Barium induced modulation of NIR emission in a neodymium cryptate complex†

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Received (in Cambridge, UK) 1st September 2006, Accepted 27th September 2006
First published as an Advance Article on the web 12th October 2006
DOI: 10.1039/b612662f

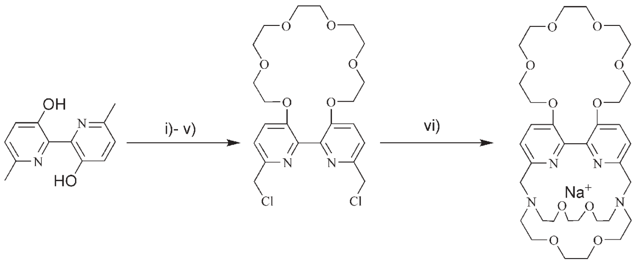
The complex $[NdL]^{III}$ is based upon a crown ether-appended ditopic cryptate ligand and demonstrates a near-infrared fluorescence response to Ba^{II}.

The design of lanthanide-based molecules for potential biomedical applications is an area of intense attention.[1] This is primarily driven by imaging modalities which can utilise the unique physical properties of various lanthanide ions, such as magnetic resonance imaging (exploiting gadolinium-derived reagents) and fluorescence (initially in time-resolved assays and more recently in microscopy).[2] For example, within the fluorescence discipline, visibly emissive, kinetically inert, Tb^{III} and Eu^{III} complexes can be utilised as optical labels in bioconjugate arrays.[3] A greater challenge is the development of emissive lanthanide complexes demonstrating optical response to endogenous analytes of bio-relevance. The approach for doing so usually requires a means of modulating the 'output' from the lanthanide 'reporter'. The key is to control the efficiency of excited state quenching of the lanthanide ion. A popular and effective approach is to control photoinduced electron transfer (PeT):[4] either in an intramolecular fashion (binding a substrate inhibits PeT and switches on emission) or intermolecularly (substrate quenches luminescence *via* electron transfer). Additionally, we have recently demonstrated that altering the degree of inner sphere hydration of a Eu^{III} complex upon binding Zn^{II} can modulate not only the spectral form, but the lifetime of the resultant phosphorescence.[5]

However, the future development of lanthanide-based probes will probably embrace the use of near-infrared (NIR) emitting ions such as Nd^{III} and Yb^{III}.[2b,6] The justification for doing so is two-fold: firstly, the use of these ions allows a greater range of sensitising chromophores to be utilised[7] (advantageous both in terms of excitation wavelength and molecular design) and secondly, emission occurring in the NIR is not complicated with biological auto-fluorescence. With improvements in detection hardware greater imaging depth within biological tissue should be possible with NIR emitting species.

Here we report the synthesis, photophysical properties and optical response to s-block metal ions, of a Nd^{III} cryptate-based complex with an appended crown ether binding site. This probe addresses many of the criteria associated with emissive lanthanide complexes: the number of coordinated solvent molecules should be minimised, the sensitising chromophore is in close proximity to the lanthanide ion ensuring efficient energy transfer, and the complex should be kinetically and thermodynamically stable, particularly when considering future *in vivo* applications.

The ditopic cryptate–crown ligand **L** was synthesised in six steps from 6,6′-dimethyl-2,2′-bipyridine-3,3′-diol (Scheme 1) and characterised by ^1H NMR spectroscopy and ESI-MS.‡ Reaction of **L** with $Nd(CF_3SO_3)_3$ in MeCN gave, after 24 h, the Nd-containing complex with an ion of appropriate isotopic distribution, in the ESI-MS at *m/z* 1118 corresponding to $\{[NdL](CF_3SO_3)_2\}^+$. The reaction times required to make this species are similar to those for other Ln-containing cryptates.[8] Taken together with the photophysical measurements described below both these factors confirm the formation of the Nd-containing cryptate complex $[NdL](CF_3SO_3)_3$, as coordination of the Nd^{III} *via* the crown ether would be virtually instantaneous and result in a heavily solvated metal ion.



Scheme 1 *Reagents and conditions*: (i) NaH, penta-(ethylene glycol)-di-*p*-tosylate, anhydrous DMF, N_2, 60 °C, (ii) *m*CPBA, DCM, RT, (iii) acetic anhydride, N_2, 120 °C, (iv) K_2CO_3, anhydrous methanol, RT, (v) thionyl chloride, DCM, reflux, (vi) diaza-18-crown-6, NaI, Na_2CO_3, MeCN, reflux.

