Non-radiative deactivation of the excited states of europium, terbium and ytterbium complexes by proximate energy-matched OH, NH and CH oscillators: an improved luminescence method for establishing solution hydration states

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The radiative rate constants for depopulation of the excited states of closely-related series of anionic, neutral and cationic europium, terbium and ytterbium complexes have been measured in H_2O and D_2O. With the aid of selective ligand deuteriation, the relative contributions of OH, NH (both amide and amine) and CH oscillators have been measured and critically assessed. Quenching of the Eu $^5D_0$ excited state by amine NH oscillators is more than twice as efficient as OH quenching. The importance of the distance between the excited Ln ion and the XH oscillator is described with recourse to published crystallographic information. The general equation, $q = A'(\Delta k_{H_2O} - k_{D_2O})_{corr}$ is presented and revised values of A' for Eu (1.2 ms), Tb (5 ms) and Yb (1 µs) given, which allow for the quenching contribution of closely diffusing OH oscillators. The relevance of such studies to the hydration state of certain gadolinium complexes is described and clear evidence provided for a break in hydration at gadolinium.

Deactivation of the luminescence from excited trivalent lanthanide ions in solution occurs by means of a vibrational energy transfer process involving high-energy vibrations of solvent molecules or of the bound ligand. Many of the early investigations of non-radiative relaxation in lanthanide systems sought to identify the nature and relative importance of these interactions.[1–10] These studies revealed that OH oscillators, *e.g.* in bound water molecules, were the most effective quenchers both in the solid-state and in solution. Other oscillators were less efficient, but clear evidence for the quenching effect of higher harmonics of NH, C–H and C=O stretching vibrations was provided.[2] It was also found that the extent of luminescence quenching by water molecules was inversely proportional to the energy gap between the emitting state and the ground state manifold,[1,2] and that each oscillator quenched the excited state independently.[7,10] The energy gap between the luminescent state and the ground state manifold is approximately 10 200 cm^{-1} for Yb^{3+}, 12 000 cm^{-1} for Eu^{3+} and 15 000 cm^{-1} for Tb^{3+}. Relatively efficient coupling of the Yb^{3+} and Eu^{3+} excited states occurs to the third vibrational overtone of proximate OH oscillators ($\nu_{OH} \sim 3300$–3500 cm^{-1}), and to the fourth harmonic in the case of Tb^{3+}, consistent with the observed less efficient quenching for Tb^{3+}, where the Franck–Condon overlap factor is less favourable. The corresponding O–D, N–D and C–D oscillators possess lower stretching frequencies and any energy matching is only possible with higher vibrational states. It was shown that—for the case of Eu and Tb—X–D oscillators were at least 200 times less effective at vibronic quenching than the corresponding X–H oscillators.[9]

In general, the rate constant for depopulation of the lanthanide excited state in water may be partitioned as the sum of the different quenching contributions [eqn. (1)]. If it is assumed

$$k_{H_2O} = k_{nat} + k_{nr} + \Sigma k_{XH} + \Sigma k_{C=O} \tag{1}$$

that in D_2O, all *exchangeable* XH oscillators do not contribute (as is likely to be the case for excited Eu, Tb and Yb complexes), then the rate equation simplifies† [eqn. (2)] (where k_{nat} is the natural radiative rate constant, k_{nr} is the rate constant for non-radiative de-excitation, and $\Sigma k_{XH}/\Sigma k_{C=O}$ are the sums of the rate constants for energy transfer to proximate matched XH and CO oscillators).

$$k_{D_2O} = k_{nat} + k_{nr} + \Sigma k_{C=O} \tag{2}$$

$$\Delta k = k_{H_2O} - k_{D_2O} = \Sigma k_{XH} \tag{3}$$

Given the predominance of OH quenching in aqueous media,[8,10] and ignoring other contributions an expression was derived that related the number of water molecules in the inner coordination sphere to the difference in the rate of quenching in H_2O and D_2O [eqn. (4)], where A is a proportionality constant

$$q = A(k_{H_2O} - k_{D_2O}) \tag{4}$$

signifying the sensitivity of the lanthanide ion to vibronic quenching by OH oscillators. For europium, A was found to be 0.525 ms^{-1} (per OH oscillator) and for terbium, 2.1 ms^{-1},[11–13] (*i.e.* $A_{Tb} = 4.2$ per bound water molecule), with an estimated uncertainty in q of ±0.5. Other less convincing and more empirical relationships have been proposed for specific classes of ligands[14] and a similar approach has been adopted in attempting to quantify the quenching effect of amine NH oscillators[15,16] in polyamine complexes of Eu and Tb. In this case, the quenching effect of an NH oscillator in Eu complexes was estimated to be 1.5 times greater than for an OH, and for terbium amine NH oscillators were reputedly half as effective as OH at quenching.

The loss of electronic energy from a luminophore to vibrational energy of a solvent molecule or ligand has been proposed[16] to occur in a similar manner to the general energy transfer formula developed by Förster.[17] A multipole–multipole Coulombic interaction between the vibrational oscillator and the luminophore is invoked wherein dipole–dipole interactions dominate. The energy transfer rate, k_{12}, between the two centres is inversely proportional to the distance between them in a $1/r^6$ relationship [eqn. (5)], in which $\bar{\nu}$ is the energy of the resonant

$$k_{12} = Cr^{-6} \tag{5}$$

$$\text{where } C_{d\text{–}d} = \left[\frac{(3e^4 f_1 f_2)}{8\pi^2 m^2 c^3 n^4 \bar{\nu}^2}\right] \int g_1(\bar{\nu}) g_2(\bar{\nu}) d\bar{\nu}$$

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† In eqns. (1) and (2), the quenching by carbonyl oscillators is highlighted: other ligand oscillators may also quench, of course, and contribute to the k_{nr} term in each case.

Table 1 Partition coefficients (log *P*) for the distribution of ^{153}Gd-radiolabelled complexes (298 K; the mean of 3 measurements is given with standard deviations in parentheses)

		Octanol		Butanol	
	Complex	PBS	water	water	PBS
Anionic	$[GdL^{1b}]^-$	−4.47(0.77)	−4.75(0.55)	−3.03(0.03)	−3.15(0.06)
	$[GdL^{1a}]^-$	−0.48(0.03)	−0.66(0.04)	0.71(0.18)	0.61(0.23)
	$[GdL^{2a}]^-$	−4.16(0.73)	−3.40(0.26)	−2.39(0.18)	−3.01(0.04)
	$[GdL^{3}]^{2-}$	−4.59(0.75)	−4.18(0.56)	−3.96(0.43)	−3.87(0.49)
Neutral	$[GdL^{9}]$	−1.91(0.05)	−2.00(0.38)	−0.50(0.02)	−0.53(0.03)
	$[GdL^{10}]$	−1.33(0.04)	−1.36(0.04)	−0.13(0.04)	−0.15(0.04)

transition, $g_1(\bar{\nu})$ and $g_2(\bar{\nu})$ are the normalised lineshapes of the emission and absorption transitions respectively, and f_1 and f_2 are the oscillator strengths of the emission transition of the luminophore and the absorption of the vibrational transition of the oscillator. Such a relationship obviously highlights the sensitivity of the rate of quenching to the distance between the lanthanide ion and a proximate oscillator. This, in turn, suggests clearly that in seeking to partition the independent quenching effects of XH oscillators, it is important initially to correlate information from closely related series of complexes of known constitution and speciation. Otherwise distances from the lanthanide to the quenching oscillator are prone to considerable variation, which may be the origin of at least some of the errors associated with previous analyses.[11–15]

As part of a programme of work focused on developing responsive lanthanide probes in magnetic resonance imaging (MRI)[18–20] and for luminescent sensors,[21,22] we have examined the luminescence behaviour of over 20 lanthanide complexes based on functionalised 12-ane-N_4 ligands. Many of these structurally homologous complexes have been characterised in detail by crystallographic and solution NMR techniques, so that a fairly large data set has been acquired from which some reliable conclusions may be drawn. Aspects of this work have appeared elsewhere in some preliminary communications.[23,24]

Quenching by bound and closely diffusing OH oscillators

In the europium, gadolinium, yttrium and ytterbium complexes of the tetrabenzylphosphinate ligand, L^{1a}, there is no metal-bound water molecule, and in the crystal lattice the nearest water is 5.6 Å away from the eight-coordinate lanthanide ion.[19,25] In aqueous solution, each of these complexes exists as one predominant (≥90%) stereoisomer with a twisted square-antiprismatic geometry at the metal ion. The rate constant for depopulation of the excited state of $[EuL^{1a}]^-$, $[TbL^{1a}]^-$ and $[YbL^{1a}]^-$ was measured in H_2O and D_2O. The difference in *k* values obtained represents the quenching effect of 'outer-sphere' water molecules, *i.e.* the quenching effect of water molecules that are diffusing sufficiently closely to the metal ion to allow vibrational energy transfer over a long distance. The measured Δk values were 0.15 ms^{-1}, 0.02 ms^{-1} and 0.11 μs^{-1} for the Eu, Tb and Yb complexes respectively. These values probably set a lower limit on the quenching effect of unbound water molecules, because the complexed lanthanide is particularly well-shielded by the 12-N_4 ring and the hydrophobic benzylic P-substituents. Indeed the relative hydrophobicity of the complexes has been highlighted in measurements of the log *P* value of the corresponding ^{153}Gd complexes, in a standard octanol–phosphate buffered saline partitioning experiment. A value of −0.48 was measured which compares to −4.77 for the more hydrophilic P–Me analogue, $[GdL^{1b}]^-$, and −4.16 for the complex of dota,‡ $[^{153}GdL^{2a}]^-$. Partition coefficients under various conditions were calculated by measuring the equilibrium concentration of representative radiolabelled gadolinium-153 complexes (^{153}Gd, γ, $t_{\frac{1}{2}}$ 241 days) and serve to highlight the relative hydrophilicity of these polar complexes (Table 1).

