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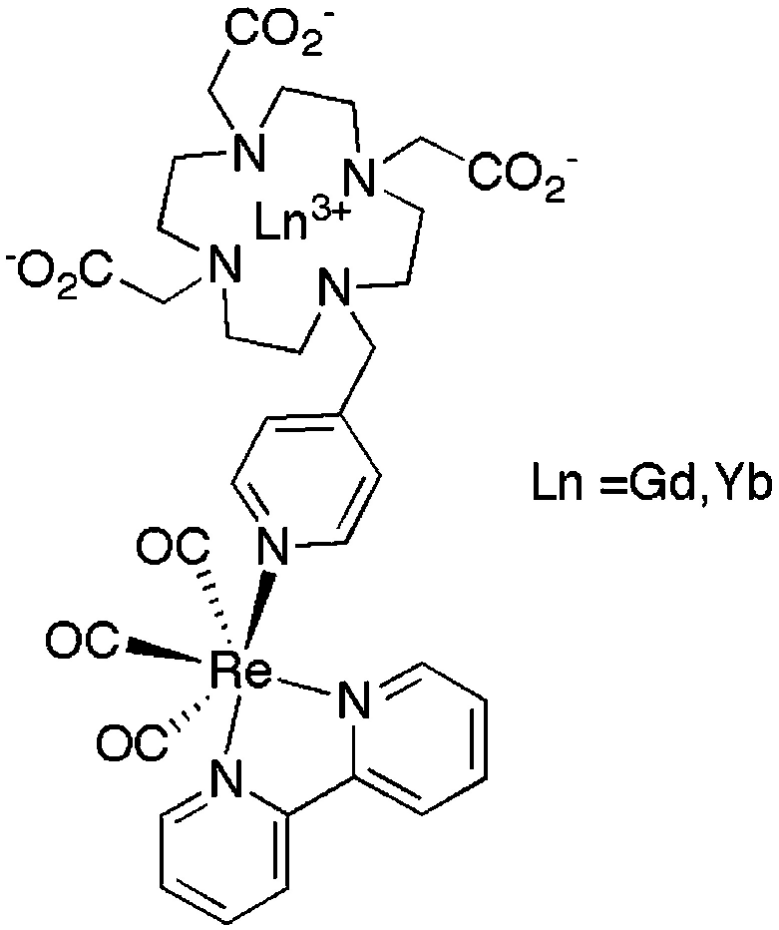

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Synthesis and Spectroscopic Properties of a Prototype Single Molecule Dual Imaging Agent Comprising a Heterobimetallic Rhenium−Gadolinium Complex

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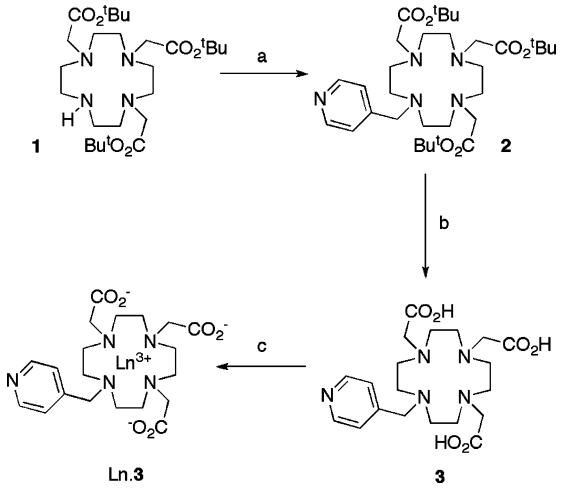
Metal complexes are increasingly of interest as imaging agents. In particular, gadolinium complexes are widely used as magnetic resonance imaging (MRI) contrast agents,[1] while the relatively long-lived luminescence from lanthanide ions and transition metal complexes makes them ideal as probes for time-gated luminescence-based assay and imaging.[2] MRI and luminescence operate with very different spatial resolution; the former is ideal for providing whole body images[3] but has spatial resolution in the 0.1 mm range, while the latter is ideal for generating high-resolution images but cannot image thick tissue samples owing to their lack of optical transparency.[4] Recently, much has been made of the possibility of using mixtures of complexes in multimodal imaging which permit simultaneous microscopy and whole body imaging.[5] The use of mixtures is, however, likely to be somewhat restricted in cases where the biodistributions of the various components differ.

Our own studies in this area have used kinetically stable building blocks in the preparation of heterometallic complexes.[6] We have concentrated on the use of d-block metal complexes as sensitizers for lanthanide luminescence in the near IR. For such applications, we have established that short-lived emission from the d-block component is desirable for optimal energy transfer. However, it became clear to us that long-lived emissive components could be combined with a gadolinium center to give a unimolecular species with potential for use in dual-mode imaging.

