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Use of Yb^{III}-Centered Near-Infrared (NIR) Luminescence To Determine the Hydration State of a 3,2-HOPO-Based MRI Contrast Agent[1]

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The synthesis, structure, and characterization of a [Yb(Tren-Me-3,2-HOPO)(H_2O)$_2$] complex are reported. As a result of its Yb^{III} emission in the near-infrared region, sensitized by the Me-3,2-HOPO chromophore, this complex can be utilized for the first time to determine the hydration state, *q*, via the luminescence lifetimes and hence the solution structure of these Me-3,2-HOPO-type ligands, which have attracted significant interest in complex with Gd^{III} as possible next-generation magnetic resonance imaging contrast agents.

It has been more than a decade since the first reports of [Gd(Tren-Me-3,2-HOPO)(H_2O)$_2$] as a potential new class of magnetic resonance imaging contrast agents.[2] The defining feature of these 1-methyl-3-hydroxypyridin-2-one (Me-3,2-HOPO)-based compounds has been the use of a hexadentate ligand design, and hence an increase in the number of metal-bound water molecules, without sacrificing complex stability compared to the typically octadentate contrast agents used commercially. Since that time, significant advances in the properties of these chelates have been steadily reported, including improvements in relaxivity,[3,4] incorporation into macromolecular architectures,[5−7] and, recently, the first direct verification of solution structure using the discovery of Eu^{III}-centered luminescence with the isomeric 1-hydroxypyridin-2-one (1,2-HOPO) chelate as a sensitizing chromophore.[8,9] Nonetheless, it has remained frustrating that direct measurements of the inner-sphere hydration state, *q*, using luminescence techniques with the parent Me-3,2-HOPO compounds have remained elusive, even when direct laser excitation of weakly absorbing *f*−*f* transitions were employed (e.g., for Eu^{III} complexes). This failing can likely be traced to the presence of a low-lying ligand-to-metal charge-transfer (LMCT) state, which efficiently quenches metal-based emission. Instead, estimates of *q* and, hence, the solution structure have relied on the fitting of relaxivity data to the Solomon−Bloembergen−Morgan equations or, where sufficiently soluble in aqueous solution, studies on the temperature dependence of the paramagnetic contribution to the water ^{17}O NMR transverse relaxation rate.[10] Recently, Beeby et al.[11] reported on a qualitative equation to determine inner-sphere hydration based on the change in lifetimes for Yb^{III} in going from H_2O to D_2O solution, and we reasoned that the lower-energy accepting state of Yb^{III} may lie below the LMCT state (which otherwise quenches Eu^{III} emission) and hence may facilitate sensitized emission from Yb^{III}. This hypothesis was borne out experimentally, and herein we describe for the first time sensitized luminescence in the near-infrared (NIR) region from a [Yb(Tren-Me-3,2-HOPO)(H_2O)$_2$] complex, and hence the direct measurement of *q* for the archetypical member of this family of compounds.

The [Yb(Tren-Me-3,2-HOPO)(H_2O)$_2$] complex was prepared in an analytically pure form using standard methodologies in MeOH as the solvent with excess pyridine as a base to ensure deprotonation of the phenolic oxygen atoms (see the Supporting Information for more details). X-ray-quality crystals of the complex were grown by slow evaporation (over several months) of a 10 μM aqueous solution in 0.1

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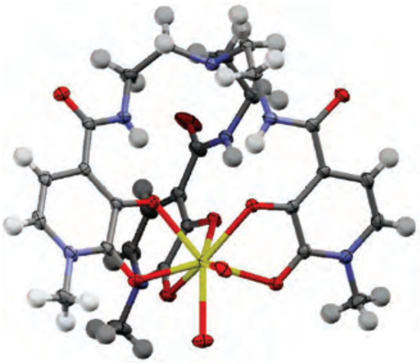

Figure 1. View of the asymmetric unit for the [Yb(Tren-Me-3,2-HOPO)$(H_2O)_2$]$\cdot$$2H_2O$ complex. Noncoordinated solvent water molecules were omitted for clarity, and thermal ellipsoids were drawn at the 50% probability level.

