Lanthanide luminescent gold nanoparticles: pH-driven self-assembly formation between Eu(III)-cyclen conjugated AuNPs and sensitising β-diketonate antenna in water

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The formation of a self-assembly between water soluble gold nanoparticles **AuNP-1**.**Eu**, functionalised with a heptadentate macrocyclic Eu(III) cyclen conjugate *via* an alkyl thiol spacer, and a naphthalene β-diketone antenna was investigated as a function of pH in water. In the study, the changes in the absorption spectra of the antenna and the gold surface plasmon resonance band, the fluorescence and the delayed Eu(III) emission of the self-assembly were all monitored. We demonstrate that the Eu(III) emission arising from the self-assembly formation on **AuNP** is significantly modulated as a function of pH, where within the physiological pH range, the emission is 'switched on' and that a direct connection can be made between theses changes and the quenching in the antenna as a function of pH.

The development of functional lanthanide complexes and conjugates is of great current interest in supramolecular chemistry, where examples of luminescent switches, sensors, logic gate mimics, cellular imaging agents and the formation of MRI and dual MRI-luminescent contrast agents have all been demonstrated.[1–6] For practical application of such devices, for instance for biological applications, it is advantageous that such devices are either incorporated into solid supports, such as water permeable hydrogels,[7] films and sol-gels,[8] or by conjugating lanthanide complexes to nanoparticles (**NP**),[9,10] using surface modifications. In particular, the latter could lead to high loading of probes/sensors/imaging agents, *etc*, with concomitant modulation in their luminescent efficiency as well as improving both the selectivity and sensitivity of such a device. Such surface modifications also allow for the targeting of larger biological structures through multiple binding site interactions.[11] To date only a few examples of functionalised lanthanide based **NPs** have been developed, most of which have been based on the use of silica[12] and polystyrene[13] **NPs**. Very few examples of gold based lanthanide **NPs** have been developed.[13,14]

Recently, we demonstrated that heptadentate Eu(III) or Tb(III) macrocyclic cyclen complexes, which contain two metal bound water molecules, form a luminescent ternary complex in aqueous solution with either aliphatic or aromatic carboxylates,[15] or β-diketones,[16] such as **2**, which function as a sensitising antennae, displacing the coordinating water molecules from the metal centers.[17] Conjugation of an alkyl thiol group into **1**.**Eu** enabled the adsorption of **1**.**Eu** onto the surface of gold **NPs**, which led to the formation of water soluble gold nanoparticles, **AuNP-1**.**Eu**, with an average diameter of 5 nm. This system was further structurally modified, by reacting it with *ca.* 250 equivalents of **2**, yielding **AuNP-1**.**Eu-2**, which also resulted in the formation of highly luminescent, red emitting (arising from the Eu(III)) **NPs** upon excitation of the antenna.[18] We further demonstrated that **AuNP-1**.**Eu-2** could be used to sense biologically important anions in competitive media, through displacement assays. Herein, we demonstrate that the formation of **AuNP-1**.**Eu-2**, from **AuNP-1**.**Eu** and **2**, is highly pH sensitive, by observing the changes in the ground and the excited state of the β-diketone antenna, as well as in the delayed lanthanide luminescence emission. We show that within the physiological pH window, the emission arising from the antenna is "switched on", and that the self-assembly formation occurs over a wide pH range.

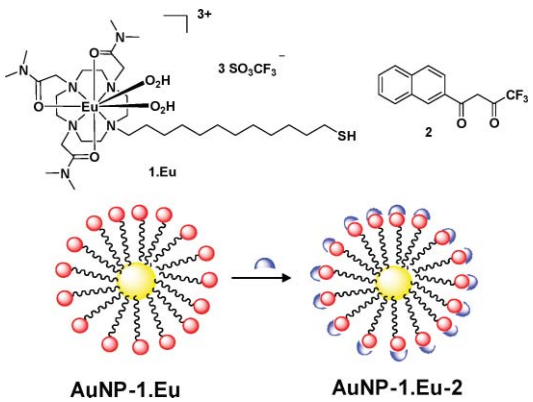

Fig. 1 The structures of **1**.**Eu** and the resulting functionalised gold nanoparticle **AuNP-1**.**Eu**, which upon reaction with **2** (shown as blue crescent) forms ternary complexes with **1**.**Eu** (shown as red balls) on the surface of **AuNP-1**.**Eu**, resulting in the formation of **AuNP-1**.**Eu-2**.

