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# [Ga<sup>3+</sup><sub>8</sub>Sm<sup>3+</sup><sub>2</sub>, Ga<sup>3+</sup><sub>8</sub>Tb<sup>3+</sup><sub>2</sub>] metallacrowns are highly promising ratiometric luminescent molecular nanothermometers operating at physiologically relevant temperatures

Elvin V. Salerno<sup>[a]</sup>, Justyna Zeler<sup>[b,c]</sup>, Svetlana V. Eliseeva<sup>[d]\*</sup>, Miguel Hernández-Rodríguez<sup>[b]</sup>, Albano N. Carneiro Neto<sup>[b]</sup>, Stéphane Petoud<sup>[d]\*</sup>, Vincent L. Pecoraro<sup>[a]\*</sup>, Luís D. Carlos<sup>[b]\*</sup>

- [a] E.V. Salerno, Prof. V.L. Pecoraro  
Department of Chemistry  
University of Michigan  
Ann Arbor, MI 48108 USA  
E-mail: vlpec@umich.edu
- [b] Dr. J. Zeler, Dr. M. Hernández-Rodríguez, Dr. A.N. Carneiro Neto, Prof. L.D. Carlos  
Department of Physics, Phantom-g, CICECO-Aveiro Institute of Materials  
University of Aveiro  
Campus de Santiago, Aveiro, Portugal  
E-mail: lcarlos@ua.pt
- [c] Dr. J. Zeler  
Faculty of Chemistry  
University of Wrocław  
Wrocław, Poland
- [b] Dr. S.V. Eliseeva, Prof. S. Petoud  
Centre de Biophysique Moléculaire  
CNRS, UPR 4301, 45071 Orléans Cedex 2, France  
E-mail : svetlana.eliseeva@cns-orleans.fr, stephane.petoud@inserm.fr

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**Abstract:** Nanothermometry is the study of temperature at the submicron scale with a broad range of potential applications such as cellular studies or electronics. Molecular luminescent based nanothermometers offer a non-contact means to record these temperatures with high spatial resolution and thermal sensitivity. A luminescent based molecular thermometer comprised of visible-emitting Ga<sup>3+</sup>/Tb<sup>3+</sup> and Ga<sup>3+</sup>/Sm<sup>3+</sup> metallacrowns (MCs) achieved remarkable relative thermal sensitivity associated with very low temperature uncertainty of  $S_T=1.9\text{ \%K}^{-1}$  and  $\delta T < 0.045\text{ K}$ , respectively, at 328 K, as an aqueous suspension of polystyrene nanobeads loaded with the corresponding MCs. They are so far the ratiometric molecular nanothermometers offering the highest level of sensitivity in the physiologically relevant temperature range.

Nanothermometry is the analysis of the temperature of submicron systems. This domain of science offers potential applications in fields such as electronics,<sup>[1]</sup> microfluidics,<sup>[2]</sup> nanomedicine,<sup>[3]</sup> and cellular studies<sup>[4]</sup> where minimal spatial-sized thermometers are desired. Luminescence based thermometry correlates temperature with either emission intensity or emission lifetime changes of luminescent systems located in the studied environment. A low temperature uncertainty ( $\delta T$ ) and a high relative thermal sensitivity of measurements ( $S_T$ ) are desirable properties.

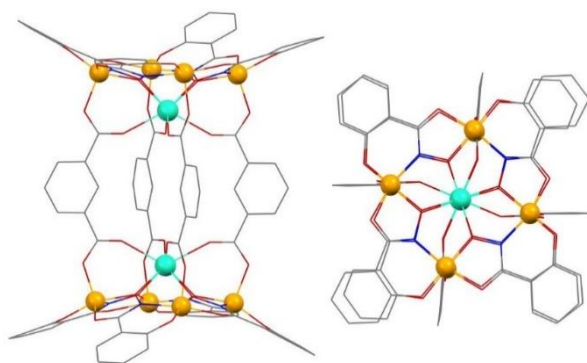
Dual-centered ratiometric luminescent thermometry is a proven intensity-based method. In this technique, the intensity ratio ( $\Delta$ ) of two

