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An Overview Of Photosubstitution Reactions Of Ru(II) Imine Complexes And Their Application In Photobiology And Photodynamic Therapy

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Abstract

This article is a short review that presents a short review of photosubstitution reactions of Ru(II) imine complexes and illustrates their use in the development of therapeutic agents. The review begins with an overview of the photophysical behavior and common photoreactions of Ru(II) imine complexes, with select examples from the literature since the 1960s. It is followed by a more detailed picture of the application of knowledge gained over the years in the development of Ru(II) complexes for photobiology and photodynamic therapy.

Graphical Abstract

Keywords

Ruthenium photochemistry; temperature dependent luminescence; photosubstitution; photodynamic therapy; imine complexes

I. Introduction

Early investigations of photosubstitution reactions of Ru(II) complexes focused on understanding the excited states involved and the mechanistic regulators of the reactions. Few would have imagined that such complexes might be injected, infused or otherwise applied for medicinal purposes. However, recent research efforts of a determined cadre of photochemists are pushing ever closer to this reality. As the understanding of photosubstitution reactions and biocompatibility of a steadily growing number of Ru(II) chromophores becomes more refined, the potential for biomedical application steadily improves. This article presents a short background of the fundamental research on the factors influencing the photoreactivity of Ru(II) complexes having metal-to-ligand charge transfer (MLCT) absorption transitions in the visible region. The vast majority of these complexes contain one or more diimine ligands (i.e. bpy = 2,2'-bipyridine, phen = 1,10-phenanthroline, and related derivatives) and one or more ligands that may be readily labilized in the excited state.

The story began with the photochemical investigation of $[\text{Ru}(\text{bpy})_3]^{2+}$.¹ Through the 1960s and early 1970s this chromophore had been investigated by a variety of groups, in part because of its relative stability in the ground state and under photolysis in protic solvents and partly because of the fact that the complex exhibited luminescence and full reversibility upon one electron oxidation and reduction. The latter behavior made the complex attractive as a chromophore for photoredox reactions and in early artificial photosynthetic systems.^{2,3} The high degree of reversibility of both oxidation and reduction rendered the complex ideal for examination of the free energy dependence of light induced electron transfer dynamics, providing a transition metal complex analog to the work of Rehm and Weller on organic photoredox reactions.⁴

The early work also included investigations of the photostability of $[\text{Ru}(\text{bpy})_3]^{2+}$ and this led to the discovery that, in water, photoaquation occurs in low yields (10^{-3} – 10^{-5}) over a wide pH range.^{5–7} Continued work on photoreactions of the complex, especially in nonaqueous solvents, where Durham and Meyer were quick to note the potential synthetic value of photosubstitution of a single bipyridine ligand to yield *cis*- $[\text{Ru}(\text{bpy})_2\text{Cl}_2]$ in methylene chloride in high yield and with a quantum yield in excess of 0.1.^{8,9} Accompanying these observations was increasing research dedicated to understanding mechanistic aspects of the photoreactions and explorations of the range of complexes undergoing this chemistry. The remainder of this article is intended to present an overview of the photophysical behavior and photosubstitution reactions of Ru(II) imine complexes, including examples of systems investigated and results of mechanistic studies. The article finishes with a detailed discussion of the use of Ru(II) imine complexes in photobiology and potential applications in medicine, with particular emphasis on the release of biologically active species initiated by

photoinduced ligand dissociation. The review is not intended to be comprehensive, but to give an overview of the photophysics and photosubstitutional behavior of Ru(II) complexes, with representative examples from the literature.

II. Ru(II) diimine complex photophysics and photochemistry

The fate of photoexcited $[\text{Ru}(\text{bpy})_3]^{2+}$ in solutions and matrices at low temperatures has been the subject of numerous reviews over the years, but the early work of Crosby and coworkers defined the charge transfer state and illustrated the splitting of the three states of the $^3\text{MLCT}$ manifold.^{10–12} A lucid and thorough review of the literature and the fundamental photophysical behavior is presented in the 1988 review by Balzani and coworkers and a general state diagram for Ru(II) diimine complexes is presented in Figure 1.¹ The longest wavelength absorption in the visible is a metal-to-ligand charge transfer (MLCT) transition. Excitation is followed by intersystem crossing to form the triplet state ($^3\text{MLCT}$) within 100 femtoseconds¹³ with an efficiency near unity. Relaxation of the triplet state to the ground state occurs over several hundred nanoseconds and includes internal conversion to form a triplet ligand field state (^3LF). This pathway was first postulated by van Houten and Watts in 1976 based on data from temperature dependent luminescence and photosubstitution of $[\text{Ru}(\text{bpy})_3]^{2+}$ in water.^{5,6,14} This work stimulated a broad range of investigations of a wide variety of Ru(II) imine complexes (*vide infra*) and the simple state diagram of Figure 1 has been used repeatedly in studies of the luminescent behavior of complexes having MLCT excited states. More recent theoretical work has provided further insight into the MLCT/LF energetics.^{15,16} An early summary of and commentary on this work was provided by Meyer; it is noteworthy that he predicts things to come with remarkable clarity in this widely cited review.¹⁷

In the early work of van Houten and Watts, the temperature dependence of $[\text{Ru}(\text{bpy})_3]^{2+}$ luminescence between 0 and 100 °C was analyzed using an expression that incorporated radiative decay and nonradiative decay from the MLCT triplet manifold of states separated by only 60 cm^{-1} and a fourth thermally equilibrated ^3LF state determined to be 3600 cm^{-1} above the lower energy manifold (eq. 1). Here E represents the energy gap between equilibrated $^3\text{MLCT}$ and ^3LF states and k_{n2} is the rate of nonradiative decay of the ^3LF state. Whatever the energy gap, the rate of forward and reverse energy transfer

$$\tau(T) = [k_r + k_{n1} + k_{n2} \exp(-\Delta E/k_b T)]^{-1} \quad (1)$$

between the two states was assumed to be fast relative to the observed relaxation. This value of k_{n2} includes all processes of the ^3LF state including dissociation of a bpy ligand to form a monodentate bpy. In this case also it is assumed that nonradiative relaxation from the $^3\text{MLCT}$ state is temperature independent.

More general formulations of internal conversion from the $^3\text{MLCT}$ state to the ^3LF state were presented by a variety of groups in the mid-1980s.^{18–20} Figure 1 includes the possibility of reverse energy transfer from the ^3LF state to the $^3\text{MLCT}$ state. The observed

rate constant for decay of the $^3\text{MLCT}$ state is given by eq. 2, where the temperature dependent process depends on the relative rate constants for back internal conversion (k_{LC}) and relaxation of the ^3LF state ($k_{\text{n2}}+k_{\text{p}}$). The two limiting

$$k_{\text{obs}}(T) = k_{\text{r}} + k_{\text{n1}} + k(T) \\ k(T) = k_{\text{CL}} ((k_{\text{n2}} + k_{\text{p}}) / (k_{\text{LC}} + k_{\text{n2}} + k_{\text{p}})) \quad (2)$$

cases are (a) when $k_{\text{n2}}+k_{\text{p}}$ is rapid relative to back internal conversion (k_{LC}) and the $^3\text{MLCT}$ to ^3LF internal conversion is the activated process or (b) when k_{LC} is much greater than $k_{\text{n2}}+k_{\text{p}}$ and the temperature dependent term for decay of the observable $^3\text{MLCT}$ state is $k(T) = A_0 \exp(-E/k_{\text{b}}T)$, where E is the energy gap between the $^3\text{MLCT}$ and ^3LF states. In addition, other kinetic conditions are possible for which all of the rate constants influence the observed decay of the $^3\text{MLCT}$ excited state and the decay may deviate significantly from exponential behavior.

Other formalisms have been put forth for analysis of temperature dependent luminescence lifetimes of Ru(II) imine complexes. For example, Rillema and coworkers²¹ found that better fits were obtained with the expression (eq. 3):

$$k_{\text{obs}} = \frac{k_{\text{r}} + k_{\text{n1}} + k_{\text{n2}} \exp(-k_{\text{n2}} \exp(-\Delta E/k_{\text{b}}T)/k_{\text{b}}T)}{1 + \exp(-\Delta E/k_{\text{b}}T)} \quad (3)$$

The exponential term in the denominator only becomes significant for values of E below 700 cm^{-1} , which is the case for several of the complexes of Table 1. While reasonable fits for the temperature dependence of many complexes were obtained with eqs. 2 or 3, some systems exhibited behavior that reflected the changes in the medium during the glass (low temperature) to fluid transition. Barigelletti and others addressed this by including an empirical expression for the solvent transition in addition to either one or two thermally activated processes (eq. 4) where B and C account for the medium

$$k_{\text{obs}} = k_{\text{r}} + k_{\text{n1}} + \frac{B}{1 + \exp[C(\frac{1}{T} - \frac{1}{T_{\text{g}}})]} + A \exp(-\Delta E/k_{\text{b}}T) \quad (4)$$

viscosity effect on luminescence and T_{g} is the glass transition temperature. This becomes particularly important when the luminescence decay is evaluated over a very broad temperature range and where the thermally activated process defined by E results in large changes in k_{obs} at temperatures well above T_{g} .

