Published in final edited form as:

Inorg Chem. 2015 February 16; 54(4): 1901–1911. doi:10.1021/ic502791y.

Solid-Phase Synthesis as a Platform for the Discovery of New Ruthenium Complexes for Efficient Release of Photocaged Ligands with Visible Light

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Abstract

Ruthenium-based photocaging groups have important applications as biological tools and show great potential as therapeutics. A method was developed to rapidly synthesize, screen and identify ruthenium-based caging groups that release nitriles upon irradiation with visible light. A diverse library of tetra- and pentadentate ligands was synthesized on polystyrene resin. Ruthenium complexes of the general formula $[\text{Ru}(\text{L})(\text{MeCN})_n]^{m+}$ ($n = 1-3$, $m = 1-2$) were generated from these ligands on solid phase, then cleaved from resin for photochemical analysis. Data indicate a wide range of spectral tuning and reactivity with visible light. Three complexes that showed strong absorbance in the visible range were synthesized by solution phase for comparison. Photochemical behavior of solution- and solid-phase complexes was in good agreement, confirming that the library approach is useful in identifying candidates with desired photoreactivity in short order, avoiding time consuming chromatography and compound purification.

Introduction

Metal complexes are actively being developed as therapeutics and tools for chemical biology.^{1–14} Despite their success in multiple arenas, our ability to rapidly synthesize, screen and identify metal complexes with desired properties has not evolved at the same pace as organic molecules, which are synthesized routinely in large libraries and screened in high throughput assays.¹⁵ Notwithstanding a few notable exceptions,^{16–19} metal complexes are usually synthesized and evaluated one molecule at a time when being developed for biological applications. This approach is less than ideal if inorganic compounds are to compete with their organic counterparts as tool compounds and therapeutics. Given that structure-activity relationships of metal complexes vary widely and are notoriously difficult

Supporting Information

General considerations, experimental procedures for preparation of **3**, **5–7**, **8a–j**, **9a–j**, **11a–j**, **12–14**, ¹H NMR spectra and LCMS characterization data for **9a–j**, X-ray crystallographic data for **12** and **14**, ¹H NMR spectra and time-resolved UV-vis data for **12–14**, including dark controls. This material is available free of charge via the Internet at <http://pubs.acs.org>.

to predict,^{20–22} more rapid methods are clearly needed to identify optimal candidates for biological applications.

One area of biology where metal complexes have made an important impact is photocaging.^{23–25} Photocaging has revolutionized our ability to study living systems, by allowing researchers to control spatial and temporal aspects of biological activity through selective deprotection or “uncaging” of active compounds.²⁶ Current photocaging methods take advantage of a variety of different protecting groups.²³ Organic-based photocages have now advanced to the point where many caged compounds are commercially available and used routinely in biological research. However, a major drawback of organic cages is that they usually require UV light, which is absorbed by nearly all species in vivo.²⁵ Metal complexes have emerged more recently as an important class of photocaging groups.^{24,27–43} They are attractive because they bind to a variety of different functional groups, including those that cannot be protected with organic-based cages such as nitriles,^{44–49} nitrogen-containing heteroaromatics⁵⁰ or thioethers.⁵¹ Thus, metal complexes offer an orthogonal approach to organic caging methods. Metal-based caging groups also carry the advantage of being labile with visible light under single-photon excitation,⁵² which is rare for organic photolabile protecting groups that are usually cleaved with UV light.^{53,54}

Of the various classes of metal-based photocaging groups, ruthenium complexes based on planar, heteroaromatic ligands have been particularly successful (Figure 1). Pioneering work in the neuroscience area proved that the Ru(bpy)₂ group (bpy = 2,2'-bipyridine) can be used to achieve high spatial and temporal control over receptor activity in live neuronal cells.^{50,52,55–62} Importantly, no toxic effects were observed from the caged neurotransmitters, or their metal-based byproducts. Later work proved that the Ru(bpy)₂ caging moiety other Ru(II) complexes with related bidentate ligands can also be used to cage cytotoxic agents^{45,47} and protease inhibitors⁴⁶ for cell-based assays.⁴⁸ In an effort to identify other photolabile protecting groups distinct from this class, we showed recently that ruthenium tri(2-pyridylmethyl)amine, Ru(TPA), is an effective cage for bioactive nitriles (see Figure 1 for ligand).⁴⁹ Although complexes of the general formula [Ru(TPA)(RCN)₂]²⁺ (RCN = bioactive nitrile) showed promising activity, including excellent stability in the dark and high levels of selectivity for enzyme inhibition under dark vs. light conditions, the potential for improvement remained. Most notably, UV light is required for efficient release of nitrile because singlet metal-to-ligand charge transfer (¹MLCT) bands for these complexes occur at $\lambda < 400$ nm. In addition, only one of the two potentially labile nitrile molecules was released upon irradiation. Therefore, we sought to develop a streamlined approach to evaluate other ligands of this class in ruthenium complexes for optimizing properties of the caging group.

