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# A turn-on luminescent europium probe for cyanide detection in water

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**A luminescent europium probe that responds to cyanide directly in water with a large nine-fold turn-on of the $Eu^{III}$ centered time-gated luminescence is presented. Unlike other $CN^-$ probes reported, the mechanism of action of $Eu^{III}$-Lys-HOPO does not rely on reaction of $CN^-$ with the probe, but on direct coordination of $CN^-$ to the $Eu^{III}$ ion concomitant with displacement of three inner-sphere water molecules. This unusual coordination of $CN^-$ with a lanthanide ion in aqueous solution was confirmed by luminescence lifetime measurements.**

Due to the high toxicity of cyanide to humans and to the environment, luminescent probes have been developed for its detection and quantification.[1] The majority of these probes rely on reactivity-based mechanisms, such as cyanohydrin formation, Michael addition, and demetallation.[1c-j, 2] Notable examples include the development of phosphonium borane by Gabbaï and coworkers,[1g] which detects cyanide in a water-methanol mixture at ppb level, and the recent development of the first europium probe for $CN^-$ by the Faulkner group, that enables detection of $CN^-$ by time-gated luminescence in pure water.[3] Time-gated luminescence detection is particularly beneficial when a complex environment is involved, as the background fluorescence can be readily gated out.[4] Current probes reported in the literature[1] suffer for the most part from the same disadvantages. Most of them do not work in pure aqueous media; most have affinity for $CN^-$ that are too low for practical applications; many require long reaction times; and many respond in a turn-off fashion whereby the luminescence intensity decreases in the presence of cyanide. Only two reactivity-based probes function in pure water. The first, developed by Gabbaï[1h], requires long reaction time (40 min) whereas the second, from Faulkner[3], displays a small (2-fold) change in luminescence intensity with $CN^-$. Importantly, both of these probes are turn-off: their luminescence decreases upon reaction with $CN^-$. Turn-off responses are disfavored since the intensity of a probe in a complex media can be quenched by factors other than the presence of the intended analyte. In order to resolve these issues, we have thought to develop probes for $CN^-$ based on a different mode of action.

Luminescent lanthanide complexes with open coordination sites, most commonly europium and terbium, are particularly well suited for the detection of coordinating anions in water.[5] One of the most common modes of action of this class of probes involves displacement of inner-sphere water molecules by a targeted anion. Since coordinated water molecules quench lanthanide luminescence, their replacement by a targeted anion increases the luminescence intensity of the lanthanide complex.[6] Because lanthanide ions are hard Lewis acids, the majority of these probes are limited to the detection of hard anions such as fluoride,[7] and oxyanions such as phosphate,[8] lactate,[9] citrate,[9-10] and hydrogen bicarbonate.[11] Probes functioning by this mechanism have not yet been reported for softer anions such as cyanide.

In devising such a probe for cyanide, the lanthanide complex must have open coordination sites and a high quantum yield. $Eu^{III}$ complexes of 1,2-hydroxypyridonate (1,2-HOPO) developed by the Raymond group are among the brightest europium complexes in water. Unfortunately, $Eu^{III}$-TREN-1,2-HOPO (Figure 1a), was reported not to respond to anions except weakly to oxalate despite its two inner-sphere water molecules (*q*).[12] With that in mind, we hypothesized that changing the

