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Ruthenium Tris(bipyridine) Complexes with Sulfur Substituents: Model Studies for PEG Coupling

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Ruthenium polypyridyl complexes are incorporated into polymers for sensing and light emitting materials applications. Coupling reactions between metal complexes and polymers are one route to polymeric metal complexes. In an effort to increase conjugation efficiency, tune materials properties, and introduce a responsive crosslink, ruthenium tris(bipyridine) derivatives with sulfur substituents were synthesized and compared to oxygen analogues. Difunctional thiols, thioesters, thioethers, and disulfides, as well as hexafunctional nonpolymeric model systems, were explored. Upon exposure to oxygen, the thiol derivative was readily oxidized. These studies guided $Ru(bpy)_3$ PEG coupling reactions with disulfide and thioether linkages, which proceeded to ∼80% and ∼60% yield, respectively. The luminescence properties of the Ru PEG derivatives and model systems were investigated. The emission spectra and lifetimes for all complexes in CH_3CN under an inert atmosphere are comparable to $[Ru(bpy)_3]Cl_2$. Lifetime data for nonpolymeric analogues fit to a single exponential decay indicating heterogeneity, suggesting sample homogeneity, whereas data for polymers fit to a multiexponential decay. In contrast to certain $[Ru(bpy)_3]^{2+}$/thiol mixtures, no intramolecular quenching by the sulfide is observed for $[Ru(bpy)_2\{bpy(CH_2SH)_2\}](PF_6)_2$. Emission spectra red shift and multiexponential decay are noted for the oxidized Ru thiol product. The rates of oxygen quenching are slower for Ru PEG derivatives than those for nonpolymeric analogues, which may be attributed to shielding effects of the polymer chain.

Introduction

Luminescent ruthenium polypyridyl complexes are well-known for their intense visible absorptions, long lifetimes, wavelength independent quantum yields, and high photostability.[1,2] Often ruthenium complexes are combined with polymers for enhanced properties and processability. Ru polymers have been utilized as oxygen,[3–5] pH,[6,7] CO_2,[8] metal ion,[9] and temperature sensors.[10] Polymeric metal complexes (PMCs), or metallosupramolecular polymers, are a class of materials featuring site-isolated metal centers in well-defined synthetic macromolecules (Figure 1, C and D). Early work focused on Ru poly(ethylene glycol) (PEG) complexes[11–14] as molten salts and electrolytes.[15–17] PEG also finds wide

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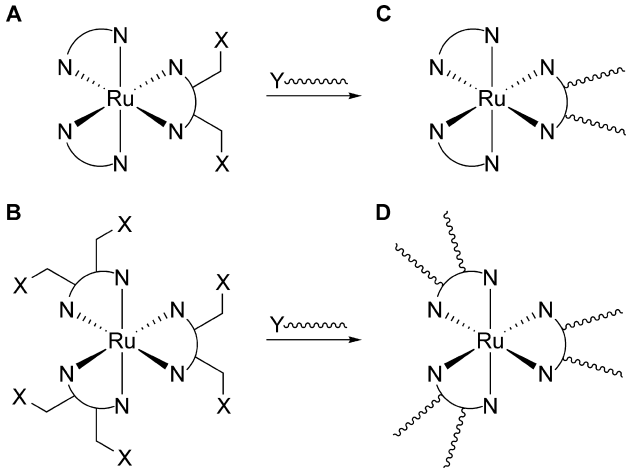

Figure 1. Schematic representation of di- and hexafunctional ruthenium tris(bipyridine)-centered polymeric metal complexes (C and D) and associated precursors (A and B), where X and Y represent reactive groups.

application in biomedicine due to its water solubility, biocompatibility, and protein nonadhesive and stealthlike properties[18,19] in surface coatings,[20] long-circulating drug delivery vehicles,[21–23] and hydrogels.[24,25] These uses also motivate the development of synthetic approaches to Ru PEG materials.

Typically, polymeric metal complexes are made by metalloinitiation, macroligand chelation, or coupling methods.[26–29] In metalloinitiation, Ru tris(bpy) complexes are modified with initiator sites for reaction with monomers. However, anionic polymerization conditions proved too harsh for making Ru PEG complexes; the activation of hydroxyl functionalized Ru tris(bpy) complexes with a strong base degraded the complex. Macroligand chelation represents an attractive alternative that has been successfully employed for bpy[11–17,30] and terpyridine[31] PEG oligomers and low molecular weight (MW) polymers. For example, $bpyPEG_2$ macroligands are made by coupling PEG with activated bpy reagents or by growing PEG from a deprotonated $bpy(CH_2OH)_2$ initiator via anionic polymerization of ethylene oxide.[32] Subsequently, the polymeric ligands are combined with Ru precursors in coordination reactions. Telechelic terpyridine polymers, terpy-PEG-terpy, have been generated using an oligomeric PEG linker ($M_n = 2000$),[33] and Ru PEG containing block copolymers are also known.[30,34] Some chelation reactions with higher molecular weight polymers require long reaction times, do not proceed to completion,[35,36] and undergo PEG chain scission, as evidenced by broadened polydispersity indices (PDIs) and molecular weights that are lower than anticipated by gel permeation chromatography (GPC). For example, the reaction of $[Ru(bpy)_2(solvento)_2]^{2+}$ complexes with $bpyPEG_2$ appears to form $[Ru(bpy)_2(bpyPEG)]^{2+}$ and PEG along with the desired $[Ru(bpy)_2(bpyPEG_2)]^{2+}$ product.[37,38] Another challenge with coupling reactions is the separation of macroligand starting materials from PMC products. Though this has been accomplished with size exclusion chromatography (SEC),[39] still efficient coupling reactions are desirable.

Here, we explored an alternative approach that is known for Ru modified proteins[40] but is less common for synthetic macromolecules, namely the coupling of polymers to functionalized metal complexes (e.g., Figure 1, A and B). This avoids reaction conditions that are damaging to the $bpyPEG_2$ macroligands. Furthermore, sulfur reagents are selected for the coupling reactions because of their increased nucleophilicity and widespread use in generating bioconjugates,[21,23,41–43] including redox responsive disulfides made from commercially available PEG reagents.[44] To generate Ru PMCs via coupling, sulfur nucleophiles can be introduced as thiol substituents on the bpy ligands of the metal complex or as end groups on the polymer. When forming sulfur functionalized Ru tris(bpy) complexes, thiols must be protected, for example, as thioesters, to avoid competition between strong sulfur donors and bpy nitrogens in chelation reactions.[45] Thiol ethers, thiol esters, and disulfides are possible via coupling reactions. In terms of properties, certain sulfur reagents are reported quenchers of Ru tris(bpy) lumines-

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cence.[46–48] Here, we investigate synthetic approaches to both nonpolymeric Ru model systems and PEG modified complexes, compare their luminescence properties to oxygen analogues, and test whether similar quenching behavior is observed for Ru/PEG blends and covalently attached Ru PEG conjugates.

