

# Activation of a PARACEST Agent for MRI through Selective Outersphere Interactions with Phosphate Diesters

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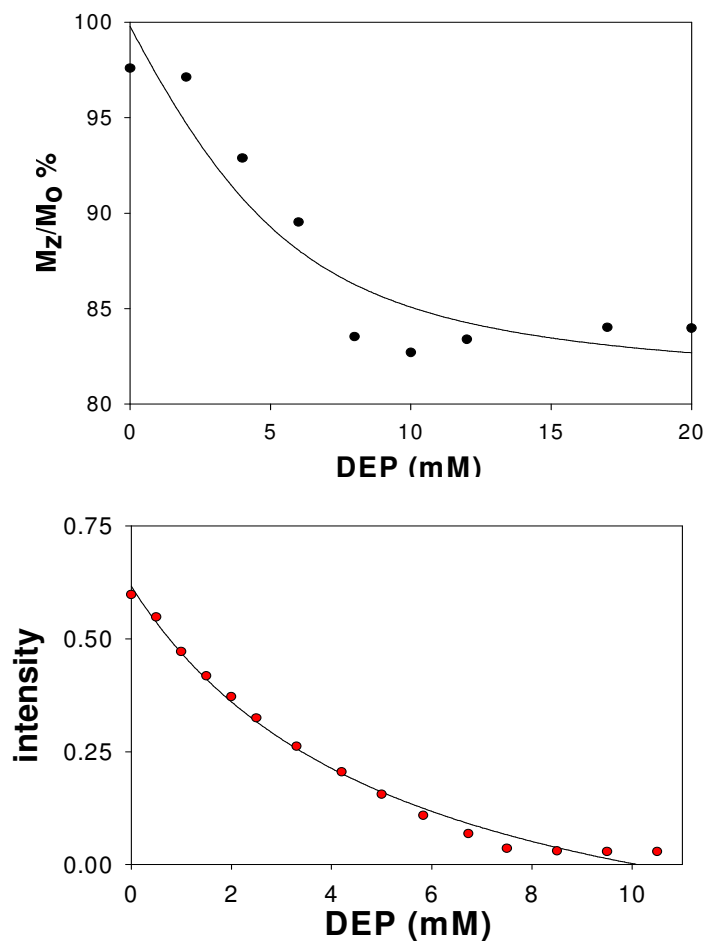


Figure S1. Top: binding isotherm from PARACEST spectra of 5.00 mM Yb(**S-THP**)<sup>3+</sup>, 20.0 mM buffer and 100 mM NaCl with addition of **DEP** at pH 7.0. Data was fit to eq S1 to give  $K_d=1.9$  mM ( $r^2=0.89$ ). Bottom: binding isotherm from the luminescence intensity of the  ${}^7F_0 \rightarrow {}^5D_0$  excitation peak at 577.7 nm ( ${}^5D_0 \rightarrow {}^7F_2$  emission) for 2.5 mM Eu(**S-THP**)<sup>3+</sup>, 20.0 mM buffer and 100.0 mM NaCl with **DEP** (0.50 mM to 11 mM) at pH 7.4. Data was fit to eq. S1 with  $K_d=2.8$  mM,  $r^2=0.99$ .

$$F = [A]_{\text{tot}} + [ML]_{\text{tot}} + K_d \quad \text{eq. S1a}$$

$$[MLA] = \frac{F - \sqrt{F^2 - 4[ML]_{\text{tot}}[A]_{\text{tot}}}}{2} \quad \text{eq. S1b}$$

$$X_{MLA} = [MLA]/[ML]_{\text{tot}} \quad \text{eq. S1c}$$

$$X_{ML} = 1 - X_{MLA} \quad \text{eq. S1d}$$

$$y = X_{ML}k_{ML} + X_{MLA}k_{MLA} \quad \text{eq. S1e}$$

$y = M_z/M_o$  %, saturation transfer effect from CEST spectra

$y$  = luminescence intensity for excitation spectra

ML = Ln(S-THP)<sup>3+</sup> complex; A = DEP anion; MLA is the complex of DEP with Ln(S-THP)<sup>3+</sup> and  $K_d$ =  
dissociation constant

$k_{ML}$  and  $k_{MLA}$  are determined from initial and final values, respectively, of luminescence intensity for luminescence titrations or percent water signal  $M_z/M_o$  % for CEST titrations.

