Stable 8-hydroxyquinolinate based podates as efficient sensitizers of lanthanide near-infrared luminescence

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Supporting Information (11 pages)

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1. Synthesis of the Ligands (Schemes 1 and 2).

N,N,N',N'-tetracyanoethyl-1,2-ethylenediamine (**1**)[1] and 7-carboxy-8-hydroxyquinoline[2] were synthesized according to literature procedures.

***N,N,N',N'*-tetraaminopropyl-1,2-ethylenediamine (2).** NaOH (2.24 g, 56 mmol) was added to a solution of **1** (3 g, 11.02 mmol) in 95% ethanol (60 mL) at 0 °C, followed by 14 mL of hydrazine 99% (288 mmol) and 1.94 g of Raney nickel (33.06 mmol) was introduced in small portions during 2 h; the solution was stirred for 6 h at rt and then refluxed for 1 h, hot-filtered and evaporated to give a colorless oil. Cycles of addition/evaporation of toluene were repeated until precipitation of NaOH occurred. Evaporation of the filtrate gave **2** as a colorless oil, which was used without further purification (2.48 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (8H, s, NH_2), 1.58 (8H, m, CH_2), 2.42-2.54 (12H, m, CH_2), 2.72 (8H, t, CH_2). ESI-MS: m/z = 289.48 $[M+H]^+$ (Calc. 289.37).

***N*-{2-{Bis-[(8-hydroxyquinoline-7-carboxamido)propyl]-amino}-ethyl}-*N'*-(8-hydroxyquinoline-7-carboxamido)-*N*-[(8-hydroxyquinoline-7-carboxamido)propyl]-propane-1,3-diamine (3, Tox).** 7-carboxy-8-hydroxyquinoline (530 mg, 2.8 mmol) was dissolved in freshly distilled thf (150 mL) under nitrogen and heated to reflux. A solution of carbonyldiimidazole (CDI, 495 mg, 3.05 mmol) in dry thf (60 mL) was added in 40 min. Then a solution of **2** (0.2 g, 0.70 mmol) in dry thf (50 mL) was added in 60 min. The mixture was stirred overnight and evaporated. The resulting orange residue was dissolved in chloroform (300 mL), successively washed with saturated NH_4Cl and brine, dried with Na_2SO_4 and evaporated to dryness. The residue was put three times through a Sephadex LH-20 column (50% MeOH-CH_2Cl_2). An orange foam **3,** eluted as a single band, was obtained (325 mg, 48%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.83 (8H, m, CH_2), 2.28 (8H, m, CH_2), 3.12 (4H, s, CH_2), 3.48 (8H, s, CH_2), 7.28 (4H, d, ArH), 7.59 (4H, dd, ArH), 7.92 (4H, d, ArH), 8.26 (4H, d, ArH), 8.87 (4H, d, ArH), 8.97 (4H, s, NH). IR (ATR): $\tilde{\nu}$ = 3460-3200, 1611, 1539, 1456 cm^{-1}. ESI-MS: m/z = 973.36 $[M+H]^+$ (Calc. 973.43), 487.83 $[M+2H]^{2+}$ (Calc. 487.54), 325.83 $[M+3H]^{3+}$ (Calc. 325.54). Anal. Calcd. for $C_{54}H_{56}N_{10}O_8 \cdot CH_2Cl_2$: C, 62.2; H, 5.7; N, 12.9. Found: C, 62.4; H, 5.5; N, 13.2.

***N*-{2-{Bis-[(5-sulfo-8-hydroxyquinoline-7-carboxamido)propyl]-amino}-ethyl}-*N'*-(5-sulfo-8-hydroxyquinoline-7-carboxamidomethyl)-*N*-[(5-sulfo-8-hydroxyquinoline-7-carboxamidomethyl)propyl]-propane-1,3-diamine (4, Tsox).** 180 mg of **3** (0.185 mmol) was placed in a round bottom flask and covered by a minimum of oleum (H_2SO_4, SO_3 30%). The mixture was stirred at rt overnight and poured on ice, yielding a precipitate which was

filtrated and washed with cold water. The collected solid **4** was dried under vacuum during 72 h to give a brown powder (198 mg, 83%). ^{1}H-NMR (400 MHz in DMSO-d_6): δ = 1.99 (8H, m, CH_2), 3.26 (8H, m, CH_2), 3.46 (8H, m, CH_2), 3.52 (4H, m, CH_2), 7.85 (4H, dd, ArH), 8.44 (4H, s, ArH), 8.96 (4H, d, ArH), 9.31 (4H, t, NH), 9.45 (4H, d, ArH). IR (ATR): 3500-3100 cm^{-1} $\tilde{\nu}$(O-H), $\tilde{\nu}$(N-H); 1637 cm^{-1} $\tilde{\nu}$(C=O), 1599, 1539 cm^{-1} $\tilde{\nu}$(C=C), $\tilde{\nu}$(C=N). ESI-TOF MS: 322.17 $[L-4H]^{4-}$ (Calcd. 321.55). Anal. Calcd. for $C_{54}H_{58}N_{10}O_{20}S_4 \cdot 8H_2O$: C, 45.1; H, 5.2; N, 9.7. Found: C, 45.1; H, 4.8; N, 9.5.