Herein, we report a library approach for accessing ruthenium complexes by solid phase synthesis that provides rapid access to new derivatives for screening photochemical behavior. Ligands designed to tune spectral properties of the ruthenium-based photocaging group were synthesized in parallel fashion on solid phase. This library was processed to form caged ruthenium complexes bound to resin, then subsequently cleaved and analyzed for photochemical reactivity. Three compounds identified from this screen were synthesized by solution phase and characterized photochemically. The data from the latter were in good

agreement with compounds from solid phase, thus validating the predictive power of our library approach. Data indicate a surprisingly wide range of spectral tuning and reactivity with light, demonstrating the utility of this screening technology, as well as the power it has to identify lead caging groups.

Results

Synthesis of Ligand Library

Our strategy for the synthesis of the ligand library was based on previous work from the Kodanko laboratory, where a single pyridine precursor bound to resin was functionalized with two components (R_1 and R_2) to create a library of polypyridyl ligands.^{63,64} The pyridine precursor chosen for the present study was derived from commercially available dimethyl pyridine-2,5-dicarboxylate (**1**, Scheme 1). Following a literature protocol,⁶⁵ selective reduction of the ester in the 2-position furnished alcohol **2**. Amidation of **2** with excess 1,3-propanediamine by heating in MeOH at 80 °C provided amine **3** in quantitative yield, where excess 1,3-propanediamine could be removed simply by azeotropic distillation from toluene.

To begin our studies with solid phase, Fmoc-protected Rink amide MBHA resin derived from polystyrene (**4**, Scheme 2) was chosen for attachment of the pyridine precursor **3**. Deprotection of the Fmoc group from **4** using 1:1 piperidine:DMF, followed by treatment with succinic anhydride in DMF furnished acid **5**. Acid **5** was coupled to amine **3** using HBTU in DMF, giving pyridylmethyl alcohol **6**, containing a 10-atom spacer between the pyridine group and the amide nitrogen bound to resin. Activation of alcohol **6** was accomplished by either mesylation or chlorination using conditions shown in Scheme 2. Mesylation with MsCl and Et₃N proceeded smoothly at RT with 100 mg or less of resin to furnish **7** ($X = \text{OMs}$). However, upon further scale up, it was difficult to observe full consumption of alcohol **6**, as judged by ¹H NMR and ESMS analysis of product cleaved from resin. Optimal conditions developed later involved heating resin to 50 °C in the presence of excess TsCl, LiCl, iPr₂EtN and MeCN, which worked routinely on scales of up to 1 g of resin, providing **7** ($X = \text{Cl}$).

A library of ten polypyridyl derivatives (**8a–j**) was accessed in 1–2 steps from monopyridine **7** ($X = \text{Cl}$ or OMs) using straightforward alkylation chemistry (Scheme 2). Full structures of the ligands prepared by this method are shown in Figure 2. Individual schemes for syntheses of **8a–h** are presented in the Supporting Information (Figure S3). In some cases, the delivery of the appropriate secondary amine resulted in nucleophilic displacement of the leaving group ($X = \text{Cl}$ or OMs), providing derivatives of **8** in one step (*Strategy A*). Alternatively, the reaction with a primary amine ($R_1\text{NH}_2$) was used to attach one group to the ligand (R_1), with a second alkylation reaction using $R_2\text{Cl}$ to complete synthesis of the tertiary amine ligand (*Strategy B*).