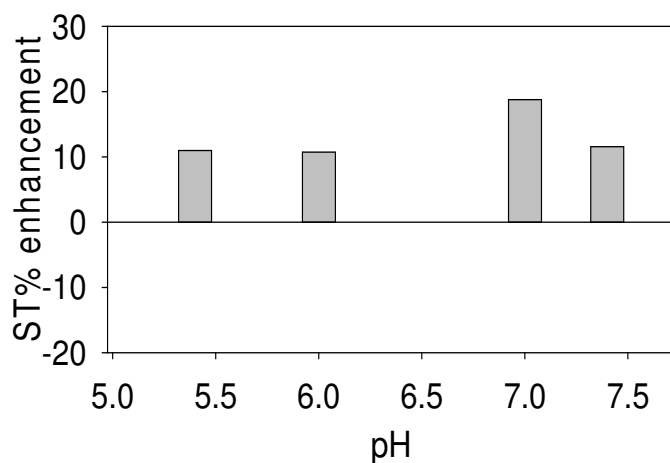


Figure S2. Data showing the difference between the PARACEST effect of a solution of Yb(S-THP)<sup>3+</sup> and DEP compared to that of a solution containing Yb(S-THP)<sup>3+</sup> alone as a function of pH in solutions containing 100 mM NaCl and 20 mM buffer. The ST% is shown at 21 ppm in solutions containing 5 mM Yb(S-THP)<sup>3+</sup> with 2 equivalents DEP compared to that in the absence of DEP.  $ST\% = (1 - M_z/M_o) \times 100$ .

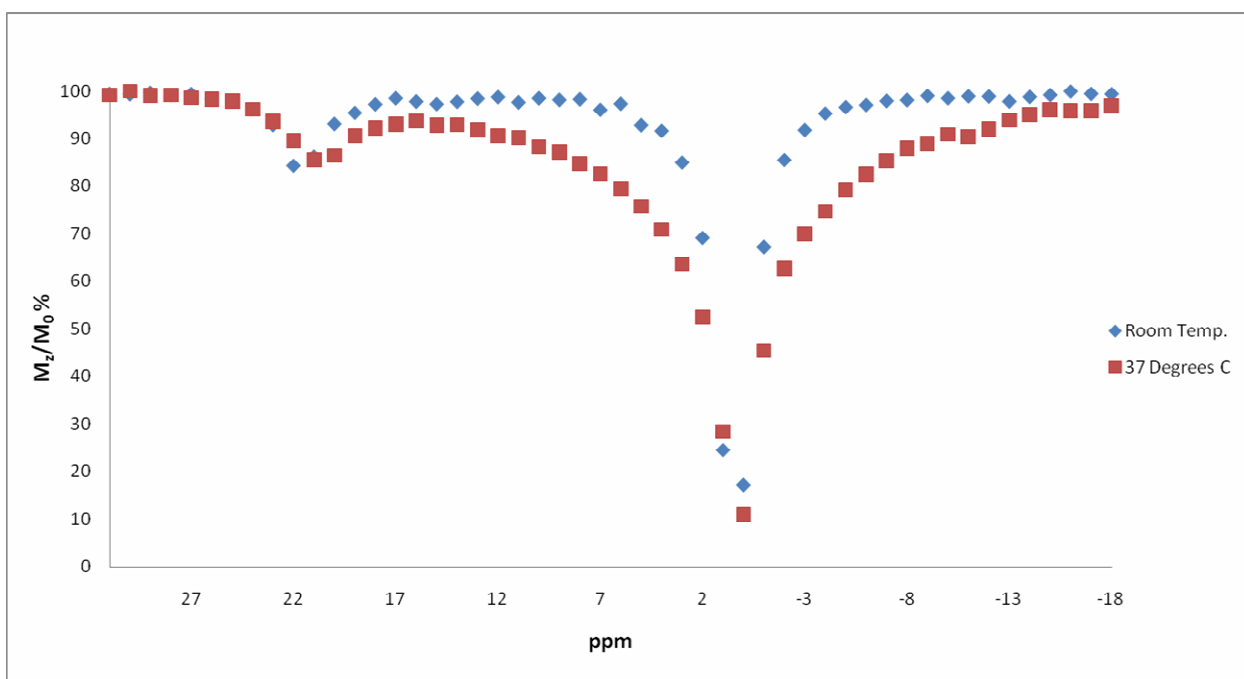


Figure S3. PARACEST spectra of 5 mM Yb(S-THP)<sup>3+</sup>, in 20 mM buffer, 100 mM NaCl at pH 7.0 and 10 mM DEP at room temperature (22 °C) as shown in blue and at 37 °C as shown in red.