***N,N,N',N'*-tetramethylaminopropyl-1,2-ethylenediamine (5).** A solution of **2** (1 g, 3.47 mmol) dissolved in a mixture of toluene (4 mL) and water (2 mL) was cooled at 5 °C, ethylchloroformate (1 g, 9.20 mmol) was added in 15 min, and KOH (843 mg, 15 mmol) in water (0.8 mL) was added in 15 min with more ethylchloroformate (1 g, 9.20 mmol). The mixture was stirred 2 h at 5 °C and then 8 h at rt. The toluene layer was separated and the aqueous one extracted with chloroform (300 mL), dried with $MgSO_4$ and evaporated to dryness. The resulting oil (1.98 g, 99 %) was used without further purifications in the next step. It was dissolved in freshly distilled thf (30 mL) and added in 30 min to a solution of $LiAlH_4$ (810 mg, 21.3 mmol) in freshly distilled thf (30 mL), heated to reflux and then the mixture was stirred overnight. KOH (1.4 g in 1.4 mL water) was added dropwise and the solution was decanted and filtrated. After evaporation to dryness, the resulting oil was distilled, yielding a colorless oil (400 mg, 33%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (4H, s, NH), 1.51 (12H, m, CH_2), 2.36-2.43 (20H, m, CH_2), 2.65 (8H, t, CH_2). ESI-MS: m/z = 345.33 $[M+H]^+$ (Calc. 344.34).

***N*-{2-{Bis-[(8-hydroxyquinoline-7-carboxamidomethyl)propyl]-amino}-ethyl}-*N*'-(8-hydroxyquinoline-7-carboxamidomethyl)-*N*-[(8-hydroxyquinoline-7-carboxamidomethyl)propyl]-propane-1,3-diamine (6, ToxMe).** This compound was prepared according to the same synthetic procedure described for the synthesis of **3** by using 7-carboxy-8-hydroxyquinoline (880 mg, 4.64 mmol) in thf (60 mL), carbonyldiimidazole (CDI, 830 mg, 5.11 mmol) in thf (60 mL), and **5** (400 mg, 1.16 mmol) in thf (120 mL); **6** was eluted as a single band and obtained as an orange foam (185 mg, 16 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.82 (8H, m, CH_2), 2.48 (8H, m, CH_2), 2.84 (4H, m, CH_2), 3.02 (12H, s, CH_2), 3.46 (8H, s, CH_2), 7.35 (4H, d, ArH), 7.47 (8H, m, ArH), 8.16 (4H, d, ArH), 8.84 (4H, d, ArH). ESI-MS: m/z = 1029.35 $[M+H]^+$ (Calc. 1028.49), 515.36 $[M+2H]^{2+}$ (Calc. 515.49). Anal. Calcd. for $C_{54}H_{56}N_{10}O_8 \cdot CH_2Cl_2$: C, 62.2; H, 5.7; N, 12.9. Found: C, 62.4; H, 5.5; N, 13.2.

***N*-{2-{Bis-[(5-sulfo-8-hydroxyquinoline-7-carboxamidomethyl)propyl]-amino}-ethyl}-*N*'-(5-sulfo-8-hydroxyquinoline-7-carboxamidomethyl)-*N*-[(5-sulfo-8-hydroxyquinoline-7-carboxamidomethyl)propyl]-propane-1,3-diamine (7, TsoxMe).** 185 mg of **6** (0.180 mmol) was placed in a round bottom flask and covered by a minimum of oleum (H_2SO_4, SO_3 30%). The mixture was stirred at rt overnight, poured on ice, and evaporated. The residue was put five times through a Sephadex G-25 column (water). The collected solid **7** was dried under vacuum during 72 h to give a brown foam (137 mg, 57%). ^{1}H-NMR (400 MHz in DMSO-d_6): δ = 1.94 (8H, m, CH_2), 2.87 (8H, m, CH_2), 3.01 (12H, m, CH_3), 3.43 (4H, s, CH_2), 3.60 (8H, m, CH_2). Anal. Calcd. for $C_{58}H_{66}N_{10}O_{20}S_4 \cdot 5H_2SO_4 \cdot 14H_2O$: C, 33.3; H, 5.0; N, 6.7. Found: C, 33.3; H, 4.9; N, 6.8.

References

1) van Duijvenbode, R. C.; Rajanayagam, A.; Koper, G. J. M.; Borkovec, M.; Paulus, W.; Steuerle, U.; Haussling, L. *Phys. Chem. Chem. Phys.* **1999**, *1*, 5649-5652.

2) Baret, P.; Beguin, C. G.; Boukhalfa, H.; Caris, C.; Laulhere, J. P.; Pierre, J. L.; Serratrice, G. *J. Am. Chem. Soc.* **1995**, *117*, 9760-9761.