After the ligand syntheses were completed, the library was evaluated by cleaving a small amount of each derivative from the resin using 95% TFA in H₂O (Figure 2), providing terminal amides **9a–j** that were characterized by LCMS (Figures S1–10) and ¹H NMR spectroscopy (Figures S12–21). LCMS analysis indicated purities for the 10 derivatives

ranged from 52–99%, with seven of the 10 compounds in >88% purity. Initially, compound **9g**, a derivative of the known ligand N4Py, was produced in <20% purity, with the remainder being unreacted **7** (X = Cl). In this case, the secondary amine used to synthesize **9g**, 1,1-di(pyridin-2-yl)-N-(pyridin-2-ylmethyl)methanamine, is a hindered nucleophile.^{63,66} Optimized reaction conditions were developed using NaI as a catalyst, MeCN as solvent and $i\text{Pr}_2\text{EtN}$, which raised the level of purity of **9g** to 88%. Synthesis of compound **9e** proceeded smoothly in the first alkylation of **7** (X = Cl) with 2-pyridylmethylamine (Scheme S3). Subsequent alkylation with 2,6-bis(bromomethyl)pyridine followed by aniline proved challenging, resulting in lower conversion to product **9e** (52% purity) under a variety of conditions, and was not optimized further.

Synthesis of Ruthenium Complex Library by Solid Phase

With a library of resin-bound polypyridyl ligands **8a–j** in hand, conditions were developed to generate ruthenium complexes with bound MeCN groups to be released photochemically. Ligands **8a–c** and **8j** contain four donor atoms and were expected to furnish complexes of the general formula $[\text{Ru}(\text{L})(\text{MeCN})_2]^{n+}$ ($n = 1, 2$) with two molecules of MeCN coordinated to the metal. Ligands **8d–i** each carry five potential donor atoms, and were expected to result in complexes of the general formula $[\text{Ru}(\text{L})(\text{MeCN})]^{n+}$ ($n = 1, 2$) with only one bound nitrile. A mixture of neutral and anionic ligands were incorporated that were expected to furnish ruthenium(II) complexes as mono- or dicationic species.

Optimization efforts began by surveying a number of conditions and ruthenium(II) precursors for metalation of the resin-bound ligands (Scheme 3, Table 1). Compound **8a**, a derivative of TPA, was used to develop the protocol because data for ruthenium(II) TPA complexes were available to use as benchmarks.^{49,67,68} Two ruthenium(II) starting materials were surveyed initially, $\text{cis-}[\text{Ru}(\text{DMSO})_4\text{Cl}_2]$, which was expected to give a mixture of complexes of the general formula $[\text{Ru}(\text{8a})(\text{DMSO})\text{Cl}]^+$ that could later be converted into $[\text{Ru}(\text{8a})(\text{MeCN})_2]^{2+}$, and $[\text{Ru}(\text{COD})(\text{MeCN})_4](\text{OTf})_2$,⁶⁹ which could potentially give access to the desired complex $[\text{Ru}(\text{8a})(\text{MeCN})_2]^{2+}$ directly in one step. Combining resin-bound **8a** with 2–10 equiv. of these ruthenium salts in the presence of solvent (DMF, EtOH or MeCN) and heat (50–80 °C) led to metallation, as judged by UV-vis spectroscopic and ESMS analysis of products cleaved from resin using 95% TFA in H_2O . Relative yields were approximated by absorbance using extinction coefficients of the species $[\text{Ru}(\text{9a})(\text{DMSO})\text{Cl}]^+$ and $[\text{Ru}(\text{9a})(\text{MeCN})_2]^{2+}$. Importantly, both species were shown to be stable for > 24 h in the TFA cleavage cocktail in the absence of irradiation, indicating decomposition does not occur to a measurable extent during 15 min cleavage from resin.

Data indicated a wide range of yields for metallation conditions surveyed. Relative to $\text{cis-}[\text{Ru}(\text{DMSO})_4\text{Cl}_2]$ (Table 1, entries 1–3), $[\text{Ru}(\text{COD})(\text{MeCN})_4](\text{OTf})_2$ is a sluggish ruthenium(II) starting material, giving <5% yield after 18 h at 50 °C in MeCN. The choice of solvent was also important. DMF, which shows superior swelling of polystyrene resin compared to MeCN, MeOH or EtOH, actually showed much lower yields for metallation (entries 1, 2 and 7). We considered at this stage that swelling properties could play a key role in optimizing formation of the ruthenium complex bound to resin, so compound **8a** was also prepared bound to Tenta-Gel resin, which shows better swelling properties than

