Diastereoselective Synthesis and Two-Step Photocleavage of Ruthenium Polypyridyl Complexes Bearing a Bis(thioether) Ligand

Michael S. Meijer and Sylvestre Bonnet

Leiden Institute of Chemistry, Leiden University, P.O. Box 9502, 2300 RA Leiden, The Netherlands

ABSTRACT: Thioethers are good ligands for photoactivatable ruthenium(II) polypyridyl complexes, as they form thermally stable complexes that are prone to ligand photostabilization. Here, we introduce a novel symmetric chelating bis(thioether) ligand scaffold, based on 1,3-bis(methylthio)-2-propanol (4) and report the synthesis and stereochemical characterization of the series of novel ruthenium(II) polypyridyl complexes \([\text{Ru}(\text{bpy})_2(L)](\text{PF}_6)_2\) \([1]−[3]−(\text{PF}_6)_2\), where \(L\) is ligand 4, its methyl ether, 1,3-bis(methylthio)-2-methoxypropane (5), or its carboxymethyl ether, 1,3-bis(methylthio)-2-(carboxymethoxy)propane (6). Coordination of ligands 4–6 to the bis(bipyridine)ruthenium center gives rise to 16 possible isomers, consisting of 8 possible \(\Lambda\) diastereoisomers and their \(\Delta\) enantiomers. We found that the synthesis of \([1]−[3]−(\text{PF}_6)_2\) is diastereoselective, yielding a racemic mixture of the \(\Lambda-\text{eq}-(S)\)-ax-OH eq-[\text{Ru}]^{2+} and \(\Delta-\text{ax}-(R)\)-eq-OH eq-[\text{Ru}]^{2+}\) isomers. Upon irradiation with blue light in water, \([1]−[3]−(\text{PF}_6)_2\) selectively substitute their bis(thioether) ligands for water molecules in a two-step photoreaction, ultimately producing \([\text{Ru}(\text{bpy})_2(\text{H}_2\text{O})_2]^{2+}\) as the photoproduct. The relatively stable photochemical intermediate was identified as \(\text{cis}−[\text{Ru}(\text{bpy})_2(\text{i}^2\text{L})(\text{H}_2\text{O})]^2\) by mass spectrometry. Global fitting of the time evolution of the UV–vis absorption spectra of \([1]−[3]−(\text{PF}_6)_2\) was employed to derive the photocleavage quantum yields (\(\Phi_{\text{CL}}\)) for each of the two photochemical reaction steps separately, revealing very high quantum yields of 0.16–0.25 for the first step and lower values (0.0055–0.0093) for the second step of the photoconversion. The selective and efficient photochemical reaction makes the photocleavable bis(thioether) ligand scaffold reported here a promising candidate for use in e.g. ruthenium-based photo-activated chemotherapy.

INTRODUCTION

The use of light as a trigger for the activation of metal-based anticancer agents has been actively researched over the last decades. In combination with ruthenium(II) complexes, light can be used either to drive the formation of reactive oxygen species through the sensitization of oxygen in photodynamic therapy (PDT) or to uncage photoactivatable complexes through ligand photosubstitution in photoactivated chemotherapy (PACT). This photolability can be enhanced through both steric and electronic effects. In our group, thioether ligands have been considered with more attention for the photocaging of bioactive ruthenium polypyridyl complexes. Several groups have shown that thioether ligands can be selectively substituted by solvent molecules, both for monodentate ligands, e.g. 2-(methylthio)ethanol (Hmte), and for bidentate chelating thioether ligands. Examples of the latter include combinations of thioether sulfur donors with nitrogen donor atoms, e.g. 2-(methylthio)methylpyridine (mmmp), as well as symmetric bis(arylthioether) ligands, e.g. 1,3-bis(phenylthio)propane (bptp). The photosubstitution of some bis(thioether) ligands was previously reported to be 5–10 times more efficient than that of comparable bis(amine) ligands. However, these reports do not always appreciate the two-step nature of the photosubstitution of such bidentate ligands, reporting the photosubstitution quantum yields as a single number. Furthermore, the bis(thioether) ligands reported previously often have limited options for further functionalization, such as the attachment of anchoring groups, which can be very useful for the development of photocleavable ruthenium complexes bound to inorganic surfaces or nanomaterials.