The tetramethylphosphinate complexes of Eu, Gd, Tb and Yb, $[LnL^{1b}]^-$, also do not possess a bound water molecule[25] and similarly exist as a single diastereoisomer in solution. They are obviously much more hydrophilic than the complexes of the tetrabenzyl analogue—as highlighted by these distribution experiments. Indeed, analysis of NMRD profiles for $[GdL^{1a}]^-$ and $[GdL^{1b}]^-$ has indicated clearly[25] that the nearest diffusing water molecule is at least 0.4 Å closer to the paramagnetic centre in $[GdL^{1b}]^-$ compared to $[GdL^{1a}]^-$. The differences in the measured rate constants in H_2O and D_2O for $[EuL^{1b}]^-$, $[TbL^{1b}]^-$ and $[YbL^{1b}]^-$ were found to be 0.26, 0.07 ms^{-1} and 0.24 μs^{-1} respectively. Clearly then, intermolecular energy transfer in solution to proximate OH oscillators may constitute a significant term in the overall quenching effect. Indeed such a conclusion has been noted previously in a singular case in the solid-state:[26] in the nine-coordinate europium complex of $Eu(oda)_3{\cdot}H_2O$ (oda is 3-oxapentandioate, or oxydiacetate), the water molecule is unbound, resides 5.05 Å from the Eu ion and was shown to contribute 0.26 ms^{-1} to the rate of quenching of the Eu ion in the lattice.

Therefore before calculating a hydration state by examining quenching rates in H_2O and D_2O, allowance must be made for the quenching effect of unbound water (or in general, solvent). Given that most of the lanthanide complexes of polyaminocarboxylates, phosphinates and phosphonates are both charged and very hydrophilic, then a correction of −0.25, −0.06 ms^{-1} and −0.20 μs^{-1} may be made for Eu, Tb and Yb complexes respectively, prior to estimating hydration states. These corrections are chosen somewhat empirically, but each represents a reasonable value, albeit subject to an error of around 25%.

When a water molecule is bound to a lanthanide ion, the metal–oxygen bond distance is fairly constant for a diverse series of anionic, neutral and cationic complexes with varying numbers of bound water molecules.[18] Values of 2.45 (±0.04) Å have been found in complexes of europium with one,[27–29] two,[30] three[31] or five[32] coordinated water molecules. Thus the quenching effect of coordinated water molecules should give rise to a fairly predictable term, for well-defined complexes of known speciation. Inspection of a considerable amount of data (Tables 2, 3 and 4) primarily relating to the quenching effects of OH oscillators in Eu, Tb and Yb complexes supports this premise. Thus, for the anionic europium complexes of L^{2a}, L^{2b} and dtpa (dtpa is diethylenetriamine pentaacetate) which possess one bound water molecule the values of $k_{H_2O} - k_{D_2O}$ are very similar, and after correcting for the quenching effect of unbound waters give Δk_{corr} values of 0.82, 0.88 and 0.90 ms^{-1} respectively. These values are the same, within the experimental error associated with such measurements. For the cationic tetraamide complexes of L^{4a}, L^{4b}, L^{4c}, L^{5a} and L^{5b}, corrected§ Δk

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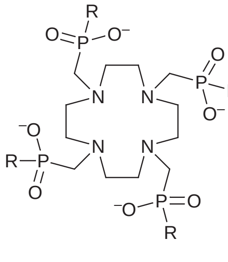
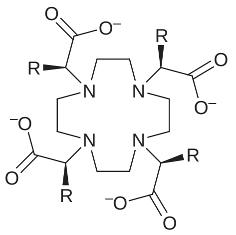
‡ dota is 1,4,7,10-tetraazacyclododecane tetraacetate.

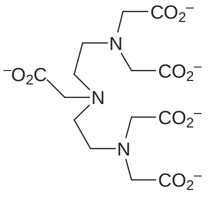
§ A correction to allow for the quenching effect of amide NH oscillators has also been applied here; see the section on NH quenching which follows.



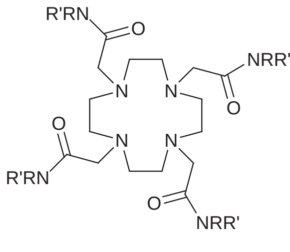
L^{1a} R = CH$_2$Ph
L^{1b} R = Me



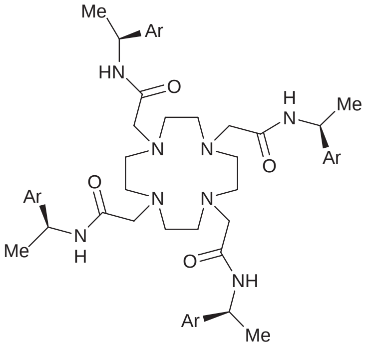
L^{2a} R = H (dota)
L^{2b} R = CH$_2$CH$_2$CO$_2^-$



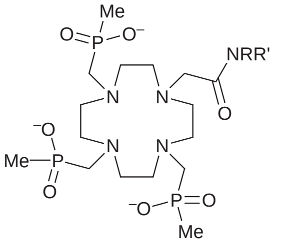
L^3 (dtpa)



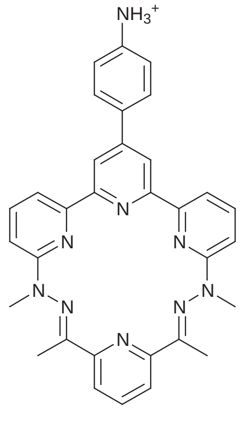
L^{4a} R = H, R' = Me
L^{4b} R = Me = R'
L^{4c} R = H = R'



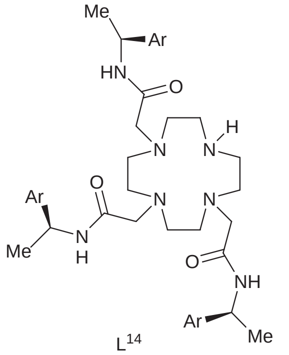
L^{5a} Ar = Ph
L^{5b} Ar = 2-C$_{10}$H$_7$
L^{5c} Ar = p-Br-Ph



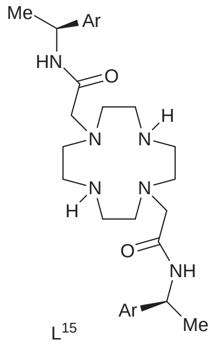
L^6 R = H, R' = Me
L^7 R = H, R' = Ph
L^8 R = R' = Me
L^9 R = R' = CH$_2$Ph
L^{10} R = R' = Bu
L^{11} R = H, R' = CH(Me)-1-C$_{10}$H$_7$
L^{12} R = H, R' = CHMePh



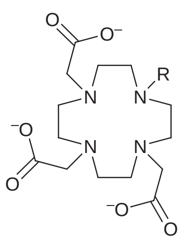
L^{13}



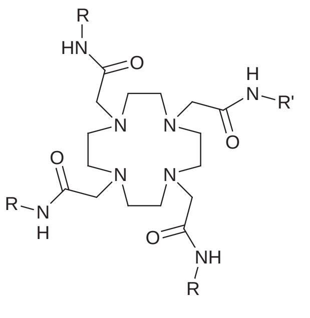
L^{14}



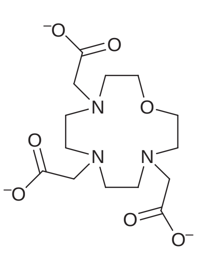
L^{15}



L^{16a} R = H (do3a)
L^{16b} R = Me



L^{17a} R = Me, R' = CH$_2$-2'-C$_{10}$H$_7$
L^{17b} R = R' = CH$_2$-2'-C$_{10}$H$_7$



L^{18}

values were obtained in the range 0.76 to 0.89. The mean value of Δk for these eight complexes is 0.83, suggesting that the appropriate proportionality constant to allow calculation of the inner-sphere hydration state is 1.2 ms [eqn. (6)]. Similar

$$q_{\mathrm{corr}} = A'\Delta k_{\mathrm{corr}} \tag{6}$$

where A' = 5 ms (Tb), 1.2 ms (Eu), 1.0 µs (Yb)

arguments in the case of terbium complexes (Table 3), suggest

Table 2 Rate constants (ms^{-1}) for depopulation of the excited states of europium complexes in H_2O and D_2O (293 K; *k* values are reproducible to ±10% ms^{-1})[a,b]

	Complex	k_{H_2O}	k_{D_2O}	Δk	Δk_{corr}[a]	q'_{corr}[d]
Anionic	$[EuL^{1a}]^-$	0.63	0.48	0.15	0	0
	$[EuL^{1b}]^-$	0.80	0.54	0.26	0.01	0.01
	$[Eu(dota)]^-$	1.60	0.53	1.07	0.82	0.98
	$[EuL^{2b}]^{5-}$	1.61	0.48	1.13	0.88	1.06
	$[Eu(dtpa)]^{2-}$	1.59	0.44	1.15	0.90	1.08
	$[Eu(edta)]^-$	2.90	0.48	2.42	2.17	2.60
Cationic	$[EuL^{4a}]^{3+}$	1.82	0.47	1.35	0.80	0.96
	$[EuL^{4b}]^{3+}$	1.60	0.54	1.06	0.81	0.97
	$[EuL^{4c}]^{3+}$[c]	1.93	0.46	1.47	0.77	0.92
	$[EuL^{5a}]^{3+}$	1.72	0.41	1.31	0.76	0.91
	$[EuL^{5b}]^{3+}$	1.92	0.48	1.44	0.89	1.07
Neutral	$[EuL^6]$	1.32	0.54	0.78	0.45	0.54
	$[EuL^7]$	1.43	0.49	0.94	0.61	0.73
	$[EuL^8]$	1.19	0.51	0.68	0.43	0.52
	$[EuL^9]$	1.25	0.52	0.73	0.48	0.58
	$[EuL^{10}]$	1.17	0.50	0.67	0.42	0.50
	$[EuL^{11}]$	1.37	0.59	0.78	0.45	0.54
	$[EuL^{12}]$	1.47	0.57	0.90	0.57	0.68
	$[EuL^{16a}]$	2.27	0.52	1.75	1.50	1.80
	$[EuL^{16b}]$	2.38	0.80	1.58	1.33	1.60

