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Controllable pH modulation of lanthanide luminescence by intramolecular switching of the hydration state†

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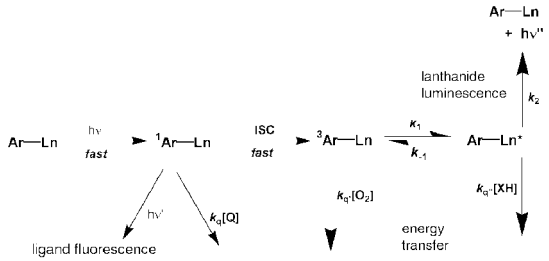
The pH dependent ligation of a pendant arylsulfonamide group allows switching between the $q = 0$ and $q = 2$ states to be reported by changes in lanthanide luminescence emission over the pH range 5.5–7.5 and in the presence of serum albumin.

The behaviour of responsive luminescent lanthanide complexes is being studied actively at present, in which changes in the lanthanide emission intensity, lifetime or polarisation are used to signal selectively concentration variations of a target analyte.[1,2] Particular attention has focused on well-defined, kinetically stable Eu and Tb complexes, and examples of pH,[3] pO_2[4] and pX[5] dependent luminescence have been reported in high salt aqueous media. These cases rely upon a perturbation either of the singlet or triplet excited states of the sensitising chromophore or the longer-lived $^5D_0$ and $^5D_4$ states of Eu and Tb respectively (Scheme 1). In the latter case, the lifetime and emission intensity are primarily determined by the nature and proximity of energy-matched XH oscillators, which quench the lanthanide excited state by vibrational energy transfer.[6] Thus reversible binding of HCO_3^- to di-aqua Eu or Tb complexes of chiral heptadentate ligands, causes displacement of the bound water molecules and an enhancement in emission intensity and lifetime as well as marked changes in emission polarisation.[5b] We now report a new example of controllable modulation of lanthanide luminescence, whereby variations in pH allow a switching between $q = 0$ and $q = 2$ states associated with the on/off ligation of an arylsulfonamide group (Fig. 1). Furthermore, by varying the structure of the macrocyclic ligand, competitive binding by endogenous anions and proteins may be suppressed, thereby paving the way for the development of complexes which operate directly in 'biological' samples (*e.g.* serum).



Scheme 1

For the preparation of the initial target complexes (Fig. 1), advantage was taken of the ring opening reaction of *N*-*p*-methoxyphenylsulfonylaziridines with secondary amines.[7] For example, reaction of *N*-*p*-trifluoromethylphenylsulfonyl-aziridine with 1,4,7-tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane in MeCN followed by TFA deprotection and metal complexation ($LnCl_3$, H_2O, pH 6) yielded the desired complexes.[8] The rate constants for decay of the Eu (and Tb) complexes were measured at pH 10 and 4 (λ_{exc} = 270 or 397 (Eu)/355 (Tb); 295 K) and gave values (Table 1) that are consistent with hydration states *q*, of 0.2 at pH 10 and 1.6 at pH 4. Profound changes in the form and intensity of the Eu emission spectra, especially the hypersensitive $\Delta J = 2$ and $\Delta J = 4$ transitions also characterised this pH change. In addition the Eu and Tb spectra, following sensitised excitation, were much more intense in the $q = 0$ régime, as not only the quenching bound OH oscillators have been displaced but also the aryl chromophore is much closer to the Ln centre, enhancing the efficiency of the intramolecular energy transfer step (Scheme 1). In accord with the hypothesis, quantum yields following excitation at 270 nm of 0.39% (pH 10) and 0.11% (pH 4) were recorded for [Eu·**1**] (R = OMe; 295 K, H_2O), and the corresponding values for [Tb·**2**] were 3.5% (pH 10) and 0.17% (pH 4).

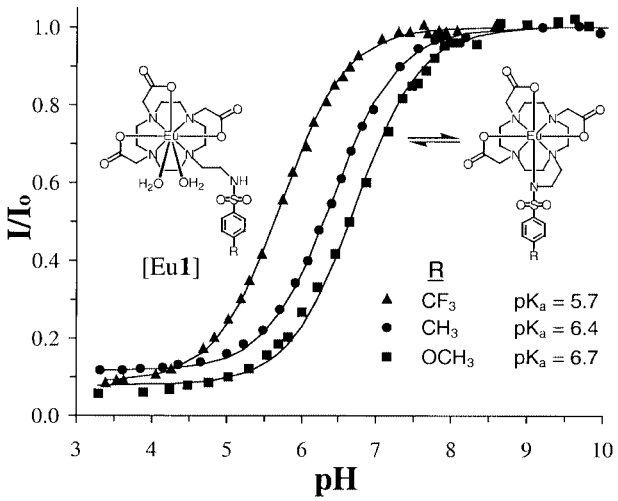


Fig. 1 pH Dependence of the europium luminescence (I/I_0) of [Eu·**1**] at 295 K (1 mM complex, 295 K, 0.1 M NaCl; λ_{exc} = 270 nm; λ_{em} = 612 nm ($\Delta J = 2$); solid lines show the fit to the experimental data).