polystyrene in protic solvents, where yields for binding to Ru(II) were higher. However, use of Tenta-Gel resin did not enhance yields for metallation with EtOH (entry 8). Optimal conditions using conventional heating methods were identified using polystyrene-based **8a**, 4 equiv of *cis*-[Ru(DMSO)₄Cl₂], EtOH as the solvent and heating at 80 °C for 18 h (entry 6). using microwave heating, cutting reaction timescales down from 18 h to 30 min (entry 7). Raising the amount of Ru(II) source to 10 equiv and heating at 120 °C for 1 h in the microwave reactor did not enhance the yield relative to 4 equiv. and 80 °C (entry 9). Thus, *cis*-[Ru(DMSO)₄Cl₂] (4 equiv.), EtOH as the solvent and heating at 80 °C for 30 min with microwave irradiation were deemed optimal for formation of the intermediate [Ru(**8a**)(DMSO)Cl]⁺.

A number of conditions were also surveyed for conversion of the resin-bound [Ru(**8a**)(DMSO)Cl]⁺ to the caged nitrile species [Ru(**8a**)(MeCN)₂]²⁺. Heating the resin in MeCN solvent lead to poor conversion to [Ru(**8a**)(MeCN)₂]²⁺ as judged by UV-vis spectroscopic and ESMS analysis of product cleaved from resin. Addition of H₂O to the MeCN medium did enhance conversion to [Ru(**8a**)(MeCN)₂]²⁺, however, full conversion was still not observed. We hypothesized at this stage that it could be difficult to obtain higher yields of [Ru(**8a**)(MeCN)₂]²⁺ because of the chloride counteranions, which are highly polar, show limited ability to solubilize dications in organic media and may not be favorable for association of the dicationic complex with the polystyrene polymer. Therefore, additives were explored that could potentially exchange with chloride, including NaBF₄, NaOAc, NaOTf and NH₄PF₆. However, significant levels of decomposition with little to no formation of product were observed. Considering these facts, an additional ruthenium(II) source was explored that already contained less polar anion than chloride. Gratifyingly, heating resin **8a** in the presence of *fac*-[Ru(DMSO)₃(O₂CCF₃)₂(H₂O)]⁷⁰ (4 equiv.) in EtOH at 80 °C for 30 min under microwave irradiation, followed by microwave irradiation in MeCN:H₂O (1:1) for 30 min at 80 °C and cleavage from resin, resulted in good conversion and provided [Ru(**9a**)(MeCN)₂](O₂CCF₃)₂ (**11a**) in 81% yield (Table 1, entry 10).

With optimal conditions developed, the library of resin-bound ligands **8a–j** was processed to Ru(II) MeCN complexes (Scheme 4). Conditions for metallation employed *fac*-[Ru(DMSO)₃(O₂CCF₃)₂(H₂O)] (4.0 equiv) in EtOH with microwave heating at 80 °C for 30 min, followed by replacement of the solvent with MeCN:H₂O and microwave heating at 80 °C for an additional 30 min. In the case of compounds **8b**, **8c**, **8d**, and **8i**, 2,6-lutidine (10 equiv) was added during step 1 for deprotonation of acidic protons. Each member of the library was cleaved from resin and screened by UV-vis spectroscopy for reactivity with visible light (30 min irradiation, λ_{irr} = 395 nm) in H₂O, with the goal of identifying complexes that exchanged H₂O for MeCN upon irradiation (Figure 3a–j).

Data from the photochemical screening indicate a range of spectral tuning, as well as reactivity with visible light. All of the complexes absorb strongly below 400 nm, with select examples showing significant absorbance from 400–500 nm (ex. **11f–g** and **11i–j**). As expected, most of the complexes are slow to react with visible light because their corresponding ¹MLCT bands lie below 400 nm (**11a–e**, **11h**). However, strong absorbance above 400 nm did not guarantee reactivity with visible light. Complex **11f**, which absorbs strongly to almost 500 nm, did not react with visible light. The N4Py derivative **14g** did

react slowly with visible light, but did not demonstrate the expected bathochromic shift for substitution of H₂O for MeCN. Complexes **11i** and **11j** did show the desired shift to longer wavelengths, with **11j** showing the most rapid spectral change upon irradiation with visible light.