Experimental Section

Materials. 4,4′-Bis(chloromethyl)-2,2′-bipyridine ($bpy(CH_2Cl)_2$),[49] $[Ru(bpy)_2\{bpy(CH_2Cl)_2\}](PF_6)_2$,[50] and $Ru(DMSO)_4Cl_2$[51] were synthesized by previously reported methods. Triethylamine (Aldrich, 99.5%) was dried over CaH_2 and distilled prior to use. The PEG reagents mPEG-SH and mPEG-OPSS (= mPEG-S-S-pyr) (Nektar) were stored in a freezer (−29 °C) in a drybox prior to use. (Note: These PEG starting materials contain high molecular weight impurities, as evidenced by bimodal GPC traces. See Figures 2 and 3. Minor peaks at low elution volumes correspond to the impurities.) Ruthenium(II) tris(bipyridine) (GFS Chemicals), ruthenium(III) chloride hydrate (Strem, 99.9% Ru), ruthenium(II) *cis*-dichlorobis(2,2′-bipyridine) dihydrate (Strem, 99%), potassium thioacetate (Fluka, 98%), sodium thiomethoxide (Aldrich, 95%), 2,2′-dithiodipyridine (Aldrich, 98%), *N*,*N*-dimethylformamide (Aldrich, 99.8% anhydrous), and all other reagents were used as received.

Methods. ^1H NMR and ^{13}C NMR (300 MHz) spectra were recorded on a Varian UnityInova 300 instrument in CD_3CN unless indicated otherwise. ^1H NMR spectra were referenced to the signal for residual protio acetonitrile at 1.940 ppm. UV/vis spectra were taken in CH_3CN solution with a Hewlett-Packard 8452A diode-array spectrophotometer. Molecular weights were determined by gel permeation chromatography (GPC) (THF, 25 °C, 1.0 mL/min) using multiangle laser light scattering (MALLS) (λ = 633 nm, 25 °C) and refractive index (λ = 633 nm, 40 °C) detection. Polymer Labs 5 μm "mixed C" columns along with Wyatt Technology Corp. (Optilab DSP interferometric refractometer, Dawn DSP Laser Photometer) and Agilent Technologies instrumentation (series 1100 HPLC) and Wyatt Technology software (ASTRA) were used in GPC analysis. Yields for Ru PEG coupling reactions were determined by GPC using ASTRA software and cumulative weight fraction analysis. Excitation and emission spectra were recorded on a SPEX Fluorolog 1680 using right angle illumination. Correction factors were applied to emission spectra to compensate for photomultiplier tube efficiencies at different wavelengths. Lifetimes were measured using a VSL-337 pulsed nitrogen laser (λ = 337 nm) (Laser Science Inc., Franklin, MA) for optically dilute solutions (A < 0.2). The luminescence signal was detected with a photomultiplier tube, averaged on a 500 MHz TDS 540 digital oscilloscope (Tektronix, Inc., Beaverton, OR), and transferred to an interfaced PC. Instrumentation was controlled by a Labview program. Data were fit to a single exponential decay using a Marquardt algorithm, unless indicated otherwise.

$Bpy(CH_2SC(O)CH_3)_2$, 1. $Bpy(CH_2Cl)_2$ (1.35 g, 5.33 mmol) was added to a blue solution of $KSC(O)CH_3$ (2.44 g, 21.37 mmol) in degassed DMF (125 mL), and the resulting solution immediately turned yellow. The heterogeneous reaction mixture was stirred at 80 °C for ∼15 h (or until TLC indicated that all $bpy(CH_2Cl)_2$ starting material was consumed). After cooling to 25 °C, solids were removed via vacuum filtration and washed with DMF and CH_2Cl_2, and the filtrate was concentrated in vacuo. The resulting crude product was dissolved in CH_2Cl_2 (∼100 mL), washed with H_2O (3 × 100 mL), and the combined aqueous layers were extracted with additional CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo: 1.75 g; 5.26 mmol; 98%. (Note: In cases when impurities were evident by thin layer chromatography or ^1H NMR analysis, the product was further purified by flash chromatography on nondeactivated silica in 60:40 hexanes/ethyl acetate.) ^1H NMR ($CDCl_3$, 300 MHz): δ 8.60 (d, J = 5.0 Hz, 2H), 8.30 (s, 2H), 7.26 (dd, J = 1.7 Hz, J = 3.3 Hz, 2H), 4.15 (s, 4H), 2.37 (s, 6H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 194.4, 156.1, 149.4, 147.8, 123.9, 121.2, 32.4, 30.3. Anal. Calcd for $C_{16}H_{16}N_2O_2S_2$: C, 57.81; H, 4.85; N, 8.43. Found: C, 57.96; H, 4.81; N, 8.39.

$[Ru(bpy)_2\{bpy(CH_2SC(O)CH_3)_2\}](PF_6)_2$, 2. The dithioacetate complex was prepared by the method of Collins et al.[50] with the following modifications. $[Ru(bpy)_2Cl_2\cdot 2H_2O]$ (0.391 g, 0.715 mmol) and **1** (0.563 g, 1.69 mmol) were stirred for 20 h in refluxing EtOH (18 mL). The reddish mixture was cooled to 25 °C and then concentrated in vacuo to ∼5 mL. After H_2O (50 mL) was added, the mixture was washed with CH_2Cl_2 (5 × 50 mL), and brine (∼5 mL) was added to clarify the emulsions. The aqueous layer was concentrated in vacuo to ∼15 mL. The addition of solid $NaPF_6$ (1.088 g, 6.48 mmol) precipitated an orange solid. The mixture was stirred for ∼5 min, and the solid was collected and washed with H_2O (∼15 mL): 0.712 g; 0.687 mmol; 91%. ^1H NMR (CD_3CN, 300 MHz): δ 8.48 (d, J = 8.4 Hz, 4H), 8.40 (s, 2H), 8.1−8.0 (m, 4H), 7.72−7.66 (m, 4H), 7.60 (d, J = 5.9 Hz, 2H), 7.43−7.29 (m, 6H), 7.31 (dd, J = 5.9 Hz, 2H), 4.22 (s, 4H), 2.36 (s, 6H). ^{13}C NMR (CD_3CN, 300 MHz): δ 157.8, 157.6, 152.5, 152.3, 151.0, 138.7, 128.5, 125.1, 32.4, 30.4. UV/vis (CH_3CN) λ_{max} (ε) = 455 nm (15 860 M^{-1} cm^{-1}). Anal. Calcd for $C_{36}H_{32}N_6O_2S_2P_2F_{12}Ru$: C, 41.74; H, 3.11; N, 8.11. Found: C, 41.50; H, 3.22; N, 7.96.

$[Ru\{bpy(CH_2SC(O)CH_3)_2\}_3](PF_6)_2$, 3. $Ru(DMSO)_4Cl_2$ (0.109 g, 0.225 mmol) and $bpy(CH_2SC(O)CH_3)_2$ (0.225 g, 0.677 mmol) were stirred for 20 h in refluxing ethanol (20 mL). The reaction mixture was cooled to 25 °C and then concentrated in vacuo. The crude product was dissolved in H_2O (∼10 mL) and filtered through a glass wool plug onto solid $NaPF_6$ (0.379 g, 2.26 mmol) to precipitate a red solid. After stirring for ∼5 min, the product was collected by vacuum filtration and washed with cold H_2O (∼10 mL): 0.253 g; 0.182 mmol; 81%. ^1H NMR (CD_3CN, 300 MHz): δ 8.37 (m, 2H), 7.53 (d, J = 5.9 Hz, 2H), 7.31 (dd, J = 1.8 Hz, J = 5.9 Hz, 2H), 4.22 (s, 4H), 2.36 (s, 6H). ^{13}C NMR (CD_3CN, 300 MHz): δ 195.3, 157.5, 152.3, 151.0, 128.4, 125.0, 32.4, 30.5. UV/vis (CH_3CN) λ_{max} (ε) = 464 nm (17 440 M^{-1} cm^{-1}). Anal. Calcd for $C_{48}H_{48}N_6S_6O_6P_2F_{12}Ru$: C, 41.53; H, 3.48; N, 6.05. Found: C, 41.24; H, 3.48; N, 5.86.