M Tris buffer at pH 7.4. The resulting structure[12] is shown in Figure 1, with full crystal data in CIF format given in the Supporting Information. The metal center is eight-coordinate (CN = 8), and the structure is isomorphous with that previously reported for the Tren-Me-3,2-HOPO ligand with Gd^{III}.[2] Coordinate bond lengths to the metal center are typical [avg. Yb−O (phenolate) ~ 2.293 Å; avg. Yb−O (keto) ~ 2.349 Å] and are slightly shorter by ca. 2.5% than those observed for Gd^{III} [avg. Gd−O (phenolate) ~ 2.358 Å; avg. Gd−O (keto) ~ 2.408 Å], as was expected because of the well-known lanthanide contraction.[13] The presence of an intermolecular hydrogen-bonding interaction between the amide N−H and phenolate oxygen atom common to this structural motif is noted, with an average N−H−O separation of ca. 1.96 Å, and the orientation of the tertiary amine lone pair from the Tren cap is directed toward the Yb^{III} metal center. Other than the differing identities of the cocrystallized solvent, the structures are essentially identical in all other aspects.

An important structural parameter that can also be obtained from the crystallographic data is the shape measure, SM,[14,15] defined as

$$\mathrm{SM} = \min\left[\sqrt{\frac{1}{m}\sum_{i=1}^{m}(\delta_i - \theta_i)^2}\right]$$

This is a measure of the agreement in the variance of dihedral angles along all edges between the polyhedron derived from the crystal structure and the idealized cases. For the eight-coordinate geometry, the three most common idealized coordination polyhedra are the bicapped trigonal-prismatic (C_{2v}), square-antiprismatic (D_{4d}), and trigonal-dodecahedral (D_{2d}) geometries, and the lowest value of SM for the three pairs represents the best fit to the closest idealized geometry. The resulting shape analysis results for the Yb^{III} and Gd^{III} complexes are summarized in Table 1. The coordination geometry of the Gd^{III} complex was previously[2] visually interpreted as a distorted bicapped trigonal prism (C_{2v}). However, inspection of the shape analysis results reveals that this complex is, in fact, closer to the trigonal-dodecahedral (D_{2d}) geometry and, hence, is isostructural with the results obtained herein for the new Yb^{III} analogue.

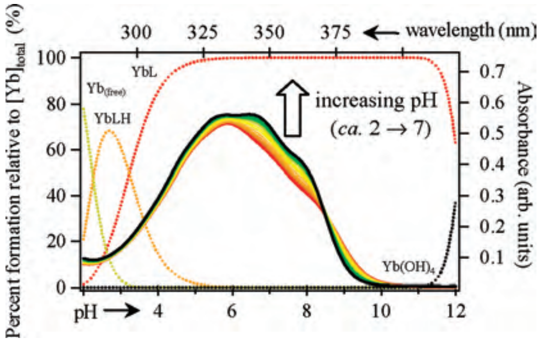

Figure 2. Speciation diagram of a ca. 25 μM [Yb(Tren-Me-3,2-HOPO)$(H_2O)_2$] complex in aqueous solution (left, bottom axes) and overlaid changes in UV−visible spectra (right, top axes) upon a change in the pH. Color code: red, free ligand spectrum (ca. pH ~2); black, fully formed complex (above ca. pH 5.5−6).

Table 1. Summary of the Shape Analysis Results for Yb^{III} and Gd^{III} Complexes of Tren-Me-3,2-HOPO

	shape measure (SM)		
complex	D_{4d}	C_{2v}	D_{2d}
[Yb(Tren-Me-3,2-HOPO)$(H_2O)_2$]	14.35	11.42	5.45
[Gd(Tren-Me-3,2-HOPO)$(H_2O)_2$]	16.04	11.50	6.52

Our attempts to determine the pM[17] of the complex by competition titration versus DTPA were unsuccessful due to evidence of ternary complex formation (see Figure S1 in the Supporting Information). Instead, the aqueous stability was assessed by spectrophotometric titration as detailed elsewhere,[16] utilizing the reported pK_a's of the Tren-Me-3,2-HOPO ligand.[2] Resulting absorption spectra versus pH are shown in Figure 2, and the stability constants determined for β_{110} and β_{111} were 20.81(2) and 24.04(2) respectively, with the site of protonation assigned to the amine backbone in accordance with previous studies.[2] These data yielded a pM[17] with Yb^{III} of 20.8, which is comparable to the previously reported[2] pGd = 20.3 with the same ligand, with the slight increase being consistent with other ligand systems (e.g., DTPA, EDTA, etc.) and attributable to the decreasing size and increasing Lewis acidity of the metal.