Results and discussion

We have previously reported the synthesis of **1**.**Eu** and the gold nanoparticle functionalised system **AuNP-1**.**Eu**.[18] As **1**.**Eu** does not contain a sensitising antenna, the hydration state of the complex was determined upon direct excitation of the Eu(III) metal center at 395 nm, and the lifetimes of the Eu(III) excited state $^5D_0$ were measured in H_2O and D_2O, as $\tau_{H2O} = 0.39$ ms and $\tau_{D2O} = 0.89$ ms. This confirmed the presence of two metal bound water

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molecules ($q \sim 2$).[19] Similarly, upon titrating **1**.**Eu** with **2** at pH 7.4 and exciting into the antenna, the formation of a ternary complex between the two was monitored by observing the appearance of the Eu(III) emissions at 595, 616, 653, 685 and 700 nm, due to the deactivation of $^5D_0 \rightarrow {}^7F_J$ ($J = 1$, 2, 3 and 4), see Fig. 2. From these changes it was clear that the hypersensitive $\Delta J = 2$ was most affected, confirming direct coordination to Eu(III), and resulting in the formation of a 1:1 ternary complex between the antenna and **1**.**Eu** (see Fig. 2, inset). The displacement of the two metal bound water molecules from **1**.**Eu** was further confirmed by lifetime measurements which gave $\tau_{H2O} = 0.28$ ms and $\tau_{D2O} = 0.30$ ms, from which a hydration state of $q = 0$ was determined.

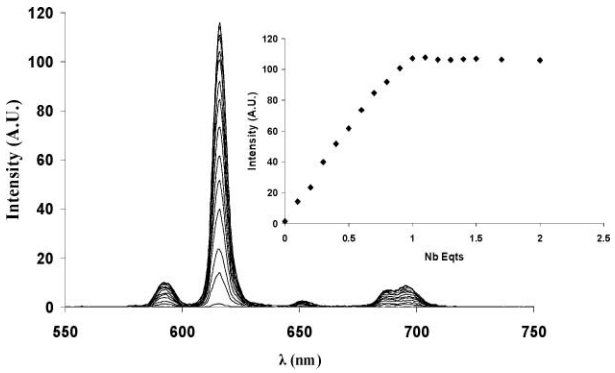

Fig. 2 Changes in the Eu(III) emission of **1**.**Eu** upon titration with **2** at pH = 7.4 (0.1M HEPES), in the presence of 0.1M TMACl. *Inset:* The changes in the $\Delta J = 2$ transition *vs.* equivalents of **2** added.

In our previous work, we had shown that at pH 7.4, **AuNP-1**.**Eu** also formed ternary complexes with **2**. Titrations showed that *ca.* 250 complexes were formed per **NP**. To evaluate the pH dependence of the self-assembly formation between **AuNP-1**.**Eu** and **2**, a solution of **AuNP-1**.**Eu** (0.2 μM Eu(III) sites; 8×10^{-4} μM **NPs**) was prepared and a 49.5 μM of **2**, *ca.* 250 equivalents, added. By excitation into the antenna at 336 nm, the characteristic Eu(III) emission arising from the $^5D_0$ excited state was observed, which was clearly visible to the naked eye under a UV lamp, demonstrating the successful formation of **AuNP-1**.**Eu-2** around neutral pH. The excited state decay from this emission was best fitted to a double exponential decay, giving lifetimes of $\tau_1 = 0.19$ ms and $\tau_2 = 0.67$ ms, indicating that the gold surface did give rise to some quenching of $^5D_0$. The Eu(III) emission arising from these **NPs** was also clearly visualized in the solid state using confocal fluorescence microscopy, as shown in Fig. 3.

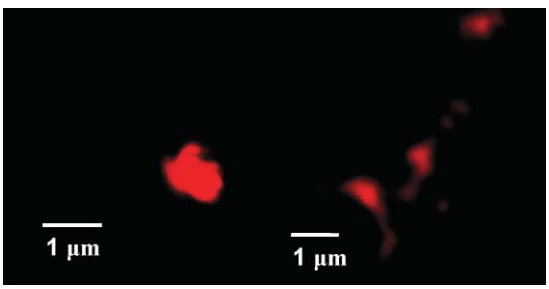

Fig. 3 Confocal fluorescence images of **AuNP-1**.**Eu-2**, showing the Eu(III) emission, arising from aggregated NPs after evaporation from aqueous pH 7.4 solution.