$[Ru(bpy)_2\{bpy(CH_2OC(O)CH_3)_2\}](PF_6)_2$, 4. The diacetate complex was prepared as described for $[Ru(bpy)_2\{bpy(CH_2SC(O)CH_3)_2\}](PF_6)_2$ using $[Ru(bpy)_2Cl_2]\cdot 2H_2O$ (0.077 g, 0.148 mmol), $bpy(CH_2OC(O)CH_3)_2$ (0.101 g, 0.336 mmol), ethanol (10 mL), and $NaPF_6$ (0.214 g, 1.28 mmol). Yield: 0.133 g; 0.132 mmol; 89%. ^1H NMR (CD_3CN, 300 MHz): δ 8.52−8.46 (m, 6H), 8.09−8.02 (m, 4H), 7.74−7.66 (m, 6H), 7.43−7.33 (m, 6H), 5.27 (s, 4H), 2.15 (s, 6H). ^{13}C NMR (CD_3CN, 300 MHz): δ 162.5 (d), 157.2 (m), 153.8, 143.3, 133.1, 131.0, 129.8, 127.8, 68.7, 25.5. UV/vis (CH_3CN) λ_{max} (ε) = 453 nm (15 170 M^{-1} cm^{-1}). Anal.

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Calcd for $C_{36}H_{32}N_6O_4P_2F_{12}Ru$: C, 43.08; H, 3.21; N, 8.37. Found: C, 42.71; H, 3.20; N, 8.34.

[Ru{bpy(CH$_2$OC(O)CH$_3$)$_2$}$_3$](PF$_6$)$_2$, 5. Method 1. $Ru(DMSO)_4Cl_2$ (0.027 g, 0.056 mmol) and bpy($CH_2C(O)CH_3$)$_2$ (0.050 g, 0.166 mmol) were stirred for 18 h in refluxing ethanol (3 mL). The reaction mixture was cooled to 25 °C and then concentrated in vacuo, forming an oil (∼1 mL). A red solid was precipitated by the addition of a saturated aqueous solution of NH_4PF_6 (0.052 g, 0.320 mmol), collected by filtration, and washed with H_2O (∼10 mL). The complex was further purified by precipitation from acetone/hexanes: 0.044 g; 0.034 mmol; 60%.

Method 2. The hexaacetate complex was prepared as described for [Ru{bpy($CH_2SC(O)CH_3$)$_2$}$_3$](PF$_6$)$_2$ using $Ru(DMSO)_4Cl_2$ (0.108 g, 0.223 mmol), bpy($CH_2OC(O)CH_3$)$_2$ (0.201 g, 0.669 mmol), ethanol (20 mL), and $NaPF_6$ (0.374 g, 2.23 mmol): 0.216 g; 0.167 mmol; 75%. ^{1}H NMR (CD_3CN, 300 MHz): δ 8.46 (s, 2H), 7.65 (d, J = 5.8 Hz, 2H), 7.36 (m, 2H), 5.27 (s, 4H), 2.15 (s, 6H). ^{13}C NMR (CD_3CN, 300 MHz): δ 171.2, 157.7, 152.5, 149.2, 126.4, 123.1, 64.0, 20.9. UV/vis (CH_3CN) λ_{max} (ε) = 459 nm (16 780 M^{-1} cm^{-1}). Anal. Calcd for $C_{48}H_{48}N_6O_{12}P_2F_{12}Ru$: C, 44.62; H, 3.74; N, 6.51. Found: C, 44.77; H, 3.92; N, 6.39.

[Ru(bpy)$_2${bpy(CH$_2$SH)$_2$}](PF$_6$)$_2$, 6. The dithiol complex was prepared by the method of Wallace and Springer[52] with the following modifications. [Ru(bpy)$_2${bpy($CH_2SC(O)CH_3$)$_2$}](PF$_6$)$_2$ (0.100 g, 0.097 mmol) was added to a Kontes flask. The flask was evacuated and backfilled with nitrogen (3×). A solution of $NaSCH_3$ (0.014 g, 0.194 mmol) in degassed CH_3OH (1.0 mL) was added, and the reaction mixture was sealed under nitrogen and stirred at 50 °C for 2 h. Aqueous HCl (1.5 mL, 0.1 M) and H_2O (5 mL) were added, and the heterogeneous mixture was extracted with CH_2Cl_2 (3 × 10 mL) and washed with brine (15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo: 0.092 g; 0.097 mmol; 99%. ^{1}H NMR (CD_3CN, 300 MHz): δ 8.53−8.47 (m, 6H), 8.10−8.01 (m, 4H), 7.76−7.70 (m, 4H), 7.62 (d, J = 5.8 Hz, 2H), 7.44−7.34 (m, 6H), 3.88 (d, J = 8.5 Hz, 4H), 2.40 (t, J = 8.5 Hz, 1H). ^{13}C NMR (CD_3CN, 300 MHz): δ 157.8 (d), 154.2, 152.5 (m), 138.6, 128.4, 127.9, 125.1, 124.7, 27.7. UV/vis (CH_3CN) λ_{max} (ε) = 455 nm (19 530 M^{-1} cm^{-1}). Anal. Calcd for $C_{32}H_{28}N_6S_2P_2F_{12}Ru$: C, 40.38; H, 2.97; N, 8.83. Found: C, 40.38; H, 3.02; N, 8.70.

[Ru{bpy(CH$_2$SH)$_2$}$_3$](PF$_6$)$_2$, 7. The hexathiol reaction was performed as described for [Ru(bpy)$_2${bpy(CH_2SH)$_2$}](PF$_6$)$_2$ using [Ru{bpy($CH_2SC(O)CH_3$)$_2$}$_3$](PF$_6$)$_2$ (0.050 g, 0.036 mmol), $NaSCH_3$ (0.015 g, 0.217 mmol), CH_3OH (2.5 mL), and HCl (3 mL, 0.1 M). Yield: 0.024 g; 0.021 mmol; 58%. ^{1}H NMR (CD_3CN, 300 MHz): δ 8.46 (m, 2H), 7.60 (d, J = 5.8 Hz, 2H), 7.37 (dd, J = 1.9 Hz, J = 5.8 Hz, 2H), 3.88 (d, J = 8.4 Hz, 4H), 2.36 (t, J = 8.4 Hz, 1.5H). ^{13}C NMR (CD_3CN, 300 MHz): δ 157.7, 154.1, 152.3, 127.9, 124.6, 27.7. UV/vis (CH_3CN) λ_{max} (ε) = 462 nm. Elemental analysis data for this air sensitive sample are as follows: Anal. Calcd for $C_{36}H_{36}N_6S_6P_2F_{12}Ru$: C, 38.06; H, 3.19; N, 7.40. Found: C, 39.08; H, 3.49; N, 7.22. (Note: C value is out of range.) The ^{1}H NMR spectrum is provided in the Supporting Information.