2. Supplementary figures

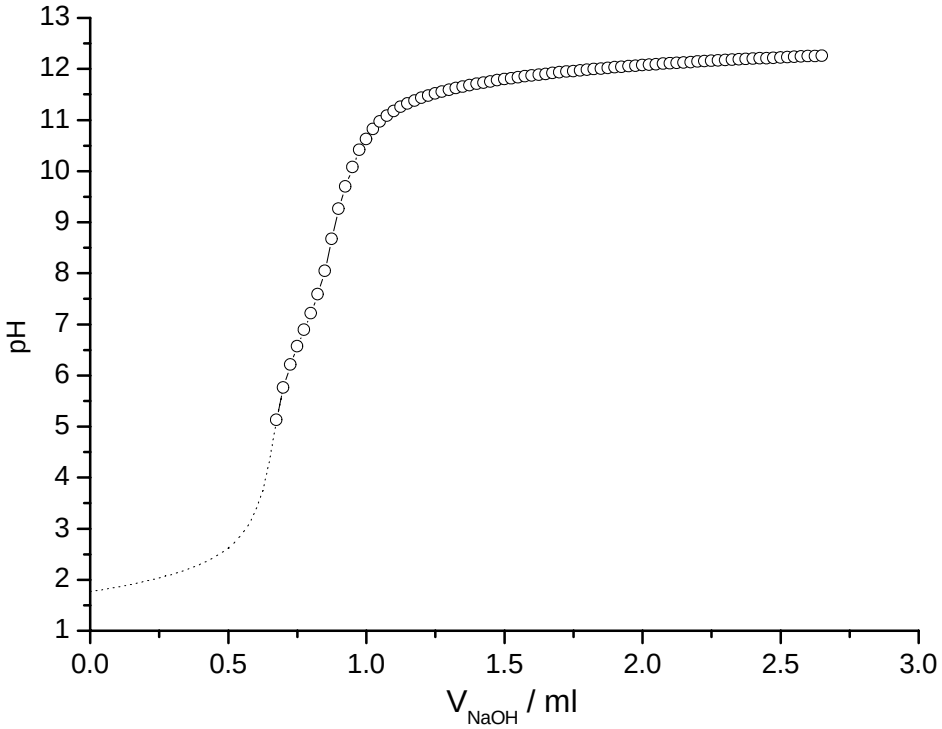

Figure S1. Potentiometric titration curve of $H_{10}L^{2+}$ with OH^- in water: [Tsox] = $9.41 \cdot 10^{-4}$ M; T = 25.0 ± 0.1 °C; μ = 0.1 M (KCl). (···) precipitation below pH = 5.5.

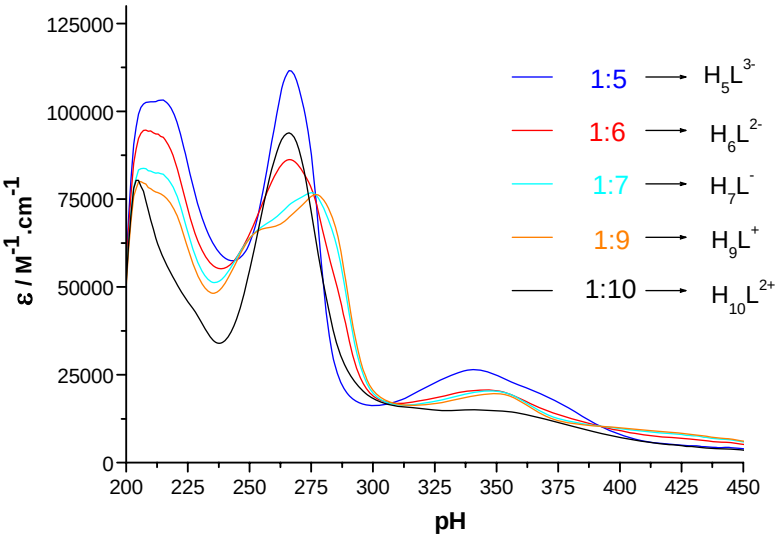

Figure S2. Calculated UV-Vis absorption spectra of the various protonated species of **Tsox**.