In this work, we report the coordination of the symmetric bidentate bis(thioether) ligand 1,3-bis(methylthio)-2-propanol (4) to ruthenium. We introduced an alcohol functionality in this ligand to allow for further functionalization; this substituent was added in a symmetrical position to prevent the formation of regioisomers upon metal coordination of the ligand. To exemplify these functionalization options, we also prepared the
Scheme 1. Chemical Structures of New Ruthenium Polypyridyl Complexes [1]–[3][PF6]2 (Left) and Complexes [7]–[10][PF6]2, Previously Reported by the Groups of Turro (Center) and Sauvage (Right).26,27

Experimental Section

General Considerations. Dry tetrahydrofuran (THF) was collected from a Pure-Solv MDS dry solvent dispenser (Demaco). 1,3-Bis(methylthio)-2-propanol (4) was obtained from Alfa Aesar. All other reagents and solvents, including cis-[Ru(bpy)2Cl2], were purchased from Sigma-Aldrich and used as received. All syntheses were conducted under an oxygen-free atmosphere using standard Schlenk line techniques. Syntheses of all ruthenium complexes were performed in an argon atmosphere in a round-bottom flask containing 1,3-bis(methylthio)-2-propanol (0.56 g, 0.50 mL, 3.70 mmol), followed by the addition of solid NaH (296 mg, 7.40 mmol, 60% dispersion in mineral oil). The resulting suspension was stirred at room temperature for 20 min to allow complete deprotonation of the alcohol. Afterward the reaction mixture was cooled to 0 °C, and iodo methane (0.63 g, 0.28 mL, 4.44 mmol) was added dropwise. The resulting suspension was stirred at room temperature for 24 h and then quenched with saturated aqueous NH4Cl (5 mL) to yield a light yellow solution. The solvent was removed in vacuo, and the residue was dissolved in H2O (40 mL) and extracted with DCM (3 × 40 mL). The organic layers were combined, washed with brine, dried over MgSO4, and concentrated by rotary evaporation. Separation of the product (Rf = 0.7) and unreacted starting compound (Rf = 0.9) was performed by column chromatography (SiO2, petrol ether 40/60/EtOAc (4/1)), ultimately resulting in 404 mg of compound 5 as a colorless oil (2.43 mmol, 66%).1H NMR (400 MHz, δ in CDCl3): 3.50 (p, J = 5.7 Hz, H2 + H4), 3.42 (s, 3H, H6), 2.74 (dd, J = 21.4, 13.6, 5.7 Hz, H3), 2.16 (s, 6H, H1 + H5).13C NMR (101 MHz, δ in CDCl3): 80.6 (C1), 75.7 (C2), 37.2 (C3 + C4), 16.8 (C5 + C6). ESI-MS in CH3OH m/z exp (calc): 205.0 (205.0, [M + K]+).1H NMR data match the literature data.11

1,3-Bis(methylthio)-2-carboxymethoxy)propane (5). Dry and deoxygenated THF (20 mL) was placed under a dinitrogen atmosphere in a round-bottom flask containing 1,3-bis(methylthio)-2-propanol (0.56 g, 0.50 mL, 3.70 mmol), followed by the addition of solid NaH (296 mg, 7.40 mmol, 60% dispersion in mineral oil). The resulting suspension was stirred at room temperature for 20 min to allow complete deprotonation of the alcohol. Afterward the reaction mixture was cooled to 0 °C, and iodo methane (0.63 g, 0.28 mL, 4.44 mmol) was added dropwise. The resulting suspension was stirred at room temperature for 24 h and then quenched with saturated aqueous NH4Cl (5 mL) to yield a light yellow solution. The solvent was removed in vacuo, and the residue was dissolved in H2O (40 mL) and extracted with DCM (3 × 40 mL). The organic layers were combined, washed with brine, dried over MgSO4, and concentrated by rotary evaporation. Separation of the product (Rf = 0.7) and unreacted starting compound (Rf = 0.9) was performed by column chromatography (SiO2, petrol ether 40/60/EtOAc (4/1)), ultimately resulting in 404 mg of compound 5 as a colorless oil (2.43 mmol, 66%).1H NMR (400 MHz, δ in CDCl3): 3.50 (p, J = 5.7 Hz, H2 + H4), 3.42 (s, 3H, H6), 2.74 (dd, J = 21.4, 13.6, 5.7 Hz, H3), 2.16 (s, 6H, H1 + H5).13C NMR (101 MHz, δ in CDCl3): 80.6 (C1), 75.7 (C2), 37.2 (C3 + C4), 16.8 (C5 + C6). ESI-MS in CH3OH m/z exp (calc): 205.0 (205.0, [M + K]+).1H NMR data match the literature data.11
(C2 + C6), 16.6 (C1 + C4). HR-MS in CH3OH m/z exp(1) (calcld): 233.0285 (233.0384, [M + Na]+).