We next carried out pH titrations on a sample of **AuNP-1**.**Eu** (0.2 μM), in water, by firstly adjusting the pH of the solution to 11, followed by the addition of 250 equivalents of **2** (50 μM in MeOH, based on Eu(III) sites), and observing the changes in the absorption, fluorescence and the delayed Eu(III) emission of **AuNP-1**.**Eu**. The overall changes observed in the UV-Vis spectra are shown in Fig. 4, and demonstrate that significant changes occur in the absorption of the antenna. Significant changes are also observed for the gold surface plasmon resonance band centred at 534 (shown in the inset in Fig. 4) as a function of pH. The results depicted in Fig. 4 demonstrate that in alkaline solution, then at pH 10.2, two major absorption bands were centred at 336 and 250 nm and two shoulders appear at 290 and 247 nm, respectively. Moreover, the gold surface plasmon resonance band of **AuNP-1**.**Eu** was also observed (see later). Upon acidification, of this solution, only a small hyperchroism was observed for the 336 nm and the 250 nm bands at pH 7 while the surface plasmon resonance band was slightly blue shifted to 526 nm. Upon further acidification, significant changes were observed and at pH 3.6, the spectra displayed a major hyperchroism for the β-diketone transitions both at 250 nm (four fold enhancements) and at 290 nm (*ca.* 50%). The opposite effect were observed for the 336 nm band. However, no clear isosbestic points are observed, which could indicate some degree of aggregation of the antenna in solution, or reflect the binding of the β-diketonate to the surface of **AuNP-1**.**Eu**.

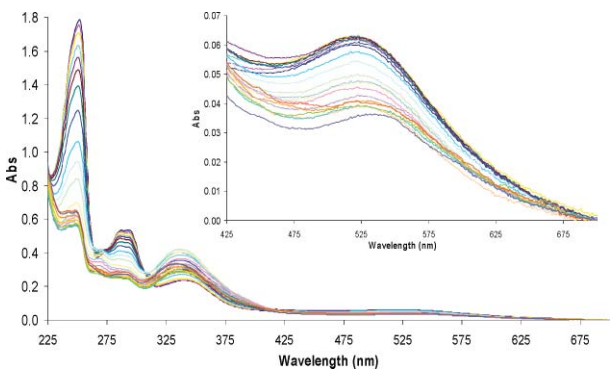

Fig. 4 The overall changes in the absorption spectra of **AuNP-1**.**Eu** (0.2 μM) and **2** (50 μM) as a function of pH from pH 10 → 3.6. *Inset*: The expanded spectra of the long wavelength absorbing surface plasmon resonance band as a function of pH.

The overall pH changes observed by plotting the absorbance at 336, 290 and 250 nm are shown in Fig. 5, and clearly demonstrate that most of the spectral changes occur within a pH window of 5–7, while some changes are also observed at more basic pH (>9). Indeed, these pH profiles mirror the results obtained for the pH titration of the antenna itself, and reflect the acidity of the α-protons of the β-diketone, due to the presence of the electron withdrawing CF_3 group. Due to the complexity of the system, we were unable to determine an accurate pK_a from these measurements. Nevertheless, an estimated value of $pK_a = 5.3$ can be obtained from these changes using:

$$pK_a(S_o) = pH - \log\frac{(Abs_{AH} - Abs_A)}{(Abs_A - Abs_{A-})}$$

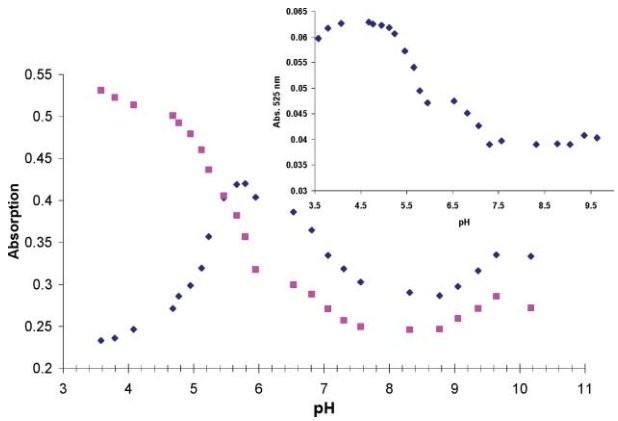

Fig. 5 Changes in the absorption spectra at 336 (◆) and 290 nm (■) of **AuNP-1**.**Eu** (0.2 μM), as a function of pH. *Inset:* The changes in the 525 nm gold surface plasmon resonance band.