In addition to photochemical screening, each of the library members was analyzed by ESMS (Table 2). Major peaks were observed for each species, along with suitable isotope patterns, corresponding to calculated m/z values for dications. Compounds **11a**, **11c–e** and **11j** all showed m/z values consistent with two bound MeCN groups. Data for **11b** were consistent with three bound nitriles, suggesting that the carboxylic acid group of ligand **9b** was not bound to ruthenium. Complexes derived from the pentadentate ligands **11f–h** all showed major species corresponding to one bound MeCN group.

Synthesis and Characterization of Complexes by Solution Phase

Based on results from our screening, three ligands were chosen for further evaluation of their corresponding Ru(II) MeCN complexes. Ligand **8f**, a derivative of the known ligand DPAbpy, was chosen because its Ru(II) MeCN complex showed significant absorption in the visible spectral range, yet no photoreactivity was detected with visible light, a surprising observation that needed to be verified by solution phase. Ligand **8g**, a derivative of the known ligand N4Py, was chosen because it also showed significant absorption at λ 400 nm. Unlike **11f**, complex **11g** did exhibit photoreactivity with visible light irradiation, but data were not consistent with substitution of H₂O for MeCN, because a bathochromic shift was not observed. Therefore a follow up study was warranted. Finally, ligand **8j**, which contains two isoquinoline moieties, was identified as the lead ligand from this study. There is a significant bathochromic shift in the absorption maximum of **11j** relative to that of **11a**, and spectral changes were observed with a low photon flux of visible light and short irradiation times that were consistent with substitution of H₂O for MeCN. However, instead of **9j**, we chose to examine the C₃ symmetric ligand TQA,⁷¹ which replaces the pyridine donor of **9j** with an isoquinoline. This substitution was expected to simplify our analysis, because only one isomer can be formed from TQA, unlike **9j**, where isoquinoline donors could adopt either a *cis* or *trans* configuration and lead to formation of two isomers.

Three Ru(II) complexes were synthesized by solution phase for evaluation against compounds from our library screen (Scheme 5). The ligands DPAbpy,⁷² N4Py⁷³ and TQA⁷¹ were synthesized using literature procedures. Treating each ligand with one equiv of *cis*-[Ru(DMSO)₄Cl₂] in MeOH at 80 °C led to rapid formation of the corresponding metal complex. Concentration and heating in MeCN:H₂O (1:1), followed by precipitation with NH₄PF₆ produced [Ru(DPAbpy)(MeCN)](PF₆)₂ (**12**), [Ru(N4Py)(MeCN)₂](PF₆)₂ (**13**) and [Ru(TQA)(MeCN)₂](PF₆)₂ (**14**) in yields of 47–75%. Complexes **12–14** were characterized by ¹H NMR and IR spectroscopies and ESMS. X-ray crystallographic data were collected for complexes **12** and **14** only, and data for **13** were described previously in the literature.⁷⁴

Diffusion of Et₂O into acetone solutions provided crystals of **12** and **14** suitable for X-ray crystallographic analysis. Select data for **12** and **14** are presented in Figure 4;. The bond distance to the single nitrile of **12**, 2.052(11) Å for Ru–N1, is considerably longer than those

measured for related complexes, such as $[\text{Ru}(\text{TPA})(\text{MeCN})_2]^{2+}$ or $[\text{Ru}(\text{bpy})_2(\text{MeCN})_2]^{2+}$.^{49,68,75–78} Metal-nitrogen bond distances to nitrile for **14** are 2.032(1) and 2.042(1) Å for Ru–N1 and Ru–N6, respectively, which are similar to $[\text{Ru}(\text{TPA})(\text{MeCN})_2]^{2+}$, with bond distances of 2.031(5) and 2.037(5) for Ru–N1 and Ru–N6, respectively.⁴⁹ In the case of **14**, Ru–N1 and Ru–N6 distances are outside the range of error, with the longer bond positioned *cis* to the basic nitrogen atom N5 (Figure 4B).