**Ruthenium Complex Synthesis.** [Ru(bpy)4](PF6)2 ([1](PF6)2). A mixture of 1,3-bis(methylthio)-2-propanol (4, 78 mg, 0.51 mmol) and cis-Ru(bpy)Cl2 (50 mg, 0.103 mmol) was placed in a 25 mL round-bottom flask, under an N2 atmosphere. A deoxygenated mixture of CH2Cl2 and H2O (10 mL, v/v, 1:1) was added. The reaction mixture was refluxed in the dark for 5 h. The resulting orange solution was cooled to room temperature, and EtOH was removed in vacuo. Water (10 mL) was added to the residue, before washing with EtO (3 × 15 mL). A saturated aqueous KPF6 solution (5 mL) was then added to the aqueous layer, and the resulting orange suspension was extracted with DCM (6 × 20 mL). The combined organic layers were washed once with half saturated aqueous KPF6 and then dried by rotary evaporation. Any excess KPF6 was removed by size exclusion chromatography in acetone, and after drying overnight under high vacuum, complex [1](PF6)2 was obtained as an orange powder (50 mg, 0.058 mmol, 57%). TLC: Rf = 0.2 (SiO2, acetone/H2O/saturated aqueous KPF6 (16/4/1)).

1H NMR (500 MHz, δ in acetone-d6): 9.87 (d, J = 5.1 Hz, 1H, H6), 9.63 (d, J = 5.6 Hz, 1H, H5), 8.88 (t, J = 8.1 Hz, 2H, H2D + H3D), 8.74 (dd, J = 8.2, 3.5 Hz, 2H, HB2 + HB3), 8.47 (tdd, J = 7.9, 2.9, 1.4 Hz, 1H, HB4), 8.18 (td, J = 7.9, 1.5 Hz, 2H, H4A + H4B), 8.08 (dddd, J = 11.2, 7.4, 5.7, 1.4 Hz, 2H, H5A + H5B), 7.84 (d, J = 5.8 Hz, 1H, H6), 7.79 (t, J = 5.3 Hz, 1H, H4), 7.52 (tdd, J = 7.2, 5.6, 1.3 Hz, 2H, HB4 + HB5), 5.33 (d, J = 4.4 Hz, 1H, −OH), 4.87 (br s, 2H, H2), 3.41 (dd, J = 13.5, 3.1 Hz, 1H, H3), 3.30 (dd, J = 13.1, 6.3 Hz, 1H, H2), 3.01 (dd, J = 13.1, 2.1 Hz, 1H, H1), 2.95–2.93 (m, 1H, H4B), 1.59 (s, 3H, H5), 1.36 (s, 3H, H3H), 1.2C NMR (101 MHz, δ in acetone-d6): 158.8, 158.7, 156.7, 157.5 (all Cq), 154.6 (C6), 154.4 (CA6), 152.2 (CA5), 152.1 (CA6), 140.0 (CA4 + CB4 + CC4 + CD4), 129.7, 129.1 (CA5 + CB5 + CC5), 128.9, 128.8 (CB5 + CC6), 126.0, 125.9 (CA4 + CD5), 125.3, 125.2 (CB4 + CD4), 129.0, 121.8 (C1), 16.1 (C1), HR-MS in CH3CN m/z exp(1): 303.5503 (303.5504, [M - 2PF6 - 2H]+), 565.0662 (565.0669, [M - 2PF6 - H]+). UV-Vis: λmax (e in M−1 cm−1) in H2O: 413 nm (5.13 × 104).

Calcld. for C21H28F12N4O3P2Mg: C, 34.91; H, 3.64; N, 6.14. Found: C, 34.91; H, 3.87; N, 5.89.

**Density Functional Theory.** Structure minimizations were performed using density functional theory (DFT) as implemented in the ADF software package from SCM (version 2017). The structures of the 16 possible A stereoisomers of [1](PF6)2 consisting of eight isomers with a chairlike metallacycle (i.e., R and S conformation for both sulfur atoms and the −OH substituent) and eight isomers with a boatlike metallacycle, were optimized in water using the conductor-like screening model (COSMO) to simulate the effect of solvent. The BLYP functional,36 combined with a TZP basis set (valence triple-ζ plus 1 polarization function) and a small frozen core for all atoms including ruthenium,35 was employed in all calculations. All boatlike structures were found to convert to chairlike structures during the structure optimization process and thus not shown.

**Photosubstitution Quantum Yields of [1]–[3](PF6)2 under Blue Light Irradiation.** UV–vis measurements on the ruthenium complexes were performed on a Cary 50 Varian spectrometer equipped with a Cary Single Cell Peltier for temperature control (T = 298 K) and stirring. For the irradiation, a LED light source was used (λ = 443 nm, fwhm = 11 nm) the photon flux of which was determined by ferrooxalate actinometry (see Table S1 in the Supporting Information). Experiments were performed in 1.0 × 1.0 cm fluorescence cuvettes (QS-111, Hellma Analytics) containing 3.0 mL of solution. A stock solution of the desired complex was prepared using demineralized water, which was then diluted to the desired working concentration (Table S1) and placed in the cuvette. Irradiations were carried out under an N2 atmosphere after deoxygenation for 10 min. The cuvettes were then gently bubbling of N2 through the sample, and the sample was kept under an inert atmosphere during the experiment by a gentle flow of N2 over the top of the cuvette. A UV–vis absorption spectrum was measured every 6 s during the experiment. Data were analyzed using Microsoft Excel 2010. The quantum yields of the photosubstitution reactions (Φps) were calculated by fitting the time evolution of the UV–vis absorption spectra of the irradiated solution using the Glotaran software package (see the Supporting Information for a full description). Mass spectrometry was performed after the irradiation reaction to identify the photoproducts.