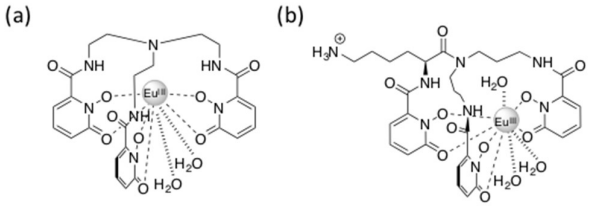


**Figure 1.** Chemical structures of (a) $Eu^{III}$-TREN-1,2-HOPO (b) $Eu^{III}$-Lys-HOPO.

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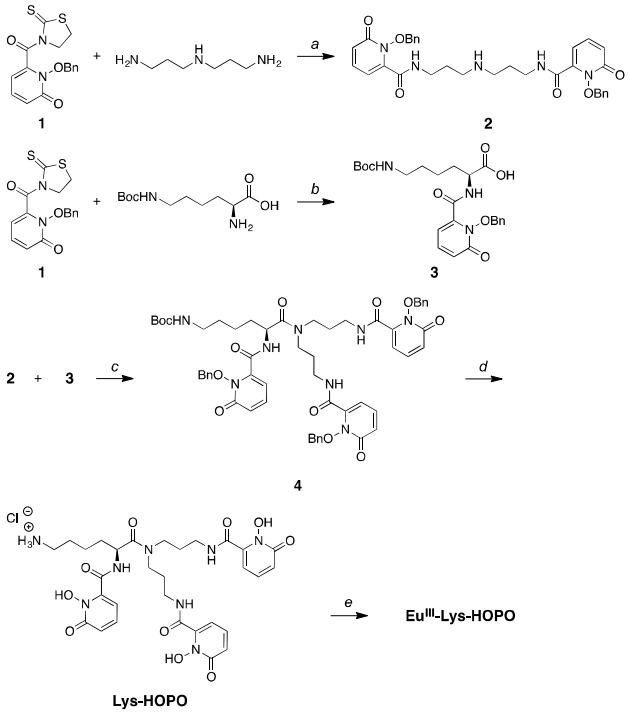
geometry of the complex from 8-coordinate ($q$=2) to 9-coordinate, ($q$=3) would favor coordination and hence detection of anions. Previous studies with similar $Gd^{III}$ complexes demonstrated that this could be achieved by modifying the cap of the ligand.[13] We thus designed $Eu^{III}$-Lys-HOPO (Figure 1b) to incorporate both the potent 1,2-hydroxypyridinonate sensitizer and a wider ligand cap that would increase the number of inner-sphere water molecules and hence favor anion coordination. The lysine side arm increases the hydrophilicity of this notoriously sparsely water-soluble class of complex.

$Eu^{III}$-Lys-HOPO was synthesized according to Scheme 1 starting from benzyl-protected and thiaz activated 1,2-hydroxypyridinone **1** that was previously synthesized in 3 steps following literature procedures.[14] In the first step, the protected HOPO arm was conjugated to the dipropylenetriamine backbone to yield the amine intermediate **2**; the attenuated reactivity of the thiazolidine group ensured that only the terminal primary amines of the backbone reacted. Separately, the HOPO(Bn) arm **1** was coupled to the BOC-protected lysine to yield the central podand **3**. The two intermediates **2** and **3** were then coupled using standard conditions to yield the protected ligand **4**. Simultaneous deprotection of the HOPO podands and the lysine side-arm under acidic conditions yielded the free ligand Lys-HOPO that was further complexed with Eu(III) under mildly basic conditions to give the final complex, $Eu^{III}$-Lys-HOPO complex.

$Eu^{III}$-Lys-HOPO is more soluble in water than the parent Eu-TREN-1,2-HOPO. When dissolved in pure water, $Eu^{III}$-Lys-HOPO exhibits the characteristic emission spectra of europium-centered luminescence with a primary peak at 615 nm (Figure S20). Uniquely, in water at pH above the pKa of HCN (9.31), the luminescence intensity of $Eu^{III}$-Lys-HOPO increases substantially, up to 9-fold, in the presence of 100 equivalents of $CN^-$ (Figure 2). In comparison, to the best of our knowledge, none of the luminescent molecular probes for $CN^-$ that function in water (as opposed to mixed solvents) display a turn-on response.




**Scheme 1** Synthesis of $Eu^{III}$-Lys-HOPO. Reagents and conditions: (a) $NEt_3$, $CH_2Cl_2$, rt, 6 hr; (b) $NEt_3$, $CH_3CN$, rt, 6 hr; (c) HATU, DIPEA, $CH_2Cl_2$, rt, 6 hr; (d) $HCl/CH_3COOH$ 1:1, rt, 6 hr; (e) $EuCl_3{\cdot}6H_2O$, pyridine, $CH_3OH/H_2O$ 1/1 (v/v), 80 °C, 6 hr.