We now report the synthesis and properties of a bimetallic complex containing a luminescent rhenium chromophore as well as a Gd^{3+} ion that can be used in MRI.

Scheme 1 outlines the preparative strategies employed to access Ln·**3**. Alkylation of the well-known triester (**1**)[7] with 4-bromomethylpyridine and sodium hydrogencarbonate gave **2**, which contains a masked heptadentate binding site. Cleavage of the *tert*-butyl esters with trifluoroacetic acid gave **3** in good yield. **3** was derivatized to form several charge-neutral lanthanide complexes (Ln = Yb, Gd, Eu). The Yb^{3+} complex showed shifted and broadened proton NMR spectra, consistent with the binding of a paramagnetic lanthanide ion in the metal binding site. While none of these complexes proved amenable to crystallization, we did manage to obtain crystals of Na·**2**. This structure (Figure 1) shows that the sodium salt adopts a twisted square antiprismatic arrangement of donor atoms with a dihedral angle of 23°, analogous with that expected for the lanthanide complexes, with the metal ion encapsulated by the ligand. It is worth noting that the pyridyl group also restricts access to the metal center in the crystalline conformation (<N(4)−C(40)−C(41) = 111.5°).

Scheme 1. Synthesis of Ln·**3**[a]



[a] Reagents and conditions: (a) 4-bromomethylpyridine·HBr, $NaHCO_3$, MeCN, Δ 24 h; (b) TFA/CH_2Cl_2 (1:1), rt, 24 h; (c) $LnOTf_3$, MeOH, Δ, 24 h.

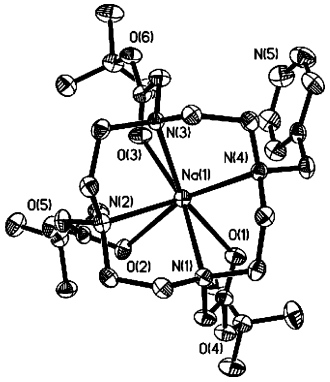


Figure 1. Thermal ellipsoid drawing of [Na·**2**]$^+$ (50%). Selected distances (Å) and angles (°): Na(1)−O(3) 2.418(3), Na(1)−N(1) 2.457(3), Na(1)−O(2) 2.604(2); O(3)−Na(1)−N(1) 163.95(9), O(3)−Na(1)−O(1) 119.44-(9), N(2)−Na(1)−N(3) 72.17(8).

The compound *fac*-$Re(CO)_3(Bpy)Cl$, **4**,[8] was prepared according to literature procedures and activated by reaction with silver triflate. Upon addition of Ln·**3** (Scheme 2), the heterobimetallic complex Ln·**3**·$Re(Bpy)(CO)_3$, **5**, was formed and purified by trituration and recrystallization. Once again, the ^1H NMR spectrum of the ytterbium complex clearly showed the presence of shifted resonances for the azamacrocycle ring and arm protons.

Time-resolved luminescence spectroscopy was used to probe both the building blocks and the bimetallic complex. Luminescence

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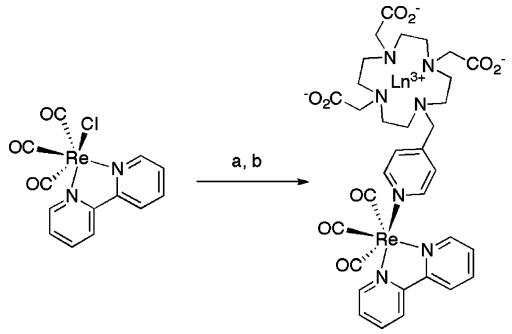
Scheme 2. Synthesis of Ln·**3**·Re(Bpy)(CO)$_3$[a]



[a] Reagents and conditions: (a) AgOTf THF/MeCN, 16 h; (b) Ln·**3**, EtOH/MeCN, Δ, 17 h.