**Photolysis Monitored by 1H NMR Spectroscopy.** Deoxygenated D2O (0.6 mL) was placed in an NMR tube containing [1](PF6)2 (1 mg) under an N2 atmosphere, resulting in an orange solution (2 mL). The tube was irradiated at room temperature using a LOT 1000 W xenon arc lamp equipped with an IR short-pass filter and a 400 nm long-pass filter. The progress of the photoreaction was monitored by 1H NMR at several time points until the steady state was reached (at 60 min irradiation).

A reference sample of cis-[Ru(bpy)3(H2O)]2+(CF3SO3)2 (cis-[14](CF3SO3)2) in D2O was prepared by the addition of a drop of trifluoro acid to a suspension of [Ru(bpy)3]2+ in D2O in the absence of light. The latter was prepared following a literature procedure.37

**Singlet Oxygen Generation and Photophysical Quantum Yield of [1]–[3](PF6)2.** The singlet oxygen generation and
phosphorescence quantum yields of $[1] - [3](\text{PF}_6)_2$ were determined by relative methods, using $[\text{Ru}(\text{bpy})_3]\text{Cl}_2$ as the standard. A full description is provided in the Supporting Information.

## RESULTS AND DISCUSSION

### Synthesis

Ligands 5 and 6 were obtained in good yields from the commercially available ligand 4 through deprotonation of the alcohol with sodium hydride, followed by nucleophilic substitution using iodomethane or bromoacetic acid as the electrophile, respectively (Scheme 2). Coordination of ligands 4−6 to the ruthenium center was achieved by refluxing an excess of the ligand (2−10 equiv) with cis-$[\text{Ru}(\text{bpy})_2\text{Cl}_2]$ in an ethanol/water mixture. Replacement of the two coordinating chlorides by ligands 4−6 was typically completed within 1.5 h, as shown by the color change of the solution from purple to orange. After anion exchange with KPF$_6$, complexes $[1] - [3](\text{PF}_6)_2$ were obtained in 55−69% yield as orange solids. The complexes were all isolated as their bis(hexafluoridophosphate) salt, as confirmed by elemental analysis. The workup of compound $[3](\text{PF}_6)_2$ was performed under acidic conditions (pH $\sim 2$) to ensure protonation of the carboxylic acid in the final solid product. All three complexes were soluble in water, despite their apolar counterions.

Coordination of the bis(thioether) ligand was clearly demonstrated by $^1$H NMR by a splitting of the signal of the thiomethyl groups, e.g., from a singlet at 2.16 ppm for ligand 5 in CDCl$_3$ to two singlets at 1.63 and 1.34 ppm for complex $[2](\text{PF}_6)_2$ in acetone-$d_6$. Further characterization of the complexes was performed using high-resolution mass spectrometry and elemental analysis.

As we used a racemic sample of cis-$[\text{Ru}(\text{bpy})_2\text{Cl}_2]$ for the synthesis of $[1] - [3](\text{PF}_6)_2$, we obtained racemic mixtures of the $\Lambda$ and $\Delta$ enantiomers for each complex. An additional stereocchemical complication is caused by the six-membered ring formed by the coordination of ligands 4−6, which induces four more sources of isomerism: the configuration (R or S) of the two sulfur atoms, the configuration of the carbon atom attached to the hydroxyl or ether group, leading to either an axial or equatorial −OR substituent, and the inversion of the six-membered metallacycle, which transforms all axial substituents on the ring into equatorial ones (see Scheme 3). With five stereogenic centers, we would expect 32 possible isomers, i.e., 16 $\Lambda$ diastereoisomers and their respective $\Delta$ enantiomers. However, due to the plane of symmetry in ligands 4−6, inversion of the six-membered ring leads to the formation of one of the other diastereoisomers: e.g., ring inversion of $\Lambda$-$\text{a-Ru}^{2+}$ (see Scheme 3) leads to the formation of $\Lambda$-$\text{h-Ru}^{2+}$. Thus, we concluded that there are eight possible $\Lambda$ diastereoisomers in total, shown in Scheme 3, all with their respective $\Delta$ enantiomers. It should be noted that the determination of enantiomer relationships is nontrivial for...
Table 1. Enantiomer Relationships for Complexes $[1]^{2+}$–$[3]^{2+}$

| Enantiomer      | $\Lambda$ | $\Delta$ |
|-----------------|-----------|-----------|
| $\Lambda$-[Ru]$_2$ | $\Lambda$-a | $\Delta$-a |
| $\Lambda$-b-[Ru]$_2$ | $\Lambda$-c | $\Delta$-c |
| $\Lambda$-d-[Ru]$_2$ | $\Lambda$-e | $\Delta$-e |
| $\Lambda$-f-[Ru]$_2$ | $\Lambda$-g | $\Delta$-g |
| $\Lambda$-h-[Ru]$_2$ | $\Lambda$-i | $\Delta$-i |

**Note:** The definition of the isomers is given in Scheme 3. The enantiomer of each isomer shown in the top line corresponds to the isomer shown in the bottom line.