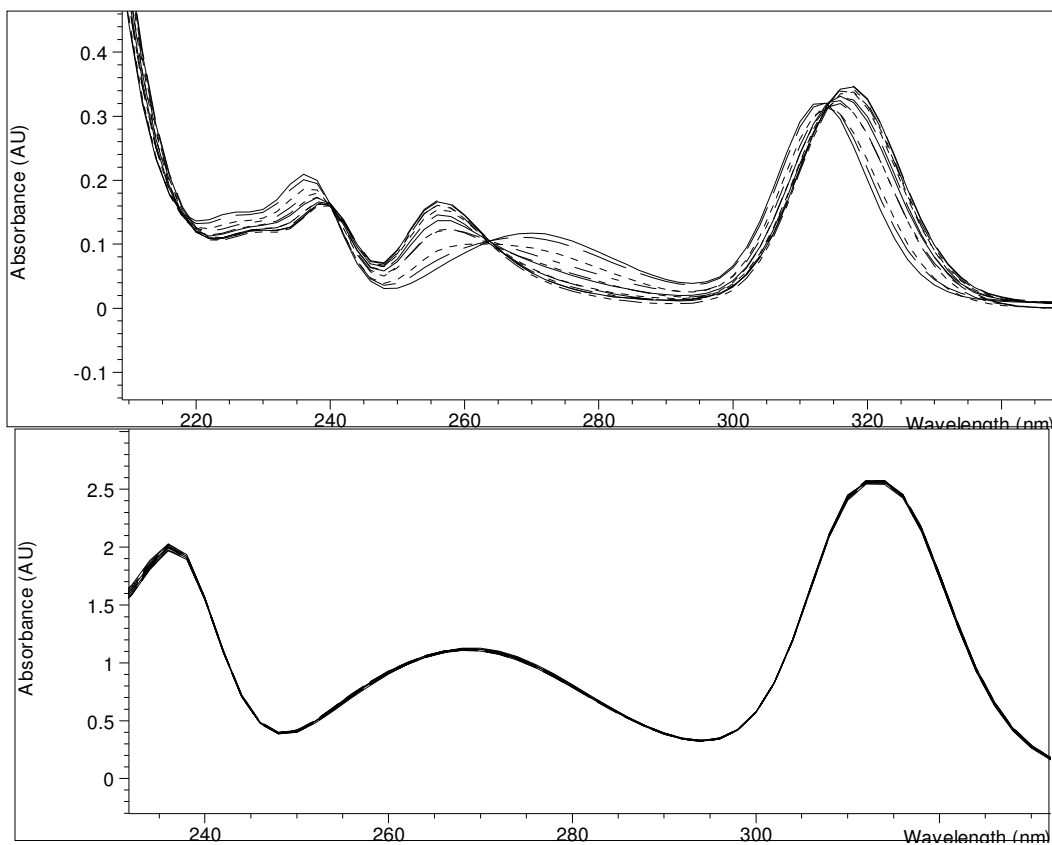
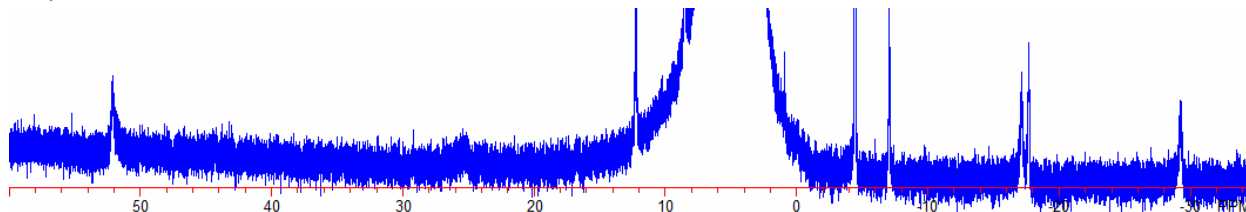
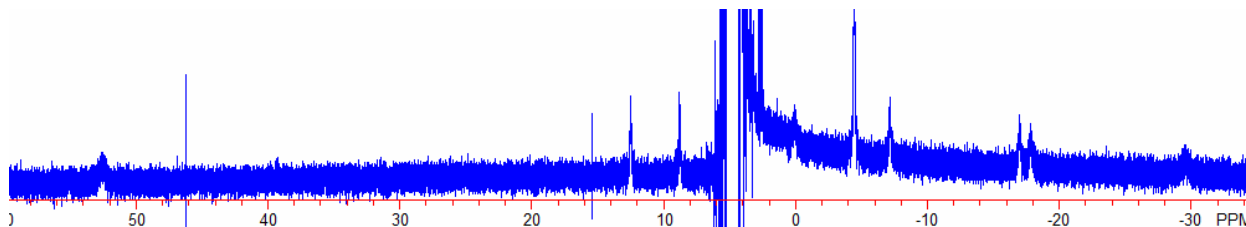