unique emitters' emission wavelengths provides a measurement of temperature with an internal calibration.<sup>[5]</sup> Molecular luminescence thermometry approaches what is perhaps the physical limit of attainable optical spatial resolution of temperature, restrained only by the diffraction limit of the optics used for detection.<sup>[6,7]</sup> It is difficult to generalize the parameters related to molecular thermometers, since while a system may excel in some respects it may be lacking in others. Generally, organic molecular fluorescent dyes have drawbacks since such systems have limited photostability depending on the intensity and duration of the light exposure and can suffer from fluorescence intensity changes that are nonrelated to temperature such as from pH, solvent viscosity or polarity, biological environment, or ionic strength.

Lanthanide based nanothermometers may derive their functionality from the temperature-dependent luminescence of lanthanide ions (Ln<sup>3+</sup>) in their compounds. Unique Ln<sup>3+</sup> photophysical properties derive from their core-like valence 4f electrons. These cations possess element-specific emission profiles with narrow bands that are specific for a given lanthanide cations and the wavelengths of which are not modified by the experimental conditions. As most f-f transitions are forbidden, free Ln<sup>3+</sup> cations are very weakly absorbing resulting in low emission intensity. This limitation can be overcome though sensitization by an appropriate coordination environment.<sup>[8]</sup>

While Ln<sup>3+</sup> thermometers are relatively common in metal organic frameworks and other solid-state systems,<sup>[9–12]</sup> self-sensitized *molecular* based systems are less common. Several such systems are: i) a Eu<sup>3+</sup> thenoyltrifluoroacetate (EuTTA) complex embedded in a polymethyl(methyl) acrylate network which has a  $\delta T$  of 0.3 K,<sup>[13]</sup>

ii) a  $\text{Tb}^{3+}$  1,1,1-trifluoro-acetylacetonate (tfac) complex with a  $S_r=5.9\%K^{-1}$  at 300 K,<sup>[14]</sup> iii) a  $\text{Tb}^{3+}$ - $\text{Eu}^{3+}$  dyad with a  $\delta T$  of 1K ( $S_r=1.876\%K^{-1}$ ) at  $\sim 200$  K,<sup>[15]</sup> and iv) a  $\text{Cu}_5$  metal cluster compound.<sup>[16]</sup> The  $\text{EuTTA}$ ,  $\text{tfac}$ , and  $\text{Cu}_5$  complexes possess respectable thermometric parameters, however, in the work related to these complexes, luminescent lifetimes were used for the determination of the relative temperatures which suffer from drawbacks such as instrumental complexity, inadequacy at mapping temperature gradients, and limited efficiency in dynamic measurements where the temperature changes are faster than the lifetime of the luminescent state of the corresponding  $\text{Ln}^{3+}$ .<sup>[5]</sup> The  $\text{Tb}^{3+}$ - $\text{Eu}^{3+}$  dyad, although notable for possessing a stoichiometric  $\text{Tb}$ - $\text{Eu}$  ratio, operates optimally at ca. 200 K, a temperature that is not suitable for biological application such as cellular temperature mapping. There is space for development of ratiometric luminescent molecular thermometers to overcome some of these challenges.



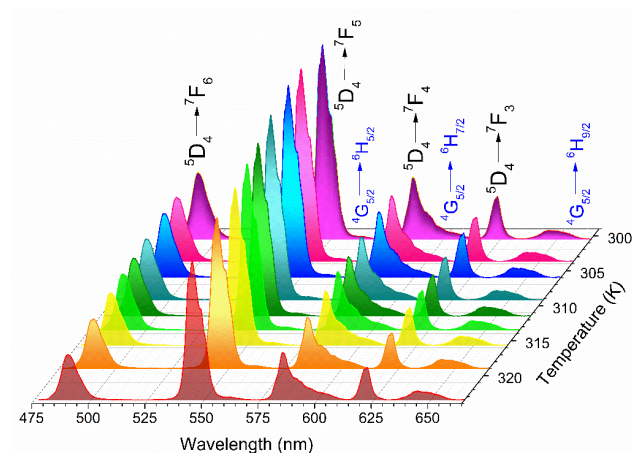
**Figure 1.** Structure of  $[\text{MC:Ln}]$  from the side (left) and top (right) views.<sup>[17]</sup> Color code: Ga, orange; Ln, green; O, red; N, blue; C, grey. Solvents, counter cations, and hydrogen atoms are omitted for clarity. CCDC Identifier: FELPUK, structure was solved on the Dy analogue.