[a] For all complexes listed, a correction to Δk of -0.25 ms^{-1} has been applied, to allow for the effect of closely diffusing OH oscillators. [b] Each *amide* NH oscillator has been assumed to contribute 0.075 ms^{-1} to the quenching of the Eu $^5D_0$ excited state. [c] The primary amide NH oscillators are diastereotopic and will quench with different efficiencies as they are different distances from the metal ion; an arbitrary reduction of 50% has been made for the second set of 4 NH oscillators, as they are at least 0.3 Å further away than the first set of 4. [d] The value of q'_{corr} has been obtained, by multiplying Δk_{corr} by 1.20.

Table 3 Rate constants (ms^{-1}) for depopulation of the excited states of terbium complexes in H_2O and D_2O (293 K; *k* values are reproducible to ±10% of the quoted value)[b]

	Complex	k_{H_2O}	k_{D_2O}	Δk	Δk_{corr}[a]	q'_{corr}
Anionic	$[TbL^{1a}]^-$	0.24	0.22	0.02	0	0
	$[TbL^{1b}]^-$	0.34	0.27	0.07	0.01	0.05
	$[Tb(dota)]^-$	0.66	0.39	0.27	0.21	1.05
	$[TbL^{2b}]^-$	0.48	0.30	0.18	0.12	0.60
	$[Tb(dtpa)]^{2-}$	0.69	0.41	0.28	0.22	1.10
	$[Tb(edta)]^-$[a]	0.93	0.29	0.64	0.58	2.90
Cationic	$[TbL^{4a}]^{3+}$	0.60	0.30	0.30	0.22	1.10
	$[TbL^{5a}]^{3+}$	0.57	0.29	0.28	0.20	1.0
	$[TbL^{5b}]^{3+}$	0.60	0.30	0.30	0.22	1.10
Neutral	$[TbL^6]$	0.31	0.23	0.08	0.02	0.10
	$[TbL^7]$	0.32	0.24	0.08	0.02	0.10
	$[TbL^8]$	0.28	0.23	0.05	0	0
	$[TbL^9]$	0.30	0.25	0.05	0	0
	$[TbL^{12}]$	0.33	0.25	0.08	0.02	0.10

[a] A 1:1 stoichiometry was used; data from reference 11 (pH 6, 10^{-3} M complex). [b] A correction of -0.06 ms^{-1} has been applied in each case, to allow for the quenching effect of closely diffusing OH oscillators, and q'_{corr} is calculated as $q'_{corr} = 5\Delta k_{corr}$.

Table 4 Rate constants (μs^{-1}) for depopulation of the excited states of ytterbium complexes in H_2O and D_2O (293 K; *k* values are reproducible to ±15%)

	Complex	k_{H_2O}	k_{D_2O}	Δk	Δk_{corr}[a]	q'_{corr}
Anionic	$[YbL^{1a}]^-$[a,b]	0.22	0.11	0.11	0	0
	$[YbL^{1b}]^-$[b,e]	0.39	0.15	0.24	0.04	0.04
	$[Yb(dota)]^-$[b]	0.67	0.17	0.50	0.30	0.30
	$[YbL^{2b}]^{5-}$[b]	1.02	0.28	0.74	0.54	0.54
	$[Yb(dtpa)]^{2-}$[b]	1.37	0.12	1.25	1.05	1.05
	$[Yb(edta)_2]^{5-}$[b]	0.46	0.09	0.37	0.17	0.17
Cationic	$[YbL^{5a}]^{3+}$[c,e]	1.43 (0.58)	0.16	1.27	1.07	1.07
	$[YbL^{5b}]^{3+}$[c,e]	1.20 (0.51)	0.20	1.00	0.80	0.80
	$[YbL^{5c}]^{3+}$[c,e]	1.30 (0.54)	0.13	1.17	0.97	0.97
	$[YbL^{13}]^{4+}$[d]	3.09	0.11	2.98	2.78	2.78
Neutral	$[YbL^7]$	0.53	0.15	0.38	0.18	0.18

[a] The value of $k_{D_2O} = 0.11$ μs^{-1} was obtained both by excitation at 970 nm and at 266 nm. [b] For excitation at 970 nm, decay curves were observed using a 1050 nm interference filter with a 40 nm bandpass, with the aid of a polariser to block scattered light from the laser source. $[Yb{\cdot}dota]^-$ exists in solution as a 4:1 mixture of a monohydrated square antiprismatic and an 8-coordinate ($q = 0$) twisted square antiprismatic complex. [c] Trifluoromethanesulfonate salts were used, with an excitation wavelength of 266 nm. [d] Excitation at 355 nm for the chloride salt; in the presence of 0.1 M NaCl, values were $k_{H_2O} = 2.50$, $k_{D_2O} = 0.13$ μs^{-1}, consistent with $q'_{corr} = 2.17$ and a structure in which one of the water molecules is replaced by a halide anion. In the presence of 0.1 M sodium lactate, $k_{H_2O} = 0.61$, $k_{D_2O} = 0.08$, consistent with replacement of *all* the bound water molecules. [e] A correction of 0.06 μs^{-1} has been applied to allow for the effect of the 4 exchangeable amide NH oscillators. The complex exists in solution (D_2O, CD_3OD, CD_3CN) as >95% of a twisted square antiprismatic structure, with $q = 1$ (^1H NMR analysis). The observation of a double exponential decay in H_2O—given the slowness of water exchange in cationic lanthanide complexes[35,36]—may correspond to the decay from a $q = 1$ species, and the *intermediate* (*i.e.* $q = 0$) for the *dissociative* water exchange mechanism.

that the appropriate proportionality constant is 5.0 ms, while for ytterbium complexes a value of 1.0 μs is reasonable (Table 4).

Bearing in mind the more accurate calculation of Δk_{corr}, these A' values are not very different from those originally suggested (4.2 for Tb, 1.05 for Eu), but probably give rise to more appropriate values for q, with a reduced uncertainty. It is important to emphasise that there is still some uncertainty associated with such estimates of hydration state. Measurement of the rate of decay of the excited state lifetimes of Eu and Tb are subject to an experimental error of ±10%, and for Yb an error of ±15% may be estimated. In addition, there is the question of the constancy of the distance between the lanthanide ion and the quenching oscillator. Although for many complexes—which exist as a single isomer in solution—the Ln–OH_2 distance, for example, is fairly constant, there are cases where a longer bond may occur or where a hydrogen bond acceptor in the ligand brings an unbound water molecule closer to the Ln ion—often termed a 'second-sphere' coordination.[33] A simple calculation of the effect of varying the Ln–OH_2 distance on the 'apparent' hydration state q, illustrates this idea. Taking a distance of 2.90 Å between the Eu (or Tb) ion and the mean position of a proton of a bound water molecule as representing a hydration state $q = 1.0$, then the effect of increasing this distance, r, on the apparent q value may be calculated, by assuming that the rate of vibrational energy transfer falls off as $1/r^6$, (Fig. 1). If the metal–water distance increases by 0.1 Å, then the apparent hydration state (*e.g.* from a luminescence measurement) may be expected to fall to 0.82; for a 0.2 Å lengthening the apparent q value will be 0.68. Interestingly, even at a distance of 3.5 Å from the metal centre, there will be a very significant residual q value. The relationship between this apparent q value, the definition of 'outer-sphere' coordination and the relevance to the relaxivity of Gd complexes is discussed further below.

Quenching effect of amide and amine oscillators

Many tetra-amide lanthanide complexes of 12-N_4 based ligands have been reported recently, and crystallographic[29,34] and solution NMR[35,36] evidence has shown clearly that there is one coordinated water molecule in the complexes of Eu, Gd and Dy. It was first noted with the europium complexes of the mono- and tetra-naphthylamides L^{17a} and L^{17b}, that with Eu^{3+} centre acting as a charge sink, the amide NH underwent H/D

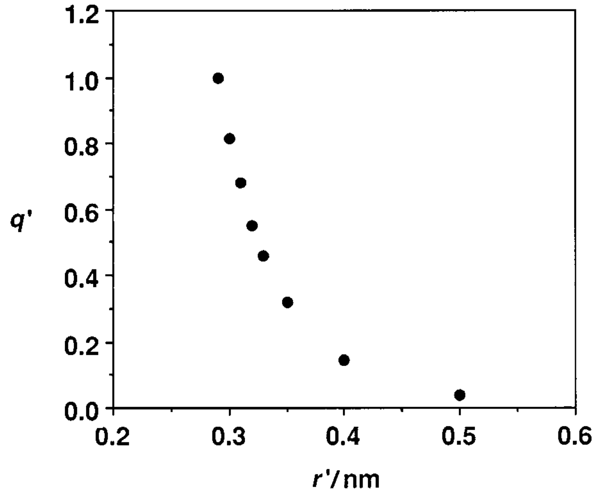


Fig. 1 Effect of varying the distance between a quenching XH oscillator and a bound lanthanide ion on the apparent hydration state q'. The distance 2.90 Å is taken to represent $q = 1$, and a $1/r^6$ relationship is assumed to define the distance dependence.