These complexes. For example, whereas the mirror image of $\Lambda$-a-[1]$_2^{2+}$ is as expected $\Delta$-a-[1]$_2^{2+}$, the enantiomer of $\Lambda$-b-[1]$_2^{2+}$ is $\Delta$-c-[1]$_2^{2+}$ because the two nonequivalent sulfur atoms in diastereoisomer b exchange with each other upon mirroring into c. A similar exchange occurs with isomers f and g. The full list of enantiomeric pairs is shown as Table 1 for convenience. According to 1D and 2D $^1$H NMR, which showed only a single set of 16 aromatic proton signals originating from the bipyridine ligands, all 3 complexes were obtained as a racemic mixture of a single diastereomer.

**Structural Characterization by NMR and DFT.** In order to gather insight into which one of the eight diastereoisomers of $[1](PF_6)_2$ was obtained, we performed a computational study of the stability of each of these isomers in aqueous solution using DFT, employing the COSMO model to simulate solvent effects. We minimized the structures of the eight $\Lambda$ diastereoisomers of $[1]^{2+}$ shown in Scheme 3, where the six-membered ring is in a chair conformation, as well as the eight possible diastereoisomers with the six-membered ring in a boat configuration. The diastereoisomers in a boat configuration either relaxed to one of the chair configurations shown above or resulted in a twisted-boat configuration with a high energy. Thus, we conclude that a boat configuration is energetically strongly disfavored for the six-membered metalacycle in $[1]^{2+}$ and that the product obtained must be in a chair configuration. The optimized structures, their structural distortion parameters, and their respective energies in water are given in Table 2, Table S2, and Figure S1. Four of the possible geometries, i.e. $\Lambda$-b-[1]$_2^{2+}$, $\Lambda$-d-[1]$_2^{2+}$, $\Lambda$-g-[1]$_2^{2+}$, and $\Lambda$-h-[1]$_2^{2+}$, were significantly higher in energy, in comparison to the other four. All of these geometries have one of the sulfur atoms in an (R)-ax orientation that leads to a steric clash of the thiomethyl group with one of the bipyridine ligands (Figure S1). Diastereoisomer $\Lambda$-(S)-eq-(S)-ax-OH$_{eq}$-[1]$_2^{2+}$ ($\Lambda$-f-[1]$_2^{2+}$ in Scheme 3) was found to be the lowest in energy, 3.7 kJ mol$^{-1}$ lower than the diastereoisomer that is second lowest, $\Lambda$-(S)-eq-(S)-ax-OH$_{eq}$-[1]$_2^{2+}$ ($\Lambda$-c-[1]$_2^{2+}$), obtained by inversion of the configuration of the carbon atom bearing the alcohol substituent. Two more diastereoisomers have relatively low energies, namely $\Lambda$-(S)-eq-(R)-eq-OH$_{eq}$-[1]$_2^{2+}$ ($\Lambda$-a-[1]$_2^{2+}$), and $\Lambda$-(S)-eq-(R)-eq-OH$_{eq}$-[1]$_2^{2+}$ ($\Lambda$-e-[1]$_2^{2+}$), where both thiomethyl groups are found in equatorial positions. The small energy differences of $\sim 4$ kJ mol$^{-1}$ between these isomers is not enough to exclude any of these four structures purely on the basis of their computed energies.