Herein we present a novel type of ratiometric luminescent-based nanothermometer based on the  $\text{Ga}_8\text{Ln}_2(\text{salicylhydroximate})_8(\text{isophthalate})_4$  metallacrown platform ( $[\text{MC:Ln}]$ , **Figure 1**) using a 1:1 mixture of  $\text{Ga}_8\text{Tb}_2$  and  $\text{Ga}_8\text{Sm}_2$  molecules.<sup>[17]</sup> These macromolecules possess an organic framework which is templated by eight diamagnetic  $d^{10}$   $\text{Ga}^{3+}$  and two  $\text{Ln}^{3+}$ . This complex can sensitize the  $\text{Ln}^{3+}$  emission through an excitation from the visible to the near-infrared (NIR) regions resulting in a remarkable luminescence intensity. We have previously demonstrated that this family of MC is well adapted for epifluorescence NIR imaging on HeLa cells.<sup>[17]</sup> Their luminescence properties and their temperature dependence have been studied here on 10 mg/mL aqueous suspensions of 100 nm amino-functionalized polystyrene nanobeads loaded with corresponding MCs ( $[\text{MC:Ln}]\text{@PS/NH}_2$ ). Data is presented for the mono-lanthanide complexes  $[\text{MC:Sm}]\text{@PS/NH}_2$  and  $[\text{MC:Tb}]\text{@PS/NH}_2$ , as well as the 1:1  $[\text{MC:Sm}]:[\text{MC:Tb}]$  mixed compound:  $[\text{MC:Sm,Tb}]\text{@PS/NH}_2$ .

The excitation spectra of  $[\text{MC:Tb}]\text{@PS/NH}_2$  and  $[\text{MC:Sm}]\text{@PS/NH}_2$  upon monitoring the sharp emission band of the corresponding lanthanide cation ( $^5\text{D}_4 \rightarrow ^7\text{F}_5$  ( $\text{Tb}^{3+}$ , 545 nm) and  $^4\text{G}_{5/2} \rightarrow ^6\text{H}_{7/2}$  ( $\text{Sm}^{3+}$ , 600 nm)) were collected at ambient temperature. Results were compared to the corresponding excitation spectra of the free MC molecules  $[\text{MC:Sm,Tb}]\text{@PS/NH}_2$  monitoring the  $^5\text{D}_4 \rightarrow ^7\text{F}_6$  ( $\text{Tb}^{3+}$ , 490 nm) and the  $^4\text{G}_{5/2} \rightarrow ^6\text{H}_{9/2}$  ( $\text{Sm}^{3+}$ , 650 nm) transitions, respectively. All excitation spectra show a series of broad bands located in the 250-370 nm wavelength range (**Figure S1a,b**). The high similarities between these different excitation spectra indicate that the electronic states located in the common chromophoric part of the MC scaffold in  $[\text{MC:Ln}]$  are used to sensitize  $\text{Tb}^{3+}$  and  $\text{Sm}^{3+}$  via an antenna effect.<sup>[8]</sup>