Having established the aqueous stability, we were interested in the photophysical properties of the Me-3,2-HOPO chromophore. The molar absorption and emission spectra for a ca. 10 μM solution of [Yb(Tren-Me-3,2-HOPO)$(H_2O)_2$] in a 0.1 M Tris buffer at pH 7.4 are shown in Figure 3. The lowest-energy ligand-centered absorption maximum is located at ca. 345 nm ($\varepsilon \sim 19\,000$ M^{-1} cm^{-1}), in accordance with our previous reports, with a more intense $\pi\pi^*$ band to higher energy at ca. 225 nm ($\varepsilon \sim 60\,000$ M^{-1} cm^{-1}). More importantly, our prediction that the Me-3,2-HOPO chro-

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[12] Crystal data: $C_{27}H_{30}N_7O_9Yb$ (769.62 g/mol), triclinic, $a = 10.1056$ (7) Å, $b = 10.6100$ (7) Å, $c = 16.8122$ (11) Å, $\alpha = 84.157(1)°$, $\beta = 79.139(1)°$, $\gamma = 66.176(1)°$, $V = 1618.81(8)$ Å^3, space group $P\bar{1}$ (No. 2), $Z = 2$, $T = 189(2)$ K, $\lambda = 0.710\,73$ Å, $\rho_{diff} = 1.58$ g/cm^3, $\mu = 2.95$ mm^{-1}, R1(F_0) = 0.028, wR2($F_0{}^2$) = 0.063, GOF = 1.021.

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[17] pM = −log $[M]_{free}$, defined as the negative log of the free metal concentration at pH 7.4 with 10 μM $[L]_{total}$ and 1 μM $[M]_{total}$.

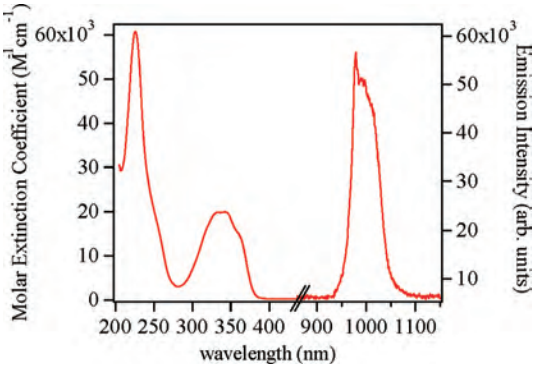

Figure 3. Electronic absorption spectrum in a 0.1 M Tris buffer at pH 7.4 (left) and steady-state NIR emission spectrum in D_2O (right) ($\lambda_{ex} = 345$ nm, 10 nm bandpass) for the $[Yb(Tren\text{-}Me\text{-}3,2\text{-}HOPO)(H_2O)_2]$ complex.

mophore may sensitize Yb^{III} was confirmed experimentally, and the characteristic metal-centered $^2F_{7/2} \leftarrow {}^2F_{5/2}$ emission band is clearly evident with a peak at ca. 980 nm, broadened due to crystal-field splitting of this transition.

Lastly, to determine the hydration state, q, of the complex, we measured the observed NIR lifetime of the complex at 980 nm upon selective N_2 laser excitation at 337.1 nm. The resulting τ_{obs} values obtained were 0.37 and 8.06 μs in H_2O and D_2O, respectively. Hence, substitution of k_H and k_D into the empirical equation given by Beeby et al., $q = A(k_H - k_D - B)$ with $A = 1\ \mu s^{-1}$ and $B = 0.2\ \mu s^{-1}$, yielded a value of $q = 2.4$. We take this noninteger result as a slight overestimate, and the residual can be accounted for by quenching due to adjacent $\nu_{C=O}$ and ν_{C-H} oscillators, which have a known[11] strong quenching effect on NIR emission. In conclusion, we have confirmed a coordination number of eight (CN = 8) in aqueous solution for the archetypical Tren-Me-3,2-HOPO ligand by NIR luminescence techniques and are now working toward similar measurements with other ligand systems (e.g., Tren-bis-HOPO-TAM).

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Supporting Information Available: Detailed synthesis of $[Yb(Tren\text{-}Me\text{-}3,2\text{-}HOPO)(H_2O)_2]$, X-ray crystallographic file (in CIF format), additional experimental details for the conditional stability constant, and photophysical characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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