where Abs_{AH}, Abs_{A} and Abs_{A-} are the absorbance of every solution, the absorbance of the protonated species and the absorbance of the deprotonated species, respectively. This value correlates well with that previously reported by Keller *et al.* of pK_a 6.23, which would enable the binding to the lanthanide centre.[21] By plotting the changes at 525 nm as a function of pH, shown as inset in Fig. 5, a pH profile similar to that observed for the band at 290 nm was obtained, demonstrating an almost 50% hyperchroism between pH 10 and 4 for the surface plasmon resonance band, and that the band was indeed affected by the changes in the antenna and hence showing a possible interaction between the surface of the **NP** and **2**.

The change in the fluorescence emission spectra of this system [**AuNP-1**.**Eu** (0.2 μM) and **2** (50 μM)] was also investigated in parallel as a function of pH. The overall changes are shown in Fig. 6, and demonstrate that the only visible emission arose from the changes in **2**, occurring with $\lambda_{max} = 460$ nm, upon excitation at 336 nm. Similar changes were observed upon exciting at 290 nm. The emission pH profile for changes occurring at 460 nm are shown as an inset in Fig. 6. The changes here occur mainly in the pH window of 4 → 6, where they mirror the changes observed for the antenna on its own and can be assigned to an excited state pK_a value of **2**, which is estimated to be *ca.* 4 from the changes observed,

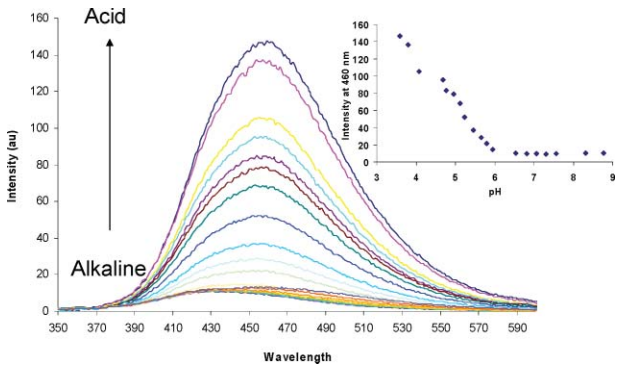

Fig. 6 Changes in the fluorescence emission spectra of **2** (50 μM) in the presence of **AuNP-1**.**Eu** (0.2 μM) as a function of pH from pH 10 → 3.6. *Inset:* The changes at 460 nm as a function of pH.

but unfortunately can not be determined accurately.[19] The blue shift observed from pH 6.5 is consistent with that observed for the antenna itself and the red shift observed after pH 9.5 may be attributed to dissociation or degradation of the self-assembly as previously observed with similar complexes.[16]

Having established that significant fluorescence changes were seen as a function of pH for the solution of **AuNP-1**.**Eu** and **2**, we next evaluated the changes in the lanthanide emission arising from **AuNP-1**.**Eu**, under identical conditions to those described above. As discussed before, no significant emission was observed from **AuNP-1**.**Eu** in the absence of the antenna, or using an antenna such as flavin monophosphate which, due to unfavourable excited state energy, was unable to sensitize the Eu(III) $^5D_0$ excited state. Hence only the self-assembly formation from **AuNP-1**.**Eu** and **2** was expected to give rise to Eu(III) emission. The changes observed in the Eu(III) emission of **AuNP-1**.**Eu** and **2** are shown in Fig. 7, and clearly demonstrate the formation of such a self-assembly. Moreover, the changes indicated that the self-assembly formation is highly pH dependent, and that all of the $^5D_0 \rightarrow {}^7F_J$ ($J = 1$, 2, 3 and 4) transitions are being, 'switched on' in more acidic media, upon excitation at the 336 nm, the λ_{max} of the antenna. The inset in Fig. 7 shows the changes observed upon excitation at 290 nm, the results of which mirror that seen upon excitation at 336 nm.