As the DFT calculations did not provide a conclusive answer, we turned to $^1$H NMR spectroscopy. The stereochemistry of the carbon atom bearing the alcohol (C$_3$ in Figure 1) could be found from the $^3$J coupling constants of the protons on the adjacent carbon atom (C$_2$). The large difference between the $^3$J coupling constant of the axial ($^3$J = 6.3 Hz) and equatorial protons ($^3$J = 2.1 Hz) suggests that the proton on C$_3$ is positioned axially, and thus the $\bar{\text{O}}$H group has to be equatorial. NOESY NMR spectroscopy further confirmed the axial position of this proton (H$_4$) by an off-diagonal correlation with the D$_6$ proton of the bpy ligand (Figure S2). As the alcohol group is equatorial, the number of possible $\Lambda$ isomers of $[1]^{2+}$ in solution was reduced to two, i.e. $\Lambda$-(S)-eq-(S)-ax-OH$_{eq}$-[1]$_2^{2+}$ ($\Lambda$-f-[1]$_2^{2+}$) and $\Lambda$-(S)-eq-(R)-eq-OH$_{eq}$-[1]$_2^{2+}$ ($\Lambda$-e-[1]$_2^{2+}$), which differ from each other by a single inversion of sulfur chirality. In order to assess whether this thiomethyl group (C$_1$ in Figure 1) was axial or equatorial, we examined the off-diagonal NOESY correlations of this group (Figure S3). We found a correlation of these protons to the A$_6$ proton of the bpy ligand, over a distance of 3.29 Å versus 5.00 Å for the equatorial and axial cases, respectively. This suggested that the thiomethyl group is oriented equatorially. However, the protons on C$_3$ also show an off-diagonal correlation to the axial proton on C$_3$, a proton that is significantly closer if the thiomethyl group is oriented axially (3.36 Å versus 4.98 Å). Finally, a weak correlation was found to the C$_3$ proton on the bipyridine ring, which is closer to thiomethyl group C$_3$ in the axial conformation (5.19 Å versus 4.98 Å). All in all, this convinced us that this thiomethyl group is at least predominantly oriented axially, yet an equilibrium between its axial and equatorial positions in solution could not be fully excluded. Thus, our NMR studies suggest that $[1]^{2+}$ is predominantly a racemic mixture of $\Lambda$-(S)-eq-(S)-ax-OH$_{eq}$-[1]$_2^{2+}$.
Oxygen Quantum Yield ($\Phi$), Photosubstitution Quantum Yields ($\Phi_{443}$) and Photosubstitution Reactivities ($\xi_{443}$) at 298 K in H$_2$O, Single Oxygen Quantum Yield ($\Phi_p$), and Phosphorescence Quantum Yield ($\Phi_\lambda$) at 293 K in MeOD for Complexes [1]–[3]([PF$_6$]$_2$) and Photochemical Intermediates [11]–[13]([PF$_6$]$_2$)

| complex | $\lambda_{max}$/nm | $\epsilon_{max}$/10$^3$ M$^{-1}$ cm$^{-1}$ | $\epsilon_{443}$/10$^3$ M$^{-1}$ cm$^{-1}$ | $\Phi_{443}$ | $\xi_{443}$ | $\Phi_\lambda$ | $\Phi_p$ ($\lambda_{max}$/nm) |
|---------|-------------------|---------------------------------|---------------------------------|--------------|--------------|--------------|---------------------|
| [1]([PF$_6$]$_2$) | 413 (5.13) | 2.95 | 0.24 | 704 | 0.008 | 2.0 $\times$ 10$^{-4}$ (624) |
| [11]([PF$_6$]$_2$) | 453 (7.02) | 6.68 | 0.0079 | 53 | <0.005 | 6 $\times$ 10$^{-5}$ (620) |
| [12]([PF$_6$]$_2$) | 412 (4.04) | 2.29 | 0.25 | 578 | 0.007 | 1.4 $\times$ 10$^{-4}$ (620) |
| [13]([PF$_6$]$_2$) | 465 (6.52) | 5.04 | 0.0093 | 47 | <0.005 | 6 $\times$ 10$^{-5}$ (620) |
| [3]([PF$_6$]$_2$) | 412 (5.18) | 2.92 | 0.16 | 474 | <0.005 | 6 $\times$ 10$^{-5}$ (620) |
| [13]([PF$_6$]$_2$) | 465 (6.77) | 6.19 | 0.0055 | 34 | <0.005 | 6 $\times$ 10$^{-5}$ (620) |

Photochemistry. All three complexes form yellow solutions in water, showing a 3MLCT absorption band around 412 nm, with molar absorption coefficients of 4.0–5.2 $\times$ 10$^5$ M$^{-1}$ cm$^{-1}$ (Table 3), typical for ruthenium(II) polypyridyl complexes containing two thioether donor ligands. Essentially no phosphorescence was observed upon irradiation of the complexes with blue light in deuterated methanol (Figure S4A), with phosphorescence quantum yields $\Phi_p$ lower than 2.0 $\times$ 10$^{-4}$. The complexes also appeared to be very poor singlet oxygen sensitizers ($\Phi_\lambda \leq 0.008$, Figure S4B), as expected from their photosubstitution properties (vide infra).