The above discussion suggests that the activated process results exclusively in population of the ^3LF state. However, the body of existing literature indicates that this is very likely not the case. Activation energies and associated prefactors are presented for a variety of Ru(II) imine complexes in Table 1.^{18,21–23} Some general trends emerge that relate to the influence

of the coordination environment on the activation parameters and the substitutional photolability. Efficiencies for populating the activated state, ^3LF or not, are obtained with eq. 5. Values for populating the activated state (Table 1) vary

$$\eta_{act}(T) = \eta_{isc}(T) \left[\frac{A \exp(-E_a/k_b T)}{k_r + k_{n1} + A \exp(-E_a/k_b T)} \right] \quad (5)$$

considerably and do not correlate intuitively with either the prefactor or the activation barrier. One very obvious trend in Table 1 is that heteroleptic complexes having one or more strong π -accepting ligands (i.e. pypm, bpz, decb, see Table 1) and the remaining coordination environment consisting of better σ -donating ligands (bpy, dmb), have activation barriers $<1000 \text{ cm}^{-1}$ and prefactors on the order of 10^7 s^{-1} . In these complexes the manifold of $^3\text{MLCT}$ states is more complex, including higher energy $^3\text{MLCT}$ states having considerably different orbital occupation. It has been postulated that thermally activated decay through states with low activation barriers and, particularly, low prefactors, corresponds to internal conversion between relatively weakly coupled $^3\text{MLCT}$ states, resulting in population of a fourth MLCT state that relaxes to the ground state more rapidly than the lower energy states of the $^3\text{MLCT}$ manifold. This state may have a higher degree of mixing with the singlet state, which would serve to increase the rate of relaxation of this fourth MLCT state.²⁴

Not shown in Table 1 are room temperature quantum yields for photosubstitution/ photosolvation. For $[\text{Ru}(\text{bpy})_3]^{2+}$ alone, it has been demonstrated that light induced bpy substitution has quantum yields that vary considerably depending on solvent (*vide infra*).^{9,20} For some of the complexes, such as those in the series of complexes containing the decb and bpz ligands, it has been shown that the homoleptic complexes undergo photoanation in CH_2Cl_2 while the heteroleptic derivatives are much less photoreactive.

Complexes of 2,2',6',2''-terpyridine (tpy) and related ligands are worth mention. The parent of this series $[\text{Ru}(\text{tpy})_2]^{2+}$ is nonluminescent at room temperature, but strongly emissive in frozen solutions at 77 K.¹ The visible absorption of the complex is Ru(II) to tpy MLCT, but, in this case, the constraints on the coordination environment imposed by the tpy ligand result in a relatively low energy ^3LF state that is readily accessible from the $^3\text{MLCT}$ state. Recent work by the Hammarström group illustrated that closely related triimine ligands with N-Ru-N angles closer to 90° yield bis-tridentate complexes with long lived luminescent $^3\text{MLCT}$ excited states in solution at room temperature.^{25–28}

III. Factors affecting photosubstitution

The results presented in Table 1 clearly illustrate that mixed ligand complexes having ligands that significantly differ in π -accepting ability almost certainly differ in the nature of the thermally activated decay process relative to homoleptic tris diimine complexes. The connection between the parameters obtained for photophysical decay and the photosubstitution efficiency was beautifully demonstrated by Allen et al. in 1983 and reiterated later by Wacholtz.^{18,29} Table 2 lists the quantum yields for photoinduced solvation

in a series of tris-diimine complexes. The results clearly illustrate that, for the mixed ligand complexes having activation barriers for nonradiative relaxation of $< 1000 \text{ cm}^{-1}$ and prefactors below 10^9 s^{-1} , for example $[\text{Ru}(\text{bpy})_2(\text{bpz})]^{2+}$ and $[\text{Ru}(\text{bpy})_2(\text{bpm})]^{2+}$, the photoreaction quantum yields are very low (Tables 1 and 2). Chloride substitution of a related series of complexes in CH_2Cl_2 , including the mixed ligand complexes $[\text{Ru}(\text{dmb})_2(\text{dec})]^{2+}$ and $[\text{Ru}(\text{dec})_2(\text{dmb})]^{2+}$, shows similar behavior: essentially no photosubstitution and very low activation energies for relaxation of the $^3\text{MLCT}$ state. The behavior is consistent with thermal activation to populate a state other than the photoreactive ^3LF state in these mixed ligand complexes.

Steric factors can also play a role in influencing photosubstitution, particularly photosubstitution products.^{30,31} For instance, Laemmel et al. illustrated that for complexes of the type $[\text{Ru}(\text{LL})_2(\text{BB})]^{2+}$ ($\text{LL} = \text{bpy}, \text{phen}$; $\text{BB} = 6,6'$ -dimethyl-2,2'-bipyridine, 2,9-diphenyl-1,10-phenanthroline, etc.),³¹ substitution on the sterically crowded BB ligand was the selective process upon irradiation. The authors illustrated how such selective photoreactions can be used in development of photochromic systems.³² Recently Sun and coworkers³³ employed transient spectroscopy to show that, for complexes having bulky diimine ligands, the ^3LF state is in fact lower in energy than the $^3\text{MLCT}$ state and relaxation to the ground state is actually slower than relaxation of the $^3\text{MLCT}$ state. Clearly some complexes have ^3LF states that are comparable in energy or lower in energy than the $^3\text{MLCT}$ state. The influence of the nature of spectator ligands on the relative gap between $^3\text{MLCT}$ and ^3LF states was examined by Caspar in the early 1980s.¹⁹ In a thorough study of the photophysical behavior of a series of $[\text{Ru}(\text{bpy})_2(\text{L})]^{2+}$ complexes, where L is imidazole, pyridine, aminoethylpyridine, pyridazine, diphenylphosphinoethane and other ligands, some included in Table 1, the authors found that the non-spectroscopic ligands exhibited a modest effect on the activation parameters for excited state relaxation, but a systematic effect on the luminescence energy (E_{00}). The authors also observed that phosphine ligands influenced the MLCT state energy to a much more significant extent than the ^3LF state energy, resulting in highly favorable population of the ^3LF state.

A capstone publication illustrating the correlation of the relative $^3\text{MLCT} - ^3\text{LF}$ energy gap on the photosubstitution efficiency was published by Ross and coworkers in the late 1980s.³⁴ Thorough examination of a large series of tris-diimine complexes having either a lowest energy $\text{Ru} \rightarrow \text{bpy}$ or a $\text{Ru} \rightarrow \text{bpz}$ $^3\text{MLCT}$ state, allowed the authors to correlate the quantum yield for ligand substitution, in this case Cl^- substitution in CH_3CN , with $E_{1/2}$, the energy difference between the first one electron reduction and oxidation potentials ($E^0(\text{Ru}(\text{III}/\text{II})) - E^0(\text{Ru}(\text{II}/\text{I}))$) and, therefore with the relative $^3\text{MLCT}$ state energy. For a given series, higher $^3\text{MLCT}$ state energies result in larger photosubstitution quantum yields, once again supporting the idea that photoreactivity is related to the ease of population of the ^3LF state.

For tris-diimine complexes, the mechanism of substitution of the bidentate ligand remains somewhat unclear. If the process is dissociative, is there evidence for a monodentate intermediate or does complete ligand loss occur rapidly following initial uncoupling of the bidentate ligand? Alternatively, is the process associative, in which case, quantum yields for photosubstitution may be dependent on the substituting ligand? In a 1986 review, Meyer outlined a mechanism that begins with $\text{Ru}-\text{N}$ cleavage in the ^3LF state.¹⁷ Tachiyashiki et

al.³⁵ found that quantum yields for photosubstitution of $[\text{Ru}(\text{phen})_3]^{2+}$ and $[\text{Ru}(\text{bpy})_3]^{2+}$ in water increased by a factor of 6–8 (relative to pH 7) with decreasing pH, with no further change occurring below pH 1. Their conclusion was that excitation resulted in formation of a monodentate intermediate that protonated, thereby inhibiting annealing of the complex to give the starting tris complex. The fact that the protonation had a larger effect for the bpy complex than the phen complex served to add support to this conjecture. A few years later they reported direct observation of a monodentate dmb intermediate, with a half-life on the order of minutes, in photolysis of $[\text{Ru}(\text{bpy})_2(\text{dmb})]^{2+}$ in acidic solution.^{36–38} Efforts by others employing mass spectroscopy to observe monodentate intermediates yielded inconclusive results that were attributed to the very short lifetimes of the intermediate species.^{39,40} Recently, the single crystal structure of a monodentate intermediate species was obtained following photolysis of solutions of various bis-di-1,2,3-triazole complexes.⁴¹ Figure 2a shows the structure of the starting bis-triazole and 2b illustrates the structure of the monodentate intermediate. What is most interesting is that the incoming acetonitrile ligand is *trans* to the coordinated singly bound bis-triazole. While the structure of the monodentate intermediate must reflect an isomerized form of the initial monodentate photoproduct, the existence of singly bound bidentate ligands formed via photolysis of tris-diimine type complexes is unequivocal.

Activation volumes for photosubstitution reactions of $[\text{Ru}(\text{bpy})_3]^{2+}$ and $[\text{Ru}(\text{phen})_3]^{2+}$ have been determined for substitution in CH_3CN and in CH_2Cl_2 .⁴² Fetterolf and Olfen showed that relaxation of the $^3\text{MLCT}$ state to the ground state involved a small negative activation volume, while $^3\text{MLCT}$ to ^3LF interconversion had a positive activation volume of approximate $10 \pm 0.4 \text{ ml mol}^{-1}$.⁴³ For the net photosubstitution reaction activation volumes were larger at room temperature and increased with increasing temperature for Cl^- substitution in CH_2Cl_2 and solvation in CH_3CN . The behavior is consistent with a dissociative model for diimine ligand substitution.

The issue of retention of configuration in photosubstitution of $[\text{Ru}(\text{LL})_3]^{2+}$ complexes was addressed in a thorough investigation by Yamagishi and coworkers.⁴⁴ Irradiation of solutions of $[\text{Ru}(\text{LL})_3]\text{Cl}_2$ ($\text{LL} = \text{bpy}, \text{phen}$) in CH_2Cl_2 solutions results in formation of $[\text{Ru}(\text{LL})_2\text{Cl}_2]$ when $\text{LL} = \text{bpy}$, but racemization occurs for the phen complex. Interestingly, the *cis*-chloro complex does not undergo racemization in solution at room temperature or upon photolysis.