Table 1 Rate constants *k* (ms^{-1}) and hydration states *q*, for decay of the lanthanide luminescence at limiting pH values (295 K, *I* = 0.1 M NaCl)

	pH/D 4			pH/D 10		
Complex	k_{H_2O}	k_{D_2O}[a]	q[a]	k_{H_2O}	k_{D_2O}	q
[Eu·**1**](*p*CF$_3$)	2.35	0.76	1.6	1.09	0.74	0.1
[Eu·**1**](*p*Me)	2.27	0.70	1.6	1.20	0.80	0.2
[Eu·**1**](*p*OMe)	2.32	0.66	1.7	1.43	0.93	0.3
[Eu·**2**]	2.21	0.65	1.6	1.11	0.72	0.2
[Tb·**2**]	0.90	0.56	1.4	0.45	0.40	0

[a] *q* Values were estimated using the equations $q^{Eu} = 1.2 (k_{H_2O} - k_{D_2O} - 0.25)$, $q^{Tb} = 5 (k_{H_2O} - k_{D_2O} - 0.06)$, which allow for contribution of unbound water molecules.[6a] Non-integral values may reflect the presence of a coordination equilibrium between the $q = 1$ and 2 states[6b] or the presence of a relatively 'long' Ln-OH_2 bond.[6a]

† Electronic supplementary information (ESI) available: examples of representative spectra of Eu and Tb complexes and their pH dependence. See http://www.rsc.org/suppdata/cc/b0/b001629m/

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Variation of the *p*-substituent in the arenesulfonyl group determines the basicity of the sulfonyl nitrogen and hence the pH at which protonation of the complex occurs. The pH dependence of the luminescence emission intensity was measured (295 K, I = 0.1 M, NaCl) for the series of terbium and europium complexes, (Fig. 1), showing behaviour in accord with the change in basicity at N. Thus the *p*-CF_3 europium complex gave a pK_a of 5.7 (±0.05) and the *p*-Me/*p*-OMe analogues yielded values of 6.4 and 6.7 respectively. The large pH-dependent changes in the form and intensity of the Eu emission allows the precise definition of pH (amenable in principle to multivariate calibration) with an estimated tolerance of ±0.1 pH units.

A limitation to the application of such complexes in a mixed salt or 'biological' background is the competititve binding of oxyanions (*e.g.* HCO_3^-, HPO_4^{2-} and lactate/citrate) or proteins (*e.g.* human serum albumin) to the q = 2 complex.[9] In order to obviate this problem, polyanionic analogues of the macrocyclic ligand were prepared by introduction of a carboxyethyl substituent α to three of the ring nitrogens.[8,10] The resultant complexes are tri- or tetra-anionic, inhibiting intermolecular anion binding to the q = 2 state. The pH-dependence of the terbium emission intensity (Fig. 2) was the same in 0.1 M NaCl and in a simulated 'clinical-anion' background—with an apparent pK_a of 6.7 (295 K). Moreover in the presence of an excess of human serum albumin (0.2 mM complex; 2 mM HSA) there was no change in the form and relative intensity of the Eu complex emission spectrum at pH 7.4, 6.9 and 5.5; the emission decay curves were also identical for each of these pH values.

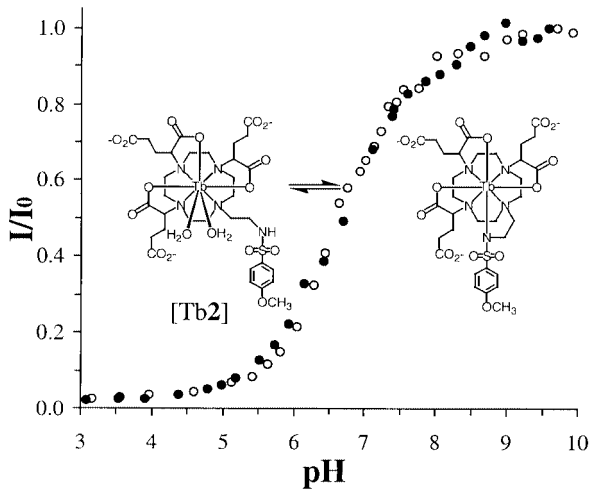

Fig. 2 pH Dependence of the terbium luminescence (I/I_0) of [Tb·**2**] at 295 K [1 mM complex; filled circles: 0.1 M NaCl, 30 mM $NaHCO_3$, 2.3 mM Na lactate, 0.13 mM citrate, 0.9 mM NaH_2PO_4; λ_{exc} = 272 nm, λ_{em} = 541 nm (ΔJ = 1); open circles: 0.1 M NaCl only; pK_a = 6.7 (±0.06)].

Such behaviour augurs well for the application of such complexes in the pH determination of serum samples, for which longer wavelength excitation (*e.g.* λ_{exc} = 355 nm) may be achieved by using a 6-phenanthridinesulfonyl group as an antenna chromophore. Moreover, the characteristics of the Eu/Tb complexes strongly suggest that the corresponding Gd complexes may be used as contrast agents to report pH changes *in vivo*. This aspect will be reported in a subsequent communication.

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