Emission spectra of  $[\text{MC:Sm}]\text{@PS/NH}_2$ ,  $[\text{MC:Tb}]\text{@PS/NH}_2$  and  $[\text{MC:Sm,Tb}]\text{@PS/NH}_2$  collected upon 340 nm excitation at room temperature show the corresponding typical emission bands of  $\text{Tb}^{3+}$  (490 nm [ $^5\text{D}_4 \rightarrow ^7\text{F}_6$ ], 545 nm [ $^5\text{D}_4 \rightarrow ^7\text{F}_5$ ], 570 nm [ $^5\text{D}_4 \rightarrow ^7\text{F}_4$ ], and 620 nm [ $^5\text{D}_4 \rightarrow ^7\text{F}_3$ ]) and  $\text{Sm}^{3+}$  (562 nm [ $^4\text{G}_{5/2} \rightarrow ^6\text{H}_{5/2}$ ], 600 nm [ $^4\text{G}_{5/2} \rightarrow ^6\text{H}_{7/2}$ ], 645 nm [ $^4\text{G}_{5/2} \rightarrow ^6\text{H}_{9/2}$ ], and 700 nm [ $^4\text{G}_{5/2} \rightarrow ^6\text{H}_{11/2}$ ]). Partial overlaps can be observed between the emission bands related to the  $^5\text{D}_4 \rightarrow ^7\text{F}_5$  ( $\text{Tb}^{3+}$ ) and  $^4\text{G}_{5/2} \rightarrow ^6\text{H}_{5/2}$  ( $\text{Sm}^{3+}$ ) transitions, and the  $^5\text{D}_4 \rightarrow ^7\text{F}_4$  ( $\text{Tb}^{3+}$ ) and  $^4\text{G}_{5/2} \rightarrow ^6\text{H}_{7/2}$  ( $\text{Sm}^{3+}$ ) transitions (**Figure S2**).

The study of the temperature changes through the emission intensity of  $[\text{MC:Sm,Tb}]\text{@PS/NH}_2$  in the physiological range (ca 298-328 K, 25-55 °C) was performed under 340 nm excitation (**Figure 2**). The integrated intensities of the emission bands related to the  $^5\text{D}_4 \rightarrow ^7\text{F}_{6,3}$  transitions of  $\text{Tb}^{3+}$  and the  $^4\text{G}_{5/2} \rightarrow ^6\text{H}_{9/2}$  transition of  $\text{Sm}^{3+}$  were monitored (**Figure 3a**). The luminescence intensities collected on two  $\text{Tb}^{3+}$  transitions ( $^5\text{D}_4 \rightarrow ^7\text{F}_{6,3}$ ) remain the same or show a slight increase from 298 K to 303 K and are followed by a significant decrease upon further heating up to 328 K. The intensity of the  $\text{Sm}^{3+}$ -based  $^4\text{G}_{5/2} \rightarrow ^6\text{H}_{9/2}$  transition is approximately constant across the temperature range examined (**Figure 3a**).



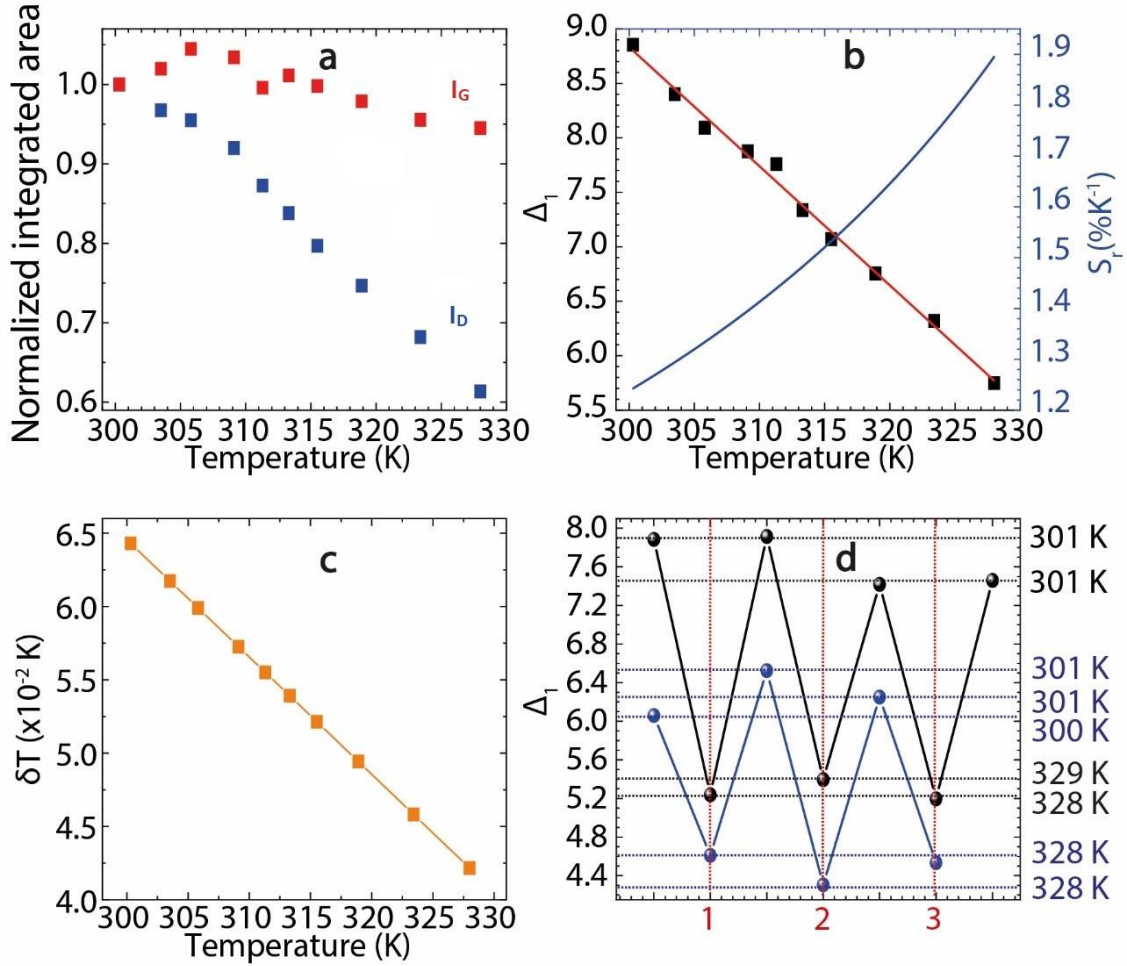
**Figure 2.** Luminescence intensities collected on 10 mg/mL aqueous suspension of  $[\text{MC:Sm,Tb}]\text{@PS/NH}_2$  beads upon excitation at 340 nm at temperatures