The absorption characteristics of $[NdL]^{III}$ are dominated by the $\pi \rightarrow \pi^*$ transition at *ca.* 340 nm. This compares with the free ligand absorption at higher energy *ca.* 310 nm, and suggests significant interaction of the Nd^{III} with the bipyridyl diimine unit, an observation that has been noted previously in bipyridine complexes.[9] Photophysical studies were conducted on solutions of $[NdL]^{III}$. Firstly, time-resolved experiments set out to determine the radiative decay characteristics of the Nd^{III} ion. Measurements were conducted in deuterated and non-deuterated methanolic solutions with excitation at 355 nm, sensitising the bipyridyl chromophore, resulting in detectable luminescence at 880, 1055 and 1340 nm

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† Electronic supplementary information (ESI) available: Experimental details, absorption, emission, ESI-MS and ^1H NMR spectra. See DOI: 10.1039/b612662f

corresponding to the $^4F_{3/2} \rightarrow {}^4I_{9/2}$, $^4I_{11/2}$ and $^4I_{13/2}$ transitions of Nd^{III}. The lifetime decays obtained were single exponential in character, suggesting one decay process, and were relatively long in duration for an 8-coordinate Nd^{III} complex (347 and 711 ns in CH_3OH and CD_3OD respectively).[10] It is possible to utilise the lifetime measurements to deduce an approximation of the inner sphere solvent coordination number (denoted by q) by application of the following equation based originally on Horrocks' work and developed further by Parker and co-workers:[11]

$$q = 290(k_{CH_3OH} - k_{CD_3OD}) - 0.4$$

Using this equation $q \approx 0$, which equates well with an encapsulating cryptate environment within which the Nd^{III} is coordinated, as opposed to the alternative 'open' crown ether site (as noted above). However, caution should be taken not to over interpret this value since the original A and B (290 ns and 0.4 respectively) constants for Nd^{III} were deduced using amino-carboxylate based ligands. The fragility of these constants has been demonstrated in the work of Faulkner *et al.* who showed that limiting the number of proximate C–H oscillators in the ligand (in their case using Lehn's cryptand)[12] elongates the Nd^{III} lifetimes, resulting in an anomalous $q = 0.43$.[13] Generally, for the rigid Lehn cryptand the hydration number of the Tb^{III}, Eu^{III} ions is usually 2–3.[9] In contrast, here the Nd^{III} coordination environment possesses two flexible aliphatic, diethyleneglycol chains and only one 2,2′-bipyridine unit. Consequently it may be that a q value for this species is more reliable than in the case of the Lehn cryptand Nd^{III} complex. However, despite the presence of C–H oscillators it is interesting that the lifetimes for $[Nd\mathbf{L}]^{III}$ are still relatively long for methanolic solution and therefore noteworthy given that the biological application of NIR emissive lanthanide probes is often inhibited by short lifetime duration.[14] For reference purposes the lifetime of $[Nd\mathbf{L}]^{III}$ was also obtained in MeCN and recorded as 470 ns. This minor elongation in lifetime compared to MeOH is probably due to the absence of an O–H oscillator in the solvent: these are known to quench lanthanide excited states very efficiently even if not directly bound (*i.e.* $q = 0$ species).

The effect on the optical properties of adding various alkali metals to $[Nd\mathbf{L}]^{III}$ was studied in acetonitrile solutions. Typically, excess metal salt ($NaClO_4$, KPF_6, $Ca(ClO_4)_2$ or $Ba(ClO_4)_2$) was added directly to the cuvette containing the MeCN solution of $[Nd\mathbf{L}]^{III}$. In terms of the absorption properties the changes are most profound for Ba^{II} with a high energy shift of the $\pi \rightarrow \pi^*$ transition to 310 nm (Fig. 1). In contrast, K^I and Na^I do not alter the absorption profile, suggesting little or no interaction with the bipyridine unit, whilst Ca^{II} causes a broadened, high energy shift to about 330 nm.