Figure S4. UV-vis spectra of 5 mM Ce(S-THP)<sup>3+</sup> in the presence of increasing concentrations of diethylphosphate (DEP) from 0, 1.00, 5.00, 10.00, 15.00, to 20.00 mM (lower spectrum showing no change) or upon addition of methylphosphate (MP) (upper spectrum) with 0.0, 1.00, 3.00, 5.00, 7.00, 10.00, 12.00, 15.00, 20.00, 25.00 mM MP at pH 6.5, 100 mM NaCl and 20 mM MES buffer.

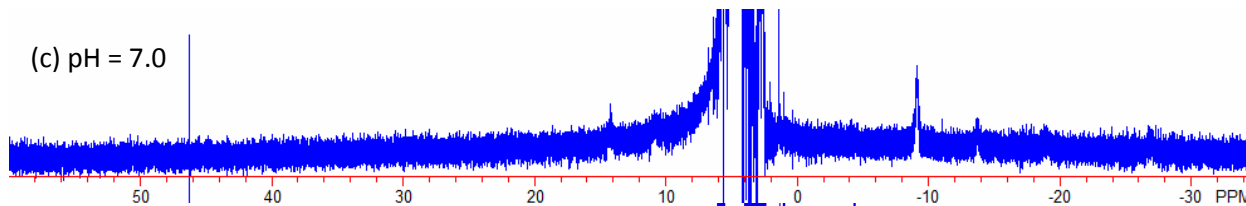
(a) pH = 0.8



(b) pH  
4.0



(c) pH = 7.0



(d) pH 7.0 and 10 mM **DEP**

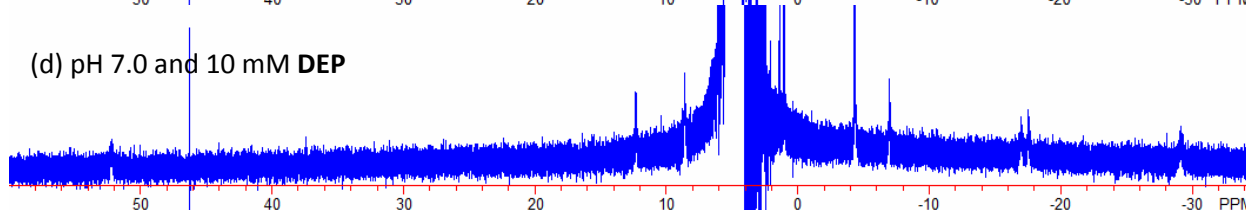
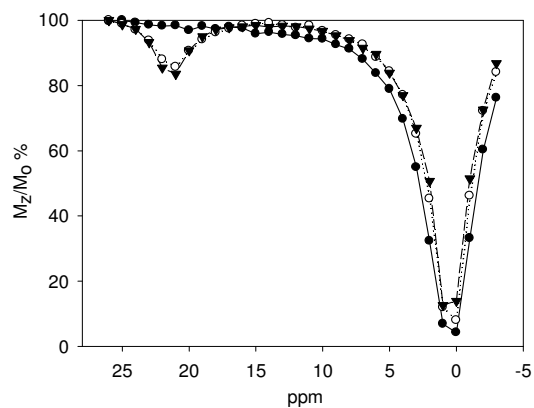
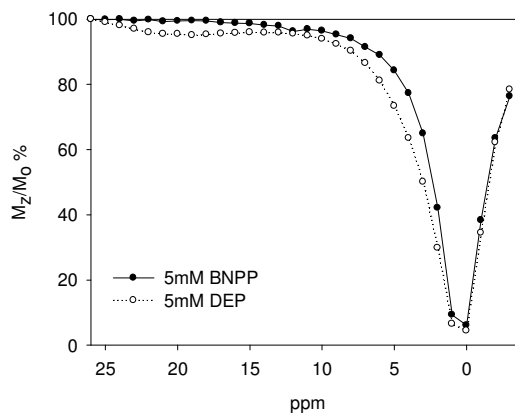