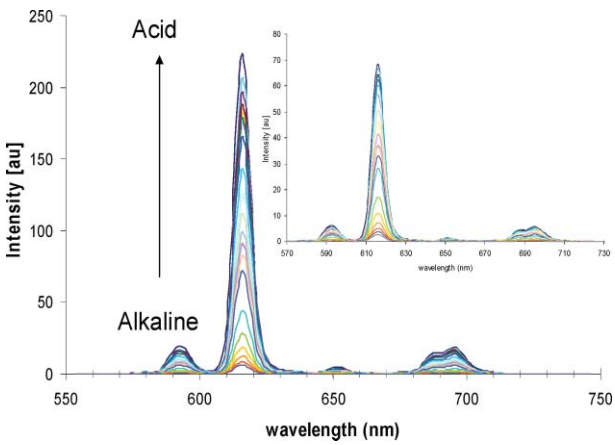

Fig. 7 Changes in the Eu(III) emission of **AuNP-1**.**Eu** (0.2 μM) and **2** (50 μM) as a function of pH from pH 10 → 3.6, upon excitation at the antenna at 336 nm. *Inset*: The changes observed in the Eu(III) emission upon excitation at 290 nm as a function of pH.

From Fig. 7, it is clear that the greatest changes are observed for the $^5D_0 \rightarrow {}^7F_2$ transition, centred at 616 nm, which is sensitive to the change in the local coordination environment of the ion. Such dramatic changes are an indication that **2** is coordinating directly to the ion centre.

The changes observed for all the transitions are plotted in Fig. 8 and clearly demonstrate the formation of the self-assembly. Those changes can be described to occur over two possible pH windows: between pH 7–9.5 and between *ca.* 4.5–6.5. While the changes occurring within the acidic media can be attributed to the antenna (which showed the same enhancement in the fluorescence), previous work in the area has shown that either heptadentate or octadentate amide functionalised macrocyclic cyclen lanthanide complexes, possessing a single or two metal bound water molecules, can undergo complex deprotonation

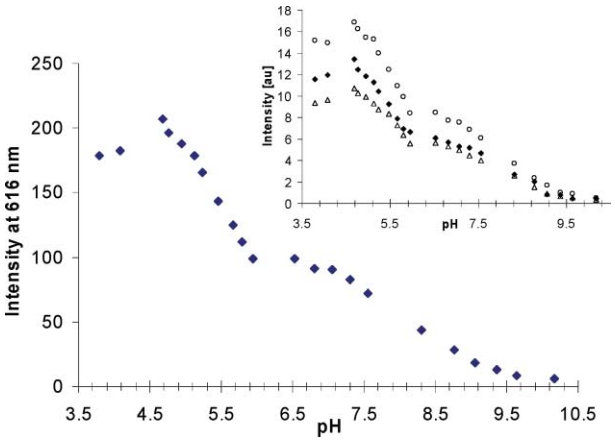

Fig. 8 Changes in the Eu(III) emission at 616 nm of **AuNP-1**.**Eu** (0.2 μM) and **2** (50 μM) as a function of pH from pH 10 → 3.6. *Inset:* the changes in the 592 (○), 688 (◆) and the 696 (△) nm bands as a function of pH.

processes where both the amides as well as the metal bound water molecules can be deprotonated.[22] Based on this information, we propose that the changes taking place within the alkaline region are significantly influenced by deprotonation of the metal complex itself or dissociation of the self-assembly. It should also be noted that the emission is not quenched in acidic media as previously reported for the formation of a ternary complex between **2** and a similar cyclen Eu(III) complex which lacks the alkyl thiol chain.† This effect could be attributed to the proximity of the **NP** with the antenna which might be affecting each other as corroborated by the changes seen in the absorption spectra for the plasmon band resonance. While we were unable to determine accurate pK_as from this profile, it clearly indicates a complex pH behaviour for the self-assembly formation between **AuNP-1**.**Eu** and **2**, within the physiological pH window, where the emission is relatively pH independent.

To further investigate the pH dependent changes in the Eu(III) emission, we also measured the lifetime of the Eu(III) decay at various pHs. The results are shown in Table 1, and again, were best fitted to a double exponential decay. The results demonstrate that the major component (τ_2) does not change much throughout the titration, except around neutral pH. This could indicate that the ternary complex is also formed in alkaline media, but is not as emissive as was observed in acidic media, as the antenna emission is quenched within the same region, *c.f.* Fig. 6. The Eu(III) emission is thus 'switched on' in parallel with the ability of the antenna to populate the $^5D_0$ excited state more efficiently. We are currently in the process of developing related systems based on the use of pH controlled self-assembly formation of lanthanide based **AuNP**.‡

† UV-Vis titrations of **2** have shown that the extinction coefficient is higher in acidic media than in neutral or basic solution. Also the compound is more emissive in acidic solution as we demonstrated herein (Fig. 6). We propose that in acidic media the enol form of **2** binds and this is followed by deprotonation of the enol to generate the enolate, aided by the Lewis acid nature of the Eu(III) centre.