[Ru(bpy)$_2${bpy(CH$_2$SSpyr)$_2$}](PF$_6$)$_2$, 8. [Ru(bpy)$_2$-{bpy(CH_2SH)$_2$}](PF$_6$)$_2$ **4** (0.027 g, 0.028 mmol) was dissolved in DMF/CH_3OH (1.5 mL each) in a Schlenk flask. A solution of 2,2′-dithiodipyridine (0.021 g, 0.094 mmol) in DMF/CH_3OH (1.0 mL each) was added dropwise to the dithiol complex solution over ∼10 min. The reaction mixture was stirred at room temperature for 5 h, the solvent was removed in vacuo, and the crude product was further purified via column chromatography with BioBeads SX-1 using acetone as the eluent: 0.031 g; 0.027 mmol; 96%. The ^{1}H NMR spectrum is provided in the Supporting Information. (Elemental analysis was not performed for this sample due to the evidence of trace impurities in the aromatic region of the ^{1}H NMR spectrum.)

[Ru(bpy)$_2${bpy(CH$_2$SS(CH$_2$)$_4$-PEG-OCH$_3$)$_2$}](PF$_6$)$_2$, 9. A DMF solution of Et_3N (1 mL, 4.0 mM) was added to a Schlenk flask containing the dithiol complex **4** (0.005 g, 0.005 mmol) and mPEG-S-S-pyr (0.052 g, 0.009 mmol). The reaction mixture was stirred at room temperature overnight (∼14 h), and then the solvent was removed in vacuo. The crude product was dissolved in a minimal amount of CH_2Cl_2 and precipitated into cold Et_2O (−78 °C) to afford an orange solid: 0.027 g; 0.002 mmol; 57%. ^{1}H NMR (CD_3CN, 300 MHz): δ 8.59−8.45 (m), 8.14−8.00 (m), 7.77−7.62 (m), 7.49−7.33 (m), 4.90 (s), 3.80−3.76 (m), 3.69−3.43 (m), 3.33−3.28 (m), 2.72 (t, J = 7.1 Hz). Percent coupling (GPC): ∼80%. UV/vis (CH_3CN) λ_{max} (ε) = 457 nm (18 100 M^{-1} cm^{-1}, based on GPC molecular weight corrected for 80% coupled product).

[Ru(bpy)$_2${bpy(CH$_2$SCH$_3$)$_2$}](PF$_6$)$_2$, 10. A solution of $NaSCH_3$ (200 μL, 0.093 mmol) in CH_3OH was added dropwise to a solution of [Ru(bpy)$_2${bpy(CH_2Cl)$_2$}](PF$_6$)$_2$ (0.035 g, 0.037 mmol) in degassed CH_3OH/DMF (2.3/2.5 mL). The reaction mixture was stirred for 4 h at room temperature and then concentrated in vacuo. The crude product was dissolved in CH_2Cl_2 (∼15 mL) and washed with H_2O (3 × 10 mL) and brine (10 mL). The organic fraction was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a red solid: 0.024 g; 0.025 mmol; 67%. ^{1}H NMR (CD_3CN, 300 MHz): δ 8.52−8.43 (m, 6H), 8.09−8.01 (m, 4H), 7.76−7.68 (m, 4H), 7.61 (d, J = 5.8 Hz, 2H), 7.44−7.31 (m, 6H), 3.81 (s, 4H), 2.03 (s, 6H). ^{13}C NMR (CD_3CN, 300 MHz): δ 157.9, 157.7, 152.6, 152.2, 151.8, 138.6, 128.4, 125.1, 37.0, 15.1. UV/vis (CH_3CN) λ_{max} (ε) = 455 nm (13 140 M^{-1} cm^{-1}). Anal. Calcd for $C_{34}H_{32}N_6S_2P_2F_{12}Ru$: C, 41.68; H, 3.29; N, 8.58. Found: C, 41.99; H, 3.42; N, 8.46.

[Ru(bpy)$_2${bpy(CH$_2$S(CH$_2$)$_4$-PEG-OCH$_3$)$_2$}](PF$_6$)$_2$, 11. NaH (0.007 g, 0.292 mmol) was suspended in DMF (20 mL) under nitrogen and a portion (1.85 mL, 0.024 mmol) was added to a Schlenk flask containing mPEG-SH (0.010 g, 0.009 mmol). A DMF solution (0.5 mL) of [Ru(bpy)$_2${bpy(CH_2Cl)$_2$}](PF$_6$)$_2$ (0.005 g, 0.005 mmol) was added dropwise to the mPEG-SNa suspension. The reaction was stirred for 18 h at 80 °C, cooled to room temperature, and quenched with CH_3OH (∼5 mL). Acidic methanol (0.5 mL HCl in CH_3OH) was added until pH ∼2 was reached, and the solvent was removed in vacuo. The crude product was dissolved in H_2O (∼5 mL), saturated $NaHCO_3$ was added until pH 8 was reached, and then the mixture was concentrated in vacuo. The polymer product was dissolved in CH_2Cl_2 and solids were removed by passage through a Celite plug. The filtrate was concentrated in vacuo to a minimal volume (∼1 mL) for dropwise addition to cold Et_2O (−78 °C), thus precipitating an orange solid: 0.027 g; 46%. ^{1}H NMR (CD_3CN, 300 MHz): δ 8.57−8.48 (m), 8.11−8.03 (m), 7.77−7.68 (m), 7.47−7.36 (m), 4.90 (s), 3.80−3.76 (m), 3.65−3.40 (m), 3.33−3.28 (m), 2.72 (t, J = 7.1 Hz). Percent coupling (GPC): ∼60%. UV/vis (CH_3CN) λ_{max} (ε) = 456 nm (19 800 M^{-1} cm^{-1}, based on GPC molecular weight corrected for 60% coupled product).

Luminescence. Lifetime data were acquired at room temperature (∼22 °C) for solutions purged with nitrogen, air (21% oxygen), or pure oxygen. All decay curves were fit to a single exponential unless indicated otherwise, in which a double-exponential equation was used:

(52) Wallace, O. B.; Springer, D. M. *Tetrahedron Lett.* **1998**, *39*, 2693–2694.

$$D(t) = \sum_{j=1}^{N} \alpha_j \exp(-t/\tau_j), \quad N = 2 \tag{1}$$

where the α's and τ's were measured by fitting the decay data to sums of exponentials using a Marquardt nonlinear least-squares algorithm. Lifetimes are reported as pre-exponential weighted lifetimes determined from[53]

$$\tau_{pe} = \sum_{j=1}^{3} \alpha_j \tau_j / \sum_{j=1}^{3} \alpha_j \tag{2}$$

This gives a good single value lifetime, which is directly comparable to intensity quenching. The full double exponential fit data are provided in the Supporting Information.

Oxygen is a dynamic or collisional quencher of the complexes. In solution, the dependence of emission intensity and lifetime with quencher concentration is given by the Stern−Volmer equations:[54]

$$\tau_0/\tau = 1 + K_{SV}[Q] \tag{3a}$$

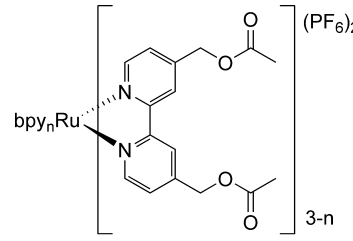
$$K_{SV} = k_q \tau_0 \tag{3b}$$

where the τ's are lifetimes, K_{sv} is the Stern−Volmer quenching constant, and k_q is the bimolecular rate constant for quenching of the excited state. The subscript 0 denotes the value of the quantity in the absence of the quencher. The Stern−Volmer quenching constants were determined by linear regression of the plots of τ_0/τ versus oxygen concentration with slopes equal to K_{SV} and the k_q's from K_{SV} and τ_0.

