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Lanthanide complexes that respond to changes in cyanide concentration in water

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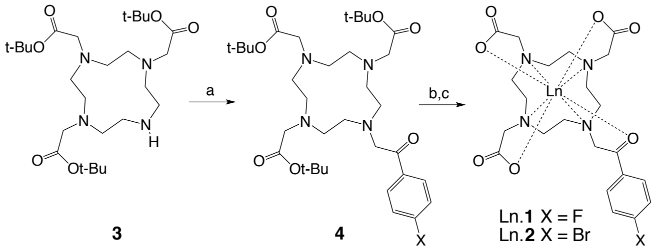
Abstract: Cyanide ions are shown to interact with lanthanide complexes of phenacylDO3A derivatives in aqueous solution, giving rise to changes in the luminescence and NMR spectra. These changes are the consequence of cyanohydrin formation, favoured by the coordination of the phenacyl carbonyl group to the lanthanide centre. These complexes display minimal affinity for fluoride and can detect cyanide at <1 μM concentrations. By contrast, lanthanide complexes with DOTAM derivatives display no affinity for cyanide in water, but respond to changes in fluoride concentration.

The detection of cyanide and fluoride ions has proved to be of considerable interest in medical/environmental monitoring, in part because both ions provide a possible route for the detection of agents used in chemical weapons.[1,2] A number of strategies have been devised that rely upon the interaction of these anions with Lewis acidic centres, with the exploitation of boron-containing receptors to this end dating back as far as the early 1960s.[3,4] However, while such approaches are highly effective in non-competitive solvents, their effectiveness generally decreases as water is introduced to the system. Systems capable of the detection of cyanide in pure water are very rare indeed, with a landmark exception being Gabbaï's phosphonium borane which signals the presence of cyanide down to the 0.2 ppm EPA regulatory threshold.[5,6] One potential problem characteristic of such compounds, however, is the competing response often encountered with fluoride and hydroxide.[3,7] These ions also have high binding affinities for the widely used -BMes$_2$ function (Mes = 2,4,6-Me$_3$C$_6$H$_2$), and consequently place a limit not only on compatible ranges of pH, but also on practical sensing applications, e.g. in drinking water.

Luminescent lanthanide complexes have been widely exploited in imaging and assay, where their long-lived emission can be readily separated from short lived fluorescence- giving rise to very low detection limits.[8] The electric-dipole forbidden nature of *f-f* absorption transitions mean that aryl chromophores are frequently used to sensitize the formation of lanthanide excited states: though some f-f transitions are magnetic dipole allowed, or can be hypersensitive to symmetry, their intensity is generally too low to be of practical use for direct sensitization. For most lanthanide complexes, sensitization is achieved via the chromophore centred triplet state, which transfers energy into the lanthanide excited state manifold.[9] The effectiveness of this energy transfer step is dependent upon the separation between the lanthanide centre and the donor triplet state. Furthermore, two mechanisms of energy transfer are possible: a Förster mechanism involving through-space energy transfer,[10] or a Dexter exchange mechanism that involves a through-bond process.[11] We have previously shown that the Dexter mechanism dominates wherever a through bond pathway is available (even up to distances in excess of 2 nm), and that it is generally much more effective than Förster energy transfer, owing to the limited spectral overlap between chromophore emission spectra and lanthanide absorption spectra.[12] Furthermore, we and others have explored the coordination of fluoride by positively charged lanthanide complexes in solution in water.[13] We have shown that fluoride coordination to the metal can have profound consequences for the spectroscopic behaviour of these systems, and demonstrated that this arises through changes to the magnetic anisotropy at the metal centre. The detection of fluoride has also been accomplished by emissive systems featuring pendant BMes$_2$ units, although here too typically with a competing response to cyanide.[14]

In the current manuscript we outline an alternative approach, in which kinetically stable lanthanide complexes (Eu.**1** and Eu.**2**) are used to probe cyanide concentration. These complexes contain a phenacyl group that coordinates to the metal centre through the carbonyl oxygen, while additionally providing an antenna chromophore that can be used to sensitize formation of the lanthanide emissive state. Thus, coordination has two effects: it facilitates energy transfer from the chromophore to the lanthanide while simultaneously polarizing the carbonyl group and increasing its susceptibility to attack by external nucleophiles. Such a binding event has the potential to disrupt the chromophore, removing the possibility of a through-bond sensitization mechanism, and changing the effectiveness of energy transfer. While cyanohydrin formation of this type has previously been employed in the detection of cyanide,[15,16] its use in conjunction with lanthanide emission offers a hitherto unexplored mechanism for signal amplification.

Complexes Ln.**1** and Ln.**2** were synthesized from the well-known triester, **3**,[17] as shown in Scheme 1. Reaction of **3** with



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Scheme 1. Synthesis of ligands and complexes. Reagents and conditions: a) dihaloacetophone, KI, K_2CO_3, MeCN, 80 °C, 48 h; b) TFA, DCM, room temperature, 24 h; c) $Ln(OTf)_3$, MeOH, 60°C, 2 d.