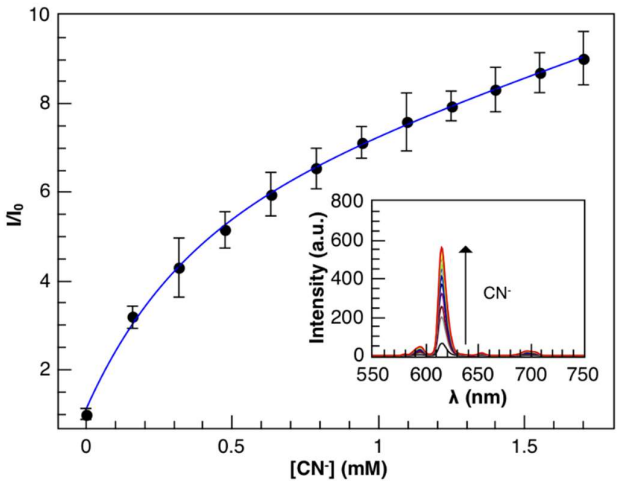



**Figure 2.** Relative time-delayed luminescence of $Eu^{III}$-Lys-HOPO as a function of $CN^-$ concentration. Error bars represent standard deviation (s.d.) $n$=3). Inset: Luminescence spectra of $Eu^{III}$-Lys-HOPO•$CN^-$ titration. I=integrated time-delayed luminescence from 550 nm to 750 nm, $I_0$=integrated luminescence of $Eu^{III}$-Lys-HOPO in the absence of $CN^-$, Experimental conditions: [$Eu^{III}$-Lys-HOPO] = 16 μM in $H_2O$, pH 9.8, $\lambda_{excitation}$ = 335 nm, delay time = 0.1 ms, excitation slit widths = 10 nm, emission slit width = 5 nm.

The substantial increase in luminescence intensity of the $Eu^{III}$ probe upon addition of $CN^-$ is in accordance with a mechanism whereby the anion directly coordinates the lanthanide, thereby displacing the inner-sphere water molecules. Since coordinated water-molecules partially quench the emission of $Eu^{III}$, their displacement results in an increase of the $Eu^{III}$-centered luminescence. The same mechanism is employed by other lanthanide-probes for the detection of anions in water.[11a, 15] The possibility that cyanide reacts with the Lys-HOPO ligand[1b] was excluded since no significant change was observed in the UV-Vis spectra (Figure S19) and in the excitation profile (Figure S20) of the complex upon addition of $CN^-$.

Further evidence of the direct coordination of $CN^-$ to the $Eu^{III}$ center was obtained by determining the number of inner-sphere water molecules ($q$) from the luminescence lifetime of the complex in $H_2O$ and $D_2O$ according to the method of Parker.[16] The results, given in Table 1, indicate that in the

| | $\tau_{H_2O}$ (ms) | $\tau_{D_2O}$ (ms) | $q$ |
|---|---|---|---|
| $Eu^{III}$-Lys-HOPO | 0.16 | 0.31 | 3.3 |
| $Eu^{III}$-Lys-HOPO + 100 eq. $CN^-$ | 0.60 | 0.78 | 0.2 |

**Table 1.** Luminescence lifetimes in $H_2O$ and $D_2O$ and number of inner-sphere water molecules ($q$) of $Eu^{III}$-Lys-HOPO in the absence and presence of 100 eq. $CN^-$ in water. Experimental conditions: [$Eu^{III}$-Lys-HOPO] = 7.6 μM, water, pH = 9.8, delay time = 0.1 ms, gate time = 0.002 ms, $\lambda_{ex}$ = 335 nm, $\lambda_{em}$ = 615 nm, excitation slit widths = 20 nm, emission slit width = 10 nm.

absence of $CN^-$, $Eu^{III}$-Lys-HOPO has three inner-sphere molecules as predicted from the expanded ligand cap. In the presence of excess $CN^-$, *q* decreases to 0. These results strongly suggest that each of the three inner-sphere water molecules of $Eu^{III}$-Lys-HOPO are replaced by $CN^-$, resulting in the formation of a 1:3 Eu:$CN^-$ complex.