Table 1. Photophysical Properties of the Complexes

complex	$\tau_{Ln}/\mu s$[a] H_2O	$\tau_{Ln}/\mu s$[a] D_2O	$\tau_{ReMLCT}/\mu s$[b]	q[c]
Yb·**3**	1.20	5.34		0.5
Eu·**3**	404	904		1.3
[Yb·**3**·Re(Bpy)(CO)$_3$]$^+$	1.47	5.30	0.12	0.4
[Gd·**3**·Re(Bpy)(CO)$_3$]$^+$			0.24	

[a] The luminescence lifetimes were obtained following excitation at 337 nm and observing the emission of Yb^{3+} complexes at 980 nm. [b] The value of τ_{ReMLCT} was determined from the emission at 600 nm. [c] Calculated[9] using $A = 1.0$ ms and $B = 0.1$ ms^{-1} for Yb^{3+} and $A = 1.2$ ms and $B = 0.25$ ms^{-1} for Eu^{3+}.

lifetimes are reported in Table 1. In the case of Ln·**3**, the gadolinium complex is nonemissive as a result of the high-energy emissive state of the metal ion. However, Yb·**3** exhibits sensitized emission with long luminescence lifetimes. The inner sphere hydration number was determined from the luminescence decay constants in H_2O and D_2O using the formula $q = A(k_{H_2O} - k_{D_2O} - B)$.[9]

The calculated values of q obtained using this equation suggest that, in solution, both Yb·**3** and [Yb·**3**·Re(Bpy)(CO)$_3$]$^+$ are in equilibrium between the dehydrated form ($q = 0$) and the monohydrate ($q = 1$), implying that the bulk and lipophilicity of the pyridyl substituent hinders close approach of solvent to the ytterbium center. By contrast, Eu·**3** has $q = 1.3$, suggesting that the complex exists in solution as a mixture of the mono- and dihydrated species, as a consequence of the greater radius of the Eu^{3+} ion. The rhenium-containing chromophore does not sensitize europium(III) emission in [Eu·**3**·Re(Bpy)(CO)$_3$]$^+$.

The compound *fac*-Re(CO)$_3$(Bpy)Cl has a very short emissive lifetime in solution (<10 ns),[10] as a result of efficient nonradiative quenching of the excited state by the bound chloride ion. When the chloride is replaced with a nitrogen donor atom from the pyridyl group in Ln·**3**, the lifetime is enhanced by around 2 orders of magnitude, depending on the lanthanide. The longest lifetime is observed for [Gd·**3**·Re(Bpy)(CO)$_3$]$^+$, where there is no competitive quenching pathway through the lanthanide ions. In the case of ytterbium, quenching of the Re ^{3}MLCT state leads to sensitized emission from the lanthanide ion, and the lanthanide emission is convoluted with the tail of the MLCT emission.

The relaxometric properties of [Gd·**3**·Re(Bpy)(CO)$_3$]$^+$ are equally interesting; the high relaxivity (8.6 mM^{-1} s^{-1} at 500 MHz) in aqueous solution is in line with the existence of a diaquo complex which tumbles slowly in solution, implying that the time-averaged structure around the Gd center in this complex is very different than that around the Yb center. In phosphate-buffered saline, the relaxivity is reduced to 3.9 mM^{-1} s^{-1} as a result of phosphate anion binding at the metal center leading to a reduction of inner sphere solvation, but the potential of these systems is clear. For Gd·**3**, the relaxivity is slightly reduced in aqueous media (5.8 mM^{-1} s^{-1} at 500 MHz) but is significantly higher in phosphate-buffered saline (4.5 mM^{-1} s^{-1} at 500 MHz). This implies that the d−f hybrid tumbles more slowly in solution than Gd·**3**, as would be expected given its greater molecular volume. These results are entirely consistent with the presence of a dihydrate complex in solution, possibly in equilibrium with a monohydrate (as with the Eu^{3+} complex). Phosphate binding is more pronounced in the case of the d−f hybrid complex, possibly as a consequence of adopting a more open conformation at the Gd^{3+} center following binding of the pyridyl pendant to the rhenium ion, suggesting that elaboration of the complex perturbs the equilibrium between the mono- and dihydrated forms.

From the results above, it is clear that the complex [Gd·**3**·Re(Bpy)(CO)$_3$]$^+$ is a potential dual imaging agent. The luminescence lifetimes are long enough to permit efficient gating of any fluorescent background (for which lifetimes of <10 ns are typical), while the gadolinium ion can be used to provide MR contrast. Heterometallic complexes such as those described here clearly have considerable potential as multimodal imaging agents. Further studies on related systems are currently in progress to optimize the MRI contrast in real systems and control the wavelength and lifetime of the ^{3}MLCT emission. Luminescence from these complexes gives a linear response over a concentration range from subnanomolar to 100 μM concentrations, but MRI contrast is likely to be poor at submicromolar concentrations. Ideally, complexes would give MRI contrast at nanomolar concentrations, enabling MR imaging of surface receptor concentrations. We are currently investigating the potential of rigid multimetallic arrays with much higher relaxivities to this end. The coordination chemistry of rhenium(I) and its analogues also provides scope for facile formation of bioconjugates and more complicated architectures.

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Supporting Information Available: Experimental detail, NMR spectra, and fitted decays for Yb complexes, relaxivity measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

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