Figure S5.  $^1\text{H}$  NMR spectra of 5.00 mM  $\text{Yb}(\text{S-THP})^{3+}$  in  $\text{H}_2\text{O}$  at (a) pH 0.8 (showing hydroxyl protons at approximately 25 ppm) and (b) pH 4 without buffer and salt, and (c) pH 7.0 with 20.0 mM buffer and 100 mM NaCl, or (d) pH 7.0 with 20.0 mM buffer and 100 mM NaCl and 10 mM **DEP**. Resonances of exchangeable hydroxyl protons were only observed at pH < 1 in  $\text{H}_2\text{O}$  or in acetonitrile mixtures.<sup>9</sup>

(a)



(b)



(c)

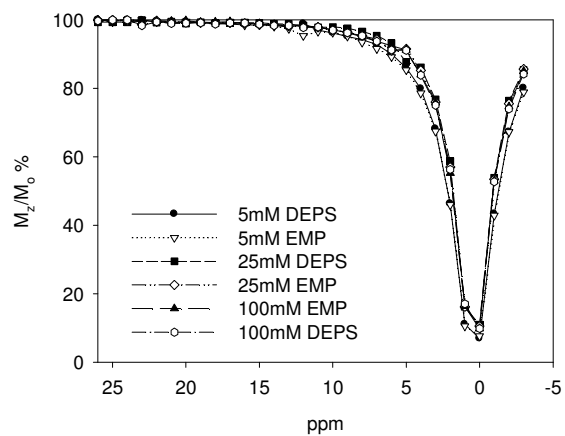


Figure S6. The CEST spectrum of 5.00 mM  $\text{Yb}(\text{S-THP})^{3+}$ , 20.0 mM MES and 100 mM NaCl at (a) pH 5.5 with addition of ( $\circ$ ) 5.00 mM **BNPP**, ( $\bullet$ ) 10.0 mM **3',5'-cAMP**, ( $\blacktriangledown$ ) 5.00 mM **DEP**. (b) pH 7.0 with addition of ( $\circ$ ) 5.00 mM **DEP**, ( $\bullet$ ) 5.00 mM **BNPP**. (c) pH 7.0 with addition of ( $\bullet$ ) 5.00 mM **DEPS**, ( $\nabla$ ) 5.00 mM **EMP**, ( $\blacksquare$ ) 25.0 mM **DEPS**, ( $\diamond$ ) 25.0 mM **EMP**, ( $\blacktriangle$ ) 100 mM **EMP**, ( $\circ$ ) 100 mM **DEPS**.