In the absence of light, complexes [1]–[3]([PF$_6$]$_2$) were found to be stable in water (Figure S5). However, all three compounds are photoreactive under blue light irradiation in water. We monitored the photoreactions of [1]–[3]([PF$_6$]$_2$) with UV–vis absorption spectroscopy and mass spectrometry. Upon irradiation of a solution of [1]([PF$_6$]$_2$) with a blue LED ($\lambda$ = 443 ± 11 nm), we observed a two-step bathochromic shift in the MLCT absorbance band of the solution (Figure 2 and Figure S6). First, the absorption maximum shifted from 413 to 453 nm, accompanied by three isosbestic points at 319, 364, and 426 nm (Figure 2A). This first reaction was completed within 5 min under the irradiation conditions used (photon flux $q_p = 2.65 \times 10^{-8}$ mol of photons s$^{-1}$), at which point the absorption maximum started to shift toward longer wavelengths again. This second reaction, in which the absorption maximum changed from 453 to 491 nm, showed isosbestic points at 314, 330, 389, and 466 nm and was significantly slower than the first photoreaction (Figure 2B). Completion of this second reaction took 1 h, at which point a steady state was reached. Mass spectrometry of the reaction mixture after irradiation (Figure S7) showed a peak at $m/z$ 247.9, corresponding to [Ru(bpy)$_2$(CH$_3$CN)$_2$]$_{2+}$ (calcld $m/z$ 248.0), formed inside the mass spectrometer from the original photoproduct [Ru(bpy)$_2$(OH$_2$)$_2$]$_{2+}$ ([14]$_{2+}$). No signals were observed that match to photoproducts resulting from expulsion of one of the bpy ligands. This result indicates that, upon blue light irradiation of [1]$_{2+}$ in water, the bis(thioether) chelate 4 is selectively substituted by two water molecules.

The intermediate species in the photoreaction was identified by mass spectrometry, by measuring a sample after the first 5 min of irradiation (Figure S8). This sample showed the peak for the photoproduct, as well as a peak for the starting compound [1]$_{2+}$ at $m/z$ 282.7 (calcld $m/z$ 283.0), and another signal at $m/z$ 303.1, identified as [Ru(bpy)$_2$(4)(CH$_3$CN)]$_{2+}$ (calcld $m/z$ 303.6), formed inside the mass spectrometer from the original photochemical intermediate [Ru(bpy)$_2$(4)-(H$_2$O)]$_{2+}$. We hypothesized that the intermediate, which is reasonably stable, is most likely six-coordinate, with ligand 4 bound in a monodentate fashion, and the second thioether

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Table 3. Lowest-Energy Absorption Maxima ($\lambda_{max}$), Molar Absorption Coefficients at $\lambda_{max}$ ($\epsilon_{max}$) and 443 nm ($\epsilon_{443}$), Photosubstitution Quantum Yields ($\Phi_{443}$) and Photosubstitution Reactivities ($\xi_{443}$) at 298 K in H$_2$O, Single Oxygen Quantum Yield ($\Phi_p$), and Phosphorescence Quantum Yield ($\Phi_\lambda$).
group is replaced by water: i.e., \([\text{Ru}(\text{bpy})_2(\kappa^1\text{H}_2\text{O})]^{2+}\) (\([\text{bpy}] = \text{pyridine}\)).\(^{39-41}\) and has also been observed for the photodissociation of the ligand bete (3,6-dithiaoctane) in \([\text{Ru}(\text{bpy})_2(\text{H}_2\text{O})_2]^{2+}\) or \([\text{Ru}(\text{bpy})(\text{mtmp})]^{2+}\)\(^{13}\).

The identity of the final products of the photoreaction was confirmed by \(^1\text{H}\) NMR spectroscopy (Figure 3). White light irradiation of a sample of \([\text{Ru}(\text{bpy})_2(\text{PF}_6)_2]\) in \(\text{D}_2\text{O}\) resulted in the formation, at the photostationary state, of a mixture of the free ligand \(4\) and of the complex cations \(\text{cis-[Ru}(\text{bpy})_2(\text{H}_2\text{O})_2]^{2+}\) (\(\text{cis-[11]}^{2+}\)) and \(\text{trans-[Ru}(\text{bpy})_2(\text{H}_2\text{O})_2]^{2+}\) (\(\text{trans-[14]}^{2+}\)). Although our experimental data do not allow us to exclude direct formation of \(\text{trans-[14]}^{2+}\) from the photochemical intermediate \([\text{11}]^{2+}\), it is most likely formed through photoisomerization of \(\text{cis-[14]}^{2+}\) to its trans isomer, as reported previously.\(^{37,42}\) As both the cis and trans isomers undergo photoisomerization, a photostationary state is obtained at the end of the irradiation experiment. Since the quantum yields for these \(\text{cis–trans}\) isomerization reactions of \([\text{14}]^{2+}\) are relatively high (\(\Phi_{450} = 0.023-0.045\) in 0.5 M \(\text{H}_2\text{SO}_4\)) in comparison to the photochemical step, we did not observe these reactions separately (whether by NMR or by UV–vis absorption spectroscopy) but they occur concomitantly.