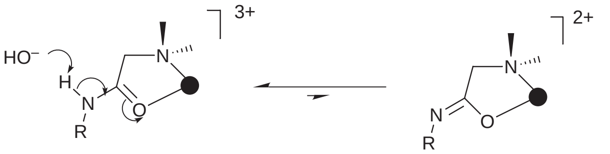


Fig. 2 Base catalysed NH/ND exchange of coordinated amide NH bonds in Eu and Yb complexes, aided by the metal centre acting as a charge sink.

Table 5 Rate constants (ms^{-1}) for depopulation of the excited states of tripositive europium and terbium amide complexes possessing two, one and no proximate amine NH oscillators (293 K; k values are reproducible to ±10% ms^{-1})[a]

Complex	k_{H_2O}	k_{D_2O}	Δk	Δk_{corr}[a]	q'_{corr}[b]
$[EuL^{5a}]^{3+}$	1.72	0.41	1.31	0.76	0.91
$[EuL^{14}]^{3+}$	3.85	1.55	2.30	1.82	2.18
$[EuL^{15}]^{3+}$	5.88	2.86	3.02	2.62	3.14
$[TbL^{5a}]^{3+}$	0.57	0.29	0.28	0.22	1.10
$[TbL^{14}]^{3+}$	0.84	0.39	0.45	0.39	1.95
$[TbL^{15}]^{3+}$	1.12	0.47	0.65	0.59	2.95

[a] Values were recorded on the trifluoromethanesulfonate salts, using a complex concentration of 1 mM at a pH of 5.5 (±0.5). [b] For europium complexes, $q'_{corr} = 1.2\ \Delta k_{corr}$, for terbium, $q'_{corr} = 5\ \Delta k_{corr}$.

exchange rapidly in D_2O (Fig. 2), whereas the corresponding yttrium (and Tb) complexes exchanged much more slowly.[37] The dried Eu complexes which had undergone H/D exchange gave rise to longer emission lifetimes, in dry acetonitrile, suggesting that deactivation of the $^5D_0$ europium excited state may occur through coupling to amide NH ($\nu_{NH} \sim 3300$ cm^{-1}) vibrational levels. Comparison of a large number of tetra-amide europium complexes (Table 2) allows the definition of the average quenching effect of an individual amide NH oscillator to be assessed as 0.075 ms^{-1}. Comparison of the behaviour of the complexes $[EuL^{4a}]^{3+}$ possessing four secondary amide oscillators—with the tertiary amide $[EuL^{4b}]^{3+}$ highlights the effect quite well: Δk values of 1.35 and 1.06 ms^{-1} were measured, which after subtraction of the effect of closely-diffusing oscillators (−0.25 ms^{-1} in each case) gives values of 1.10 and 0.81 ms^{-1}. This rate difference may be ascribed to amide NH quenching.

In the corresponding terbium tetra-amide complexes, amide NH quenching is not so apparent. This may be due to the relative inefficiency of the process, or because amide NH/ND exchange occurs sufficiently slowly at pH 5.5 that the effect is often not experimentally observed. Consider the example of the terbium complex, $[Tb{\cdot}L^{4a}]^{3+}$, it gives a rate constant of 0.30 ms^{-1} in D_2O that is pH independent in the range 4 to 12. At pD 5.9, H/D exchange does not occur over a period of 3 hours, monitoring by ESMS and FTIR. The cationic tetra-amide complexes of Tb (Table 3) therefore exhibit corrected q values close to unity, without allowing for any amide NH quenching.

For the ytterbium complexes examined, ^1H NMR analysis revealed that amide NH/ND exchange does occur rapidly on the experimental timescale. Thus $[Yb{\cdot}L^{5a}]^{3+}$ shows an amide NH resonance at −13.8 ppm (200 MHz, 293 K) in CD_3CN that is absent in D_2O and CD_3OD. These chiral cationic complexes exist in solution in a twisted square antiprismatic coordination, as revealed by the close correlation of their proton NMR dipolar shifts with that of those complexes which are known to possess this geometry, such as the 8-coordinate $[Yb{\cdot}L^{1a}]^-$ (X-ray analysis)[19] and the minor isomer of $[Yb{\cdot}dota]^-$.[38] The complex $[Yb{\cdot}L^{5c}]^{3+}$ was examined in detail; samples of the dried NH and amide ND labelled complexes (prepared by stirring in D_2O for 10 mins at 293 K) were dissolved in dry acetonitrile and the rate of decay of the Yb luminescence monitored in degassed solution following excitation at 266 nm. Double exponential decay was observed, with rate constants of 0.15 and 0.39 μs^{-1} and 0.20/0.44 μs^{-1} for the amide NH and ND complexes respectively. The difference in k values, corresponding to the combined quenching effect of 4 amide NH oscillators (*ca.* 0.05 μs^{-1}) is small compared to the effect of proximate OH oscillators. The observation of double exponential decay was also observed in aerated solution.

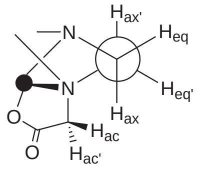
The effect of *amine* NH quenching in europium and terbium complexes has been reported previously, although the effectiveness has apparently differed markedly in the systems studied.[14,15,39] Again, a key issue to check is the extent to which H/D exchange occurs on the experimental timescale. It is instructive to compare the quenching rates in D_2O for a structurally-related series of di-, tri- and tetra-amide complexes in which there are two, one and no amine NH oscillators bound to the metal ion. Given that the amine NH oscillator is likely to be more or less the same distance from the lanthanide ion in each case, and that $^1H/^2H$ NMR and FTIR ($\nu_{NH} = 3250$ cm^{-1}) studies show that NH/ND exchange does *not* occur under ambient conditions in the complex, then the quenching contribution of the independent NH oscillator can be assessed in this series. The values obtained (Table 5), suggest that for terbium each oscillator contributes 0.09 (±0.01) ms^{-1} to the rate of quenching, while for europium the process is much more efficient with a value of *ca.* 1.2 (±0.02) ms^{-1} per NH. Obviously, this is only a small data set, from which it is presumptuous to draw a general conclusion, but the importance of the effect is beyond doubt. For excited europium complexes, quenching by amine NH oscillators, notwithstanding the longer M–NH distance, is at least twice as efficient as OH vibrational energy transfer, a figure which is in reasonable agreement to the singular example reported by Balzani.[39] The larger quenching effect of amine NH oscillators compared to amide NH groups most likely reflects the much shorter distance to the lanthanide ion in the former case.

Quenching effect of ligand CH oscillators

Following early reports of the quenching effect of CH oscillators,[2] more recently attention has been focused on the quenching of lanthanide luminescence by high-energy vibrational CH modes in the ligand itself.[23,40–43] This effect is particularly important for complexed lanthanide ions with a relatively small energy gap between the luminescent state and a lower-lying level, such as Nd^{3+}, Ho^{3+} and Tm^{3+}. It is important again to consider the importance of distance on vibrational quenching: most complexed lanthanide ions are often directly bound to OH or NH oscillators where the minimum distance to the lanthanide ion is between, say, 2.9 Å for OH (*e.g.* Eu/Tb) and 3.1 Å for NH. The majority of aromatic CH ($\nu_{CH} \sim 3050$ cm^{-1}) or aliphatic CH ($\nu_{CH} \sim 2950$ cm^{-1}) oscillators are necessarily at a greater distance from the metal ion, and it is difficult to imagine how *any* CH oscillator can be closer than, say, 3.4 Å from the complexed Ln^{3+} ion, in a given complex of Eu and Tb. Therefore, in assessing the importance of CH quenching, we have chosen to examine structurally well-defined complexes wherein the distances from the Ln^{3+} ion to the different types of CH oscillator have been determined. The two cases considered involve the $q = 0$ Ln complexes of L^{1a} [19,25] and the complexes of dota L^{2a},[27,44–46] for each of which a good deal of crystallographic data is available.

The average distances between the diastereotopic methylene hydrogens and the Eu^{3+} or Lu^{3+} ion in $[Ln(dota)\cdot H_2O]^-$ have been calculated from the published crystal strucures and are shown in Fig. 3. For $[Eu(dota)\cdot OH_2]^-$, for example, four of the CH_2CO hydrogens are close to the Eu centre (average distance is 3.75 Å), while the other diastereotopic set of 4 hydrogens is more remote and average 4.39 Å from the bound ion. In the saturated 12-membered ring, 4 sets of diastereotopic hydrogens may be identified with the pseudo-axial positions closest to the Eu centre (at 3.68 and 3.82 Å, on average), and the pseudo-equatorial hydrogens are so much further away (4.5 Å), that they are unlikely to cause significant quenching. A similar analysis for $[EuL^{1b}]^-$ shows a slightly more compact structure (Fig. 4), with the benzylic hydrogens 4.1 Å distant from the lanthanide ion.