ranging from 298 to 328 K. The transitions are labeled in black for Tb<sup>3+</sup> and in blue for Sm<sup>3+</sup>.

The relationship between Tb<sup>3+</sup> and Sm<sup>3+</sup> integrated emission intensities can be used as a ratio-thermometric measurements in order to evaluate the temperature of the [MC:Sm,Tb]@PS/NH<sub>2</sub>

environment. We define  $\Delta_1 = I_D/I_G$  where  $I_G$  and  $I_D$  are the integrated areas of the  ${}^4G_{5/2} \rightarrow {}^6H_{9/2}$  (Sm<sup>3+</sup>) and  ${}^5D_4 \rightarrow {}^7F_6$  (Tb<sup>3+</sup>) transitions, respectively. The temperature evolution of  $\Delta_1$  from 298 K to 328 K can be fitted as a linear function is shown in **Figure 3b**.

From this fitting process, the relative sensitivity ( $S_r$ ) can be estimated according to the equation:



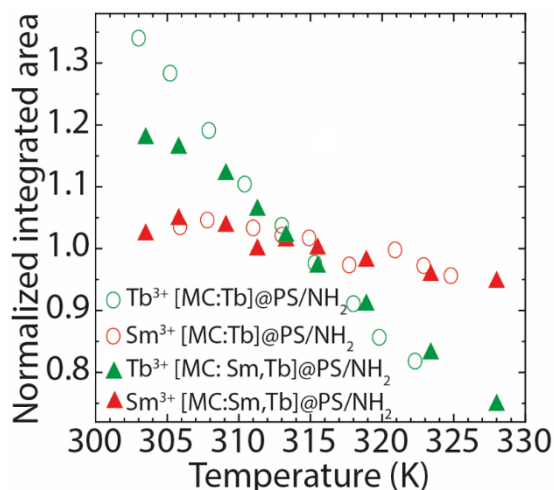
**Figure 3.** Thermometric behavior of the 10 mg/mL aqueous suspension of [MC:Sm,Tb]@PS/NH<sub>2</sub> beads upon excitation at 340 nm in the temperature range 298 - 328 K. **(a)** Temperature evolution of  $I_G$  (Sm<sup>3+</sup>,  ${}^4G_{5/2} \rightarrow {}^6H_{9/2}$ ) (red) and  $I_D$  (Tb<sup>3+</sup>,  ${}^5D_4 \rightarrow {}^7F_6$ ) (blue) from 298 K to 328 K. **(b)** The experimental thermometric parameter  $\Delta_1$  is given in black, while the fitted  $\Delta_1$  is given by the red curve and  $S_r$  is shown by the blue curve. **(c)** The temperature uncertainty,  $\delta T$ , was calculated using the thermometric parameter  $\Delta_1$ . **(d)** The temperature cycling experiment was carried out twice with an intermediary period of 3 months. The black and blue dots represent the first and second experiments respectively, showing reversibility around 99.89% and 99.92% in 3 consecutive cycles.

