COMMUNICATION

ChemComm
www.rsc.org/chemcomm

The nature of the counter-anion can determine the rate of water exchange in a metal aqua complex†

Alessandro Barge,[a] Mauro Botta,*[a] David Parker*[b] and Horst Puschmann[b]

[a] *Dipartimento di Scienze e Tecnologie Avanzate, Universita degli Studi del Piemonte Orientale, Corso Borsalino 54, I-10131 Alessandria, Italy. E-mail: mauro.botta@unito.it*

[b] *Department of Chemistry, University of Durham, South Road, Durham, UK DH1 3LE. E-mail: david.parker@dur.ac.uk*

Received (in Cambridge, UK) 25th February 2003, Accepted 23rd April 2003
First published as an Advance Article on the web 16th May 2003

The nature of the counter-anion determines the water exchange rate for a series of cationic gadolinium complexes in aqueous solution, as a consequence of the ordering effect that the anion imposes on the structure of the second hydration sphere.

Whilst some progress has been made in understanding the effect of ions on the structure and exchange dynamics of aqueous solutions, there remains a distinct lack of unequivocal experimental data which might help to explain various ion-specific effects. Examples include our inability to provide a compelling explanation for ion-pairing preferences in reverse-phase and ion chromatography[1] or a satisfactory rationalisation of the ability of salts to induce protein precipitation (Hofmeister series).[2] Sound empirical hypotheses have been put forward to account for the charge-density dependent strength of hydration and its relationship to biological organisation and structure,[3] and more recent computational work has put these ideas on a firmer footing.[4] Charge densities govern water/ion interactions and define the relative importance of both water structure electrostatics, *i.e.* ion-water dipole interactions, and the extent of hydrogen bonding involving water/water hydrogen bonds. More charge dense ions cause strong electrostatic ordering, breaking hydrogen bonds and creating a well-defined second sphere of hydration. Larger ions do not perturb the bulk water hydrogen bonding array significantly. These low charge density ions are termed 'chaotropes' ($I^- > Br^- > Cl^-$) to distinguish them from 'kosmotropes' (*e.g.* Mg^{2+}, Na^+, phosphates), characterised by positive and negative water entropies respectively.[5]

From the coordination chemist's viewpoint, our understanding of reaction mechanisms at a metal centre in aqueous solution has advanced rather slowly since Eigen, Wilkins' and Margerum's early work.[6] The simple water/ligand exchange reaction at a metal ion is generally considered to be insensitive to the nature of the ligand in the second coordination sphere, *i.e.* to be a reaction controlled by the rate of water association or dissociation.[7] Information on this process is obtained by variable T and P ^{17}O and ^1H NMR studies and Merbach's group in particular have highlighted details of the water interchange reaction, with positive volumes of activation characterising a more dissociative interchange process.[7] From a structural chemist's viewpoint, accurate neutron diffraction and neutron scattering data on solids and concentrated salt solutions are allowing information to be built up about the local hydration spheres of anions and cations and the dependence of each on concentration and counter ion.[8]

Over the past five years, it has become more evident that the nature of the second hydration sphere is critically important in defining the kinetics of water exchange at metal ion centres.[9] This is of particular importance in lanthanide chemistry, where an understanding of the factors determining water exchange rates is needed in seeking to improve the efficacy of contrast agents used in MRI.[10] Recently, we reported how the solvent accessible surface area around such complexes is determined by the lipophilicity of the ligand substituents.[11] The slowest exchange rates were observed for complexes that did not assist the approach of second sphere water molecules and possessed the smallest solvent accessible surface area. Here, we extend these ideas to establish how the nature of the counter-anion in cationic gadolinium complexes determines the rate of dissociative water exchange and hence the proton relaxivity of solutions containing these complexes.

