.5 M at 298 K)¹² so that the relaxivity increase in this pH range, which is a reversible phenomenon, cannot be ascribed to partial dissociation of the complex and/or to dissociation of one or more of the pendant arms with a resulting increase of the hydration number. A clue to the understanding of the acid-catalyzed process which leads to the increase of the

proton exchange rate has been gained by measuring the longitudinal relaxation times T_1 of the ^{19}F nuclei of the counter anions $(\text{CF}_3\text{SO}_3)^-$. A sufficiently intense ^{19}F resonance was observed in a 2 mM solution of $[\text{Gd}(\text{DTMA})](\text{CF}_3\text{SO}_3)_3$ in the presence of 20-fold excess of $\text{CF}_3\text{SO}_3\text{Na}$. The relaxation time of the ^{19}F resonance is constant ($\sim 75 \text{ ms}$) in the pH range from 8 to 2, then it abruptly increases as the pH decreases to indicate a longer distance between the paramagnetic Gd(III) center and the fluorinated anion.

We believe that the observed behavior is consistent with the occurrence of long-lived,¹³ strong ion pair interactions at $\text{pH} > 2$ which are progressively weakened as the pH of the solution is decreased. Support for this view has been gained from the observation that the ^{19}F T_1 significantly increases upon displacement of triflate by an excess of phosphate or sulfate or chloride anions. The ion pairs are intimately involved with the array of hydrogen bonds between the water molecules forming the hydration sphere of the two ions. The breakup of the ion-pair adduct seems to be related to the formation of a preferential pathway for the exchange of the water protons from the inner coordination sphere to the bulk which likely involves a proton transfer to the second hydration sphere hydrogen-bonded water molecules, as recently has been shown to occur for hexaaquarhodium(III) cations.¹⁴

In summary, this work reports for the first time a distinct evaluation of the water and prototropic exchange rates for a gadolinium(III)-coordinated solvent molecule. The results, which have a direct impact in the current research of contrast agents for magnetic resonance imaging, suggest that it is possible to obtain equivalent proton relaxivity values by exploiting different routes, namely base/ OH^- catalysis of prototropic exchange and proton catalysis of the ion-pair dissociation promoting coordinated water protons exchange in strongly acidic media.

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Supporting Information Available: Text describing materials and methods (1 page). See any current masthead page for ordering information and Internet access instructions.

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(13) In the case of the phosphate salt of the Eu(III) complex we succeeded in observing separate ^{31}P resonances for the free and bound anion. Furthermore, it is worth noting that the presence of strong electrostatic interactions between the anions and the metal complex, localized near the water coordination site, may account for the pH independence of the ^{17}O transverse relaxation rate, which indicates equal exchange rates for the aquo and hydroxo Gd(III) complexes.

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(11) ΔH^\ddagger (kJ mol^{-1}) = 27.1 ± 5.0 ; ΔS^\ddagger ($\text{J K}^{-1} \text{ mol}^{-1}$) = -64.7 ± 15.0 .

(12) Determined by monitoring the relaxivity increase of a 1.5 mM aqueous solution of the complex as a function of time, at 20 MHz and 298 K. This relaxivity increase follows the acid-catalyzed release of the free Gd^{3+} aquoion.