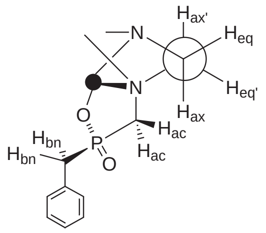
Selectively deuteriated complexes of dota, L^{2a}, were prepared with deuterium replacing hydrogen either in the acetate methylene groups or in the 12-membered ring. In the former case, enolisation of the bound carboxylate occurs sufficiently readily at pD 11.5 and 70 °C to allow selective deuteriation of the CH_2CO positions. The extent of isotopic substitution was assessed by negative electrospray mass spectrometry and by ^1H NMR integration: in each case a value of 90(±2)% was obtained. Isotopic substitution in the ring required the synthesis of per-deuterated cyclen, which was carried out using conventional methodology (Scheme 1). Combined mass spectral and ^1H NMR analysis of the derived europium complex indicated that 92(±2)% deuterium incorporation had been achieved. Perdeuteriated complexes $[Ln[^2H_{22}]dota]$ were then prepared following H/D exchange (72 h) of the acetate side



Complex	r_{Hac}	$r_{Hac'}$	r_{Hax}	$r_{Hax'}$	r_{Heq}	$r_{Heq'}$
$[Eu(dota)]^-$	3.75[b]	4.39	3.74[c]	3.78	4.50	4.49
$[Y(dota)]^-$	3.68	4.23	3.68	3.72	4.35	4.39
$[Lu(dota)]^-$	3.65	4.18	3.65	3.70	4.31	4.32

[a] Mean distances from the Ln ion to the hydrogen atom are given in Å; data from references 27, 44 and 45.
[b] Two shortest distances are 3.48 and 3.52 Å.
[c] Two shortest distances are 3.54 and 3.70 Å.

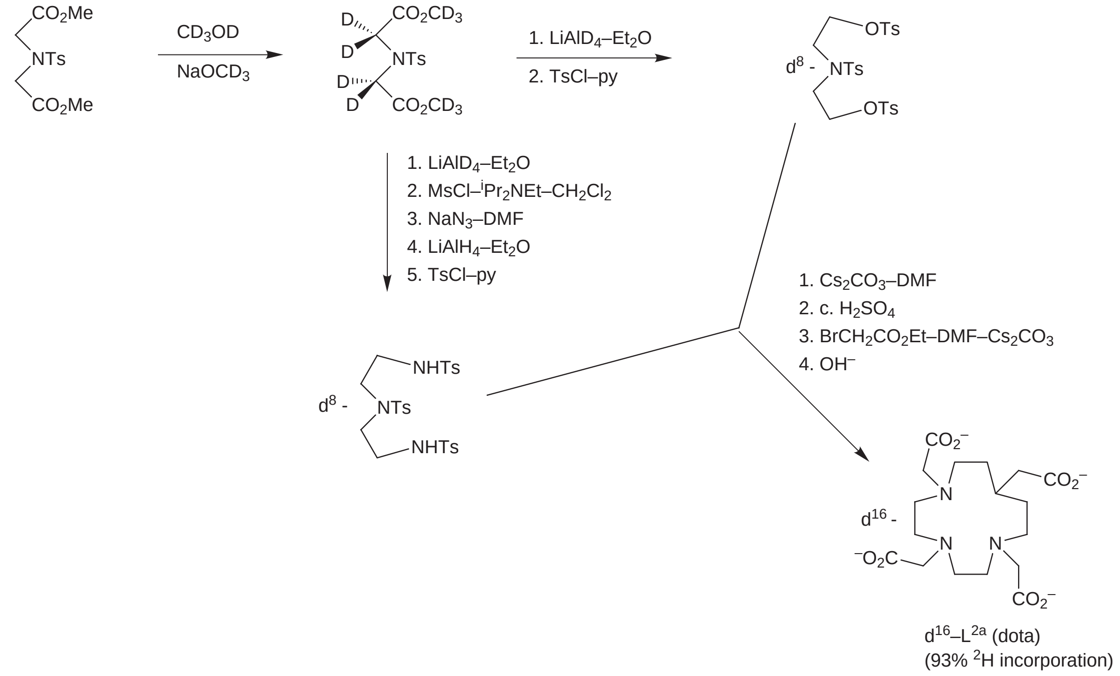
Fig. 3 Distances between ligand hydrogen atoms and the bound lanthanide ion, from published crystallographic data of lanthanide complexes of dota.



Complex	r_{Hac}	$r_{Hac'}$	r_{Hax}	$r_{Hax'}$	r_{Heq}	$r_{Heq'}$	r_{Hbn}
$[EuL^{1b}]^-$	3.58	4.19	3.65	3.78	4.50	4.48	4.11
$[YL^{1b}]^-$	3 .51	4.15	3.56	3.74	4.45	4.42	4.09

[a] Mean distances from the Ln ion are given in Å; data from references 19 and 25.

Fig. 4 Distances between ligand hydrogen atoms and the Y or Eu ion in tetrabenzylphosphinate complexes. Data are taken from published crystallographic sources.



Scheme 1

Table 6 Rate constants for depopulation of the excited states of protiated and selectively deuteriated europium and ytterbium complexes in H_2O and D_2O (293 K; ms^{-1} for Eu and Tb complexes, μs^{-1} for Yb)

Complex	k_{H_2O}	k_{D_2O}	Δk	Mean contibution per CH oscillator/s^{-1}
$[EuL^{1a}]^-$	0.63	0.48	0.15	~+5 (CH_2Ph)
$[Eu[^2H_7]L^{1a}]^{-\,a}$	0.60	0.44	0.16	
$[Eudota]^-$	1.60	0.53	1.07	+45 (NCH_2CO)
$[Eu[^2H_7]dota]^{-\,b}$	1.44	0.36	1.08	
$[Eu[^2H_{15}]dota]^{-\,c}$	1.41	0.30	1.11	+28 (axial ring CH)
$[Eu[^2H_{22}]dota]^{-\,b}$	1.29	0.24	1.05	
$[Tb(dota)]^{-\,d}$	0.57	0.35	0.22	−6 (axial CH)
$[Tb[^2H_{15}]dota]^-$	0.60	0.40	0.20	
$[Yb(dota)]^-$	^{e}	0.17		+11 000 (axial ring CH)
$[Yb[^2H_{15}]dota]^{-\,c}$	^{e}	0.086		
$[Yb[^2H_7]dota]^-$	^{e}	0.125		+13 000 (NCH_2CO)

[a] Mass spectral and ^1H NMR analysis confirmed that there was 87% (±3) H/D exchange in the benzylic methylene hydrogens. [b] 90% (±2) incorporation of ^2H at the NCH_2CO sites was measured by ^1H NMR and negative-ion ESMS. [c] The per-deuteriated 12-N_4 tetra-amine was prepared separately, followed by alkylation with $BrCH_2CO_2Et$, hydrolysis in base and complexation with $Ln(OAc)_3$. [d] A similarly small increase in rate was found for $[Tb[^2H_7]dota]^-$ in both H_2O and D_2O. [e] Double exponential decay was observed.

arms at pD 11.5 and 343 K. In the case of the tetraphosphinate ligand L^{1a}, H/D exchange was only performed at the more remote benzylic site. This incorporation was carried out by taking the corresponding tetraethylphosphinate ester into CD_3OD (in the presence of 1% $NaOCD_3$), and H/D exchange was observed by ^1H NMR to occur only at the benzylic positions with 87% ^2H-incorporation. Following acid hydrolysis and metal complexation no further change in the level of ^2H-incorporation was observed.

Rate constants for depopulation of the lanthanide excited states were measured in H_2O and D_2O for the selectively and per-deuteriated complexes and results are collated in Table 6. The more remote benzylic CH oscillator (4.1 Å distant) in $[EuL^{1a}]$ contributes little to the overall quenching and only a small change was noted. In the dota terbium complexes examined, a very small *increase* in the rate constants was observed, consistent with earlier reports,[41] perhaps suggestive of a marginally better overlap with CD harmonics than CH although the effect is within experimental error. Much more marked quenching effects were observed with the CH_2CO and ring NCH_2 oscillators for Eu and Yb. For the acetate methylene hydrogens, only 4 of the hydrogens are sufficiently close to quench (Fig. 3). Each C–H oscillator may be estimated to contribute 45 s^{-1} and 13 000 s^{-1} to the quenching of the excited Eu and Yb ion respectively. This partial deuteration reduces the rate constant for quenching by about 33% in D_2O, in each case. For the ring C–H oscillators, it is more difficult to break down the individual contributions. If it is assumed that the eight more distant pseudo-equatorial CH oscillators (Fig. 3) do not quench at all, then the longer lifetime ($\tau = 1/k$) associated with ring deuteriation may be estimated to involve an individual contribution of *ca.* 28 s^{-1} for Eu and 11 000 s^{-1} for Yb.

What is clear from the above discussion and the data in Table 6, is that there are significant enhancements in luminescence lifetime to be achieved for Eu and Yb complexes by isotopic substitution of both the ring and side-arm methylene groups.[40–43] Such improvements are of importance in the development of practicable long-lived luminescent probes,[21,22] but are much smaller in magnitude than the quenching effect of bound and closely diffusing OH and amine NH oscillators. It is worth emphasising again, that CH quenching, in Eu and Yb complexes at least, is less important as a consequence of the $1/r^6$ dependence of energy transfer and the relatively long C–H/Ln distances that are always found in such ligated species.

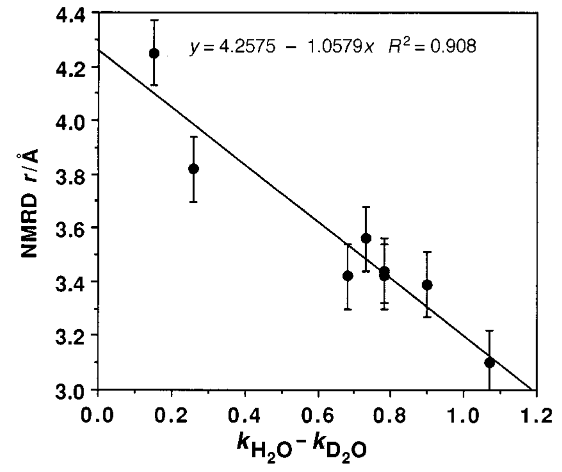


Fig. 5 Correlation between the NMRD derived distance in eight Gd complexes (refs. 33, 47 and 55) and the quenching effect of OH oscillators on the luminescence of the corresponding Eu complexes (given as the difference in the radiative rate constants in H_2O and D_2O).