2-chloro-4'-fluoroacetophenone or 2,4'-dibromoacetophenone, using a procedure derived from that already used to prepare other phenacyl DO3A derivatives,[18] afforded the protected pro-ligands **4a** and **4b**, respectively. Deprotection with trifluoroacetic acid and subsequent complexation with the appropriate lanthanide triflate yielded the respective metal complexes. The NMR spectra of the europium complexes (Eu.**1** and Eu.**2**) are very similar, and bear strong resemblance to the spectra reported for other lanthanide complexes of phenacylDO3A derivatives.[18] Resonances corresponding to the axial ring protons are observed in the range 25-36 ppm (for the dominant diastereoisomer) and are consistent with a broadly square anti-prismatic (SAP) geometry at the metal centre.

Both complexes also exhibited sensitized luminescence in aqueous solution, and the lifetimes in H_2O and D_2O were used to calculate the inner sphere hydration at the metal centre using the equation:

$$q = 1.2(\tau_{H2O}^{-1} - \tau_{D2O}^{-1} - 0.25)$$

where q is the number of inner sphere water molecules, and τ_{H2O}^{-1} and τ_{D2O}^{-1} are the observed luminescence lifetimes in H_2O and D_2O, respectively (in milliseconds).[19] The results are summarized in Table 1, and show that both Eu.**1** and Eu.**2** feature nine-coordinate lanthanide ions with one bound solvent molecule.

Table 1. Photophysical properties of Eu.**1** and Eu.**2** in aqueous solution.

	τ_{H2O}/ms	τ_{D2O}/ms	q
Eu.**1**	0.62	2.16	1.1
Eu.**2**	0.61	2.52	1.2

Addition of cyanide to aqueous solutions of Eu.**1** and Eu.**2** resulted in a dramatic reduction in the observed luminescence intensity in each case. The luminescence *lifetimes* in water, however, remained unchanged within error, even following the addition of a large excess of cyanide, suggesting that there is no displacement of water from the inner coordination sphere of the lanthanide metal. Furthermore, the steady state emission spectra of Eu.**1** (Figure 1) show that the change in emission intensity is broadly consistent across all the peaks in the lanthanide emission spectrum. Given that the $^5D_0$-$^7F_2$ transition in europium(III) species is hypersensitive to local coordination environment, the lack of a dramatic change in the relative intensities of the peaks in the spectrum is consistent with the continued coordination of water.

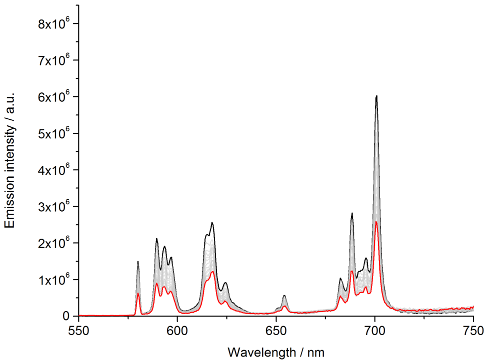

Figure 1. Changes in the Eu.**1** emission spectra in H_2O upon addition of KCN; λ_{ex} = 266 nm, exit slits 1 nm. Start of titration (black), end of titration (red; 1.5 equiv.) and intermediate concentrations (grey).

The changes in the relative ratios of the intensities of the peaks in the spectrum corresponding to the $^5D_0$-^7F_n transitions were then used to estimate binding constants for association with cyanide (Table 2) using DYNAFIT to model behaviour and assess binding models.[20] While these 1:1 stoichiometric binding constants are relatively low in magnitude, little directly comparable data is available in pure water, and the apparent selectivity over fluoride, especially for Eu.**2**, is high (vide infra). Interaction with hydroxide can be ruled out under these conditions: in studies on related systems we have shown that the pK_a of the complexed ligand is >10.2.[18]

Table 2. Affinity constants for cyanide and fluoride.

	K_{CN}/M^{-1}	K_F/M^{-1}
Eu.**1**	94.2 [80.3 – 110.7]	2.1 [1.9-2.3]
Eu.**2**	142.7 [135.9 – 173.1]	1.5 [1.46-1.57]
Eu.**5**	No binding	26.1 [24.9-27.4]

95% confidence limits are shown in square brackets

The ^1H NMR spectra of Eu.**1** and Eu.**2** also exhibited marked changes when cyanide was added. These are exemplified in Figure 2, which clearly shows the emergence of new species upon the addition of cyanide to Eu.**1**. Combined with the luminescence data and the associated binding constants, it is clear that there is a well-defined interaction between cyanide and the europium complex, since collisional quenching would not explain the observed behaviour. It is also clear that the new species is in slow exchange with Eu.**1** on the timescale of the NMR experiment.