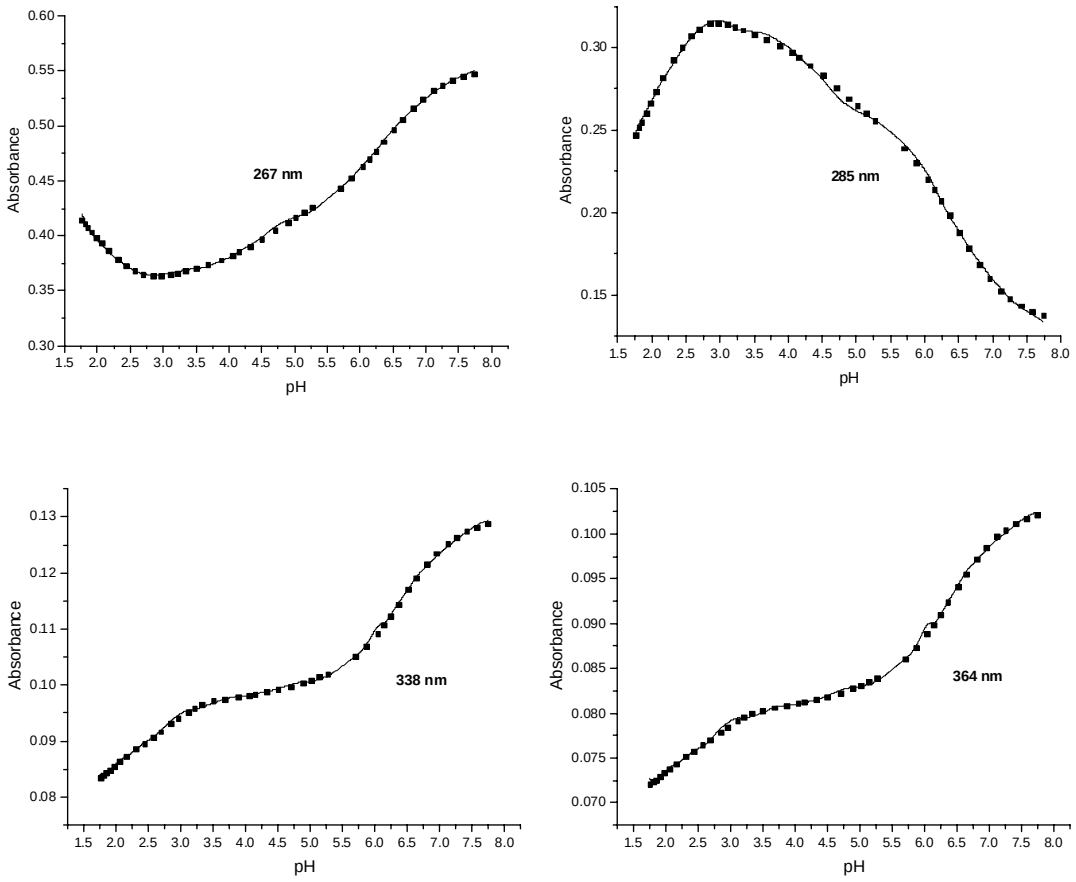

Figure S3. Absorbance variation of **Tsox** at different wavelengths in function of pH.

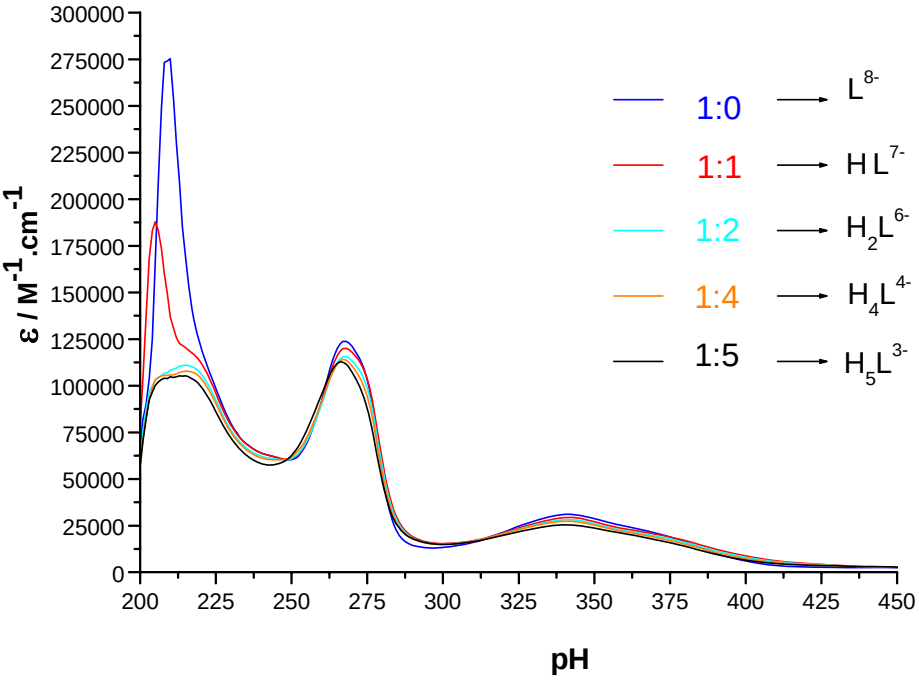

Figure S4. Calculated UV-Vis absorption spectra of the various protonated species of **Tsox**.