The changes to the electronic absorption spectra of **12**, **13**, and **14** in H_2O at room temperature were monitored as a function of irradiation time to detect generation of any photochemical products. No change in the absorption spectrum of **12** was observed following irradiation ($\lambda = 395$ nm) for 1 h (Figure S38). The irradiation of **13** in H_2O with $\lambda = 395$ nm results in a shift in the absorption maximum from 348 nm to 361 nm, whereas the peak at 420 nm blue shifts to 408 nm with clear isosbestic points at 368 nm and 412 nm (Figure 5A). This process, occurring with $\Phi_{400} = 0.019(3)$, is not consistent with substitution of CH_3CN with H_2O because a shift of the MLCT band at 420 nm to lower energy is expected. Further irradiation causes a red shift of the 420 nm peak (Figure 5B), suggesting that substitution of CH_3CN may occur as a secondary process following the first photoinduced event. The first event is presumed to correspond to the substitution of one of the coordinated pyridyl substituents from the N4Py ligand with H_2O , a point that is explored by ^1H NMR spectroscopy with the results described below. Irradiation of **14** with $\lambda = 395$ nm, Figure 5C, causes a red shift of the absorption maximum from 418 nm to 425 nm with an isosbestic point at 420 nm and $\Phi_{400} = 0.027(1)$. This red shift of the MLCT band is consistent with formation of the corresponding mono-aqua complex upon substitution of one CH_3CN . Further irradiation results in a further red shift to 460 nm (Figure 5D), consistent with substitution of the second CH_3CN ligand with H_2O . Indeed, a second isosbestic point is apparent in Figure 5D for the changes to the absorption spectrum at longer irradiation time at 398 nm.

To confirm the nature of the photoproducts formed during the photolysis of **13** and **14**, the changes to the ^1H NMR spectrum of each complex was monitored as a function of irradiation time in D_2O with $\lambda = 395$ nm. In D_2O in the dark, no changes were observed (Figures S39, S40), confirming that the complexes are stable in solution in the absence of light. Figure 6A depicts the changes in the NMR spectrum of **14** upon irradiation in D_2O . In 180 min, a clean progression to a single photoproduct is observed, assigned to the mono-aqua species, labeled M in Figure 6A. Most notably, the loss of the singlet at 2.32 ppm concurrent with the evolution of a singlet at 2.06 ppm (free CH_3CN) indicates substitution of bound CH_3CN with D_2O . By comparison with the previously reported $[\text{Ru}(\text{TPA})(\text{CH}_3\text{CN})_2]^{2+}$ analogue,⁴⁹ the photosubstituted CH_3CN is assigned as the ligand *trans* to the quinoline group (N6, Figure 4B), as this CH_3CN chemical shift is more shielded than the CH_3CN *trans* to the amine (2.92 ppm). A schematic representation of this ligand exchange is shown in Figure 6B. This experiment confirms the ability of **14** to release a nitrile ligand and coordinate a solvent molecule when irradiated with visible light at early irradiation times. It should be noted that after 180 min of irradiation, the integration of the peak corresponding to remaining bound CH_3CN ligand begins to decrease, together with a continued increase in free CH_3CN . At 360 min of irradiation, peaks corresponding to the

bis-aqua product are discerned in the ^1H NMR spectrum, labeled B in Figure 6A. This finding, together with the presence of an isosbestic point a longer irradiation times in the absorption spectra (Figure 5B), is indicative that the first step shown in Figure 6B is followed by the exchange of the second CH_3CN ligand with prolonged photolysis.

The photoproduct(s) formed upon irradiation of **13** in D_2O were also studied by ^1H NMR and the results are shown in Figure 7. Unlike **14**, the bound CH_3CN singlet at 2.81 ppm does not show a clear decrease concurrent with only free CH_3CN evolution; instead, as the singlet at 2.81 ppm decreases, a new peak at 2.86 ppm increases as well as a small increase of free CH_3CN at 2.06 ppm. Additionally, the singlet at 6.62 ppm, assigned as the methine proton, decreases and two new additional singlets at 6.08 and 6.35 ppm appear with irradiation. The aromatic region becomes more complicated with new peaks arising at 6.98, 7.80, 8.25, and 8.84 ppm. The shift is consistent with a small change in the environment around the CH_3CN protons upon exchange of one coordinated pyridyl ring for a solvent molecule. The ^1H NMR results are consistent with the presence of multiple photoprocesses upon visible light irradiation, where the dominant pathway is the dissociation of a coordinated N4Py pyridyl ring from the ruthenium center, but with CH_3CN exchange for a solvent molecule also operative to a smaller extent, the methine proton singlet upfield is consistent with one of the pyridyl rings being released and replaced by solvent.