Complexes of $[Gd\cdot\mathbf{1a}]^{3+}$ with differing counter anions were prepared following literature procedures from the ligand and the appropriate Gd salt, or by ion exchange from the chloride salt using an Amberlite anion exchange resin. For the parallel series of europium complexes, proton NMR measurements examining the ratio of the square antiprismatic to twisted square antiprismatic isomers in D_2O revealed a constant value of 4 : 1 at 298 K. For each gadolinium complex, the relaxivity was measured (20 MHz, 298 K) and the water exchange rate at 298 K assessed following variable temperature ^{17}O NMR measurements of the transverse ^{17}O relaxation rate, analysing the data using the Swift–Connick approximation. For purposes of comparison, data for the related complexes, $[Gd\cdot\mathbf{1b}]^{3+}$ [12] and the two anionic complexes $[Gd\cdot\mathbf{2}]^-$ and $[Gd\cdot\mathbf{3}]^-$ [13] — containing an integral carboxylate group — are also included.

In the pH range 6 to 8, these complexes exhibited no change in relaxivity, ruling out any pH dependent prototropic contribution to the observed proton relaxivity. The plot of proton relaxivity *versus* the measured water exchange rate (Fig. 1) reveals some important features. Within the halide series, the iodide complex exchanges water most rapidly and the relaxivity order follows the same sequence: $I^- > Br^- > Cl^-$. The acetate complex showed intermediate behaviour, and for complexes with an integral carboxylate anion the Ala-based complex, $[Gd\cdot\mathbf{2}]^-$ exchanged more rapidly than the β-Ala isomer, $[Gd\cdot\mathbf{3}]^-$; the latter may possess greater conformational freedom for the carboxylate anion to engage in hydrogen bonding. Complexes containing nitrate, trifluoromethanesulfonate, trifluoroacetate, and chloride counterions exchange water more slowly and the sulfate complex exchanged water most slowly of all.

The relaxivity tends to the limit expected for a complex where only the outer-sphere contribution to the measured proton relaxivity is operative [$\tau_m > T_{1m}$, eqn. (1)].

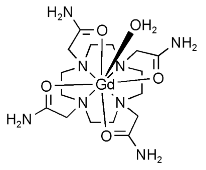
$$R_{1p}^{is} = \frac{C_{tot}q}{55.6\,(T_{1m}+\tau_m)} \qquad (1)$$

Implicit in eqn. (1) (where R_{1p}^{is} is the inner sphere paramagnetic contribution to the measured relaxivity, τ_m is the mean water exchange rate, q is the number of bound water molecules, C_{tot} is the complex concentration (mM) and T_{1m} is the longitudinal relaxation time of the coordinated water protons) is the definition of the other limit, when $\tau_m < T_{1m}$ and the relaxivity tends to the value expected for a low molecular weight, mono-aqua Gd complex with a relatively fast water exchange rate, *i.e.* the value of 3.8 to 4.3 $mM^{-1}\,s^{-1}$ (298 K, 20 MHz) for related complexes such as $[GdDTPA]^{2-}$ and $[GdDOTA]^-$.[10]

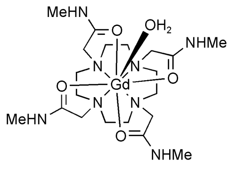
---

† Electronic supplementary information (ESI) available: representative NMRD profile (298 K) and ^{17}O-NMR analysis for the chloride complex. See http://www.rsc.org/suppdata/cc/b3/b302211k/