$$S_r = \frac{1}{\Delta} \frac{\partial \Delta}{\partial T} \quad (1)$$

Temperature uncertainties ( $\delta T$ , **Figure 3c**) were calculated as:

$$\delta T = \frac{1}{S_r} \frac{\delta \Delta}{\Delta} \quad (2)$$

Where  $\delta \Delta$  is derived from the experimental uncertainty.<sup>[5]</sup> This system demonstrates a  $\delta T < 0.07$  K throughout the examined range and a maximum  $S_r = 1.9$  % K<sup>-1</sup> at 328 K (**Figure 3b**). The thermometric behavior is similar whether using the  ${}^5D_4 \rightarrow {}^7F_3$  or  ${}^5D_4 \rightarrow {}^7F_6$  Tb<sup>3+</sup> transition (**Figures S4, S5 and Table S1**), however the  ${}^5D_4 \rightarrow {}^7F_6$  emission is used here due to an overall lower dispersion of  $\delta T$ .



**Figure 4.** Integrated emission signals of  $\text{Sm}^{3+}$  ( $^4\text{G}_{5/2} \rightarrow ^6\text{H}_{9/2}$ ) and  $\text{Tb}^{3+}$  ( $^5\text{D}_4 \rightarrow ^7\text{F}_6$ ) in  $[\text{MC:Sm}]@PS/\text{NH}_2$ ,  $[\text{MC:Tb}]@PS/\text{NH}_2$ , and  $[\text{MC:Sm,Tb}]@PS/\text{NH}_2$  samples normalized to the average integrated intensity. The emission intensities are very similar between the mixed and mono-lanthanide  $\text{Tb}^{3+}/\text{Sm}^{3+}$  samples.

To evaluate the mechanisms of nanothermometer action, the luminescence lifetimes and intensities of  $[\text{MC:Sm}]@PS/\text{NH}_2$ ,  $[\text{MC:Tb}]@PS/\text{NH}_2$ , and  $[\text{MC:Sm,Tb}]@PS/\text{NH}_2$  were measured as a function of temperature. Since the integrated intensities of  $\text{Sm}^{3+}$  bands are fairly similar when comparing the  $[\text{MC:Sm}]@PS/\text{NH}_2$  and  $[\text{MC:Sm,Tb}]@PS/\text{NH}_2$  (**Figure 4**), there is no significant energy transfer from  $\text{Tb}^{3+}$  to  $\text{Sm}^{3+}$ , corroborated by theoretical calculations (Ln-to-Ln energy transfer section in the Supporting Information).

Experimental emission decays of  $\text{Sm}^{3+}$  measured on the  $^4\text{G}_{5/2}$  level on  $[\text{MC:Sm}]@PS/\text{NH}_2$  and  $[\text{MC:Sm,Tb}]@PS/\text{NH}_2$  are both best fitted with bi-exponential functions resulting in individual lifetime values that can be considered as temperature independent (**Figure S6**, **Tables S3**, **S4**).

The temperature dependences of integrated intensities of  $\text{Tb}^{3+}$  emission bands for  $[\text{MC:Tb}]@PS/\text{NH}_2$  and  $[\text{MC:Sm,Tb}]@PS/\text{NH}_2$  samples are comparable, however changes are more significant for the former sample (**Figure 4**). There is a notable decrease in integrated emissive intensity as temperature increases. There are two distinct observed luminescence lifetimes of the  $\text{Tb}^{3+}$  excited  $^5\text{D}_4$  level (**Figure S7** and **Table S5**, **S6**). Globally, we can notice a decrease in observed luminescence lifetimes as temperature increases.