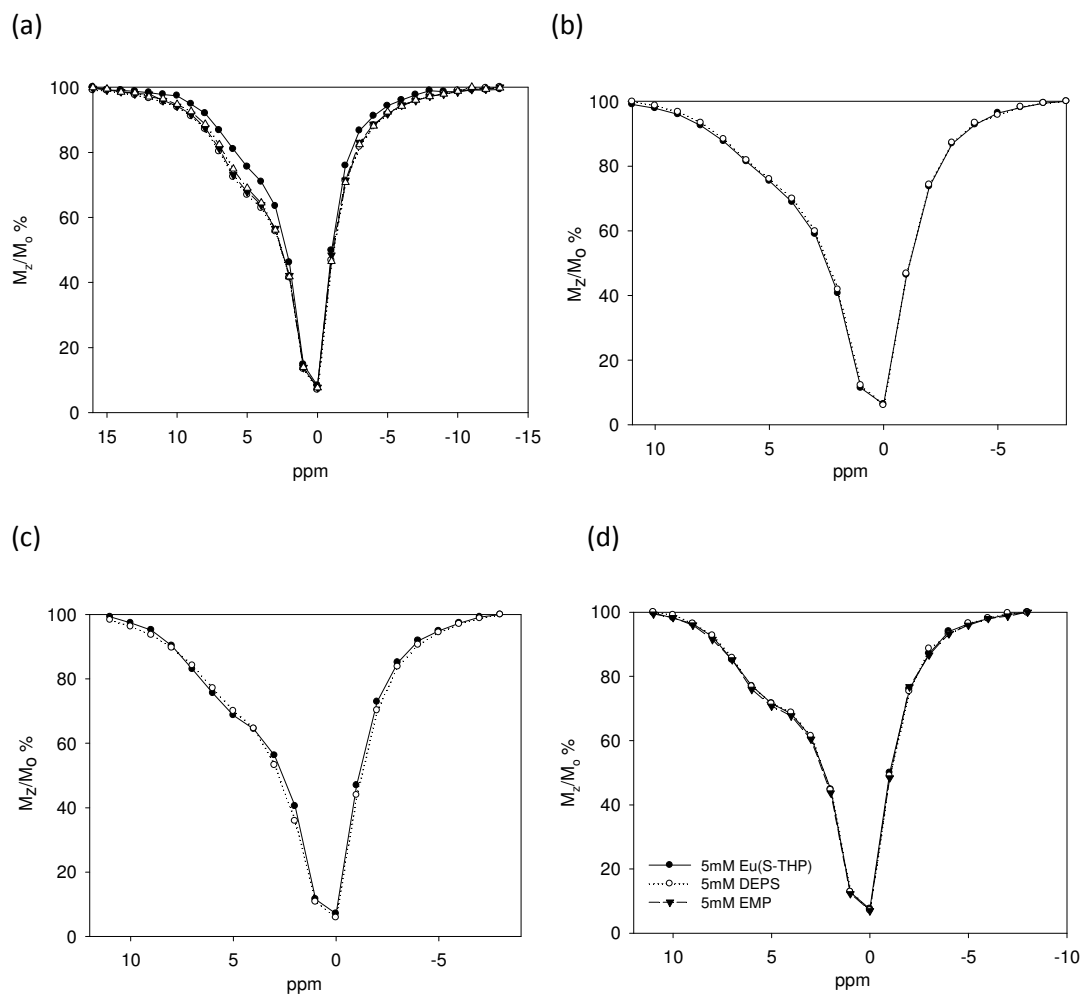


Figure S7. The CEST spectrum of 5.00 mM Eu(**S-THP**), 20.0 mM MES and 100 mM NaCl (a) with addition of **BNPP** at pH 6.5. (●) without **BNPP**, (○) 5 mM **BNPP** immediately after addition, (▼) and (Δ) after 1 day and 7 days, respectively. Minimal hydrolysis of **BNPP** (1%, 3%, respectively) was observed. (b) at pH 6.6, (●) without **NPPC**, (○) with addition of 10.0 mM **NPPC**. (c) at pH 6.5 (●) without **3',5'-cAMP**, (○) with addition of 7.5 mM **3',5'-cAMP**. (d) at pH 6.5, (●) complex, (○) with addition of 5mM **DEPS**, (▼) with addition of 5 mM **EMP**.