Relationship to the hydration state of Gd complexes in solution (the 'Gd-break')

There are further conclusions to be drawn from an examination and comparison of the data in Tables 2 and 3. There is a clear difference, for example, between the corrected hydration states of the seven mono-amide triphosphinate complexes of europium and terbium which have been examined. In the case of terbium, there are evidently *no* proximate OH oscillators, while for the europium complexes non-integral values of q_{corr} were found ranging from 0.50 to 0.68. ^{31}P NMR and ^1H NMR analyses had revealed that for all of these complexes, one predominant (>90%) stereoisomer exists in aqueous solution.[33,47] This stereoisomer is undoubtedly a twisted square antiprismatic structure because there is a remarkably close correspondence in the form and intensity of the circularly polarised luminescence (CPL) spectra of these Eu and Tb monoamidetriphosphinate complexes and those of their tetraphosphinate analogues.[48¶] This latter class of complexes has been shown to possess *no* bound water (Eu–Yb), and to adopt a twisted antiprismatic structure along the lanthanide series.[19] The 'partial' hydration of the Eu complexes has been explained in terms of a 'second-sphere' hydration,[47] wherein the carbonyl group of the amide serves as a hydrogen bond acceptor to a closely diffusing water molecule, thereby shortening the mean distance of approach of water molecules to the polar lanthanide ion. The break in hydration occurs at gadolinium, and many other apparent discontinuities in the thermodynamic properties or aquation states of lanthanide ions have been noted previously.[50]

The measurement of the hydration states of Gd complexes in aqueous solution is of particular interest to the design and performance of gadolinium contrast agents that are frequently used in magnetic resonance imaging. The relaxivity (the increment of the water proton relaxation rate per unit concentration of Gd complex) of such contrast agents is directly proportional to the number of bound water molecules. In addition, the longitudinal proton relaxation rate varies with the distance from Gd to the water proton in a $1/r^6$ relationship. Thus, in cases where there is partial hydration of the lanthanide ion ($0 < q \leq 1$), then reduced relaxivity values are to be expected. Such is the case for the Gd complexes of mono-amidetriphosphinates[18,47] for which relaxivity values (20 MHz, 298 K) of *ca.* 3 mM^{-1} s^{-1} were found. Furthermore the fitting of observed NMRD profiles of

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¶ By comparison, square-antiprismatic lanthanide complexes show *much* more intense and quite different Eu and Tb CPL spectra, associated with the greater helical twist at the metal centre.[22,29,49]

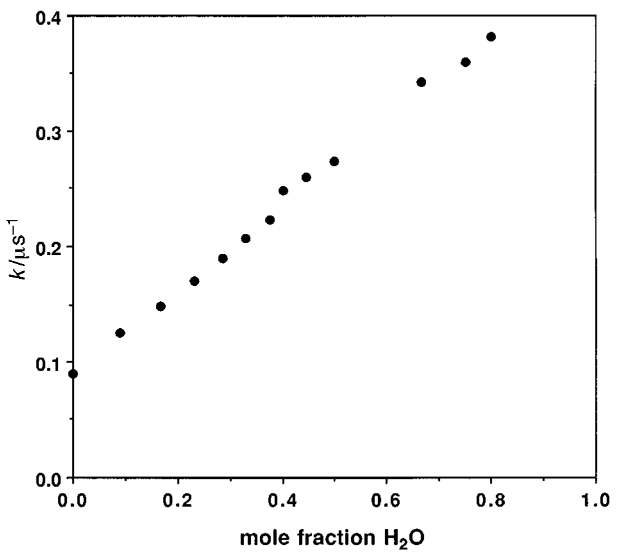

Fig. 6 Relationship between the mole fraction of H_2O in H_2O–D_2O mixtures and the radiative rate constant for depopulation of the excited Yb ion in $Yb(edta)_2$ [293 K, pH 6, 1 mM $Yb(CF_3SO_3)_3$, 5 mM edta].

gadolinium complexes allows the Gd–water proton distance to be estimated with some confidence.[51] The correlation between the NMRD-derived distance *r* and the Δk values (uncorrected for outer-sphere contributions) for the corresponding Eu complexes is reasonable (Fig. 5). This result also follows naturally from the analysis depicted in Fig. 1, and suggests that—in this case at least—the Gd complexes resemble the corresponding Eu complexes more than their Tb analogues.

As the distance between a Gd centre and a water proton increases, the *rate* of dissociative water exchange (τ_m) will increase. Maximising τ_m values is an important goal in the design of effective paramagnetic contrast agents: if τ_m is too slow, as is the case for square antiprismatic tetra-amide complexes,[35,36] then this may limit the observed relaxivity. In the central (Eu, Gd, Tb) lanthanide complexes of dota and the achiral tetra-amide analogues (*e.g.* $[LnL^{4a}]^{3+}$), there are two predominant diastereoisomers in solution—the mono-capped square-antiprismatic complexes (twist angle 40°) and the related *twisted* square-antiprismatic structure (twist angle *ca.* 29°). These isomers interconvert by arm-rotation fairly slowly at ambient temperatures (*ca.* 30 s^{-1} at 298 K) and recent work has highlighted the much *faster* rate (>10^3 times) of dissociative water exchange in the twisted square-antiprismatic complexes.[36] Moreover, all of the published Eu/Gd–OH_2 distances in mono-capped square-antiprismatic complexes show a relatively short Ln–OH_2 bond (say 2.44 Å)[28–30] whereas the singular published report of a long (2.56 Å) Gd–OH_2 bond[52] occurs in a mono-capped *twisted* square-antiprismatic complex of the ligand L^{18}. Therefore, when examples occur of non-integral hydration in Eu or Tb complexes, provided that the solution distribution of isomers is appreciated, then they *may* be related to the presence of a significant proportion of a twisted square-antiprismatic structure, with a long Ln–OH_2 bond, a reduced q_{corr} value and a relatively fast τ_m value. Such may be the case for the complex of (*RRRR*)-L^{2b} [q^{Eu}_{corr} = 1.06, with a 4 : 1 isomeric ratio in favour of the twisted square-antiprismatic structure; *but* q^{Tb}_{corr} = 0.60 with an approximate 2 : 1 ratio [^1H NMR] of twisted/square-antiprismatic structures].[28] A further example may be given by the complexes of L^{16a} (do3a) and the *N*-methylated analogue L^{16b}, for which q^{Eu}_{corr} values of 1.80 and 1.60 have been measured (Table 2). While undoubtedly these complexes[52] possess two bound water molecules in solution, one Eu–OH_2 bond is likely to be significantly longer than the other giving rise to the lower measured *q* values (see Fig. 1).

Finally this sort of analysis highlights the rather indistinct boundary between inner- and outer-sphere hydration states and serves to emphasise that the $q = 0$ and $q = 1$ states are boundary conditions between which a spectrum of non-integral solvation states may exist, determined by local hydrophobicity and the presence or absence of H-bond donor/acceptor groups. Indeed, it is perhaps worth adding that the current distinction between inner-, second- and outer-sphere hydration states is a purely arbitrary one, and a robust single theory of relaxation is required that accommodates each contribution seamlessly, based primarily on the distance effect and the weighted local concentration of proximate exchangeable protons.

Summary

A revised method for assessing '*q*' values in Eu, Tb and Yb complexes

In conclusion, the measurement of the rates of depopulation of the excited states of Eu, Tb and Yb in H_2O and D_2O affords a useful method for estimating the hydration state of the lanthanide ion, provided that a correction is applied to allow for the contribution of closely diffusing OH, and where appropriate, amine or amide NH oscillators. In the latter two cases, care must be taken to establish whether H/D exchange has occurred prior to measurement in the deuteriated solvent. A general equation may then be used [eqn. (6)], to calculate the hydration

$$q_{corr} = A'\Delta k_{corr} \qquad (6)$$

state *q*, in each case [where A' = 5 ms (Tb); 1.2 ms (Eu); 1.0 μs (Yb)]. Correction factors in Δk for outer sphere water molecules are -0.25 ms^{-1} for Eu, -0.06 ms^{-1} for Tb and -0.20 μs^{-1} for Yb and a correction of -0.075 ms^{-1} should be made for carbonyl-bound amide NH oscillators with Eu. This revised method should reduce the uncertainty associated with such a procedure, and where non-integral results are obtained, then consideration should be given to other factors. These include: the equilibrium distribution[38] of lanthanide complexes in which there is one or no water molecule bound, the possibility of a relatively 'long' Ln–OH_2 bond or the occurrence of a well-defined 'second-sphere' of hydration.

Finally it is also worth noting that these luminescence methods strictly afford the solvation state of the *excited* lanthanide complex. In the case of Eu and Tb, the emissive timescale is about 10^4 times slower than the rate of water exchange at a Ln ion, so that the measurement should accurately reflect the solvation state of the ground-state. This is not the case with Yb complexes, as the observed rates of luminescence decay (0.1 to 3 μs^{-1}) (Table 4) are similar to, or slower than, the water exchange rate, particularly for neutral or cationic complexes. Therefore it is possible to observe luminescence from the $q = 1$ and $q = 0$ states, simultaneously, observing for example, the intermediate in dissociative water exchange. Further details of this aspect will be reported subsequently.