Although coordination of $CN^-$ to lanthanide complexes in aqueous solution has not been previously reported, bridging cyano-lanthanide structures are not unprecedented. Numerous such structures have been reported for use such as magnetochemistry,[17] thermally structural changes,[18] or solid-state light emitters.[19] Do note that in these solid-state structures, however, the cyanide ligand bridges the lanthanide to another transition metal ion. This is unlikely to occur in our system due to the absence of transition metal ions.

As shown in Figure 2, the time-gated luminescence intensity of $Eu^{III}$-Lys-HOPO increases incrementally upon addition of cyanide. In accordance with the luminescence lifetime studies that indicate replacement of all three inner-sphere water molecules of the europium probe, the titration data was fitted to the stepwise formation of a 1:3 $Eu^{III}$-Lys-HOPO:$CN^-$ complex. Fitting was performed according to the method reported by Thordarson (see SI for details).[20] As is commonly observed, the results, shown in Table 2, indicate that binding affinity decreases with each subsequent addition of $CN^-$ ($K_{a1} > K_{a2} > K_{a3}$). $Eu^{III}$-Lys-HOPO has moderately high affinity for cyanide. The first association constant, $K_{a1}$, is ten-fold higher than that of the other europium probe that functions in water developed by Faulkner.[3] The cumulative association constant, $\beta_3 = 1.39\times10^8$ $M^{-3}$, is comparable to the probe developed by Gabbaï in mixed water/MeOH.[1h] The turn-on response of this probe and its efficacy in pure water renders it a promising candidate for further environmental applications.

| | | |
|---|---|---|
| $K_{a1}$ | EuL + $CN^-$ ⇆ EuL•CN | 1,500 $M^{-1}$ |
| $K_{a2}$ | EuL•CN + $CN^-$ ⇆ EuL•$(CN)_2$ | 420 $M^{-1}$ |
| $K_{a3}$ | EuL•$(CN)_2$+ $CN^-$ ⇆ EuL•$(CN)_3$ | 220 $M^{-1}$ |

**Table 2.** Stepwise association constants, $K_a$, of $Eu^{III}$-Lys-HOPO with $CN^-$ in $H_2O$ at pH 9.8. Charges omitted for clarity.

The selectivity of $Eu^{III}$-Lys-HOPO for other anions is shown in Figure S23 (white bars). The europium complex does not bind $Cl^-$, $Br^-$, $I^-$, $CH_3CO_2^-$, $SO_4^{2-}$, and $NO_3^-$. The probe is, however, also responsive to three other hard anions at pH 10 that commonly coordinate lanthanides;[5, 15e, 15f, 16, 21] Phosphate, carbonate, and to a lesser extent fluoride increase the metal-centered luminescence of the probe 12-fold, 7-fold and 2-fold, respectively. Interestingly, the parent Eu-TREN-1,2-HOPO was reported not to bind to either of these three anions.[12] As predicted, a minor change in the structure of the ligand that opens up a coordination site can have substantial influence on the affinity of a lanthanide complex for coordinating anions. Nonetheless, except for phosphate, sequential addition of cyanide returns the 9-fold increase in luminescence observed upon addition of $CN^-$ (Figure S23, grey bars). This increase is identical to that of the control suggesting that neither carbonate nor fluoride affect the ability of $Eu^{III}$-Lys-HOPO to detect cyanide.