Results and Discussion

Ruthenium complexes with sulfur substituents were synthesized as models for polymer coupling reactions and their luminescence properties were explored. Either the metal complex or the polymer may be functionalized with nucleophiles (e.g., RSH) or electrophiles (e.g., RCl, RSSpyr) for coupling reactions. Thioacetates are precursors to thiols that can serve as protecting groups to prevent the coordination of sulfur to Ru ions during complex formation (Scheme 1). Specifically, $bpy(CH_2SC(O)CH_3)_2$ (**1**) was synthesized by the reaction of $bpy(CH_2Cl)_2$ with $KSC(O)CH_3$ in DMF to afford a brownish solid in 98% yield.[55,56] $Bpy(CH_2SC(O)CH_3)_2$ was then combined with $Ru(bpy)_2Cl_2$ in refluxing ethanol, followed by precipitation with $NaPF_6$ to afford $[Ru(bpy)_2\{bpy(CH_2SC(O)CH_3)_2\}](PF_6)_2$ (**2**) in 91% yield.[50] A hexafunctional Ru thioacetate complex $[Ru\{bpy(CH_2SC(O)CH_3)_2\}_3](PF_6)_2$ (**3**) can also be obtained in 81% yield through the reaction of $bpy(CH_2SC(O)CH_3)_2$ with $Ru(DMSO)_4Cl_2$ in refluxing ethanol, followed by precipitation with $NaPF_6$.

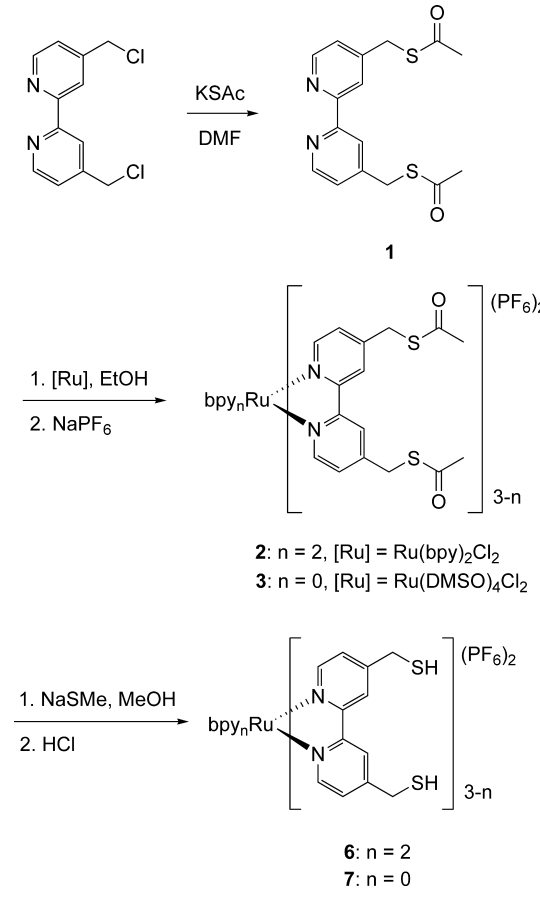
Using similar methods, oxygen derivatives were synthesized for comparison. $Bpy(CH_2C(O)CH_3)_2$ ligands were prepared by reported methods[55] for coordination to Ru precursors as described for thioacetate functionalized complexes. $[Ru(bpy)_2\{bpy(CH_2OC(O)CH_3)_2\}](PF_6)_2$ (**4**) and $[Ru\{bpy(CH_2OC(O)CH_3)_2\}_3](PF_6)_2$ (**5**) were obtained in 75% and 89% yield, respectively.[50]



4: n = 2
5: n = 0

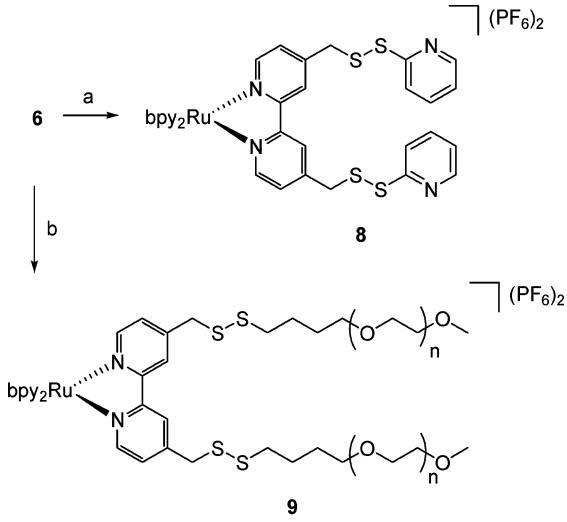
Ru thioacetate complexes provide a facile route to nucleophilic Ru thiol complexes (Scheme 1). Initial attempts to synthesize $[Ru(bpy)_2\{bpy(CH_2SH)_2\}](PF_6)_2$ (**6**) involved the hydrolysis of Ru dithioacetate, **2**, with NaOH followed by an acidic workup; however, unprotected thiols readily oxidize to form disulfides under these conditions. ^{1}H NMR analysis of the Ru thiol product revealed a multiplet at the methylene position (3.8 ppm) rather than the doublet expected for Ru bound bpyCH_2SH, suggesting thiol oxidation. Wallace and Springer[52] have shown that thioacetates can be selectively reduced to thiols using a sacrificial reductant, NaSMe, in methanol at room temperature; hence, this method was explored. Due to the poor solubility of the Ru dithioacetate, **2**, at room temperature, the deprotection

Scheme 1



(53) Carraway, E. R.; Demas, J. N.; DeGraff, B. A. *Anal. Chem.* **1991**, *63*, 332–336.
(54) Kautsky, H. *Trans. Faraday Soc.* **1939**, *35*, 216–219.
(55) Smith, A. P.; Corbin, P. S.; Fraser, C. L. *Tetrahedron Lett.* **2000**, *41*, 2787–2789.
(56) Zheng, T.-C.; Burkart, M.; Richardson, D. E. *Tetrahedron Lett.* **1999**, *40*, 603–606.

Scheme 2



reaction was heated at 50 °C to create a homogeneous solution. The reaction was quenched with aqueous HCl and an orange precipitate resulted. The stoichiometry of NaSMe proved to be crucial in this reaction. An excess of NaSMe or incomplete reduction gave rise to a CH_3SH impurity that was difficult to remove. To avoid this and also Ru complex impurities, stoichiometric amounts of NaSMe were required. Reactions are typically complete after two hours. The Ru dithiol product **6** was obtained in essentially quantitative yield and was stable when stored under N_2 in the dark even after several months time. Synthesis of a hexafunctional thiol complex, **7**, was also attempted in a similar fashion, and experimental details are provided; however, due to the instability of thiols to oxidation, an analytically pure sample was not obtained.