Evidence for crossing between the $^3\text{MLCT}$ and ^3LF states and ligand substitution on the ps time scale exists for some systems. One recent example, from Greenough, Roberts, et al., presents a transient spectroscopic and computational evaluation of photoinduced nicotinamide (NA) loss in the system $[\text{Ru}(\text{bpy})_2(\text{NA})_2]^{2+}$ in aqueous solution.⁴⁵ Excitation is followed by ultrafast formation of the $^3\text{MLCT}$ state ($\sim 100 \text{ fs}$) which then leads to ligand loss in $< 1 \text{ ps}$ to form a pentacoordinate intermediate. This then either collapses to the starting bis-NA complex or undergoes solvation to make the aquo complex over a period of a few hundred ps. Computational analysis of the process supports the idea that the $^3\text{MLCT}$ state and ^3LF state are strongly coupled prior to ligand loss and exact characterization of one or the other state being directly linked to ligand loss is not possible with this system. Others have claimed ligand loss initiated by routes other than population of the ^3LF state (*vide*

infra). Loss of the second NA from $[\text{Ru}(\text{bpy})_2(\text{NA})(\text{OH}_2)]^{2+}$ occurs on a much longer time scale.

IV. Case studies of photosubstitution

A. Complexes with a single imine ligand

Microsecond flash photolysis studies of pyridine substitution in complexes of the type $[\text{Ru}(\text{NH}_3)_5(\text{pyX})]^{2+}$ (pyX = a variety of substituted pyridine derivatives)⁴⁶ resulted in the postulate that an intermediate species is observed immediately after the excitation pulse ($\sim 30 \mu\text{s}$) that is not the excited state; the authors postulated the existence of an $\eta^5\text{-py}$ bound species that either relaxed back to the starting complex or went on to aquate. By modern standards, the existence of an intermediate species at such long times following excitation is surprising. The transition linked to photoreaction in these complexes was sensitized with a variety of organic dyes (singlet and triplet sensitizers) and was found to be a state with an energy between 17,000 and 17,700 cm^{-1} .⁴⁷ In related work, CN bound cyanopyridines of the type $[\text{Ru}(\text{NH}_3)_5(\text{xNC-py})]^{2+}$ (x = 2, 3 or 4) were irradiated in aqueous solution and found to undergo only aquation of the ammine or cyanopyridine ligands and no evidence was found of linkage isomerism.⁴⁸

B. Substitution of monodentate ligands

An interesting study of stereospecificity in photosubstitution was provided by Suen and cohorts in the photolysis of $[\text{Ru}(\text{tpy})(\text{L})_3]^{2+}$ and $[\text{Ru}(\text{tpy})(\text{L})_2\text{Cl}]^+$ complexes (L = CH_3CN , py, pyMe = 4-methylpyridine).⁴⁹ The reactions below summarize some of the observed behavior in a non-coordinating solvent:

and, in acetonitrile solutions:

The second reaction provides evidence that substitution occurs along the axis of the complex with the weakest ligand field. The work provides several examples of weak axis labilization accompanied by no rearrangement. However, photolysis of *-trans*- $[\text{Ru}(\text{tpy})(\text{py})_2\text{Cl}]^+$ yields a product that results in rearrangement of the monodentate Cl, but the yield is very low. Coe et al. examined a series of $[\text{Ru}(\text{tpy})(\text{X})(\text{Y})(\text{Z})]^{n+}$ complexes (X,Y,Z = Cl^- , py, 4-ethylpyridine, *N,N*-dimethylaminopyridine, triphenylphosphine and trifluoroacetate in various combinations). Ligand loss photochemistry occurred only for $[\text{Ru}(\text{tpy})(4\text{-ethylpyridine})_3]^{2+}$, but all the complexes examined exhibited strong temperature dependent luminescence between 90 and 200 K that was attributed to the $^3\text{MLCT}$ to ^3LF internal conversion process.⁵⁰

An interesting extension in the use of sterically bulky bidentate ligands to influence the selectivity of substitutional photochemistry was reported by Knoll et al.⁵¹ Irradiation of complexes of the type $[(\text{tpy})\text{Ru}(\text{LL})(\text{py})]^{2+}$ ($\text{LL} = 6,6'$ -dimethyl-2,2'-bipyridine or 2,2'-biquinoline) in CH_3CN solutions resulted in selective loss of pyridine, but with quantum yields at least 100 fold greater than that of the complex with $\text{LL} = \text{bpy}$. Crystallographic data suggests that ground state distortion of the py ligand may play a significant role in the nature and relative efficiency of the excited state photoreaction.

Complexes of the type $[\text{Ru}(\text{bpy})_2(\text{L}_2)]^{2+}$ are of interest for potential applications in photodynamic therapy as they are easily prepared and should exhibit selective loss of L. The bis-acetonitrile complex exhibits very high quantum efficiency for loss of CH_3CN in various nonaqueous solvents (Table 2).⁵² Photolysis of $[(\text{bpy})_2\text{Ru}(\text{NO}_2)(\text{CN})]$ in aqueous solution results in selective loss of the NO_2^- ligand to yield the aquo complex.⁵³ The complex and related derivatives exhibit weak luminescence in solution at room temperature and substitution is postulated to proceed through a ^3LF state. Here again, the NO_2^- containing axis of the complex is weakest and loss of the monodentate ligand dominates. Irradiation of $[(\text{bpy})_2\text{Ru}(\text{NH}_3)(4,4'\text{-bpy})]^{2+}$ in CH_3CN leads to selective loss of 4,4'-bpy;^{54,55} quantum chemical calculations on this system indicate the labilization occurs through a ^3LF state, but the calculations do not point to 4,4'-bpy substitution vs. NH_3 . This same group has reported other interesting studies of photosubstitution of monodentate ligands in Ru(II) imine complexes.^{56–58}

The potential synthetic utility of photosubstitution of a monodentate ligand and replacement with a bidentate ligand (the reverse of the above mentioned synthetic scheme of Durham.) was put forth by Mulhern et al. Using $[(\text{bpy})\text{Ru}(\text{CO})_2\text{Cl}_2]$ and $[\text{Ru}(\text{bpy})(\text{dmb})(\text{CO})_2]^{2+}$ as the chromophores, light induced loss of CO in the presence of bidentate chelating ligands led to generation of a variety of heteroleptic diimine complexes.⁵⁹ The initial photoreaction of $[(\text{bpy})\text{Ru}(\text{CO})_2\text{Cl}_2]$ does involve CO loss to yield a solvent complex in coordinating solvents.⁶⁰

C. Intramolecular sensitization of photoinduced ligand loss

One initiative in control of photosubstitution processes has been to push light absorption as far to the red as possible in sensitization of ligand loss, potentially better enabling *in vivo* applications. A recent investigation by Bahreman and coworkers explored the use of yellow light absorbing chromophores as sensitizers for reactive triplet excited states of Ru(II) imine chromophores.⁶¹ By covalently linking a rhodamine B (RhB) derivative to a $[\text{Ru}(\text{tpy})(\text{bpy})(\text{Hmte})]^{2+}$ ($\text{Hmte} = 2\text{-methylthioethan-1-ol}$) chromophore for which irradiation resulted in loss of the S bound Hmte ligand, the authors were able to establish that the bound RhB was indeed effective in sensitizing the reactive excited state. While the quantum yield for Hmte loss did not change upon irradiation of the RhB chromophores at 570 nm, the observed rate of ligand loss increased significantly as a result of the increase in efficiency of light harvesting. Energy transfer from the RhB to the triplet manifold of the complex was illustrated by the complete quenching of the RhB fluorescence.

V. Photosubstitution reactions not involving ^3LF excited states

While the majority of published work on light induced ligand loss in Ru(II) imine containing complexes is linked to reactions from ^3LF states, other dissociation mechanisms have been put forth in systems that deserve mention here. One involves photoreaction of a boron-dipyrromethene (BODIPY) modified Ru(II) bipyridyl arene complex, $[\text{Ru}(\text{cym})(\text{bpy})(\text{py-BODIPY})]^{2+}$ ($\text{cym} = \eta^6\text{-}p\text{-cymene}$ and $\text{py-BODIPY} = 4\text{-BODIPY-pyridine}$, Figure 3).⁶² Excitation of the complex into the BODIPY absorption at approximately 500 nm results in py-BODIPY loss ($\Phi_{\text{rxn}} = 0.04$), but excitation into the $^1\text{MLCT}$ state of the complex with 315 nm, a wavelength at which the absorption of the coordinated BODIPY is negligible, results in no observable loss of the pyridyl ligand. In addition, the fluorescence intensity of the coordinated py-BODIPY is much lower than that of the free ligand. While energy and electron transfer processes of the py-BODIPY excited singlet state with the Ru(II) complex are both possible, energy transfer is unlikely to result in ligand loss since direct excitation of the Ru localized transitions did not give rise to photosubstitution. Zhou et al. have postulated that intra-molecular electron transfer leads to a coordinated cation radical having a greatly weakened Ru-py bond, as depicted in Figure 3.