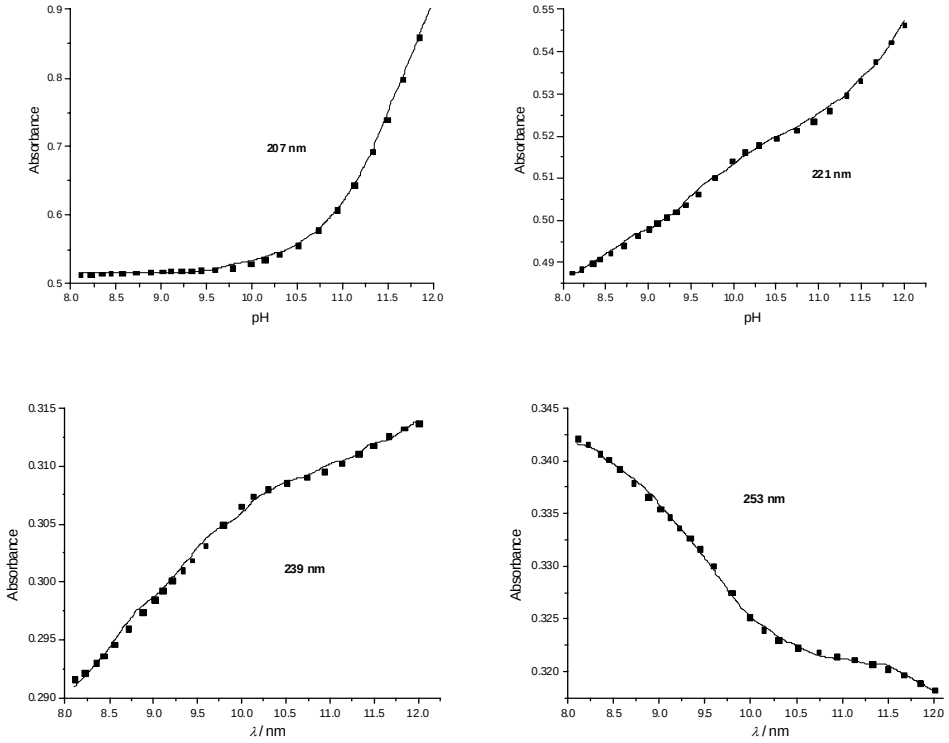

Figure S5. Absorbance variation of **Tsox** at different wavelengths in function of pH.

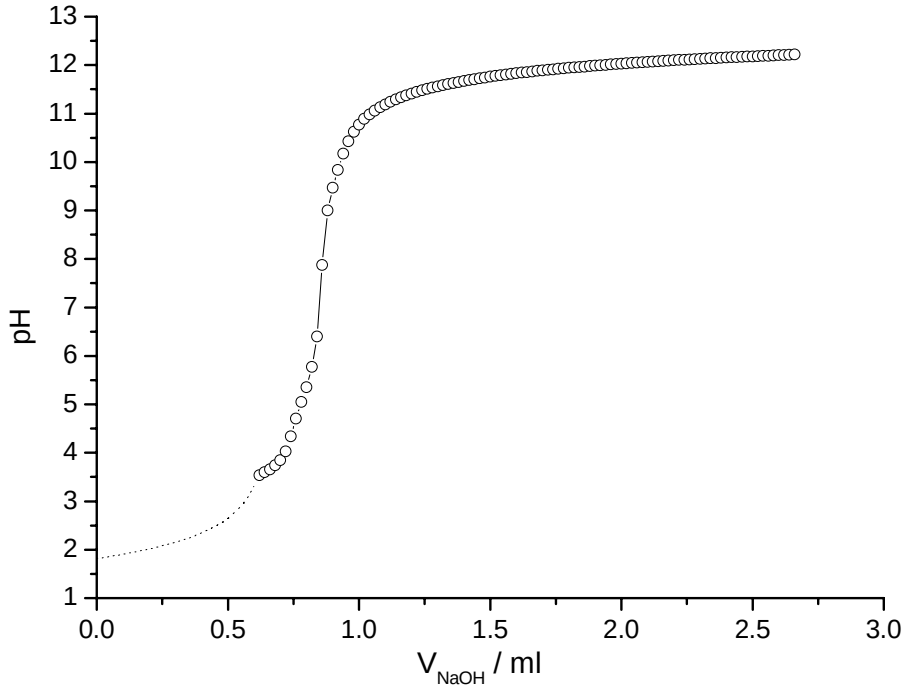

Figure S6: Potentiometric titration curve with OH^- of $H_{10}L^{2+}$ and 1 equivalent of Eu^{III} in water: [**Tsox**] = $9.41 \cdot 10^{-4}$ M; T = 25.0 ± 0.1 °C; μ = 0.1 M (KCl). (…) precipitation below pH 3.5.