‡ The back pH titrations were also carried out, and the changes in the absorption spectra and the fluorescence emission as well as in the Eu(III) emission. All showed the dissociation of the self-assembly.

Table 1 Lifetimes measured from the Eu(III) emission of a solution of **AuNP-1**.**Eu** (0.2 μM) and **2** (50 μM) as a function of pH[a]

pH	τ_1 (ms)	τ_2 (ms)
3.8	0.14	0.67
5.7	0.15	0.60
7.0	0.12	0.47
7.4	0.19	0.67
9.0	0.11	0.59
9.9	0.08	0.58

[a] Excitation at 336 nm.

Conclusions

Herein, we have presented the results from our investigation into pH-controlled self-assembly formation between the Eu(III) based **AuNP-1**.**Eu** and the β-diketone **2**.

We have shown that the changes in the absorption spectra can be assigned to the deprotonation of the α-proton in **2**, but also to changes in the surface plasmon resonance band of the **AuNP**, which potentially could be due to aggregation effect that is pH dependent. The changes observed for the absorption spectra and the fluorescence emission spectra mirror that observed for the antenna itself. However, the most significant changes were observed in the lanthanide emission, which signified the formation of the desired self-assembly between **AuNP-1**.**Eu** and **2**, as a function of pH. While the fluorescence emission showed evidence for the deprotonation of the α-proton, the changes in the Eu(III) emission demonstrated the direct binding of the antenna to the Eu(III) ion in **AuNP-1**.**Eu**, and demonstrating the formation of lanthanide luminescent **AuNP**. These results also demonstrate that while the fluorescence of the antenna is enhanced in acid media, its ability to populate the Eu(III) excited states is also enhanced within the same pH window.

We are in the process of developing other such lanthanide based **NP** supramolecular device for use in luminescence imaging and sensing.

Experimental

Spectroscopic titrations

All absorption spectra were recorded on a Varian UV-Vis spectrophotometer and all luminescence spectra were performed on a Varian Carey Eclipse Fluorescence spectrophotometer.

The concentration of nanoparticles in a typical experiment was 0.2 mM in water, to which was added 250 eq of diketone **2** in MeOH (50 mM). The amount of MeOH added was always less than 1% of the total volume of the solution.

The pH titrations were carried out by adjusting the pH of a stock solution containing **AuNP-1**.**Eu** and **2**, by adding either NaOH or HCl. All the spectra were recorded after 5 min of equilibration time. The absorption spectra were recorded from 250 to 400 nm using excitation and emission slit widths of 1 nm with a medium scan speed. Fluorescence emission spectra were collected by exciting at 336 nm and scanning from 340 to 700 nm. Slit widths were 10 nm and 5 nm for excitation and emission respectively.

Time-delayed luminescence spectra were collected by exciting at 336 nm and scanning from 550 to 750 nm, with a delay time of

0.1 ms, a gate time of 10 ms, a data interval of 1 nm, an average time of 0.1 s and a decay time of 0.02 s. Slit widths were 5 nm for excitation and emission.

Europium luminescence lifetimes were measured by recording the decay of the emission intensity at 616 nm. The signals were analyzed as double-exponential decays.

Fluorescence imaging

Confocal fluorescence imaging was carried out by JM at The Confocal Microscopy Division of the School of Biochemistry and Immunology, Trinity College Dublin, using an Olympus FluoViewTM FV1000 laser scanning microscope, based on a 1 × 81 motorized inverted microscope, 3 confocal detectors and a transmitted light detector, AOTF laser control and 4 laser systems. The samples of **AuNP-1**.**Eu** were made up at a concentration of 5.0×10^{-6} M in H_2O at pH = 7.4 (HEPES buffer) and a samples of this solution (evaporated samples) imaged on a glass plate by observing the emission at 618 nm (the $\Delta J = 2$ band).

Acknowledgements

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