VI. Photoisomerization processes of Ru(II) imine complexes

There are relatively few reports of light induced isomerization reactions of Ru(II) imine complexes, but they are certainly worth mentioning in the context of reactivity from charge transfer versus ligand field excited states. An interesting example was reported by Hirahara et al.⁶³ in the light induced isomerization of $[\text{Ru}(\text{tpy})(\text{pynp})(\text{OH}_2)]^{2+}$ ($\text{pynp} = 2\text{-(2-pyridyl)-1,8-naphthyridine}$). The complex has proximal and distal isomers (Scheme 1) and it was found that irradiation of the distal aquo complex resulted in formation of the proximal isomer, but no isomerization is observed on irradiation of the proximal isomer. The process was believed to proceed via loss of the aquo ligand from the $^3\text{MLCT}$ state followed by isomerization of the penta-coordinate intermediate and reformation of the proximal aquo complex. It appears the rate determining step is the loss of water from the $^3\text{MLCT}$ state. Pyridyl triazole ligands provide an interesting opportunity to observe formation and annealing of monodentate intermediates through intramolecular isomerization. Scheme 2 illustrates the case for $[\text{Ru}(\text{bpy})_2(\text{HPTNx})]^{2+}$ ($\text{HPTNx} = 3\text{-(pyrid-2-yl-1,2,4-triazole)}$; $x = 2$ or 4), reported by Wang in the early 1990s.⁶⁴ Through a combination of pH dependent luminescence, spectrophotometric and HPLC studies, it was established that the pyridyl triazole bound in the 2 position isomerized under photolysis to the triazole coordinated in the 4 position, reaching a steady state favoring the ligand coordinated in the 4 position (4:1). In addition, both complexes lose the pyridyl triazole ligand upon photolysis in CH_2Cl_2 in the presence of Br^- , but the complex with the pyridyl triazole bound in the 2 position underwent competitive isomerization and photoanation. The work serves as affirmation of formation of monodentate intermediates from bidentate ligands in the process of net loss of the bidentate ligand. Irreversible photoisomerization of Ru(II) complexes of the closely related 1-methyl-3-(pyridin-2-yl)-1,2,4-triazole was also reported by Fanni et al.⁶⁵

There have been a variety of very thorough reports from the Rack group on S to O photoisomerism in Ru(II) imine complexes of DMSO.^{66–70} Detailed redox, photochemical,

transient kinetic and computational results strongly suggest the reactive excited state for the photoisomerization process is *not* a ^3LF state.^{71,72} Isomerization occurs from the $^3\text{MLCT}$ state and the efficiency is strongly dependent on the nature of the ligand *trans* to the coordinated DMSO.

VII. Photosubstitution reactions of Ru(II) complexes in various microenvironments

The medium effect on the luminescence behavior of Ru(II) imine complexes has been appreciated for many years, since early investigations of their photophysical behavior in solution vs. rigid media at low temperatures. More recently others have examined photosubstitution and photoisomerization of complexes such as $[\text{Ru}(\text{bpy})_2(\text{py})_2]^{2+}$ in room temperature matrices (i.e. PMMA) and silica sol-gel monoliths and have found strong inhibition of the photoreactions.⁷³

In work pertinent to the behavior of Ru(II) complex chromophores serving as dyes in dye sensitized solar cells, Meyer and coworkers investigated the temperature dependent luminescence behavior of several complexes including $[\text{Ru}(\text{bpy})_2(\text{CN})_2]$, $[\text{Ru}(\text{bpy})(\text{NCS})_2]$ and $[\text{Ru}(\text{dcb})_2(\text{NCS})_2]^{4-}$ (dcb = 4,4'-dicarboxy-2,2'-bipyridine) in CH_3CN , propylene carbonate and adsorbed on mesoporous TiO_2 surfaces. The two bpy-containing chromophores exhibited a single activated process from the $^3\text{MLCT}$ state that was assigned as population of a $^3\text{MLCT}$ state approximately 800 cm^{-1} above the triplet state manifold. The prefactor for this activated process was between 10^8 and 10^9 s^{-1} , at least three orders of magnitude smaller than that typically observed for population of the ^3LF state. For the dcb complex, two activated processes were required to fit the experimental data; these corresponded to a process with a small barrier (750 cm^{-1}) and a second with a barrier of 4600 cm^{-1} and a prefactor of between 10^{14} and 10^{15} s^{-1} , clearly indicative of ligand field population. Given the room temperature radiative and nonradiative decay of $[\text{Ru}(\text{dcb})_2(\text{NCS})_2]^{4-}$ in CH_3CN , the efficiency of population of the ^3LF state is around 7%.⁷⁴ Interestingly, irradiation of $[\text{Ru}(\text{dcb})_2(\text{NCS})_2]^{4-}$ adsorbed on mesoporous TiO_2 does not result in photosubstitution, even at elevated temperatures. The postulate is that the activation barrier for interconversion between $^3\text{MLCT}$ and ^3LF states is larger for the complex adsorbed on the mesoporous support.

VIII. Photobiological applications of Ru(II) imine complexes

The ligand exchange from Ru(II) diimine complexes that takes place upon irradiation with visible light represents an alternative to traditional photodynamic therapy (PDT) strategies. Traditional PDT utilizes a photosensitizer prodrug that absorbs light in the therapeutic window (600–900 nm) to form a long-lived excited state which sensitizes the formation of cytotoxic $^1\text{O}_2$ via energy transfer.^{75–77} The first FDA-approved PDT agent, Photofrin®, is used to treat esophageal and head and neck cancers.⁷⁸ Metal complexes with relatively long-lived excited states, typically intraligand $^3\pi\pi^*$ or $^3\text{MLCT}$ in nature, have been investigated as potential PDT agents, and these efforts are thoroughly discussed.^{79–83} Because PDT treatment depends on the availability of $^3\text{O}_2$ in the vicinity of the photosensitizer, the efficacy of PDT drugs is hindered by the hypoxic nature of solid tumors.^{84,85} This challenge

has inspired the efforts of many researchers to design visible light-activated metal complexes with therapeutic activities that do not solely rely on the availability of $^3\text{O}_2$, termed photochemotherapy (PCT) or photoactivated chemotherapy (PACT).^{79,86} Two strategies that exploit photoinduced ligand exchange in Ru(II) diimine complexes, light-activated cisplatin analogs that covalently bind to DNA and photolabile cages for selective drug delivery, are reviewed herein. Additional strategies for photoinduced ligand dissociation include MLCT or MMCT (metal-to-metal charge transfer) state-induced Cl^- dissociation from a Pt or Rh metal center, respectively.^{87,88} Other important PCT schemes, such as light-induced oxidation of DNA, photocrosslinking, and H-abstraction, are discussed elsewhere.^{89–92} Additionally, photoinduced ligand exchange has been employed in the controlled release of neurotransmitters to study neuron activity.^{93–98}

The photorelease of one or more monodentate ligands from a Ru(II) complex affords a species with open coordination site(s) available for covalent binding to DNA. In solution in the dark, no ligand dissociation occurs, such that irradiation provides spatiotemporal control over covalent DNA binding. This concept builds on the idea initially developed by Barton, et. al. that incorporates thermally dissociable Cl^- ligands in Ru(II)-diimine complexes to facilitate covalent binding to DNA.⁹⁹ The ability to activate a drug only in the area exposed to light circumvents the systemic toxicity associated with platinum therapeutic and other drugs that rely on thermal ligand exchange for activation and coordination to DNA. Sadler and coworkers have developed a series of Ru(II)-piano stool complexes that undergo such light activated ligand substitution. The electronic absorption spectrum of $[(p\text{-cym})\text{Ru}(\text{bpm})(\text{py})]^{2+}$ (Figure 4) has a maximum at 383 nm ($\epsilon = 2.31 \times 10^4 \text{ M}^{-1}\text{cm}^{-1}$) that tails into the visible region due to overlapping ^1LF and $^1\text{MLCT}$ transitions, and the lowest energy excited state has significant ^3LF character.¹⁰⁰ Irradiation of the complex with $\lambda_{\text{irr}} = 400\text{--}600 \text{ nm}$ for ~ 8 hours promotes the exchange of py for a solvent H_2O molecule to form $[(p\text{-cym})\text{Ru}(\text{bpm})(\text{OH}_2)]^{2+}$. In D_2O in the presence of one equivalent of 9-ethylguanine (9-EtG), irradiation of $[(p\text{-cym})\text{Ru}(\text{bpm})(\text{py})]^{2+}$ with visible light promotes the formation of $[(p\text{-cym})\text{Ru}(\text{bpm})(9\text{-EtG})]^{2+}$, where the Ru(II) center binds to the N7 position of 9-EtG; the lack of adduct formation in the presence of 9-ethyladenine (9-EtA) points at the selectivity for G by the complex.¹⁰¹ Enhanced dark interactions with pUC19 DNA were observed with $[(p\text{-cym})\text{Ru}(\text{bpm})(4,4'\text{-bpy})]^{2+}$ (Figure 4) compared to the py analogue due to the ability of the extended ligand to intercalate.¹⁰¹ Under ambient light, $[(p\text{-cym})\text{Ru}(\text{bpm})(\text{py})]^{2+}$ and $[(p\text{-cym})\text{Ru}(\text{bpm})(4,4'\text{-bpy})]^{2+}$ are cytotoxic toward A2780 human ovarian cancer cell lines with IC_{50} values of 9.0 and 61.1 μM , respectively.

In the $[(p\text{-cym})\text{Ru}(\text{bpm})(\text{py})]^{2+}$ architecture, the replacement of the py ligand with py-substituted tumor-targeting peptides, L, to form $[(p\text{-cym})\text{Ru}(\text{bpm})(\text{L})]^{2+}$, where L = py-Arg-Gly-Asp (py-RGD) and py-octreotide (octreotide is a cyclic octapeptide), shown in Figure 4, leads to similar photoreactivity, with the generation of the $[(p\text{-cym})\text{Ru}(\text{bpm})(\text{OH}_2)]^{2+}$ photoproduct which forms a monoadduct with either G base in 5'-dCATGGCT-3' sequence when incubated overnight.¹⁰² When irradiated in the presence of the oligonucleotide for 9 hours, an additional GG chelate was observed via loss of the *p*-cymene ligand. The same experiment with 5'-dAGCCATG-3' demonstrates that the complex is also able to form GG chelates between non-adjacent G bases. The observation of only Ru(II)-G adducts in a peptide-oligonucleotide strand, Phac-His-Gly-Met-linker-p5'-dCATGGCT, reveals that the

metal complex is selective for G nucleobases, even in the presence of His and Met which are known to coordinate to metal centers.