The incorporation of disulfides into polymers offers the advantage of a cleavable linkage in reducing environments. Disulfides have been introduced into imaging agents[57,58] and gene[59] and drug[43,60] delivery vectors. Disulfide PEG products are accessible through reaction of an alkyl thiol with mPEG-S-S-pyr. Attempts to synthesize a nonpolymeric disulfide $[Ru(bpy)_2\{bpy(CH_2SSpyr)_2\}](PF_6)_2$ (**8**) involved the reaction of Ru dithiol **6** with 2,2′-dithiodipyridyl (Scheme 2). Several solvent conditions were screened, including CH_2Cl_2, DMF, and a CH_3OH/DMF (1:1) cosolvent system. Reactions in CH_2Cl_2 did not work well due to the formation of an oily precipitate during the course of the reaction. Furthermore, the ^{1}H NMR spectrum showed a multiplet rather than the expected singlet for the -C*H*$_2$SSpyr resonance (4.17 ppm). Modeled after work by Smith et al.,[61] 1:1 CH_3OH/DMF solvent conditions worked better; the reaction mixture remained homogeneous and a singlet was observed in the ^{1}H NMR spectrum for the product methylene protons. The byproduct from this coupling reaction is HS-pyr, which is a yellow substance with a UV/vis absorbance at ∼360 nm.[62] Purification of the disulfide product **8** by precipitation from acetone/hexanes and BioBead size-exclusion chromatography removed some of the HS-pyr byproduct, but ^{1}H NMR integration of the methylene resonance (bpyC*H*$_2$SSpyr) versus the highly complex aromatic region (i.e., HS-pyr, unreacted or partially reacted Ru complex, and 2,2′-dithiodipyridyl complex) suggested that some impurities remained (see Supporting Information for the ^{1}H NMR spectrum). Even though it proved difficult to obtain analytically pure products of the disulfide complex **8**, these exploratory studies provide important insight for polymer coupling. Due to differences in solubility, it may be possible to separate the HS-pyr byproduct from polymer products by precipitation.

The knowledge gained from the nonpolymeric disulfide analogue **8**served as a starting point for polymer coupling reactions with a commercially available PEG reagent. Electrophilic mPEG-S-S-pyr was combined with Ru dithiol, **6**, to produce Ru disulfide-PEG, **9** (Scheme 2). Aliquots of the reaction run in DMF were taken over 18 h and the extent of polymer coupling to the difunctional Ru thiol precursor complex was determined by GPC analysis based on the cumulative molecular weight of the injected sample. The reactions showed ∼70% coupling after five hours, but were typically run for ∼14 h in an attempt to increase product yields. Different Et_3N loadings (0.5, 1, 2 equiv) were tested to explore the effects of base. With 2 equiv of Et_3N, a nonluminescent product was obtained, suggesting degradation of the complex. Reactions run with 1 equiv of Et_3N also resulted in dark reaction mixtures. A base loading of 0.5 equiv proved optimal, affording luminescent products and resulting in ∼80% coupling (Figure 2), in accord with similar PEG reactions in the literature.[63] Polymer products were purified by precipitation from CH_2Cl_2 into cold diethyl ether (−78 °C). This method removed the yellow byproduct and excess triethylamine; however, unreacted or mono-substituted PEG products were difficult to separate from Ru disulfide-PEG, **9**. This is common in coupling reactions involving polymer reagents and products. Further separation of Ru disulfide-PEG from mPEG-S-S-pyr and mono-substituted Ru disulfide-PEG was attempted using BioBeads in benchtop size-exclusion chromatography; however, for this method to work well, greater than a factor of two difference in polymer molecular weights is recommended. Here, the polymer product, starting material, and likely monofunctional impurity are at the molecular weight cutoff. Preparative scale GPC could be more useful to purify products from unreacted polymer starting material.

As an alternative, Ru complexes can be functionalized with electrophilic sites for reaction with PEG nucleophiles (e.g., mPEGOH, mPEGSH). A halomethyl complex, $[Ru(bpy)_2$-

(57) Lee, Y.; Mo, H.; Koo, H.; Park, J. Y.; Cho, M. Y.; Jin, G.-W.; Park, J. S. *Bioconjugate Chem.* **2007**, *18*, 13–18.
(58) Cerritelli, S.; Velluto, D.; Hubbell, J. A. *Biomacromolecules* **2007**, *8*, 1966–1972.
(59) Neu, M.; Germershaus, O.; Mao, S.; Voigt, K.-H.; Behe, M.; Kissel, T. *J. Controlled Release* **2007**, *118*, 370–380.
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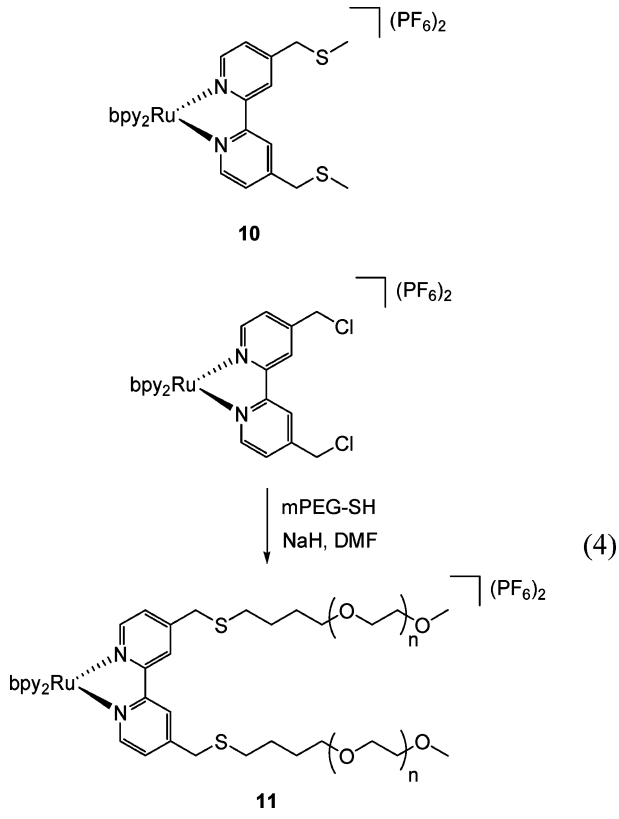
(61) Smith, A. B., III; Savinov, S. N.; Manjappara, U. V.; Chaiken, I. M. *Org. Lett.* **2002**, *4*, 4041–4044.
(62) Egwim, I. O. C.; Gruber, H. J. *Anal. Biochem.* **2001**, *288*, 188–194.
(63) Murthy, N.; Campbell, J.; Fausto, N.; Hoffman, A. S.; Stayton, P. S. *Bioconjugate Chem.* **2003**, *14*, 412–419.

$\{bpy(CH_2Cl)_2\}]^{2+}$, was synthesized by previously reported methods.[50] Initial attempts to couple $[Ru(bpy)_2\{bpy(CH_2Cl)_2\}]^{2+}$ with mPEGOH and NaH in DMF showed no evidence of reaction by GPC analysis after ~18 h. Reagents with stronger sulfur nucleophiles were explored for comparison. A nonpolymeric thioether analogue $[Ru(bpy)_2\{bpy(CH_2SCH_3)_2\}]^{2+}$ (**10**) was produced in good yield via the reaction of $[Ru(bpy)_2\{bpy(CH_2Cl)_2\}]^{2+}$ with NaSMe in 1:1 MeOH/DMF. A thioether polymer, **11**, was also targeted (eq 4). Reaction of mPEG-SH and $[Ru(bpy)_2\{bpy(CH_2Cl)_2\}]^{2+}$ in DMF with Et_3N as the base showed ~30% coupled product by GPC analysis (Figure 3). Alternatively, when NaH was stirred with mPEG-SH followed by dropwise addition of $[Ru(bpy)_2\{bpy(CH_2Cl)_2\}]^{2+}$ in DMF solution, coupling improved to ~60%. Though it was not possible to separate the Ru polymer product from the PEG starting material and monosubstituted Ru PEG product by precipitation or BioBeads separation, preparative GPC may prove useful here.