Irradiation of complexes \([\text{2}]^{2+}\) and \([\text{3}]^{2+}\) resulted in very similar photoreactions, as shown in Figures S9 and S10. The UV–vis absorption spectra indicate formation of the same final photoproduct \([\text{14}]^{2+}\), passing through the monodentate photochemical intermediates \([\text{12}]^{2+}\) and \([\text{13}]^{2+}\), as confirmed by mass spectrometry (Figures S11–S14). The quantum efficiencies of the two photochemical steps for each photoreaction were derived using global fitting of the time evolution of the UV–vis absorption spectra, using the Glotaran software package (Table 3 and Figures S15–S17).\(^{36}\) The phosphorescence quantum yields \(\Phi_{443}\) were found to be similar across all three complexes, with \(\Phi_{443} = 0.24, 0.25, \) and 0.16 for the first step of the photoreaction for \([\text{1}]^{2+}, [\text{2}]^{2+},\) and \([\text{3}]^{2+}\), respectively. The second step of the photoreaction was characterized by the photostationary quantum yields of 0.0079, 0.0093, and 0.0055, respectively. These quantum efficiencies are similar to those observed earlier for the second reaction step of bidentate pyridine-thioether ligands\(^{13}\) and slightly lower for ruthenium polypyridyl complexes bearing two photocleavable monodentate ligands, such as \(\text{cis-[Ru}(\text{bpy})_2(\text{py})]^{2+}\) (\(\text{py} = \text{pyridine}\)).\(^{39-41}\)

Scheme 4. Two-Step Photosubstitution Reactions Observed upon Blue Light Irradiation of Solutions of \([\text{1}]^{2+}–[\text{3}]^{2+}\) in \(\text{H}_2\text{O}\)

![Scheme 4](attachment://scheme4.png)
In this work, we have shown that the coordination of ligands 4–6 to the cis-Ru(bpy)2 scaffold under reflux in an EtOH/H2O mixture is diastereoselective, yielding complexes [1]–[3](PF6)2 as a racemic mixture of two enantiomers: namely, Δ-(S)-eq-(S)-ax-OHeq-[Ru]2+ and Δ-(R)-ax-(R)-eq-OHeq-[Ru]2+. DFT calculations showed this isomer to be the most energetically favorable, suggesting that under such conditions the synthesis is under thermodynamic control. As the obtained isomer was also found to have the smallest bond angle variance (σ2), we hypothesize that minimization of the steric hindrance induced by the thioether ligands is a major driving force for the formation of this isomer. As we obtained the same diastereoisomer that was reported for complexes [9](PF6)2 and [10](PF6)2, we conclude that the diastereoselectivity is not determined by the nature of the thioether substituent or by the chelate ring size. According to DFT, the substituent on the C3 carbon in [1]–[3](PF6)2 does force the chelate ring in a chair conformation, rather than a half-chair conformation as observed in the X-ray structures of [9](PF6)2 and [10](PF6)2.

All three complexes were found to be stable in the dark in aqueous solution but undergo efficient ligand substitution reactions upon irradiation with blue light. In all three cases, a selective substitution of the bis(thioether) ligand in two steps was observed, leading to the formation of the bis(aqua) complex [Ru(bpy)2(H2O)2]2+ ([14]2+). The reaction mechanism was found to be identical with that reported for complexes [7](PF6)2 and [8](PF6)2. A 30-fold difference in efficiency between the two steps of the photoreaction was observed, which, in combination with a high time resolution in the irradiation experiments, allowed us to determine the photosubstitution quantum yields for the individual steps, rather than the overall quantum yield. It also allowed us to identify the photochemical intermediate as the k′-mono(thioether), mono(aqua) complex by mass spectrometry. Substitution of the alcohol group by a methoxy or carboxylate group, as in complexes [2](PF6)2 and [3](PF6)2, does not have an effect on the diastereoselectivity of the synthesis or on the selectivity of the photosubstitution reaction. Only small differences were observed in the efficiency of the photosubstitution reactions. Thus, functionalized bis(thioether) ligands are promising candidates for the binding of cis ruthenium-based PACT complexes to inorganic surfaces, as they can be functionalized, do not form too many isomers, and can be efficiently photocleaved.

## ASSOCIATED CONTENT

* Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.9b01669.

NMR spectra, spectroscopic details for photosubstitution, singlet oxygen generation, and phosphorescence quantum yield measurements, mass spectra after irradiation, dark stability measurements of ruthenium complexes, and computational details, including calculated geometries and structural parameters (PDF)

## AUTHOR INFORMATION

### Corresponding Author

*E-mail for S.B.: bonnet@chem.leidenuniv.nl.

**ORCID**

Michael S. Meijer: 0000-0003-0877-2374
Sylvestre Bonnet: 0000-0002-5810-3657

### Notes

The authors declare no competing financial interest.

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