A series of Ru(II) bis-bidentate complexes featuring two *cis*-monodentate ligands were designed by Turro and coworkers to be kinetically inert to ligand substitution in solution in the dark while efficiently exchanging monodentate ligands with coordinating solvent molecules under visible light irradiation, thus providing light-activated cisplatin analogs. The electronic absorption spectroscopy of *cis*-[Ru(bpy)₂(NH₃)₂]²⁺ (Figure 5) features Ru→bpy ¹M LCT transitions centered at 490 nm (ε = 8210 M⁻¹cm⁻¹) and the irradiation of the complex in aqueous solution forms the bis-aquated complex *cis*-[Ru(bpy)₂(OH₂)₂]²⁺ from the sequential substitution of each NH₃ ligand with H₂O (Φ₃₅₀ = 0.024(2); Φ₄₀₀ = 0.018(2)).¹⁰³ *Cis*-[Ru(bpy)₂(OH₂)₂]²⁺ covalently binds to G bases in 5'-AGTGCCAAGCTTGCA-3' or 5'-TGCAAGCTTGGCACT-3' with λ_{irr} > 345 nm for 10 min, and enhanced binding is observed in the strand with two adjacent guanines. This result suggests that the complex prefers to form 1,2-intrastrand crosslinks in a manner similar to cisplatin. Further evidence for this interaction was demonstrated by the decrease in the thermal denaturation temperature of the annealed 15-mer strands by 5 °C because an intrastrand crosslink kinks the DNA strand, causing destabilization and lower melting temperature. Similarly, cisplatin decreases the melting temperature of a 20-mer sequence by 8 °C. Additionally upon irradiation of [Ru(bpy)₂(NH₃)₂]²⁺ with λ > 345 nm for 15 min, the complex covalently binds to linearized pUC18 DNA, and no interaction was observed in the dark.

Because the absorption of low energy visible and NIR light is important for PCT applications, Turro and coworkers designed a Ru(II) complex featuring a σ-donating bidentate ligand to destabilize the Ru(dπ) orbitals, thus lowering the Ru→L ¹MLCT transition energy.^{104,105} The deprotonated phenylpyridine (phpy⁻) ligand in *cis*-[Ru(phpy)(phen)(CH₃CN)₂]⁺ (Figure 5) provides red-shifted absorption bands with maxima at 461 nm and 486 nm (ε = 11,599 M⁻¹cm⁻¹ and 10,842 M⁻¹cm⁻¹) relative to the analogous *cis*-[Ru(phen)₂(CH₃CN)₂]²⁺ (λ_{max} = 420 nm, ε = 8,600 M⁻¹cm⁻¹ in CH₃CN),¹⁰⁶ and the absorption of the former extends to wavelengths beyond 600 nm. The CH₃CN ligands were chosen because the quantum yields for nitrile ligand exchange are generally greater than those measured for the exchange of amine and pyridine. The irradiation of *cis*-[Ru(phpy)(phen)(CH₃CN)₂]⁺ with 450 nm light in the presence of excess Bu₄NCl in CH₂Cl₂ yields the monosubstituted complex [Ru(phpy)(phen)(CH₃CN)Cl] with Φ₄₅₀ = 0.25.¹⁰⁵ This complex covalently binds to linearized plasmid DNA when irradiated for 20 min with λ 420 nm, and no coordination is observed when the complex and DNA are incubated in the dark. The light and dark toxicities of *cis*-[Ru(phpy)(phen)(CH₃CN)₂]⁺ toward OVCAR-5 human advanced ovarian epithelial cancer cells were investigated. The relatively high dark LC₅₀ of 1.0 μM is likely due to thermal ligand exchange in the presence of glutathione (GSH) which is in high concentration in cells; however, irradiation with 690 nm light for 100 s results in a 14-fold enhancement in toxicity. This significant increase in toxicity toward cancer cells upon irradiation with red light is important in the development of useful PCT agents.

Enhanced cancer cell death with Ru(II) complexes that undergo ligand exchange for covalent DNA binding can be achieved by incorporating an additional pathway for cell death via $^1\text{O}_2$ production. Ligands with extended π -systems, such as benzo[*l*]dipyrido[3,2-*a*:2,3-*h*]quinoxaline (dppn), typically provide low-lying, long-lived $^3\pi\pi^*$ excited states that are efficient sensitizers for $^1\text{O}_2$ production. The dual-active compound *cis*-[Ru(bpy)(dppn)(CH₃CN)₂]²⁺ (Figure 5) absorbs efficiently in the visible region due to Ru→bpy and Ru→dppn_{prox} $^1\text{MLCT}$ transitions.¹⁰⁷ Following $^1\text{MLCT}$ state formation, thermal population of the dissociative ^3LF state and the $^3\pi\pi^*$ can occur competitively, leading to either exchange of CH₃CN for solvent ($\Phi_{400} = 0.002(3)$ in H₂O) or production of $^1\text{O}_2$ ($\Phi_{460} = 0.72(2)$ in MeOH), respectively. The complex is cytotoxic toward HeLa cells when irradiated with 466 ± 20 nm light with an IC₅₀ value of 0.47 ± 0.02 μM and a phototoxicity index, PI, of 1110 (PI = dark IC₅₀/irr IC₅₀). The PI values for the analogous complexes [Ru(bpy)₂(dppn)]²⁺ (irr IC₅₀ = 0.39 ± 0.06 μM) which only produces $^1\text{O}_2$ and *cis*-[Ru(bpy)₂(CH₃CN)₂]²⁺ (irr IC₅₀ = 223 ± 94 μM) which only undergoes ligand exchange were 282 and 6.4, respectively, highlighting the impact of dual photoactivity to elicit cell death.

A common drawback of typical PDT drugs is the patient's light sensitivity for extended periods of time following treatment, which can cause severe skin damage. One proposed method to circumvent this problem uses a Ru(II) complex that requires two modes of activation to undergo ligand dissociation, visible light irradiation and a reducing agent, thus resulting in enhanced selectivity of the PCT agent.¹⁰⁸ Cancer cells are known to have elevated intracellular GSH concentrations, providing a more reducing environment compared to healthy cells,¹⁰⁹ such that limiting photochemical ligand lability to only regions with elevated GSH levels provides enhanced selectivity. A complex that contains two redox-active 4,4'-azopyridine (AzPy) ligands, *cis*-[Ru(bpy)₂(AzPy)₂]²⁺ (Figure 5), was designed such that it is stable upon irradiation ($\lambda_{\text{irr}} > 470$ nm) in the absence of GSH, explained by the low energy Ru→AzPy $^3\text{MLCT}$ state that precludes thermal population of the dissociative ^3LF state. The absorption spectrum of *cis*-[Ru(bpy)₂(AzPy)₂]²⁺ features a maximum at 453 nm with contributions from Ru→bpy and Ru→AzPy $^1\text{MLCT}$ transitions, with the latter on the low energy tail, extending to 600 nm. In aqueous solution with a 100-fold excess of GSH, the reduced species *cis*-[Ru(bpy)₂(py-NH-NH-py)₂]²⁺ (py-NH-NH-py = 1,2-di(pyridin-4-yl)hydrazine) was identified by ESI-MS, while no peak for the original *cis*-[Ru(bpy)₂(AzPy)₂]²⁺ complex remained. The substantial decrease in the absorption band between 400 and 600 nm and evolution of an emission band centered at 633 nm that occur within 10 minutes of exposure to GSH are consistent with the reduced product formation. Irradiation of the reduced species *cis*-[Ru(bpy)₂(py-NH-NH-py)₂]²⁺ in H₂O with $\lambda > 470$ nm produces a red shift in the absorption band from 450 nm to 482 nm, consistent with the exchange of one py-NH-NH-py ligand with water to form [Ru(bpy)₂(py-NH-NH-py)(OH₂)]²⁺. In the reduced complex, the lowest-lying $^3\text{MLCT}$ state is Ru→bpy in nature which is destabilized enough to undergo thermal population of the dissociative ^3LF state. A control complex, *cis*-[Ru(bpy)₂(Et₂N-AzPy)₂]²⁺ (Et₂N-AzPy = 4-(4-diethylaminophenylazo)pyridine, Figure 5), was used, which does not undergo such photoreactivity because the electron-donating nature of the diethylaniline substituent precludes the ligand from reduction by GSH. Irradiation of *cis*-[Ru(bpy)₂(AzPy)₂]²⁺ in the

presence of GSH and pUC19 DNA with $\rightarrow > 470$ nm for 25 minutes following incubation in the dark for 20 minutes led to covalent binding of the complex to DNA, an effect that was not observed in the absence of light nor in the absence of GSH. This DNA binding assay validates the dual activation of monodentate ligand dissociation from Ru(II) diimine complexes.

The strategy of designing light-activated Ru(II)-diimine complexes to covalently bind to DNA in a manner similar to cisplatin has also been employed with bidentate ligand dissociation. Glazer and coworkers have developed a series of complexes that exchange a bidentate ligand with two solvent molecules by the addition of steric bulk to the dissociating ligand. Two complexes featuring biq ligands that are sterically demanding and possess low-lying π^* orbitals for lower energy MLCT transitions, $[\text{Ru}(\text{phen})_2(\text{biq})]^{2+}$ and $[\text{Ru}(\text{phen})(\text{biq})_2]^{2+}$ (shown in Figure 6), absorb low energy light with $\lambda_{\text{max}} = 525$ and 550 nm, respectively, and the absorption extends up to 700 and 800 nm, respectively.¹¹⁰ Irradiation with red and NIR light promotes dissociation of a biq ligand in each complex and subsequent covalent binding of the respective metal fragment to pUC19 DNA. The related complex $[\text{Ru}(\text{bpy})(\text{biq})_2]^{2+}$ undergoes similar photochemistry and covalently binds to linearized pUC18 DNA upon irradiation with $\lambda = 630$ nm for 15 min.¹¹¹ The steric bulk of the biq ligands causes distortion of the pseudooctahedral geometry which is proposed to stabilize the ^3LF state from which ligand dissociation occurs.