Luminescence and oxygen quenching were explored for the Ru complexes (**2**−**11**). Nonpolymeric di- and hexafunctional $[Ru(bpy)_3]^{2+}$ analogues with oxygen and sulfur substituents exhibited lifetimes that are comparable to the $[Ru(bpy)_3]Cl_2$ parent complex. The absorption, emission, and quenching properties of the complexes are provided in Table 1. Both polymeric and nonpolymeric Ru complexes exhibited similar absorption and emission spectra. Representative examples for the Ru thioacetate **2** are provided in Figure 4. Emission decay curves were fit to a single exponential, suggesting the presence of one luminophore in a uniform environment. Stern−Volmer and bimolecular

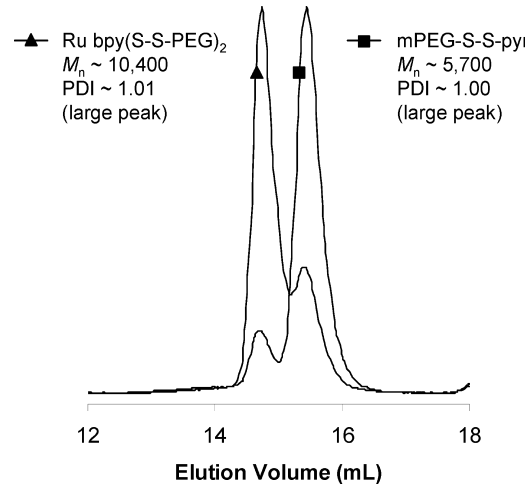


Figure 2. Refractive index GPC overlay of mPEG-S-S-pyr (■) commercial starting material and Ru disulfide-PEG (▲) coupled product in THF.

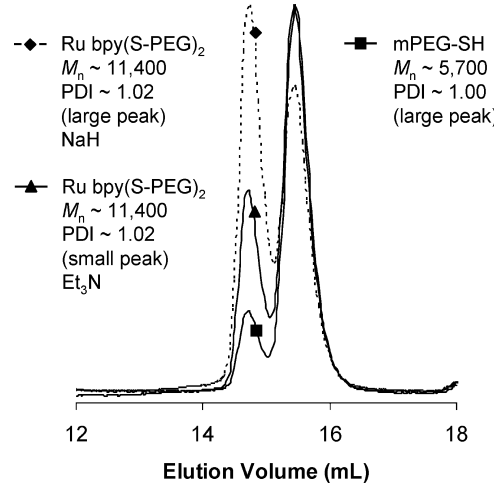


Figure 3. GPC overlay of mPEG-SH (■) and Ru thioether-PEG products (◆,▲). Coupling increased with NaH (◆) versus triethylamine (▲) as a base.

quenching constants show similar quenching behavior for these nonpolymeric analogues, as indicated by comparable k_q values.

In some cases, thiols are known to quench the excited state of $[Ru(bpy)_3]^{2+}$ with sulfur oxidation and concomitant metal reduction.[46–48] Luminescence of $[Ru(bpy)_3]^{2+}$ is quenched by thiolates such as dithyldithiocarbamate (dtc)[46] or sodium benzothiolate in acetonitrile solution[47] or by 4-mercaptopyridine in aqueous solution. $[Ru(bpy)_3]^{2+}$ is reduced to $[Ru(bpy)_3]^{+}$, and disulfide oxidation products are formed. In these examples, the sulfur groups were not covalently attached to the Ru complex. However, in this study, when $-CH_2SH$ groups are present as substituents, **6**, the excited state of $[Ru(bpy)_3]^{2+}$ is not quenched. If the thiol group in **6** were functioning as an intramolecular quencher, then the lifetime should be significantly shorter than for $[Ru(bpy)_3]^{2+}$, but this is not the case. Under an argon atmosphere, the lifetimes of the Ru dithiol complex and $[Ru(bpy)_3]^{2+}$ are the same (τ_o = 1067 ns) (Table 1). ^1H NMR analysis and single exponential emission decay suggest that a single luminophore is present in solution. After exposure to oxygen, a red-shifted emission λ_{max} was observed and corresponding

Table 1. Luminescence Lifetimes and Oxygen Quenching Data for Ru(II) Complexes[a] in CH_3CN

complex[a]	λ_{max} (nm)	ε (M^{-1} cm^{-1})	τ_0[b] (ns)	τ_{air}[c] (ns)	τ_{O_2}[d] (ns)	K_{SV}[e] (M^{-1})	$k_q \times 10^{-9}$[f] (M^{-1} s^{-1})
$[Ru(bpy)_3]^{2+}$	451	14340	1067	158	37	3061	2.87
$[Ru(bpy)_2\{bpy(CH_2SC(O)CH_3)_2\}]^{2+}$	455	15860	1056	188	47	2376	2.25
$[Ru\{bpy(CH_2SC(O)CH_3)_2\}_3]^{2+}$	464	16970	1180	184	49	2550	2.16
$[Ru(bpy)_2\{bpy(CH_2OC(O)CH_3)_2\}]^{2+}$	453	15170	1073	197	49	2293	2.14
$[Ru\{bpy(CH_2OC(O)CH_3)_2\}_3]^{2+}$	459	16780	1090	212	54	2111	1.94
$[Ru(bpy)_2\{bpy(CH_2SH)_2\}]^{2+}$	455	19530	1067	190[i]	45[i]	2501	2.34
$[Ru(bpy)_2\{bpy(CH_2OH)_2\}]^{2+}$	454	17750	1059	157	39	2863	2.70
$[Ru(bpy)_2\{bpy(CH_2SCH_3)_2\}]^{2+}$	455	13140	1018	181	48	2244	2.20
$[Ru(bpy)_2\{bpy(SS\text{-}PEG\text{-}OCH_3)_2\}]^{2+}$	457	18100[g]	1134[i]	251[i]	75[i]	1564	1.38
$[Ru(bpy)_2\{bpy(S\text{-}PEG\text{-}OCH_3)_2\}]^{2+}$	456	19800[h]	1174[i]	219[i]	55[i]	2231	1.90

[a] Emission $\lambda_{max} = 630$ nm. [b] τ_0 = lifetime in absence of oxygen. [c] τ_{air} = lifetime in air saturated solution. [d] τ_{O_2} = lifetime in oxygen saturated solution. [e] K_{SV} = Stern−Volmer quenching constant. Values obtained are within ± 5% standard deviation unit. [f] k_q = bimolecular quenching rate constant. [g] Based on GPC molecular weight, corrected for 80% coupled product. [h] Based on GPC molecular weight, corrected for 60% coupled product. [i] Lifetime data fit to double exponential. Pre-exponential weighted lifetimes are reported.

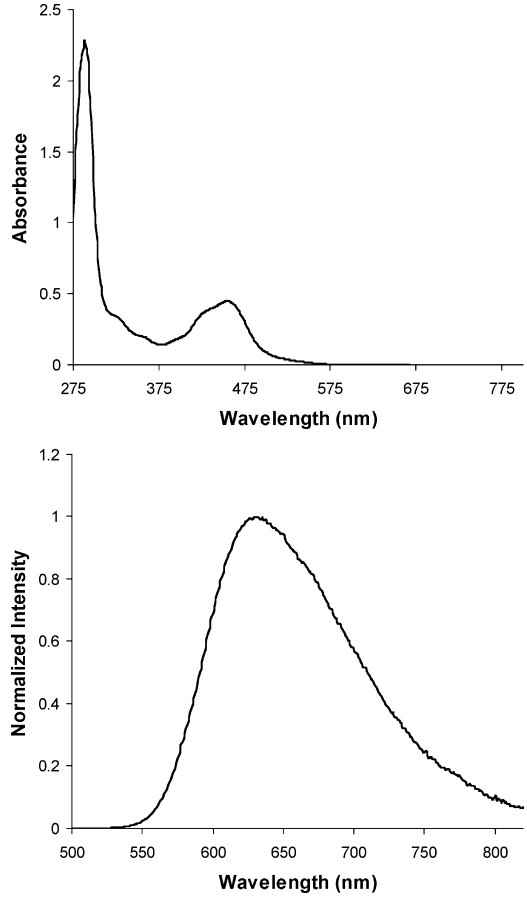


Figure 4. UV−vis (top) and emission (bottom) spectra of Ru dithioacetate, **2**, in CH_3CN solution.