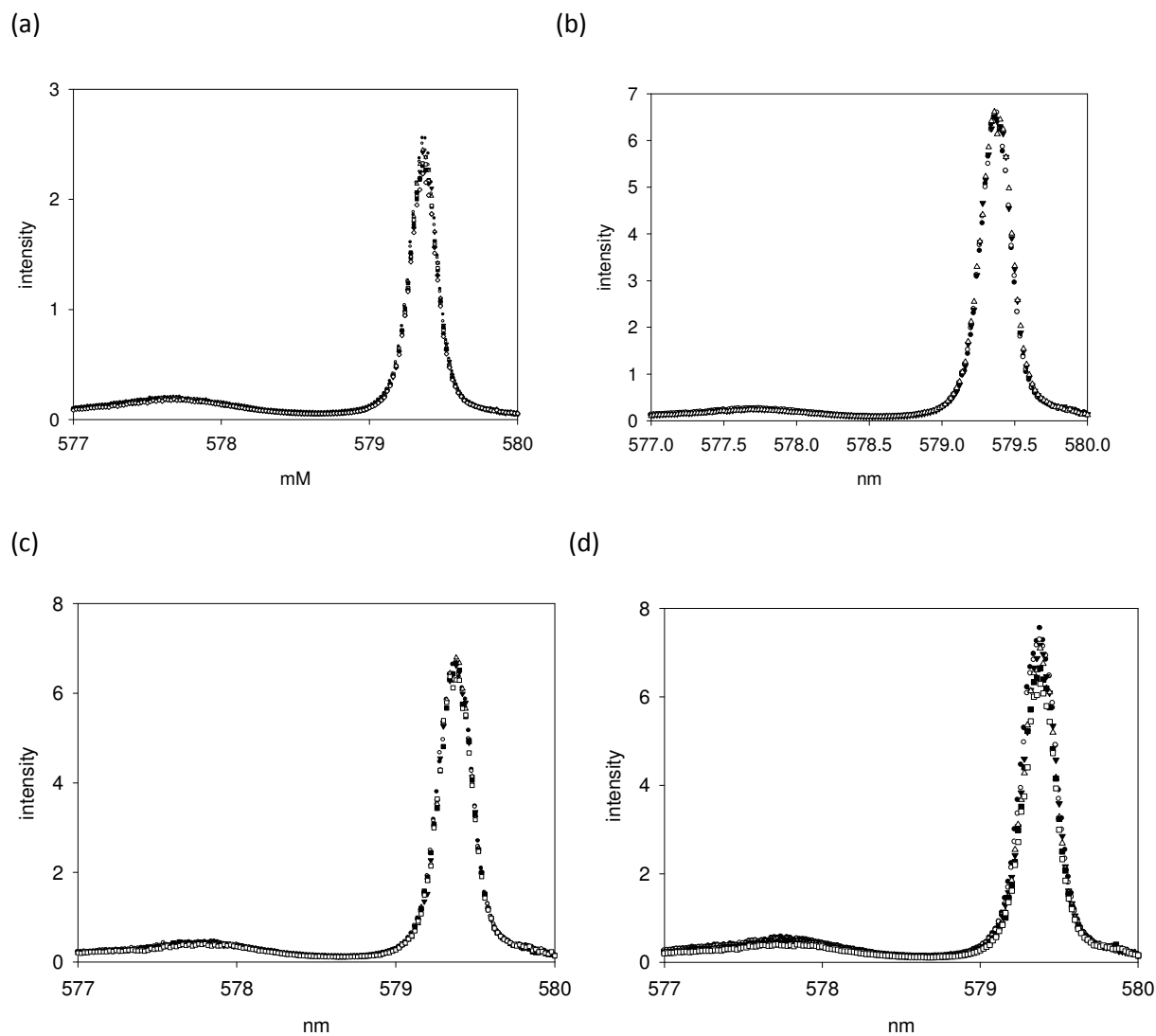


Figure S8.  ${}^7F_0 \rightarrow {}^5D_0$  excitation spectra of  $\text{Eu}(\text{S-THP})^{3+}$  in 20.0 mM buffer and 100.0 mM NaCl (a) **NPPC** added to 1.0 mM  $\text{Eu}(\text{S-THP})^{3+}$  at pH 7.5, ( $\bullet$ ) 0.0 mM, ( $\circ$ ) 1.0 mM, ( $\blacktriangledown$ ) 2.0 mM, ( $\Delta$ ) 3.0 mM, ( $\blacksquare$ ) 4.0 mM, ( $\square$ ) 5.0 mM, ( $\blacklozenge$ ) 6.0 mM, ( $\diamond$ ) 8.0 mM. (b) **3',5'-cAMP** added to 2.0 mM  $\text{Eu}(\text{S-THP})^{3+}$  at pH 7.2, ( $\bullet$ ) 0.0 mM, ( $\circ$ ) 2.0 mM, ( $\blacktriangledown$ ) 6.0 mM, ( $\Delta$ ) 10.0 mM. (c) **EMP** added to 2.5 mM  $\text{Eu}(\text{S-THP})^{3+}$  at pH 7.4, ( $\bullet$ ) 0.0 mM, ( $\circ$ ) 2.5 mM, ( $\blacktriangledown$ ) 5.0 mM, ( $\Delta$ ) 7.5 mM, ( $\blacksquare$ ) 10 mM, ( $\square$ ) 12.5 mM. (d) **DEPS** added to 2.5 mM  $\text{Eu}(\text{S-THP})^{3+}$  at pH 7.4, ( $\bullet$ ) 0.0 mM, ( $\circ$ ) 1.25 mM, ( $\blacktriangledown$ ) 2.5 mM, ( $\Delta$ ) 5.0 mM, ( $\blacksquare$ ) 7.5 mM, ( $\square$ ) 10 mM.