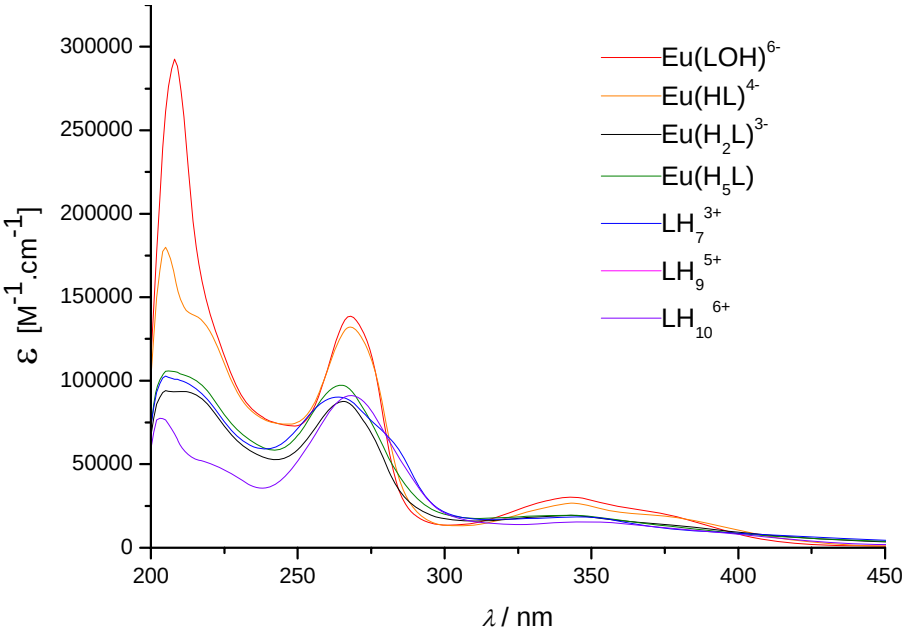

Figure S7. Calculated UV-Vis absorption spectra of the various protonated species of **Tsox** in presence of one equivalent of Eu^{III}.

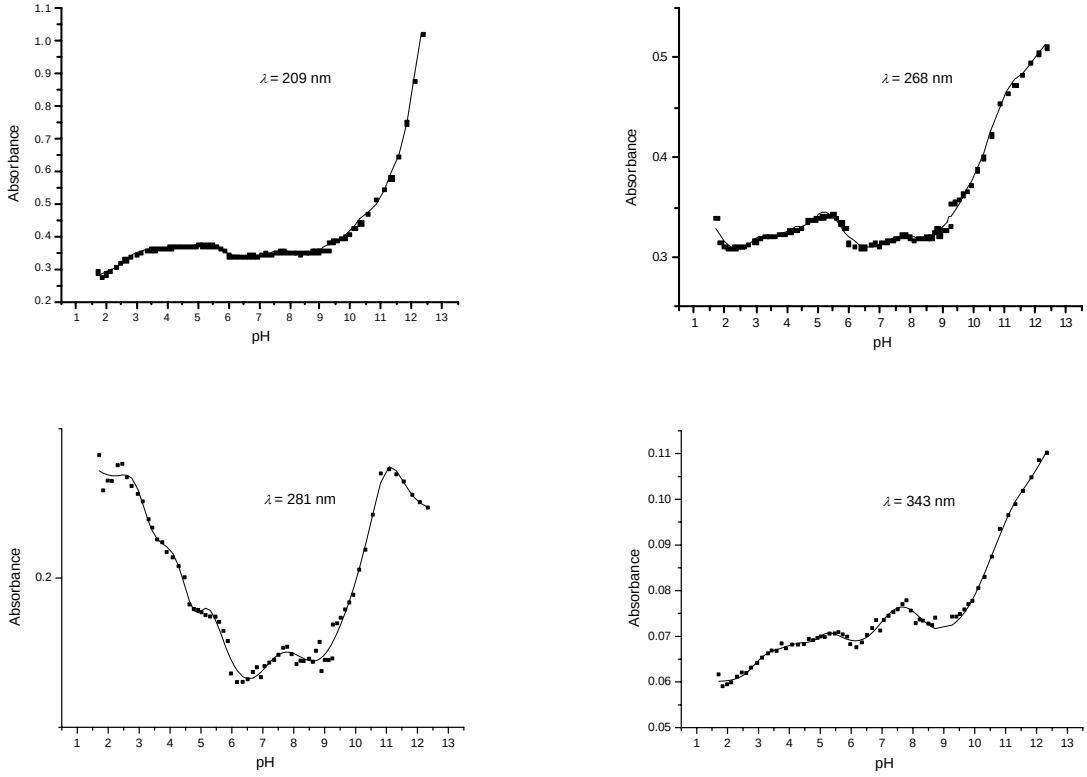

Figure S8. Absorbance variation of **Tsox** in presence of one equivalent of Eu^{III} at different wavelengths in function of pH