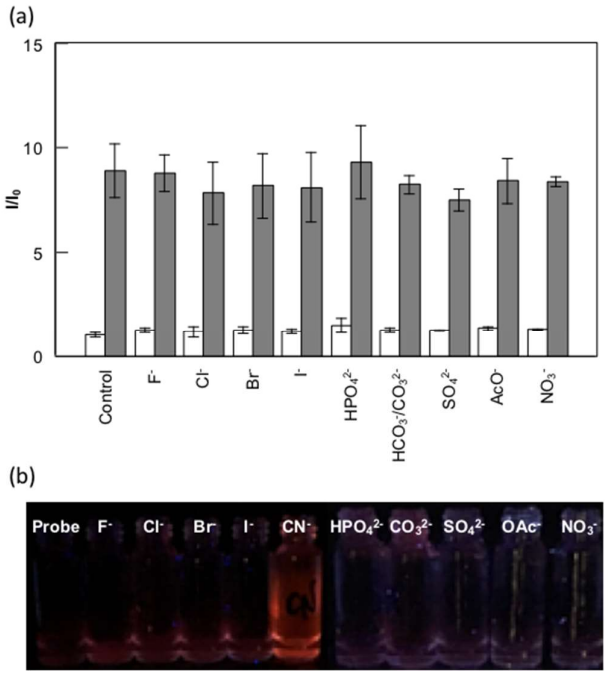



**Figure 3** a) Selectivity of $Eu^{III}$-Lys-HOPO to various environmentally-relevant anions. White bars represent the time-delayed relative luminescence intensity after addition of 100 eq. of the appropriate anions (NaF, NaCl, NaBr, NaI, NCN, $NaHPO_4$, $NaHCO_3$, $Na_2SO_4$, NaOAc, and $NaNO_3$) and 100 eq. of $CaCl_2$. Grey bars represent the time-delayed relative luminescence intensity after subsequent addition of 100 eq. of NaCN. Experimental conditions: I=integrated time-delayed luminescence from 550 nm to 750 nm, $I_0$=integrated luminescence of $Eu^{III}$-Lys-HOPO in the absence of any anion, [$Eu^{III}$-Lys-HOPO] = 16 μM in $H_2O$, pH 9.8, $\lambda_{excitation}$ = 335 nm, delay time = 0.1 ms, excitation slit widths = 10 nm, emission slit width = 5 nm. Error bars represent s.d., *n* = 3. b) Photo of $Eu^{III}$-Lys-HOPO solutions in water with 100 eq. of corresponding anions and 100 eq. of $CaCl_2$ illuminated with a hand-held UV lamp

Selectivity over phosphate and fluoride is a common problem with lanthanide and cyanide probes, respectively. Notably, interference from all three competing anions can be eliminated by simple addition of a soluble $Ca^{2+}$ salt such as $CaCl_2$ $Ca^{2+}$ forms highly stable and insoluble salts with $F^-$, $HPO_4^{2-}$, and $CO_3^{2-}$. As shown in Figure 3a (white bars), in the presence of 1 equivalent $CaCl_2$ per competing anion, the luminescence of $Eu^{III}$-Lys-HOPO only turns on in the presence of $CN^-$. Under these conditions, neither $HPO_4^-$, $HCO_3^-/CO_3^{2-}$, $F^-$, $Cl^-$, $Br^-$, $I^-$, $CH_3CO_2^-$, $SO_4^{2-}$, nor $NO_3^-$ affect the response of the europium probe. Importantly, the subsequent addition of 100 equivalent of $CN^-$ restores the 9-fold increase in metal-centered luminescence (Figure 3a, grey bars), demonstrating that in the presence of $Ca^{2+}$, the competing anions do not affect the determination of cyanide concentration. Notably, this 9-fold increase in luminescence enables naked-eye detection of cyanide with a hand-held UV light (Figure 3b).

In summary, a europium complex for the time-gated luminescence detection of $CN^-$ in pure water is presented. $Eu^{III}$-Lys-HOPO demonstrates a 9-fold increase in luminescence intensity in the presence of $CN^-$ and is highly selective over competing anions of environmental relevance in the presence of $Ca^{2+}$. Moreover, unlike other molecular probes for cyanide, $Eu^{III}$-Lys-HOPO is not a reactivity-based probes but functions via

direct and reversible coordination of the lanthanide ion by $CN^-$ concomitant with displacement of three inner-sphere water molecules.

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## Conflicts of interest

The authors declare no conflict of interest.

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A europium complex functions as a turn-on luminescent probe for cyanide in pure water via coordination of the anion.