Because the MCs are embedded in 100 nm polystyrene beads, they may experience different environments that may induce complex interactions. More specifically, we must take into account that MCs located in the core of the beads have less motional freedom and are more protected from interactions with solvent molecules than those located closer to the surface. This could explain why luminescence decays of  $^4\text{G}_{5/2}$  and  $^5\text{D}_4$  emitting levels are biexponential. Indeed, luminescence decays are monoexponential for the  $\text{Sm}^{3+}$  ( $\tau_{\text{obs}} = 117(1)$

$\mu\text{s}$ ) and  $\text{Tb}^{3+}$  ( $\tau_{\text{obs}} = 1410(1)$   $\mu\text{s}$ ) MCs in the solid state.<sup>[17]</sup> These observed solid state lifetimes are longer but close to the corresponding 'longer' lifetime values found for aqueous suspension of  $[\text{MC:Tb}]@PS/\text{NH}_2$ ,  $[\text{MC:Sm}]@PS/\text{NH}_2$ , and  $[\text{MC:Sm,Tb}]@PS/\text{NH}_2$  beads.<sup>[14]</sup>

This nonradiative relaxation is derived from back-transfer to the triplet state of the salicylhydroxamate ligand. The ligand triplet state was previously determined in the solid state as  $E_{\text{T}}^* = 21,980$   $\text{cm}^{-1}$  via phosphorescence spectra.<sup>[17]</sup> The intramolecular energy transfer (IET) from ligands states to the  $\text{Tb}^{3+}$  in  $[\text{MC:Tb}]@PS/\text{NH}_2$  were estimated using the theory introduced by Malta *et al.*<sup>[18,19]</sup> The theoretical analysis (Supporting Information) indicates that the sensitization energy comes from the singlet state instead of the triplet one. This is associated with the energetic positions of these donor states, the  $\text{T}_1$  state is not in a viable energetic position (the best acceptor state is  $^7\text{F}_6 \rightarrow ^5\text{D}_4$  with  $\Delta E = 1536$   $\text{cm}^{-1}$ ) while the  $\text{S}_1$  is in good resonance with three acceptor states:  $^7\text{F}_6 \rightarrow ^5\text{H}_7$  ( $\Delta E = -129$   $\text{cm}^{-1}$ ),  $^7\text{F}_5 \rightarrow ^5\text{H}_6$  ( $\Delta E = 407$   $\text{cm}^{-1}$ ), and  $^7\text{F}_5 \rightarrow ^5\text{H}_5$  ( $\Delta E = -469$   $\text{cm}^{-1}$ ). By selection rules on the quantum number  $J$ , the last three are allowed for the exchange mechanism while  $^7\text{F}_6 \rightarrow ^5\text{D}_4$  is forbidden by the same mechanism. The  $^7\text{F}_5$  level is also considered in the calculations due to an abnormally longer lifetime and an important role in the IET process.<sup>[20–23]</sup> Once the energy populates  $\text{Tb}^{3+}$  by the ligand's  $\text{S}_1$  level, the population in higher  $\text{Tb}^{3+}$  states tends to decay non-radiatively until reaching the emissive level of  $\text{Tb}^{3+}$  ( $^5\text{D}_4$ ). In this process, non-radiative energy losses occur in intermediate energy levels through backward energy transfer to  $\text{T}_1$ . This is what happens when the populations reach the  $^5\text{G}_5$  and  $^5\text{G}_6$  levels, donating back the energy to the ligand  $\text{T}_1$  state with a rate on the order of  $8 \times 10^6$   $\text{s}^{-1}$  in the pathways involving the  $^5\text{G}_{5,6} \rightarrow ^7\text{F}_{5,6}$  transitions (also dominated by the exchange mechanism). Indeed, another study demonstrated that  $\text{Tb}^{3+}$ -ligand triplet energy transfer is an effective channel for  $\text{Tb}^{3+}$  thermal emission dependence.<sup>[14]</sup>  $\text{Sm}^{3+}$ , with a lower energy emissive state ( $^4\text{G}_{5/2} \rightarrow ^6\text{H}_{5/2}$ ), is further from the ligand triplet state with a forward IET rate of  $1.9 \times 10^{10}$   $\text{s}^{-1}$  and therefore less likely to back-transfer energy ( $\sim 70$   $\text{s}^{-1}$ ) thus explaining its temperature-constant lifetimes.