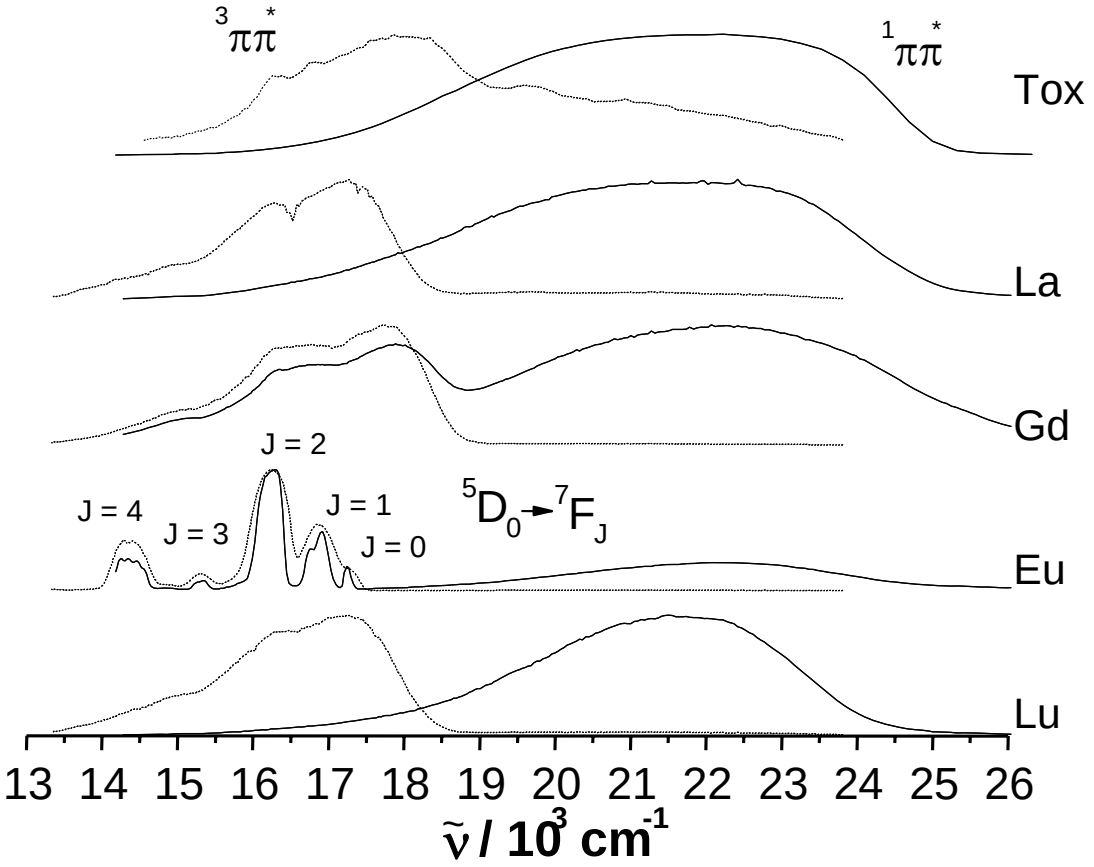

Figure S9. Luminescence spectra of **Tox** and its 1:1 complexes $6 \cdot 10^{-5}$ M in methanol at 77 K without time delay (solid line) and with a 0.05 ms time delay (dotted line).

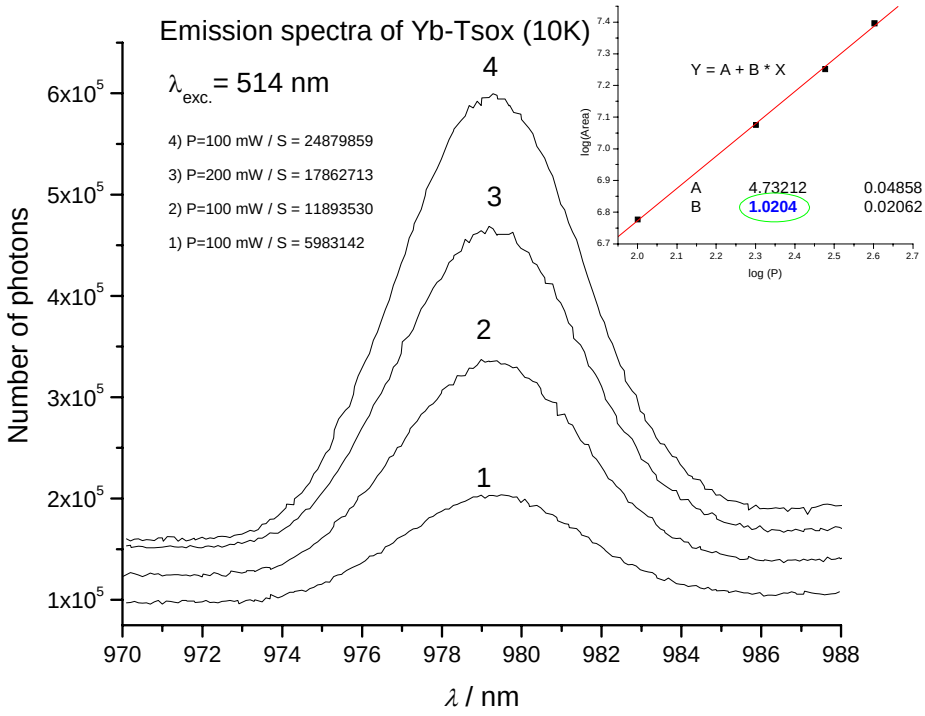

Figure S10. Luminescence intensity of the Yb-**Tsox** (λ_{an} = 979 nm) complex versus the power of the laser (514 nm) at pH 7.4 in HBS buffer at 10 K.