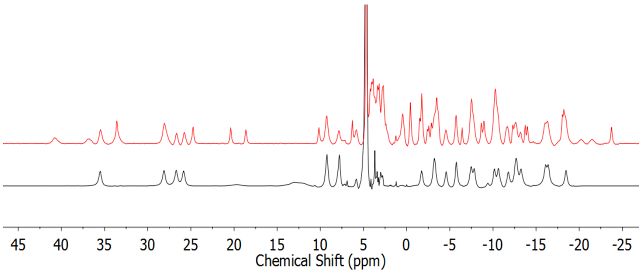

Figure 2. ^1H NMR spectra of Eu.**1** without cyanide (black) and with cyanide (red) (D_2O, 298 K, 400 MHz).

With coordination of cyanide to the metal being ruled out on the basis of the essentially unchanged luminescence lifetimes, an interaction between the ligand and cyanide can be hypothesized. It is well known that cyanide reacts with carbonyl compounds to form cyanohydrins, a phenomenon presumably exacerbated in the case of the systems studied here by coordination of the carbonyl oxygen at europium (Scheme 2). Crucially, such a binding event would also rationalize the spectroscopic observations made above. Thus, formation of the cyanohydrin derivative disrupts the interaction between the phenacyl chromophore and the lanthanide centre, ruling out a Dexter exchange mechanism by disrupting the through-bond pathway for exchange, and enforcing a less efficient through space pathway for energy transfer. Thus, cyanide uptake in this fashion lowers the intensity of the observed emission. NMR-wise, the bulk of the cyanide group in a cyanohydrin will inevitably influence the balance between SAP and TSAP (twisted square anti-prismatic) coordination at the lanthanide centre, and the increase in intensity of resonances corresponding to TSAP isomers (e.g. the peaks around 20 ppm in Figure 2) can therefore be ascribed to cyanohydrin formation. These observations are borne out by changes in the IR spectra (particularly to the band at 1713 cm^{-1} corresponding to the carbonyl region, see SI Figure s4) and by observed changes to the ^{13}C NMR of the corresponding lutetium complex Lu.**1** on addition of cyanide (SI Figure s5).

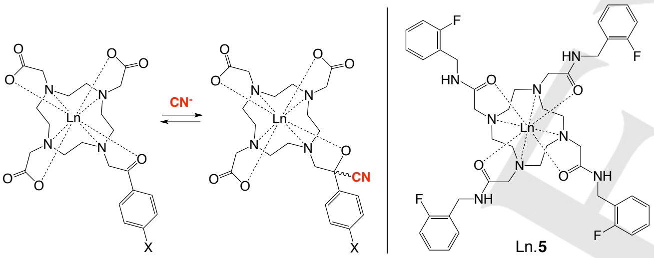

Figure 3. (left) Proposed interaction between phenacyl DO3A complexes and cyanide in water; (right) non-phenacyl 'control' systems Ln.**5**.

To obtain further evidence for the proposed detection mechanism, we also investigated whether cyanide interacts with other lanthanide containing systems, in particular using complex Eu.**5** to assess whether any interaction occurs in the absence of the pendant ketone function. In this case, no change was observed in either the luminescence or NMR spectra following addition of cyanide, lending further credence to the hypothesis that cyanide interacts with the carbonyl group in the phenacyl chromophore.

With this in mind, we also explored fluoride binding by Eu.**1**, Eu.**2** and Eu.**5**. As might be expected, given the greater residual charge on the lanthanide centre, Eu.**5** displayed dramatically higher affinity for fluoride than the phenacylDO3A derivatives (Table 2). In all cases, we can infer binding of fluoride at the lanthanide centre from the changes in the luminescence spectra (and particularly from changes to the relative intensities of the hypersensitive $^5D_0$-$^7F_2$ transition). Thus, Eu.**1** and Eu.**2** both respond to cyanide in water, but respond only weakly to fluoride (and respond to the two ions in different ways) while Eu.**5** responds only to changes in fluoride concentration, and is unresponsive to cyanide. This raises the prospect of differentiating between the two ions using lanthanide probes and thereby enabling not only effective methods for probing cyanide contamination of (fluoridated) drinking water, but also a mechanism for distinguishing cyanide-containing chemical warfare agents such as GA (Tabun) from fluorophosphonate esters such as GB (Sarin) and GD (Soman).

In summary, our results have shown that ligand structure can be exploited in the design of ion responsive systems. It is possible to use the Lewis acidity of the lanthanide centre to change the behaviour of coordinated chromophores, and thus modulate the intensity of emission. The preparation of complexes that exhibit this response in water at low (mM) concentrations opens the door to the development of effective and stable responsive complexes that can be used in challenging environments.

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Keywords: detection • cyanide • fluoride • lanthanide complexes • energy transfer

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COMMUNICATION

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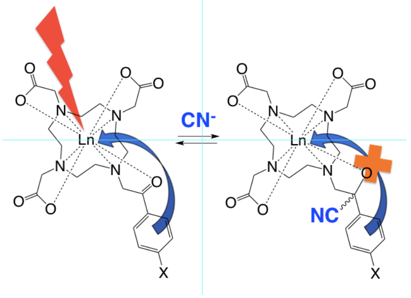

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