A similar series of Ru(II) complexes utilize steric bulk from methyl substituents to facilitate efficient dissociation of a bidentate ligand to afford Ru(II)-containing moieties that covalently bind to DNA. Complexes with the general formula $[\text{Ru}(\text{bpy})_2(\text{NN})]^{2+}$ were reported, where NN = 6,6'-dimethyl-2,2'-bipyridine (Me_2bpy), = 7,10-dimethylpyrazino[2,3-*f*][1,10]phenanthroline (Me_2dpq), or 3,6-dimethyldipyrido[3,2-*a*:2',3'-*c*]phenazine (Me_2dppz), shown in Figure 6, and their photochemistry and photoinduced coordination to DNA were investigated.^{112–114} The irradiation of $[\text{Ru}(\text{bpy})_2(\text{Me}_2\text{bpy})]^{2+}$ and $[\text{Ru}(\text{bpy})_2(\text{Me}_2\text{dpq})]^{2+}$ with $\lambda = 450$ nm and $[\text{Ru}(\text{bpy})_2(\text{Me}_2\text{dppz})]^{2+}$ with $\lambda = 400$ nm results in dissociation of the methyl-substituted ligand, and the resulting $\text{Ru}^{\text{II}}(\text{bpy})_2$ fragment was reported to covalently bind to duplex and quadruplex DNA. Photocytotoxicity toward HL60 leukemia and A549 lung cancer cells was observed upon treatment with $[\text{Ru}(\text{bpy})_2(\text{Me}_2\text{bpy})]^{2+}$ and $[\text{Ru}(\text{bpy})_2(\text{Me}_2\text{dpq})]^{2+}$ and irradiation with $\lambda = 450$ nm for 3 minutes, resulting in IC_{50} values as low as $1.1 \mu\text{M}$ and PI values up to 208. Related strained complexes were recently incorporated into cross-linked polymeric nanoassemblies to tune the hydrophobicity, photochemical activation, pH, and solution ionic strength in metal complex photodelivery.¹¹⁵ Additionally, $[\text{Ru}(\text{bpy})_2(\text{Me}_2\text{dppz})]^{2+}$ also acts as a photochemical DNA sensor due to the DNA light-switch behavior of dppz-type ligands.¹¹⁴ In polar protic solvent, the lowest energy excited state is a dark state, but when intercalated into DNA (or in nonpolar solvent), the dark state is higher in energy compared to the bright state. From the bright state, thermal population of the ^3LF state can occur, thus leading to dissociation of the Me_2dppz ligand.

In an attempt to decrease the dark toxicity of metal complexes with planar ligands, some of which exhibit strong intercalation between the DNA bases, nonplanar analogues to dpq and Me_2dpq , 2,3-dihydro-1,4-dioxino[2,3-*f*]-1,10-phenanthroline (dop) and 2,3-dihydro-1,4-

dioxino[2,3-*f*]-2,9-dimethyl-1,10-phenanthroline (Me₂dop; Figure 6) were utilized in the complexes [Ru(bpy)₂(Me₂dop)]²⁺ and [Ru(Me₂phen)₂(dop)]²⁺ (Me₂phen = 2,9-dimethyl-1,10-phenanthroline).¹¹⁶ Despite the use of non-intercalating ligands, the affinity for DNA when incubated in the dark was not significantly decreased. Irradiation with $\lambda > 400$ nm in aqueous solvent causes exchange of a bulky, methyl-substituted ligand with two H₂O molecules. When HL60 human promyelocytic leukemia cells were exposed to [Ru(bpy)₂(Me₂dop)]²⁺ or [Ru(Me₂phen)₂(dop)]²⁺ and irradiated with $\lambda > 400$ nm, the cells were killed with greatly enhanced efficiency compared to the dark toxicities, as evidenced by the irradiated IC₅₀ values of 0.65 ± 0.10 μ M and 0.16 ± 0.01 μ M, and PI values of 52 and 1880, respectively. The dark IC₅₀ of [Ru(Me₂phen)₂(dop)]²⁺, > 300 μ M, is especially noteworthy, highlighting the fact that the dark DNA affinity probed by gel assays provides a poor prediction of dark cytotoxicity.

A series of [Ru(bpy)₂(LL)]²⁺ complexes, where LL = 3,6-dithiaoctane (bete), 1,2-bis(phenylthio)ethane (bpte), ethylenediamine (en), or 1,2-dianilinoethane (dae), shown in Figure 6, were designed to probe the effects of electronic structure on photoinduced dissociation of the bidentate ligand, LL.¹¹⁷ The compounds with LL = bete and bpte exhibit absorption maxima of 422 nm and 404 nm, respectively, while those values for the analogous LL = en and dae compounds are observed at 485 nm and 469 nm, respectively. It is believed that the shift is due to the ability of S-bound ligands to stabilize the Ru(d π) orbitals to a greater extent than N-bound ligands. The longer Ru-LL bond distances calculated in the ³MLCT excited state when LL = bete or bpte compared to the N-containing ligands are consistent with the greater efficiency of LL dissociation in CH₂Cl₂ with excess Cl⁻ and $\lambda_{\text{irr}} = 400$ nm for [Ru(bpy)₂(bete)]²⁺ and [Ru(bpy)₂(bpte)]²⁺, $\Phi_{400} = 0.019(1)$ and $0.016(3)$, respectively, compared to [Ru(bpy)₂(en)]²⁺ and [Ru(bpy)₂(dae)]²⁺ with $\Phi_{400} = 0.002(1)$ and $0.003(1)$, respectively. The irradiation of [Ru(bpy)₂(bete)]²⁺ in the presence of 5'-GMP in aqueous media with visible light for 10 minutes followed by incubation at 37 °C in the dark for 4 hours affords the [Ru(bpy)₂(5'-GMP)]²⁺ adduct. Additionally, the complexes covalently bind to linearized pUC18 DNA following irradiation with $\lambda = 395$ nm for 4 minutes. The S-containing compounds bind to nucleic acids more efficiently compared to the N-containing compounds, consistent with the trends in LL exchange quantum yields.

The photoinduced exchange of a bidentate ligand with two solvent molecules from the Ru^{II}(bpy)₂ caging group was utilized to provide a metal complex that can simultaneously covalently bind to DNA and cleave DNA in hypoxic conditions upon visible light irradiation.¹¹⁸ The irradiation of an aqueous solution of [Ru(bpy)₂(py-SO₃)]⁺ (Figure 6) with $\lambda = 470$ nm causes a shift in the Ru $\rightarrow$ bpy ¹MLCT transition from 460 nm to 490 nm with an isosbestic point at 478 nm. The absorption of the photoproduct is consistent with the formation of *cis*-[Ru(bpy)₂(OH₂)₂]²⁺. In the presence of pBR322 plasmid DNA in a deoxygenated solution, photolysis causes both a retardation of the supercoiled DNA migration, indicative of covalent binding, as well as formation of the open circular DNA band, indicative of single strand cleavage. The DNA cleavage is proposed to arise from a hydroxyl radical (OH $\cdot$) formed from H₂O upon the release of a py-SO₃ $\cdot$ radical from the metal complex. Despite the dual activity in the gel shift assays, [Ru(bpy)₂(py-SO₃)]⁺ exhibits low phototoxicity toward human pulmonary adenocarcinoma A549 cells when irradiated with visible light, likely due to either poor cellular uptake or inappropriate cellular

localization. The effects of substituents on the bpy ligands were investigated with a series of $[\text{Ru}(\text{R}_2\text{bpy})_2(\text{py-SO}_3)]^+$ complexes, where $\text{R} = -\text{OCH}_3$, $-\text{CH}_3$, or $-\text{COOCH}_3$.¹¹⁹ The $\text{py-SO}_3^\bullet$ radical dissociation is sensitive to the R group due to the $^3\sigma(\text{Ru-O}) \rightarrow \pi^*(\text{R}_2\text{bpy})$ CT character of the excited state that promotes Ru-O bond cleavage, and consequently the complexes with more electron donating R groups ($\text{R} = -\text{OCH}_3$ or $-\text{CH}_3$), thus lower $^3\sigma(\text{Ru-O}) \rightarrow \pi^*(\text{R}_2\text{bpy})$ state energies, release $\text{py-SO}_3^\bullet$ less efficiently.

In addition to the ability of the Ru(II) fragment to bind to DNA and other biomolecules, the ligand(s) that are released may also be biologically active. In fact, the spatiotemporal control of drug release is a growing field in the application of photoinduced ligand dissociation from Ru(II)-diimine complexes.^{79,80} The bioactive molecule is inactive when it is coordinated to a Ru(II) complex, but upon irradiation with visible light, the molecule is exchanged with a solvent molecule and becomes available for therapeutic activity. The photochemical delivery of 5-cyanouracil (5CNU), which is a structural analog to the commonly used chemotherapy drug 5-fluorouracil, was investigated using *cis*- $[\text{Ru}(\text{bpy})_2(5\text{CNU})_2]^{2+}$ and $[\text{Ru}(\text{tpy})(5\text{CNU})_3]^{2+}$, shown in Figure 7.^{120,121} Visible light irradiation of these complexes causes the dissociation of two equivalents of 5CNU to form *cis*- $[\text{Ru}(\text{bpy})_2(\text{OH}_2)_2]^{2+}$ and *trans*- $[\text{Ru}(\text{tpy})(5\text{CNU})(\text{OH}_2)_2]^{2+}$. The quantum efficiencies when irradiated with 400 nm light were measured to be $\Phi_{400} = 0.16(4)$ for the formation of the mono-aqua $[\text{Ru}(\text{bpy})_2(5\text{CNU})(\text{OH}_2)]^{2+}$ and $\Phi_{400} = 0.022(2)$ for the bis-aqua *trans*- $[\text{Ru}(\text{tpy})(5\text{CNU})(\text{OH}_2)_2]^{2+}$ complexes. In addition to the ability to release 5CNU, the aquated photoproducts also covalently bind to linearized plasmid DNA, such that it is possible to release three equivalents of therapeutic agents for each metal complex: two equivalents of 5CNU and one of the aquated metal complex. The phototoxicity of $[\text{Ru}(\text{tpy})(5\text{CNU})_3]^{2+}$ was investigated with HeLa cells, and irradiation of the cells incubated with the metal complex with $\lambda = 400$ nm for 1 hour resulted in an LC_{50} value of $156 \pm 18 \mu\text{M}$, which is consistent with the LC_{50} value of 5CNU alone, $151 \pm 33 \mu\text{M}$, indicating that under the conditions of irradiation of the cell cultures, only one 5CNU molecule is released.