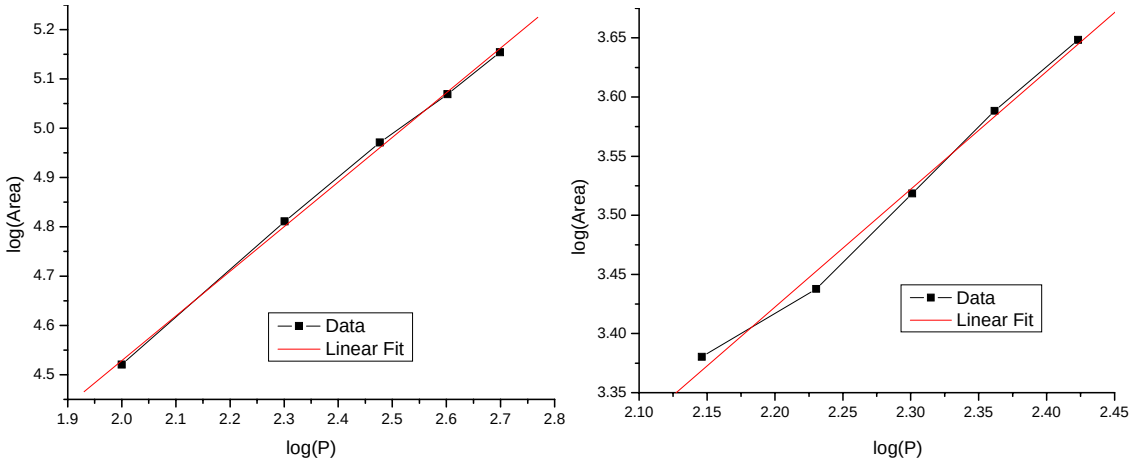

Figure S11. Luminescence intensity of the Yb-**Tsox** (λ_{an} = 979 nm) complex versus the power of the laser (Left: 580 nm, Right: 355 nm) at pH 7.4 in HBS buffer at 10 K

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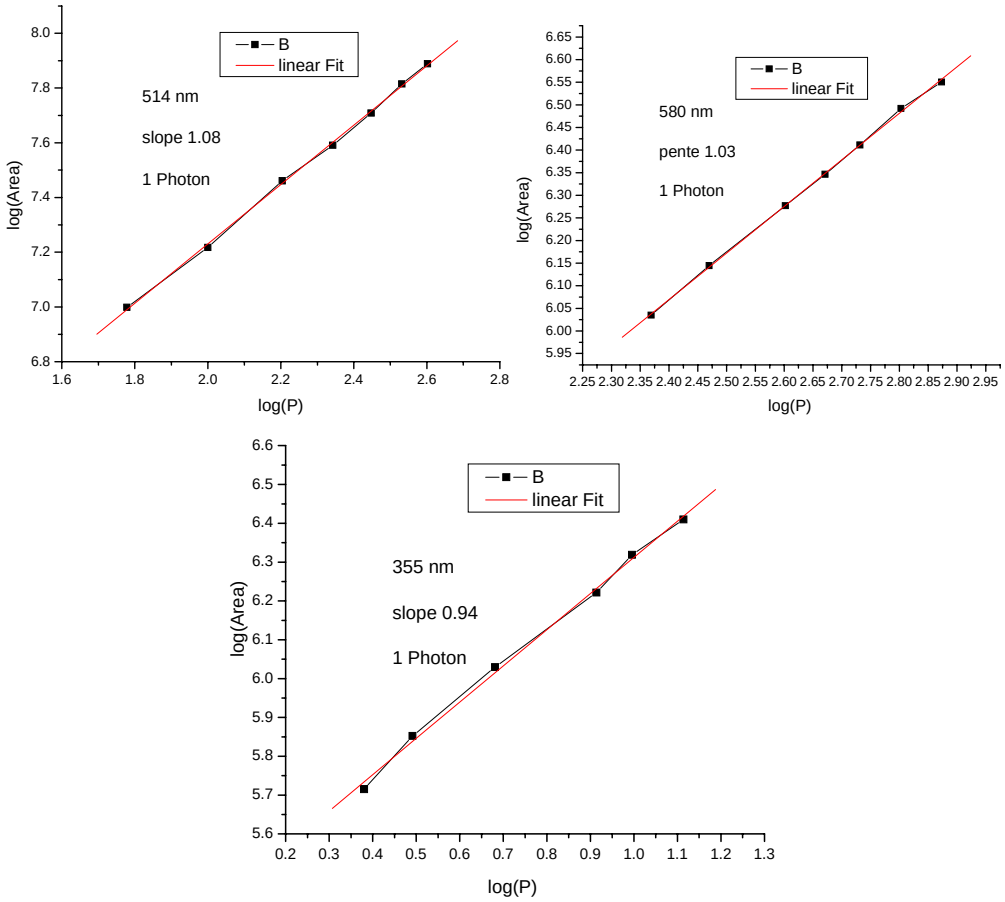

Figure S12. Luminescence intensity of the Yb-**TsoxMe** (λ_{an} = 979 nm) complex versus the power of the laser (355, 514 and 580 nm) at pH 7.4 in HBS buffer at 10 K.