The performance of this novel generation of  $[\text{MC:Sm,Tb}]@PS/\text{NH}_2$  thermometer as an aqueous suspension has been compared to other nanothermometers incorporating two different visible-emitting  $\text{Ln}^{3+}$  ions (**Table S2**). The  $[\text{MC:Sm,Tb}]@PS/\text{NH}_2$  beads analyzed in the physiological temperature range exhibit generally comparable performances to most solid state ratiometric thermometers (**Table S2**), however several solid state ratiometric systems offersuperior thermal sensitivity in the physiological temperature range. These systems, including metal-organic frameworks<sup>[24,25]</sup> or nanoparticles,<sup>[26]</sup> offer high sensitivity and some modifiability, but they are inherently solid state systems requiring non-miniscule dimensions for stability, and which often depend upon energy transfer between ions for the



thermometric mechanism. Although [MC:Sm,Tb]@PS/NH<sub>2</sub> was prepared as molecular units within nanobeads to confer biocompatibility, we can assume that this system mainly behave as discrete molecular units (especially in respect to sensitization and emission). This is a fresh approach to Ln<sup>3+</sup> based thermometry and provides another avenue for future applications such as cellular thermal imaging.

This mixed Sm<sup>3+</sup>-Tb<sup>3+</sup> metallacrown system has demonstrated behavior as a ratiometric luminescent molecular thermometer with S<sub>r</sub> of 1.9 %K<sup>-1</sup> at 328 K and is an effective nanothermometer for the physiological temperature regime with  $\delta T$  measured <0.045 K at 328 K. This is among the most sensitive visible emission based nanothermometers of any type in the physiological range, and is especially notable for being molecular-based and water-stable. These properties are highly promising in respect to temperature sensitivity and precision while opening the possibility for enhanced spatial resolution.

Several metallacrowns are capable of sensitizing Ln<sup>3+</sup> emission from the UV-visible to the near-infrared domains. Several of them have shown excellent resistance to photobleaching.<sup>[17,27–29]</sup> Future work will examine in greater details their thermometric potential. Additionally, we will seek to modify these systems to overcome the present limitations of sensitization in the UV and requirement to solubilize in nanobeads for aqueous stability.

This study performed with metallacrowns constitutes a broader demonstration of the effectiveness of a molecular approach to nanothermometry. As opposed to Ln<sup>3+</sup>-doped solid-state systems, molecules possess a uniform environment surrounding each luminescent cation. This can lead to more consistent emitting processes and thus reduced uncertainty related to each measurement.

In addition to the nanometer sizes of these novel thermometers, MC molecules are also relatively easy to modify using the wealth of chemical techniques with a limited synthetic effort. Such high level of tunability could lead to the improvement of lanthanide sensitization and thermometric sensitivity,<sup>[30]</sup> control the regions of thermometric effectiveness, enhance solubility, or even promote cellular uptake or binding via appendages such as antibodies.<sup>[31]</sup> These newly developed metallacrown nanothermometers illustrate the promise of such an approach.

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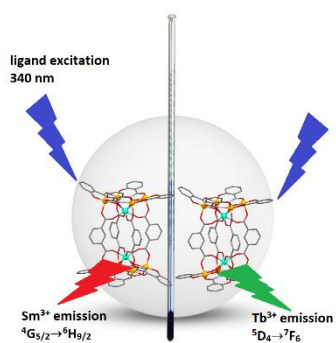
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## Entry for the Table of Contents



**Metallacrown based thermometry.** Mixtures of luminescent  $\text{Ga}^{3+}/\text{Tb}^{3+}$  and  $\text{Ga}^{3+}/\text{Sm}^{3+}$  metallacrowns proved to be highly sensitive luminescent molecular thermometers. These were placed in polystyrene nanobeads for aqueous stabilization and demonstrate the promise of a molecular approach to nanothermometry.