Experimental

Distribution experiments for ^{153}Gd-labelled complexes

The ^{153}Gd-labelled complexes of L^{1a}, L^{1b}, L^{2a}, L^3, L^9 and L^{10} were prepared in an ammonium acetate buffered aqueous solution at pH 6.8, as described in references 53 and 54. Four solvent mixtures were made up, consisting of octanol–water, octanol–phophate-buffered-saline, butanol–water and butanol–phosphate-buffered saline. A Dulbeccos A (pH 7.3) solution of phosphate buffered saline was used. For each of the above four mixtures, three different volume ratios were used [0.5 ml/0.5 ml; 0.75 ml/0.25 ml; 0.25 ml/0.75 ml], and to each of these twelve mixtures was added 5 or 10 mL of the ^{153}Gd radiolabelled complex in 0.15 M NH_4OAc solution. The solutions were shaken for 3 hours on a vertical turntable and then centrifuged for two minutes to separate the phases. Duplicate 100 μL samples were taken from each phase of the tube and their radioactivity counted using an LKB Compugamma instrument. Partition coefficients were calculated for each volume ratio and the mean values were determined for three sets of samples. Data are collated in Table 1.

Luminescence measurements

Details of the instrumentation and data-handling procedures used for determining emission lifetimes of europium and terbium complexes have been described elsewhere.[49] Measurement of the emission lifetimes of ytterbium was carried out using the signal observed with a nitrogen-cooled germanium photodiode/amplifier (North Coast EO-817-P), operating in high sensitivity mode. For complexes with an aromatic chromophore, indirect excitation at 266 nm was used, whereas for direct excitation of the Yb ion, the output from a YAG driven optical parametric oscillator was used, producing photons at 970 nm. Emission was observed in the low energy tail of the emission band using a 1050 nm interference filter with a 40 nm bandpass, with the aid of a polariser to block scattered light from the laser source. Decays were analysed by iterative reconvolution and non-linear least squares analysis of the instrument response profile with a single exponential function. Further details and a discussion of the validity of the method can be found in reference 43. For rather short lifetimes (<1 µs, typically), the short duration 'spike', arising from scattered light was sufficiently intense to prevent accurate measurement, following direct excitation. In these cases, the longer lifetimes were determined first in D_2O and then in D_2O–H_2O mixtures with an increasing mole fraction of H_2O. Lifetimes were determined by discarding the early data points and fitting the remaining data points to an exponential decay. In certain cases, the value of the lifetime was estimated by extrapolation; an example of this approach is given in Fig. 6, for the behaviour of $[Yb(edta)_2]^{5-}$ [5 mM edta, 1 mM $Yb(CF_3SO_3)_3$, 293 K, direct excitation at 970 nm, pH 6].

Synthesis and characterisation

Details of the synthesis and characterisation of the lanthanide complexes of L^1–L^{17} have been given elsewhere[19,20,28,29,33,35,37,49,52,54,55] and in references quoted therein. *J* Values are given in Hz and *δ* values in ppm throughout. Ether refers to diethyl ether.

Bis(trideuteriomethyl) *N-p*-tolylsulfonyl-5-aza-2,2,4,4-tetradeuteriopentane-1,5-dioate. An excess of deuteriomethanol (30 mL) was added to the fully protiated title compound (1.46 g, 4.5 mmol) and sodium metal added (10 mg, 0.43 mmol). The resulting solution was heated under argon for two hours. The cooled solution was treated with ion exchange resin (Dowex 50W, H^+ form) and stirring continued for 5 minutes. The solution was filtered and solvent removed under reduced pressure to give a colourless semi-crystalline solid (1.54 g, 92%); mp 96–98 °C. δ_H (200 MHz, $CDCl_3$) 2.42 (s, 3H, Ar-*Me*), 7.31 (d, 2H, *J* = 8), 7.59 (d, 2H, Ar-H); δ_C ($CDCl_3$) 15.2 (s, Me), 47.5 (pent., CD_2, *J* = 21), 51.5 (sept., CD_3, *J* = 22), 127.3 (Ar, CH), 129.5 (Ar, CH), 136.4 (Ar-CC), 143.8 (Ar, CS), 169.1 (CO); δ_D ($CHCl_3$) 3.62 (s, 6D, OCD_3), 4.17 (s, 4D, CD_2); ν_{max} 3056 (ArCH), 2361 (w), 2263 (w), 2182 (w), 2081 (w), 1742 (s, CO), 1595, 1496 (m) cm^{-1}. Found: C, 47.6; H, 5.31; N, 4.09%. $C_{13}H_7D_{10}NO_6S$ requires: C, 48.0, H, 5.22; N, 4.30%.

***N-p*-Tolylsulfonyl-1,1,2,2,4,4,5,5-octadeuterio-3-azapentane-1,5-diol.** Lithium aluminium deuteride (0.275 g, 8.3 mmol) was added gradually to a solution of the tetra-deuterio ester (1.0 g, 3.3 mmol) in dry THF (50 mL) and the mixture was heated under reflux for 2 hours. After cooling, water (10 mL) was added and solvents removed under reduced pressure. The residue was partitioned between ether (50 mL) and dilute hydrochloric acid (50 mL, 1 M), and the aqueous layer extracted three times with ether (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and solvents removed under reduced pressure to yield a colourless solid (0.68 g, 82%), mp 90–91 °C. δ_H ($CDCl_3$) 2.44 (s, 3H), 7.34 (d, 2H), 7.71 (d, 2H); δ_D ($CHCl_3$) 3.23 (s, 4D), 3.83 (s, 4D); δ_C ($CDCl_3$) 21.5 (Me), 52.0 (pent., CD_2N), 61.1 (pent., CD_2O), 127.3 (ArCH), 129.8 (CH), 135.2 (CC), 143.7 (CS); *m/z* (ammonia-CI) 268 (M^+ + 1), 285 (M + NH_4^+); ν_{max} 3232 (br, OH), 2236 (CD), 2200 (w), 2086 (w), 1596 (Ar ring), 1490 (w), 1336 (s) cm^{-1}. Found: C, 49.4; H, 6.49; N, 5.08%. $C_{11}H_9D_8NO_4S$ requires: C, 49.1; H, 6.32; N, 5.20%.

***N-p*-Tolylsulfonyl-1,5-bis(*p*-tolylsulfonyloxy)-3-aza-1,1,2,2,4,4,5,5-octadeuteriopentane.** A solution of the diol (0.46 g, 1.72 mmol) and freshly recrystallised toluene-*p*-sulfonyl chloride (2.6 g, 13.6 mmol) in dry pyridine (15 mL) was held at −18 °C for 2 weeks. The mixture was poured onto crushed ice, with stirring and the resultant precipitate filtered, washed with water (3 × 20 mL) and dried under vacuum to give a colourless solid (0.81 g, 82%). δ_H ($CDCl_3$) 2.43 (s, 3H, ArMe), 2.46 (s, 6H, ArMe), 7.29 (d, 2H, *J* = 8.2), 7.36 (d, 4H, *J* = 8.0), 7.61 (d, 2H, *J* = 8.2), 7.76 (d, 4H); δ_D ($CHCl_3$) 3.33 (s, 4D), 4.08 (s, 4D); ν_{max} 3066 (w, ArH), 2956 (w), 2916 (w, CH), 2161 (CD), 2034 (CD), 1596 (Ar ring), 1494 (w), 1340 (s), 1163 (s), 971 cm^{-1}. Found: C, 52.2; H, 4.92; N, 2.57%. $C_{25}H_{21}D_8NO_8S_3$ requires: C, 52.2; H, 5.04; N, 2.43%.

***N-p*-Tolylsulfonyl-1,5-bis(methylsulfonyloxy)-3-aza-1,1,2,2,4,4,5,5-octadeuteriopentane.** A solution of diisopropylethylamine (0.474 mL, 6.12 mmol) in dichloromethane (25 mL) was added to a stirred solution of the deuterium labelled diol (0.75 g, 2.79 mmol) in dichloromethane (25 mL) at 0 °C and methanesulfonyl chloride (1.07 mL, 6.12 mmol) added by syringe over a period of 15 minutes. After 30 minutes, the mixture was washed successively with saturated sodium carbonate solution (30 mL), water (30 mL) and dilute hydrochloric acid (30 mL, 1 M). The organic layer was dried over potassium carbonate and solvent removed under reduced pressure to yield a pale yellow oil. Trituration with a little dry methanol encouraged crystallisation giving a pale yellow solid (1.14 g, 96%), mp 61–62 °C. δ_H ($CDCl_3$) 2.44 (s, 3H, Me), 3.06 (s, 6H), 7.36 (d, 2H, *J* = 8), 7.71 (d, 2H). δ_C ($CDCl_3$) 21.5 (CMe), 37.4 (SMe), 127.2 (CH), 130.0 (CH), 134.8 (CC), 144.3 (CS); δ_D ($CHCl_3$) 3.46 (s, 4D), 4.38 (s, 4D). ν_{max} 3030 (w), 2939 (w), 2364 (w, CD), 1597 (Ar ring), 1326 (s), 1171(s), 960 (s), 815 (s), 669 (s), 522 (s) cm^{-1}. Found: C, 37.2; H, 5.15; N, 3.10%. $C_{13}H_{13}D_8NO_8S_3$ requires: C, 36.9; H, 4.96; N, 3.31%.