Time-resolved data were obtained for the NIR emitting Nd^{III} components, the lifetimes being determined as 500, 420, 424, and 440 ns for addition of Na^I, K^I, Ca^{II} and Ba^{II} respectively. This is probably within error (*i.e.* ±10%) of the measurement obtained for the free complex $[Nd\mathbf{L}]^{III}$ (470 ns) and suggests binding an alkali metal in the crown does not significantly disrupt the coordination environment of the neighbouring cryptate-bound lanthanide ion. However, in the case of Ba^{II} which revealed the most profound changes in the absorption spectrum, the intensity of the Nd^{III} emission at 1055 nm is reduced significantly following excitation at 335 nm (Fig. 2). The possibility of Nd^{III} displacement can be discounted, firstly, on the grounds that upon addition of Ba^{II} the lifetime does not significantly change (and hence there is no change in the coordination environment) and secondly, the intensity of Nd^{III} emission does not significantly decrease upon addition of Na^I, K^I, or Ca^{II}.† Rather, this corresponds well with the UV-vis data which show a decrease in the absorptivity at 335 nm following Ba^{II} addition and essentially point to bipyridyl mediated modulation of the lanthanide emission at this wavelength.

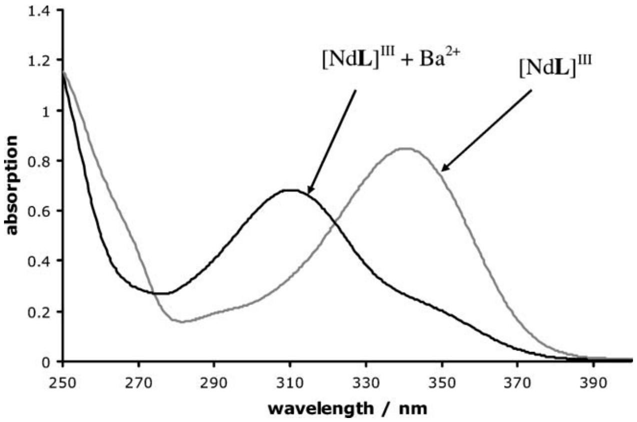

Fig. 1 Absorption spectra of $[Nd\mathbf{L}]^{III}$ upon addition of $Ba(ClO_4)_2$ in MeCN.

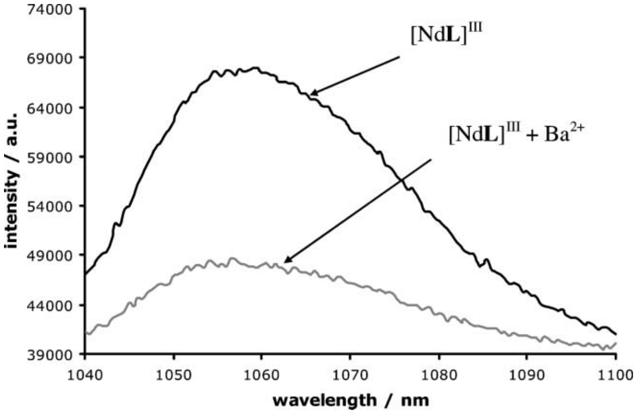

Fig. 2 Uncorrected NIR emission spectrum of $[Nd\mathbf{L}]^{III}$ in MeCN ($\lambda_{ex} = 335$ nm). NB The background count on the detector is typically 38 000–39 000 cps.

One possible reason why addition of barium ions to the crown ether unit has such an effect on the optical properties is the coordination of the two oxygen atoms directly bonded to the 2,2′-bipyridine unit. We have shown that in similar systems coordination of these oxygen atoms can affect the NCCN torsion angle of the bipyridine unit, forcing it away from planarity.[15] Undoubtedly such a change would have a dramatic effect on the absorption profile.

This work demonstrates, for the first time, that by appropriate ligand design, Nd^{III} NIR emission can be modulated by s-block metal ions. Future work will focus upon the incorporation of the smaller crown-5 and crown-4 units within this ditopic ligand which will hopefully show a response to biologically important metal ions such as Li^I, Na^I, Mg^{II} and Ca^{II}.

We thank the Universities of Huddersfield and Cardiff for support.

Notes and references

‡ The ligand **L** was synthesised in 6 steps from 6,6′-dimethyl-2,2′-bipyridine-3,3′-diol. ^{1}H NMR (500 MHz, CDCl$_3$, J in Hz) δ 7.37 (2H, d, J = 8.4), 7.30 (2H, d, J = 8.4), 4.26 (m, 2H), 4.16 (m, 2H), 4.07 (d, J = 13, 2H), 3.90–3.46 (m overlapping, 26H), 3.42 (m, 2H), 3.33 (d, J = 13, 2H), 3.00 (m, 2H), 2.85 (m, 4H), 2.69 (m, 2H), 2.61 (m, 4H). ESI-MS: m/z 699 $\{\text{NaL}\}^+$. Full details are given in the ESI.

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