The photorelease of drugs from Ru(II) complexes has also been investigated with protease inhibitors based on nitrile-modified peptides. This concept was first demonstrated using a peptide known to inhibit the cysteine protease inhibitor papain, Ac-Phe-NHCH₂CN (Figure 7).¹²² The nitrile acts as the warhead that the cysteine thiolate in the active site of papain attacks reversibly, causing papain inhibition. The coordination of the inhibitor to a Ru(II) center protects it from this reactivity with papain, thus generating a caged system that can be activated with light.¹²³ The irradiation of *cis*- $[\text{Ru}(\text{bpy})_2(\text{Ac-Phe-NHCH}_2\text{CN})_2]^{2+}$ with 400 nm light causes the exchange of each peptide ligand with a solvent water molecule in a two-step process, forming the $[\text{Ru}(\text{bpy})_2(\text{Ac-Phe-NHCH}_2\text{CN})(\text{OH}_2)]^{2+}$ intermediate with $\Phi_{400} = 0.080(4)$ and the *cis*- $[\text{Ru}(\text{bpy})_2(\text{OH}_2)_2]^{2+}$ product with an overall efficiency (reactant to product) of $\Phi_{400} = 0.00091(7)$. This overall quantum yield is significantly lower than the value reported for *cis*- $[\text{Ru}(\text{bpy})_2(\text{CH}_3\text{CN})_2]^{2+}$ of 0.21, likely due to the lower solubility of Ac-Phe-NHCH₂CN in aqueous solution compared to that of CH₃CN, such that recombination of the fragments is favored instead of their escape from the solvent cage. The activity of papain is inhibited by Ac-Phe-NHCH₂CN with $\text{IC}_{50} = 638$ nM, while when bound to the Ru(II) metal in *cis*- $[\text{Ru}(\text{bpy})_2(\text{Ac-Phe-NHCH}_2\text{CN})_2]^{2+}$ the IC_{50} value was measured to be $9.8 \mu\text{M}$ in the dark, but decreases to 295 nM when irradiated with $\lambda_{\text{irr}} = 395$

nm for 10 minutes. This result indicates that each Ru(II) complex releases two equivalents of Ac-Phe-NHCH₂CN. An analogous experiment with *cis*-[Ru(bpy)₂(CH₃CN)₂]²⁺ provides an IC₅₀ value > 500 μM, consistent with the notion that the Ru(II) complex photoproduct has no impact on the enzyme activity. The light-activated inhibition of cathepsins B, K, and L were also investigated with *cis*-[Ru(bpy)₂(Ac-Phe-NHCH₂CN)₂]²⁺, and in each case, the irradiated metal complex is up to two times more potent than the inhibitor alone, and light activation results in 6- to 33-fold greater activity.

The investigation of light-activated cysteine protease inhibition using a Ru^{II}(bpy)₂ cage was expanded using the cathepsin K inhibitors Cbz-Leu-NHCH₂CN and Cbz-Leu-Ser(OBn)-CN, both pictured in Figure 7, with IC₅₀ = 36 nM and 28 nM, respectively.¹²⁴ The irradiation of *cis*-[Ru(bpy)₂(Cbz-Leu-NHCH₂CN)₂]²⁺ and *cis*-[Ru(bpy)₂(Cbz-Leu-Ser(OBn)-CN)₂]²⁺ with 400 nm light undergoes the same stepwise ligand exchange in H₂O as described for the Ac-Phe-NHCH₂CN complex, providing reactant to intermediate Φ₄₀₀ values of 0.050(6) and 0.021(2), respectively, and overall reactant to product Φ₄₀₀ values of 0.0067(4) and 0.0045(6). In the dark, *cis*-[Ru(bpy)₂(Cbz-Leu-NHCH₂CN)₂]²⁺ and *cis*-[Ru(bpy)₂(Cbz-Leu-Ser(OBn)-CN)₂]²⁺ inhibit cathepsin K with IC₅₀ = 560 μM and 2.2 μM, respectively, and their activities are greatly enhanced by 35- and 88-fold upon visible light irradiation for 15 minutes (irradiated IC₅₀ = 16 nM and 25 nM, respectively). These IC₅₀ values are consistent with the release of two equivalents of Cbz-Leu-NHCH₂CN and one equivalent of Cbz-Leu-Ser(OBn)-CN. The slower release of Cbz-Leu-Ser(OBn)-CN observed in the photolysis experiments monitored by electronic absorption spectroscopy is consistent with the release of only one equivalent of peptide during the course of the enzyme inhibition experiment. Caging of two molecules of Cbz-Leu-NHCH₂CN was also achieved using the Ru^{II}(TPA) moiety, where TPA = tris(2-pyridylmethyl)amine, affording the complex [Ru(TPA)(Cbz-Leu-NHCH₂CN)₂]²⁺.¹²⁵ Ligand exchange with this complex, however, requires UV light (365 nm), and only the nitrile ligand *trans* to the pyridyl group is exchanged with a solvent H₂O molecule (Φ₃₅₀ = 0.011(1)). In the dark, the IC₅₀ value of [Ru(TPA)(Cbz-Leu-NHCH₂CN)₂]²⁺ is 5.6 μM; an 89-fold increase in inhibitory activity occurs upon irradiation with 365 nm, providing an IC₅₀ value of 63 nM. No inhibition of cathepsin K was observed with 500 μM of the control complex, [Ru(TPA)(CH₃CN)₂]²⁺, in the light or dark, indicating that the metal complex does not impact cathepsin K activity.

Ru(II)-diimine complexes have also been utilized for the photochemically controlled delivery of synthetic peptides coordinated to the metal through histidine residues to control the activity of Ni(II)-dependent peptide nucleases with spatial and temporal control.¹²⁶ The Arg-Gly-His (RGH) tripeptide, which features an imidazole side chain from the His residue and chelates Ni(II) to form a metallopeptide that exhibits endonuclease activity, was coordinated to a Ru(II) complex to afford [Ru(bpy)₂(PPh₃)(RGH)]²⁺ (shown in Figure 7) to prevent the peptide from chelating Ni(II). Irradiation of the complex with 455 nm light releases the RGH peptide and forms the aquated Ru(II) complex, [Ru(bpy)₂(PPh₃)(OH₂)]²⁺. The efficiency of ligand dissociation was determined for the [Ru(bpy)₂(PPh₃)(His-Boc)]²⁺ precursor (His-Boc = Boc-protected histidine) to be Φ ≈ 0.06 (λ_{irr} = 455 nm). Upon incubation with cellular components such as H₂O₂, GSH, histidine, and Ni(II) for 24 h, the complex remains stable, confirming the effectiveness of the Ru^{II}(bpy)₂(PPh₃) cage. The endonuclease activity of [Ru(bpy)₂(PPh₃)(RGH)]²⁺ was assayed using pcDNA 3.1 Neo

plasmid. Irradiation of $[\text{Ru}(\text{bpy})_2(\text{PPh}_3)(\text{RGH})]^{2+}$ in the presence of the plasmid and $\text{Ni}(\text{ClO}_4)_2$ produces nicked circular DNA in a manner similar to the incubation of RGH and $\text{Ni}(\text{ClO}_4)_2$, which forms the metallopeptide in situ, with the plasmid. Incubation of the plasmid with $[\text{Ru}(\text{bpy})_2(\text{PPh}_3)(\text{RGH})]^{2+}$ and $\text{Ni}(\text{ClO}_4)_2$ in the dark results in no DNA cleavage, confirming the utility of this metal complex as an effective cage for histidine-containing peptides.

IX. Summary

This review has attempted to present an overview of the photophysical behavior and common photoreactions of Ru(II) imine complexes, with select examples from the literature since the 1960s, and also to provide a more detailed picture of the use of knowledge gained over the years in the development of Ru(II) complexes for use in photobiology and photodynamic therapy. This recent research has furthered the understanding of the photoreactivity of Ru(II) imine complexes and has provided elegant examples of the exploitation of both the photophysical and photochemical behavior of particular complexes in the development of novel therapeutic agents.

Acknowledgments

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Biographies

Jessica K. White received her B.S. in Chemistry from the University of Dayton in 2008. In 2013, she earned her Ph.D. from Virginia Tech under the direction of the late Prof. Karen J. Brewer while studying excited state dynamics and photocatalytic properties of Ru(II),Pt(II) supramolecular complexes. She is currently a postdoctoral researcher with Prof. Claudia Turro at The Ohio State University studying photoinduced ligand dissociation from metal complexes. Beginning in Fall 2016, she will be an Assistant Professor in the Department of Chemistry and Biochemistry at Ohio University. Her research interests involve the photochemistry of metal complexes with applications in photochemotherapy.