***N-p*-Tolylsulfonyl-1,5-diazido-3-aza-1,1,2,2,4,4,5,5-octadeuteriopentane.** To a solution of the deuterium labelled mesylate (0.25 g, 0.59 mmol) in DMF (5 mL) was added sodium azide (1.5 g) and the resulting suspension was stirred under argon at 40 °C for 12 hours. The reaction mixture was diluted with ether (100 mL) and washed with aqueous lithium chloride solution (2 × 20 mL, 1 M) and then water (8 × 25 mL). The organic layer was dried over potassium carbonate and solvent removed under reduced pressure to yield a colourless solid (0.18 g, 95%) which was used without further purification. Mp 40–42 °C. δ_H ($CDCl_3$) 2.45 (s, 3H, ArMe), 7.35 (d, 2H, *J* = 8.1), 7.72 (d, 2H); δ_D ($CHCl_3$) 3.27 (s, 4D), 3.51 (s, 4D); δ_C ($CDCl_3$) 21.6 (Me), 48.2 (pent.), 50.0 (pent.), 127.2 (CH), 130.0 (CH), 135.8 (CC), 144.1 (CS); ν_{max} 3362 (w), 3058 (w, ArCH), 2922 (w, CH), 2195 (CD), 2093 (NNN), 1593 (m), 1489 (s), 1339 (s), 1280 (s), 1168 (s), 677 (s), 601 cm^{-1}. Found: C, 42.0; H, 4.88; N, 29.9%. $C_{11}H_7D_8N_7O_2S$ requires: C, 41.6; H, 4.73; N, 30.9%.

***N-p*-Tolylsulfonyl-3-aza-1,1,2,2,4,4,5,5-octadeuteriopentane-1,5-diamine.** A solution of the azide (10.5 g, 3.31 mmol) in dry THF (10 mL) was added slowly to a stirred suspension of lithium aluminium hydride (0.314 g, 8.28 mmol) in THF (10 mL) under argon at −10 °C. After addition was complete, the temperature was raised to 10 °C for 30 minutes. To the mixture was added sodium hydroxide solution (5%, 0.7 mL) and the mixture stirred for 12 hours. The resulting precipitate was filtered off and solvents removed under reduced pressure to yield a pale yellow oil (0.83 g, 99%). For elemental analysis, a sample of the oil was dissolved in dry ether (10 mL) and dry HCl gas passed through the solution resulting in the formation of a colourless precipitate of the hydrochloride salt. The remainder of the material was used directly in the next step of the synthesis. δ_H ($CDCl_3$) 2.38 (s, 3H, Me), 7.26 (d, 2H, $J = 8.2$), 7.65 (d, 2H); δ_C ($CDCl_3$) 21.5 (Me), 40.3 (pent., CD_2N, $J = 21$), 51.8 (pent., CD_2N), 127.2 (CH), 129.8 (CH), 136.1 (CC), 143.4 (CS); *m*/*z* (CI) 266 ($M^+ + 1$). Found: C, 38.7; H, 6.32; N, 12.0%. $C_{11}H_9D_8N_3SO_2\cdot 2HCl$ requires: C, 39.1; H, 6.26; N, 12.4%.

1,3,5-Tris(*p*-tolylsulfonyl)-3-aza-1,1,2,2,4,4,5,5-octadeuteriopentane-1,5-diamine. *N*-Tosylation was effected using standard conditions (TsCl–pyridine) as described in the literature,[56] yielding a colourless solid in 75% yield. δ_H ($CDCl_3$) 2.38 (s, 9H, Me), 5.25 (br s, 2H, NHTs), 7.26 (d, 6H, $J = 8$), 7.62 (d, 6H); *m*/*z* (FAB, glycerol) 682 ($M^+ + 1$).

1,4,7,10-Tetrakis(*p*-tolylsulfonyl)-2,2,3,3,5,5,6,6,8,8,9,9,11,11,12,12-hexadecadeuterio-1,4,7,10-tetrazacyclododecane. 1,3,5-Tris(*p*-tolylsulfonyl)-3-aza-1,1,2,2,4,4,5,5-octadeuteriopentane-1,5-diamine (0.8 g, 1.4 mmol) and caesium carbonate (1.83 g, 5 mmol) were vigorously stirred in dry DMF (75 mL) and a solution of *N*-*p*-tolylsulfonyl-1,5-bis(*p*-tolylsulfonyloxy)-3-aza-1,1,2,2,4,4,5,5-octadeuteriopentane (0.80 g, 1.4 mmol) in dry DMF (50 mL) added over 6 hours. The mixture was heated for 15 h at 75 °C. Solvent was removed under reduced pressure and the product isolated following the published procedure[56] to give a white solid (800 mg, 78%), mp 277–279 °C. δ_H ($CDCl_3$) 2.44 (s, 12H, Me), 3.43 (br, 1H, residual CHD), 7.33 (d, 8H, $J = 8$), 7.69 (d, 8H); *m*/*z* (DCI) 804 ($M^+ + 1$).

2,2,3,3,5,5,6,6,8,8,9,9,11,11-Hexadecadeuterio-1,4,7,10-tetraazacyclododecane. Detosylation was carried out using concentrated sulfuric acid, following the detailed published procedure,[56] to give the desired amine as a colourless solid. Mp 100–102 °C. δ_D ($CHCl_3$) 2.69; δ_C ($CDCl_3$) 46.0 (pent., $J = 21$); *m*/*z* (CI) 189 ($M^+ + 1$), 188 (M^+ {as $H(^2H)_{15}$} + 1).

1,4,7,10-Tetrakis(ethoxycarbonylmethyl)-2,2,3,3,5,5,6,6,8,8,9,9,11,11-hexadecadeuterio-1,4,7,10-tetraazacyclododecane. A suspension of the labelled amine (59 mg, 0.31 mmol), ethyl bromoacetate (0.141 mL, 1.27 mmol) potassium iodide (10 mg) and caesium carbonate (564 mg, 1.73 mmol) in DMF (20 mL) was stirred under argon at 80 °C for 18 h. Solvent was removed under reduced pressure and the residue suspended in dichloromethane (20 mL), and filtered through Celite which was thoroughly washed with dichloromethane (2 × 10 mL) and chloroform (2 × 10 mL). The combined filtrates were evaporated and a colourless solid obtained (145 mg, 87%) which was hydrolysed directly without further purification. δ_H ($CDCl_3$) 1.27 (t, 12H, $J = 7.2$), 3.19 (br s, 8H, CH_2CO), 4.19 (q, 8H, CH_2O); δ_C ($CDCl_3$) 14.0 (Me), 47.8 (br), 51.5 (br), 54.9 (CH_2CO), 61.1 (CH_2O), 173.5 (CO); *m*/*z* (ES+) 555 ($M^+ + 1$).

1,4,7,10-Tetrakis(carboxymethyl)-2,2,3,3,5,5,6,6,8,8,9,9,11,11-hexadecadeuterio-1,4,7,10-tetraazacyclododecane. The ethyl ester (145 mg, 0.26 mmol) was dissolved in sodium hydroxide solution (1 M, 3 mL) and left at room temperature for 18 h. Hydrochloric acid (1 M, 3.1 mL) was added to give a solution pH of *ca.* 2.5. The volume was reduced until a crystalline solid began to form which was separated by filtration to give a colourless solid (99 mg, 75%). Crystallographic analysis of the ligand obtained under similar crystallisation conditions revealed that the solid was the oxonium salt of the [monodeprotonated (on carboxy group) dihydrochloride salt].[57] δ_H (pD 5) 3.24 (br t, 1H residual CHD), 3.61 (s, 8H); δ_C (pD 5) 48.8 (pent., CD_2N), 56.9 (CH_2CO), 178.6 (CO).

Lanthanide complexation

The Eu, Tb and Yb complexes were made from the deuteriated ligand and the metal oxide using standard conditions, reported elsewhere.[27,45] In each case, NMR integration and analysis of the negative ion ESMS spectra gave mean values for the level of deuterium incorporation of 93% (±2).

[Eu[$^2H_{15}$]dota]$^-$. δ_H (D_2O, pD 5, 295 K, 300 MHz, major isomer only quoted) 32.6 (residual axial ring CH), −2.69 (residual equatorial ring CH′), −8.50 (residual equatorial ring CH), −9.77 (residual axial ring CH′), −16.4 (4H, CHCO), −18.1 (4H, CH′CO); *m*/*z* (ESMS−) 566.6 (90%), 568.3 (22), 569.1 (100), 570.1 (16).

Deuterium exchange in the CH_2CO groups in the complex was undertaken at pD = 11.5 by heating [Eu(dota)]$^-$ at 65 °C for 24 hours, monitoring H/D exchange by ^1H NMR, following the reduction in intensity of the signals at *ca.* −16 and −18 ppm. The level of ^2H incorporation was assessed to be 90% (±2).

[Yb[$^2H_{15}$]dota]$^-$. δ_H (D_2O, pD 5, 293 K, 200 MHz: major isomer only quoted) 134.4 (residual CH axial), 24.8 (CH′ equatorial), 20.5 (CH equatorial), −38.0 (4H, CHCO), −45.7 (CH axial), −85.3 (4H, CH′CO); *m*/*z* (ESMS−) 586.8 (38%), 588.2 (65), 589.3 (54), 590.2 (100), 591.3 (15), 592.3 (37).

[Tb[$^2H_{15}$]dota]$^-$. δ_H (D_2O, pD 5, 293 K, 65.6 MHz: major isomer only quoted) +267 (4H, CHCO), 141.5 (residual CH axial), 86.3 (4H, CH′CO), −97.3 (residual CH′ equatorial), −101.3 (residual CH equatorial), −410 (residual CH′ axial); *m*/*z* (ESMS−) 574.7 (100), 576.0 (17).

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