Discussion

Combinatorial chemistry, diversity-oriented synthesis and other compound library approaches have made a major impact in chemical biology and drug discovery.^{79–85} Methods for synthesizing large libraries of organic compounds have advanced to the point where a single researcher can synthesize hundreds of thousands of compounds in a week.¹⁵ In comparison to organic compounds, methods to synthesize libraries of inorganic compounds are grossly underdeveloped. Most attention has focused on the discovery of metal-based catalysts for organic reactions,^{86–88} selective metal-binding agents,^{89–91} and new photosensitizers.⁹² Peptide- and oligonucleotide conjugates of metal complexes have been synthesized by solid phase for biological applications, and these compounds have enjoyed great success as biologically active agents and tool compounds.^{93–102} However, their synthesis often involves late-stage attachment of the complex (or ligand) to the biomolecule, where the coordination environment of the complex is preset. Surprisingly, even though there is an enormous amount of chemical space that remains unexplored, studies that apply combinatorial chemistry to vary and tune the coordination sphere of biologically active inorganic compounds are rare.^{16–19} To the best of our knowledge, library approaches had not been applied yet towards discovery of new metal-based caging groups, a class of inorganic compounds with many important biological applications.^{30,32–40,46,48–50,52,55,57–62,103–105}

The solid phase synthesis and screening platform described in this manuscript allowed us to rapidly identify complexes that release their ligands with visible light. Three examples with varied reactivity were synthesized and fully characterized, and the photochemical behavior of the complexes was in good agreement between solid- and solution-phase compounds (Figures S41–43). Thus, our library approach was validated as a method for identifying lead

caging groups. Solid-phase synthesis carries numerous advantages over its solution-phase counterpart, including the ability to perform reactions on small scale, and isolate compounds by simple filtration, thereby avoiding time consuming and often tedious purifications of ligand precursors, ligands and metal complexes, which all can be challenging. Removing the need for compound isolation and chromatography is a major advantage, especially for researchers that do not carry a strong experimental skill set in synthesis. Key to this study, only 1–2 compounds out of the 10 surveyed actually reacted with visible light in the desired manner to release bound nitriles. Synthesizing and characterizing the photochemistry of each of these 10 complexes would have taken considerable effort. The synthesis and screening approach we adopted allowed us to direct our efforts in synthesis and full characterization toward the most promising compounds only.

The library members from this study displayed a wide range of reactivity with visible light. Many of the examples showed little if any photochemical activity, an observation easily explained by the fact that most compounds did not absorb strongly in the visible region. Indeed, photochemistry is observed for many of the compounds surveyed when irradiated with in the MLCT bands with UV light.¹⁰⁶ However, several of the compounds prepared absorb well in the visible range, and either do react when irradiated with visible light to follow a non-desired pathway, such as the pyridine release observed with complex **13**, or are not photoactive with visible light at all (ex. **12**). Thus, absorbing in the visible range did not guarantee nitrile release with visible light, an observation that has been reported with other caging strategies.⁴⁰ The lead compound established from this study was complex **14**, which acts much like its congener $[\text{Ru}(\text{TPA})(\text{MeCN})_2]^{2+}$,⁴⁹ with the selective release the nitrile ligand positioned *trans* to quinoline upon irradiation with short irradiation times. Complex **14**, however, does provide numerous advantages over $[\text{Ru}(\text{TPA})(\text{MeCN})_2]^{2+}$, including efficient release of MeCN with visible light and larger quantum yield, $\Phi_{400} = 0.027(1)$ for **14** vs. $\Phi_{350} = 0.012(1)$ for $[\text{Ru}(\text{TPA})(\text{MeCN})_2]^{2+}$. In order to explain the wide range of reactivity with light, computations were carried out with compounds **12–14** and other examples.¹⁰⁷ Time-dependent density functional theory (TD-DFT) calculations, the focus of a separate manuscript, have provided significant insight into the disparity of reactivity for these complexes, which are all derived from very similar ligands. These data have allowed us to assign many of the optical bands observed in absorption spectra of the complexes as ¹MLCT transitions, which fall in the UV to visible range. Preliminary assessment of the data indicates that barrier for internal conversion between the lowest energy ³MLCT state and the dissociative triplet metal centered (³MC) states is a key factor that controls the outcome and selectivity of nitrile release with these complexes. Results of these studies will be published elsewhere.