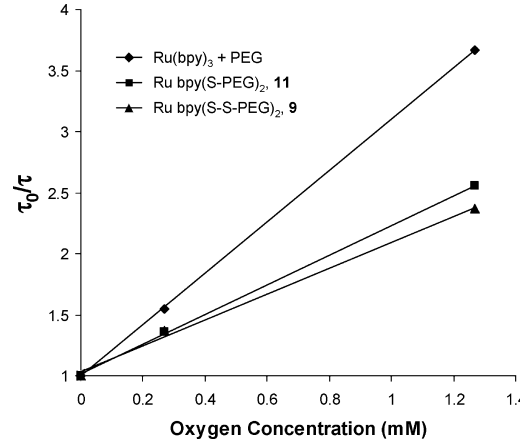


Figure 5. Lifetime Stern−Volmer quenching plot for the $Ru(bpy)_3$/PEG blend, Ru disulfide-PEG (**9**), and Ru thioether-PEG (**11**) by molecular oxygen in aqueous solution.

emission decay data were fit to a multiexponential, indicative of multiple species in solution. Given that thiols are unstable to air oxidation,[46–48] this could account for the mixture of luminescent products. A linear Stern−Volmer plot using pre-exponential lifetimes was obtained for **6**, indicating that dynamic quenching is the predominant process.

Oxygen quenching studies were also performed with Ru disulfide-PEG, **9**, and Ru thioether-PEG, **11**, products in acetonitrile solution. Here, emission decay curves were fit to a multiexponential. This may be due to different luminophore microenvironments[2] or a mixture of mono- and disubstituted Ru PEG species. Similar to the nonpolymeric analogues, the lifetimes of both Ru disulfide-PEG and Ru thioether-PEG in CH_3CN solution were 1018 and 1147 ns, respectively. Oxygen quenching experiments resulted in bimolecular quenching rates, k_q, of 1.38×10^{-9} M^{-1} s^{-1} for the disulfide and 1.90×10^{-9} M^{-1} s^{-1} for the thioether PEG complex. In comparison to $[Ru(bpy)_3]^{2+}$ and other nonpolymeric analogues, lower k_q values were observed. Shielding effects are noted with covalent attachment of polymers to metal complexes.[36,64] Polymer chains can slow oxygen diffusion and thus hinder physical contact at the metal center. The k_q value for Ru thioether-PEG is higher, approaching values for nonpolymeric analogues, perhaps due to the lower polymer coupling yield and the likely higher percentage of the monoPEGylated complex, which may be more accessible to the quencher. In contrast, Ru disulfide-PEG was obtained in higher yield and lower k_q values were observed.

Oxygen quenching studies of Ru disulfide-PEG and Ru thioether-PEG were also performed in aqueous solution for comparison. $[Ru(bpy)_3]^{2+}$ and a $[Ru(bpy)_3]^{2+}$/HO-PEG-OH blend were also explored as controls to evaluate the effect of PEG on the luminescence properties of Ru tris(bpy) in solution versus chemical attachment. Two equivalents of HO-PEG-OH were used in binary mixture measurements to correlate with metal/polymer ratios in Ru PEG PMCs. Lifetime Stern−Volmer plots were fit with linear regression (Figure 5). Lifetimes and rates of quenching for $[Ru(bpy)_3]^{2+}$

(64) Vogtle, F.; Plevoets, M.; Nieger, M.; Azzellini, G. C.; Credi, A.; De Cola, L.; De Marchis, V.; Venturi, M.; Balzani, V. *J. Am. Chem. Soc.* **1999**, *121*, 6290–6298.

Table 2. Luminescence Lifetimes and Oxygen Quenching Data for Ru(II) Complexes in H_2O

complex	τ_0[a] (ns)	τ_{air}[b] (ns)	τ_{O_2}[c] (ns)	K_{SV}[d] (M^{-1})	$k_q \times 10^{-9}$[e] (M^{-1} s^{-1})
$[Ru(bpy)_3]^{2+}$	611	391	167	2094	3.43
$[Ru(bpy)_3]^{2+}$ + PEG	618	394	167	2097	3.40
$[Ru(bpy)_2\{bpy(SS\text{-}PEG\text{-}OCH_3)_2\}]^{2+}$	555[f]	406[f]	235[f]	1087	1.96
$[Ru(bpy)_2\{bpy(S\text{-}PEG\text{-}OCH_3)_2\}]^{2+}$	520[f]	383[f]	204[f]	1229	2.36

[a] τ_0 = lifetime in absence of oxygen. [b] τ_{air} = lifetime in air saturated solution. [c] τ_{O_2} = lifetime in oxygen saturated solution. [d] K_{SV} = Stern−Volmer quenching constant. Values obtained are within ± 5% standard deviation unit. [e] k_q = bimolecular quenching rate constant. [f] Lifetime data fit to double exponential. Pre-exponential weighted lifetimes are reported.

and the $[Ru(bpy)_3]^{2+}$/PEG blend are comparable (Table 2); the presence of PEG in solution does not affect luminescence properties in a significant way. Though luminescence lifetimes, τ_0, for Ru disulfide-PEG and Ru thioether-PEG complexes (Table 2) are not affected by PEG covalent attachment, decreased rates of quenching, k_q, indicate polymer shielding effects. Similar properties have been observed for other Ru tris(bpy) polymers.[36,64]

Conclusion

A series of nucleophilic and electrophilic Ru tris(bpy) derivatives with sulfur and oxygen substituents were synthesized for use in model studies and PEG coupling reactions. Thiol functionalized Ru complexes were achieved using thioacetate-substituted bpy ligands to prevent competing coordination of sulfur to Ru ions. The reduction of the Ru thioacetate complex, **2**, leads to the dithiol complex, **6**, which serves as a precursor to materials with disulfide linkages, **9**. Alternatively, thiol PEG reagents can react with $[Ru(bpy)_2\{bpy(CH_2Cl)_2\}]^{2+}$ to produce PMCs with thioether linkages, **11**. Luminescence lifetimes and oxygen quenching behavior of nonpolymeric analogues were similar to the parent compound, $[Ru(bpy)_3]^{2+}$. In contrast to certain Ru tris(bpy) thiol reagent mixtures,[46–48] intramolecular quenching of the excited state by the sulfide was not observed for the Ru complex **6** with thiols as substituents. Lifetimes of Ru PEG materials were similar to $[Ru(bpy)_3]^{2+}$; however, rates of quenching were slower for ruthenium polymeric metal complexes due to shielding effects.

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Supporting Information Available: ^1H NMR spectra for compounds **1**−**11** and double exponential fit lifetime data. This material is available free of charge via the Internet at http://pubs.acs.org.

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