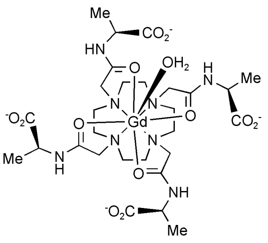
DOI: 10.1039/b302211k



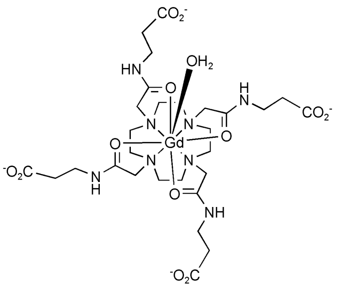
[Gd.1a]$^{3+}$



[Gd.1b]$^{3+}$



[Gd.2]$^-$



[Gd.3]$^-$

The nitrate complex of [Gd·**1a**]$^{3+}$ also exhibits a slow water exchange rate, limiting the inner sphere contribution to the measured relaxivity. This complex has been examined by X-ray crystallography,‡ following crystallisation from aqueous solution. The structure reveals the complex in the major square antiprismatic form, with a highly ordered array of hydrogen bonding between the Gd-bound water and the three second sphere waters and nitrate anions (Fig. 2, Gd–O = 2.466(2) Å with each of the water hydrogens tilted away from the Gd–O vector). The Gd-bound water molecule acts as a hydrogen bond acceptor (O5–O3W), and as a hydrogen-bond donor to another water molecule in the asymmetric unit (*i.e.* a second-sphere water: O5–O2W) and to a disordered nitrate anion (73/27 disorder over two sites). The hydrogen bond network is completed by bonds between the ligand amide NH donors and oxygen acceptors which are either water molecules(N31–O1B), nitrate counter-ions (N41–N10) or an amide carbonyl in an adjacent complex (N31–O3A). Attempts to solve the X-ray structures of complexes containing bromide and iodide anions were frustrated by significant disorder in the location of two of the anions. In the case of the chloride complex, the high solubility in water has precluded obtaining suitable crystals for analysis in this series of complexes. That the bromide and iodide complexes are indeed disordered in the crystal lattice accords with their chaotropic tendency and the faster rates of water exchange measured.

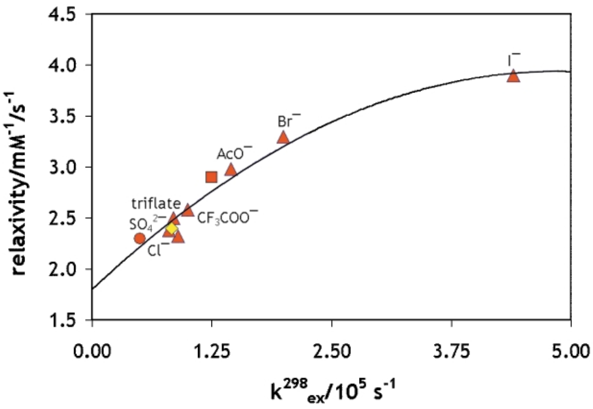


Fig. 1 Variation of proton relaxivity (298 K, 20 MHz) with water exchange rate (^{17}O NMR, 298 K) for the series of cationic gadolinium complexes, [Gd·**1a**·OH$_2$]$^{3+}$, varying the nature of the anion shown, (nitrate = diamond). Data for the anionic complexes with an integral carboxylate, [Gd·**2**·OH$_2$]$^-$ and [Gd·**3**·OH$_2$]$^-$, are shown for comparison [13] (circle and square respectively), and for [Gd·**1b**·OH$_2$](CF$_3$SO$_3$)$_3$, (not shown), relaxivity is 2.5 mM^{-1} s^{-1} and k_{ex} = 0.59 × 10^5 s^{-1} (298 K).[12]

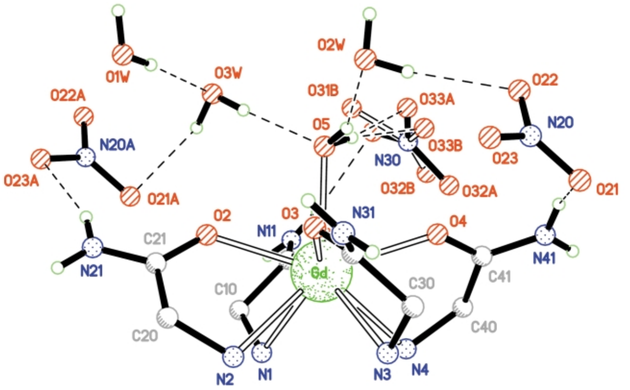


Fig. 2 View of the hydrogen bonding network in the crystal lattice for [Gd·**1a**(H$_2$O)](NO$_3$)$_3$·3H$_2$O (120 K); the nitrate N30 is disordered over two sites (73/27 occupancy modelled).

In summary, anions imposing order on the second sphere of hydration, either by electrostatic ordering or through the establishment of a network of hydrogen bonds, can give rise to slower rates of water exchange at the proximate gadolinium centre compared to less charge dense ions that lack the ability to break up the hydrogen bond network between water molecules around the metal centre.

We thank EPSRC for support; this work was undertaken under the auspices of the EC/ESF COST Action D-18.