Professor Claudia Turro received her B.S. with Honors (1987) and Ph.D. (1992) degrees in Chemistry from Michigan State University and joined the Department of Chemistry at The Ohio State University in 1996, following graduate work on excited state dynamics of transition metal complexes and electron transfer processes relevant to biology. Her research program spans the areas of time-resolved spectroscopy, excited states reactivity of transition

metal complexes, and bioinorganic chemistry, including systems with applications in therapeutics, diagnostics, and solar energy conversion. Professor Turro received the Early Career Award from the National Science Foundation in 1998 and the Arnold and Mabel Beckman Foundation Young Investigator Award in 1999. She was named a 2010 Fellow of the American Chemical Society (ACS) and a 2011 Fellow of the American Association for the Advancement of Science. Professor Turro was elected as President of the Inter-American Photochemical Society in 2012 and Chair of the ACS Division of Inorganic Chemistry in 2016. She received the 2014 College of Arts and Sciences Susan M. Hartmann Mentoring and Leadership Award the 2014 Inter-American Photochemical Society Award in Photochemistry, the 2016 Columbus ACS Section Award, and the 2016 Edward W. Morley Medal presented by the Cleveland Section of the ACS.

Professor Russell Schmehl received his B.S. in Chemistry in 1976 from Roanoke College. He received a Ph.D. from the University of North Carolina in 1980 under the direction of David Whitten and also did postdoctoral work at UNC in the lab of Royce Murray. In 1982 he joined the faculty of Tulane University and is was promoted to full Professor in 1993. Between 2009 and 2011 he served as interim Graduate Dean in Tulane's School of Science and Engineering. His research has focused on the design, synthesis, photophysical and photochemical investigation of second and third row transition metal complexes and has resulted in over 100 publications in peer reviewed journals. Specific areas of study have included intramolecular energy transfer between charge transfer and ligand localized excited states, the development of light harvesting ensembles of chromophores and, more recently, development of efficient sacrificial photoinduced electron transfer systems for generation of potent reductants in solution. Between 2002 and 2012 he served as American editor of the Journal of Photochemistry and Photobiology and in 2014 he received the Outstanding Researcher Award from Tulane's School of Science and Engineering.

Highlights

- A review of temperature dependent luminescence of Ru(II) imine complexes is presented.
- The efficiencies of photosubstitution reactions of Ru(II) imine complexes are reviewed.
- Mechanistic aspects of photosubstitution reactions are reviewed.
- An overview of photosubstitution reactions in biological systems is presented.

Figure 1.
States diagram of typical Ru(II) imine complexes.

Figure 2.

(A) Drawing of the bis-triazole complex and (B) structure of the monodentate intermediate species formed upon photolysis in CH_3CN .

Figure 3.

Postulated ligand to ligand charge transfer state intermediate associated with pyridine ligand loss in $[\text{Ru}(\text{cym})(\text{bpy})(\text{py-BODIPY})]^{2+}$ (S = solvent).

Figure 4. Structural representation Ru(II)-piano stool complexes that release a monodentate ligand, L, upon visible light irradiation and covalently bind to DNA.

Figure 5.
Structural representations of complexes that covalently bind to DNA upon photodissociation of monodentate ligands.

Figure 6.

A series of Ru(II) diimine complexes that undergo photoinduced bidentate ligand dissociation followed by covalent binding to DNA.

Figure 7.
Structural representations of Ru(II) diimine complexes that release a bioactive molecule upon visible light irradiation.

Scheme 1.

Scheme 2.

Table 1

Parameters obtained from measurements of temperature dependent luminescence decay of various Ru(II) imine complexes.

Complex, medium	$k_{\text{r+n}}, \times 10^{-5} \text{ s}^{-1}$	A_0 (or k_{a2}), s^{-1}	E_a (or E), cm^{-1}	τ_{act} , 298 K	ref.
[Ru(bpy) ₃] ²⁺ , H ₂ O	12.2	10 ¹³	3600	0.19	5
[Ru(bpy) ₃] ²⁺ , MeOH/EtOH	2.2	1.4 × 10 ¹⁴	3950	0.77	24
[Ru(tpy)(bpy)(AN)] ²⁺ , PN/BN ^b	1.7	2 × 10 ¹⁴	1600	1.0	22
[Ru(pypm) ₃] ²⁺ , MeOH/EtOH	11	5 ± 3 × 10 ¹³	3340	0.82	21
[Ru(pypm) ₂ (bpy)] ²⁺ , MeOH/EtOH	17	1.3 ± 0.2 × 10 ⁷	480	0.43	21
[Ru(bpy) ₂ (pypm)] ²⁺ , MeOH/EtOH	12	2 ± 0.4 × 10 ⁷	550	0.54	21
[Ru(dmb) ₂ (py) ₂] ²⁺ , MeOH/EtOH ^b	7.1	4 ± 5 × 10 ¹⁵	3200	1.0	21
[Ru(bpm) ₂ (py) ₂] ²⁺ , MeOH/EtOH	8.7	3 ± 17 × 10 ¹⁷	4800	0.97	21
[Ru(bpy) ₂ (py) ₂] ²⁺	8.2	1.7 × 10 ¹³	3410	0.42	19
[Ru(bpz) ₃] ²⁺	3.3	8 ± 2 × 10 ¹²	3325	0.21	29
[Ru(bpy) ₂ (bpz)] ²⁺	7.4	4 ± 3 × 10 ⁹	2100	0.18	29
[Ru(bpy) ₂ (bpz)] ²⁺	21	3 ± 9 × 10 ⁷	800	0.23	29
[Ru(bpy) ₂ (pn)] ²⁺ , MeOH/EtOH	10	1 ± 2 × 10 ¹²	2814	0.56	23
[Ru(dmb) ₃] ²⁺ , CH ₂ Cl ₂	5.3	3 ± 4 × 10 ¹¹	2740	0.52	18
[Ru(dmb) ₂ (decb)] ²⁺ , CH ₂ Cl ₂	4.1	4 ± 1 × 10 ⁶	450	0.53	18
[Ru(decb) ₂ (dmb)] ²⁺ , CH ₂ Cl ₂	4.1	5 ± 1 × 10 ⁶	610	0.40	18
[Ru(decb) ₃] ²⁺ , CH ₂ Cl ₂	3.3	3 ± 4 × 10 ⁷	1180	0.23	18
[Ru(bpy) ₂ (biq)] ²⁺ , MeOH/EtOH	14	2 × 10 ⁷	420	0.65	24
[Ru(biq) ₃] ²⁺ , MeOH/EtOH	4.5	1.7 × 10 ¹³	2700	0.99	24
[Ru(bpy) ₂ (NMI) ₂] ²⁺ , CH ₂ Cl ₂	25	1.5 × 10 ¹³	3500	0.21	19
[Ru(bpy) ₂ (AEP)] ²⁺ , CH ₂ Cl ₂	9.1	4.5 × 10 ¹³	3240	0.89	19
[Ru(bpy) ₂ (pyd) ₂] ²⁺ , CH ₂ Cl ₂	3.4	1.5 × 10 ¹⁴	2710	0.99	19

AN = CH₃CN, dmb=4,4'-dimethyl-2,2-bipyridine, pypm = 2-(2'-pyridyl)pyrimidine, bpm = 2,2'-bipyrimidine, bpz = 2,2'-bipyrazine, en = ethylenediamine, decb=4,4'-dicarboxyethyl-2,2'-bipyridine, biq = 2,2'-biquinoline, NMI = N-methylimidazole, AEP= 2-aminoethylpyridine, pyd = pyridazine b. PN/BN = propionitrile/butyronitrile glass; MeOH/EtOH = Methanol/Ethanol glass.

Table 2

Room temperature photosubstitution quantum yields.

Complex	Solvent	Ligand	θ_{rxn}	$\eta_{\text{act}}, 298 \text{ K}$	ref.
$[\text{Ru}(\text{bpy})_3]^{2+}$	CH_2Cl_2	Cl	0.049	0.84	18
$[\text{Ru}(\text{bpy})_3]^{2+}$	CH_3CN	CH_3CN	0.029	0.46	29
$[\text{Ru}(\text{bpy})_2(\text{py})_2]^{2+}$	CH_3CN	Cl	0.006	0.42	21
$[\text{Ru}(\text{bpy})_2(\text{bpz})(\text{py})_2]^{2+}$	CH_3CN	Cl	0.0008	--	21
$[\text{Ru}(\text{bpy})_2(\text{NCCCH}_3)_2]^{2+}$	CH_3OH	CH_3OH	0.82	--	52
$[\text{Ru}(\text{bpm})_3]^{2+}$	CH_3CN	CH_3CN	0.48	0.71	29
$[\text{Ru}(\text{bpm})_2(\text{bpy})]^{2+}$	CH_3CN	CH_3CN	$<10^{-3}$	0.07	29
$[\text{Ru}(\text{bpy})_2(\text{bpm})]^{2+}$	CH_3CN	CH_3CN	$<10^{-4}$	0.10	29
$[\text{Ru}(\text{bpz})_3]^{2+}$	CH_3CN	CH_3CN	0.45	0.74	29
$[\text{Ru}(\text{bpz})_2(\text{bpy})]^{2+}$	CH_3CN	CH_3CN	0.035	0.18	29
$[\text{Ru}(\text{bpy})_2(\text{bpz})]^{2+}$	CH_3CN	CH_3CN	$<10^{-4}$	0.20	29
$[\text{Ru}(\text{dmb})_3]^{2+}$	CH_2Cl_2	Cl	0.005	0.52	18
$[\text{Ru}(\text{dmb})_2(\text{decb})]^{2+}$	CH_2Cl_2	Cl	$<10^{-3}$	0.53	18
$[\text{Ru}(\text{decb})_2(\text{dmb})]^{2+}$	CH_2Cl_2	Cl	$<10^{-3}$	0.40	18
$[\text{Ru}(\text{decb})_3]^{2+}$	CH_2Cl_2	Cl	0.012	0.23	18