Notes and references

‡ *Crystal data* for [Gd·**1a**(H$_2$O)](NO$_3$)$_3$·3H$_2$O: $C_{16}H_{40}GdN_{11}O_{17}$, M_r = 815.84, T = 120(2) K, λ(Mo-Kα) = 0.710073 Å, triclinic, space group $P1$, a = 10.2067(2), b = 10.3352(2), c = 16.0092(3) Å, α = 91.6440(10), β = 99.2690(10), γ = 116.0800(10)°, V = 1487.57(5) Å^3, D_c = 1.821 Mg m^{-3}, Z = 2, μ(Mo-Kα) = 2.323 mm^{-1}, reflections collected/unique 12937/6435 [R_{int} = 0.0261], final R indices [$I > 2\sigma(I)$]: R_1 = 0.0191 and wR_2 = 0.0487 [6262], R indices (all data): R_1 = 0.0196 and wR_2 = 0.0491. Data collected on a Bruker SMART CCD 6K area detector diffractometer. CCDC reference number 204855. See http://www.rsc.org/suppdata/cc/b3/b302211k/ for crystallographic data in CIF or other electronic format.

1 J. M. Roberts, A. R. Diaz, D. T. Fortin, J. M. Friede and S. D. Piper, *Anal. Chem.*, 2002, **74**, 4927.

2 F. Hofmeister, *Arch. Exp. Pathol. Pharmakol.*, 1888, **24**, 247; M. G. Cacace, E. M. London and J. J. Ramsden, *Quart. Rev. Biophys.*, 1997, **30**, 241.

3 K. D. Collins, *Biophys. J.*, 1997, **72**, 65.

4 B. Hribar, N. T. Southall, V. Vlachy and K. R. Dill, *J. Am. Chem. Soc.*, 2002, **124**, 12302.

5 E. A. Krestov, *Thermodynamics of Solvation: Solution and Dissolution, Ions and Solvents, Structure and Energetics*, Horwood, New York, 1991.

6 M. Eigen, *Pure Appl. Chem.*, 1963, **6**, 105; R. G. Wilkins and M. Eigen, *Adv. Chem. Ser.*, 1965, **49**, 55; T. W. Swaddle, *Comments Inorg. Chem.*, 1991, **12**, 237; D. W. Margerum, in *Coordination Chemistry*, ed. A. E. Martell, ACS Monograph, ACS, Washington, DC, **vol. 174**, 1978, ch. 1; D. T. Richens, *The Chemistry of Aqua Ions*, Wiley, Chichester, 1997.

7 S. Cossy, L. Helm and A. E. Merbach, *Inorg. Chem.*, 1989, **28**, 2699.

8 J. E. Enderby and G. W. Neilson, *Adv. Inorg. Chem.*, 1989, **34**, 195.

9 S. Aime, A. Barge, M. Botta, D. Parker and A. S. de Sousa, *J. Am. Chem. Soc.*, 1997, **119**, 4767; A. Blemzen, F. Foglia, E. Furet, L. Helm, A. E. Merbach and J. Weber, *J. Am. Chem. Soc.*, 1996, **118**, 12777; M. Botta, *Eur. J. Inorg. Chem.*, 2000, 399; D. Parker, R. S. Dickins, H. Puschmann, C. Crossland and J. A. K. Howard, *Chem. Rev.*, 2002, **102**, 1977.

10 P. Caravan, J. J. Ellison, T. J. McMurry and R. B. Lauffer, *Chem. Rev.*, 1999, **99**, 2293.

11 S. Aime, A. Barge, M. Botta, F. Fedeli, A. Mortillaro, D. Parker and H. Puschmann, *Chem. Commun.*, 2002, 1120.

12 S. Aime, A. Barge, J. I. Bruce, M. Botta, J. A. K. Howard, J. M. Moloney, D. Parker, A. S. de Sousa and M. Woods, *J. Am. Chem. Soc.*, 1999, **121**, 5672.

13 S. Aime, A. Barge, M. Botta, J. A. K. Howard, R. Kataky, M. P. Lowe, J. M. Moloney, D. Parker and A. S. de Sousa, *Chem. Commun.*, 1999, 1047.