Conclusions

In conclusion, we have described a new platform for discovering metal-based caging groups that provides rapid access to new derivatives for screening photochemical behavior. A representative library of 10 compounds was produced that contained a range of different donors, denticities and coordination geometries. Absorption and photoreactivity with visible light was screened, resulting in the identification of several compounds that demonstrated interesting behavior worthy of further investigation. Three new analogs were synthesized by

solution phase, and data for compounds were in good agreement with the corresponding complexes from solid phase, thus validating the predictive power of the library approach. The wide range of reactivity with visible light amongst the library of compounds illustrated the need to prescreen compounds for their photochemical behavior, before efforts were directed towards solution phase synthesis and full characterization, an inherently tedious but necessary process. In general terms, this study represents an important example of why combinatorial, library-based approaches should be applied towards the development of inorganic complexes for biological applications. Such studies are currently underway in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge the National Institutes of Health (EB 016072) and Wayne State University (Rumble Fellowship to R.S.) for their generous support of this research.

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Planar Heteroaromatics *Ligands Containing Trialkylamines*

Figure 1.
Planar heteroaromatic ligands found in ruthenium-based caging groups and ligands derived from trialkylamines

Figure 2.
Structures of polypyridyl ligand library bound to resin (**8a–j**) and cleaved for analysis (**9a–j**)

Figure 3.

Changes in the electronic absorption spectra upon irradiation with visible light (λ_{irr} 395 nm) in H_2O of complexes **11a–j** for 0 (black), 5 (red), 15 (green) and 30 (blue) min.

A **B** **Figure 4.**

Perspective view of the dications [Ru(DPAbpy)(MeCN)]²⁺ (**A**) and [Ru(TQA)(MeCN)₂]²⁺ (**B**) derived from **12** and **14**, respectively. Thermal ellipsoids are shown at 50% probability. Hydrogen atoms are omitted for clarity. Select bond lengths (Å) and angles (deg) for [Ru(DPAbpy)(MeCN)]²⁺ (**A**); Ru–N1, 2.052(11); Ru–N2, 2.060(12); Ru–N3, 2.085(12); Ru–N4, 1.986(14); Ru–N5, 1.954(11); Ru–N6, 2.052(11); N1–Ru–N6, 97.6(4). Select bond lengths (Å) and angles (deg) for [Ru(TQA)(MeCN)₂]²⁺ (**B**); Ru–N1, 2.032(1); Ru–N2, 2.067(1); Ru–N3, 2.052(1); Ru–N4, 2.061(1); Ru–N5, 2.042(1); Ru–N6, 2.042(1); N1–Ru–N6, 87.50(4).

Figure 5.

Electronic absorption spectra of **13** irradiated for 0, 0.5, 1, 4, 7, and 15 min (A) and 15, 40, and 85 min (B) and **14** irradiated for 0, 0.5, 1, and 2 min (C) and 2, 5, 20, and 60 min (D), in H_2O upon irradiation with $\lambda = 395$ nm.

Figure 6.

^1H NMR spectra following irradiation of **14** in D_2O with $\lambda_{\text{irr}} = 395 \text{ nm}$ for 0, 15, 45, 90, and 180 min; the label M indicates signal from the mono-aqua intermediate and B from the bis-aqua product formed upon irradiation with selected integrations shown parentheses (A) and schematic representation of the first ligand exchange process of the complex (B).

Figure 7.
 ^1H NMR spectra following irradiation of **13** in D_2O with $\lambda_{\text{irr}} = 395$ nm for 0, 30, 60, and 120 min. Stars indicate new signals evolved upon irradiation.

Scheme 1.
Synthesis of pyridine precursor 3

Scheme 2. Solid phase synthesis of the polypyridyl ligand library (**8a-j**)

Scheme 3.

Three methods (A-C) explored for synthesis of Ru(II) complexes [Ru(**9a**)(DMSO)Cl]Cl (**10a**) and [Ru(**9a**)(MeCN)₂](X)₂ (**11a**, X = OTf, O₂CCF₃). See Table 1 for more details.

Scheme 4.
Synthesis of Ru(II) MeCN complex library

Scheme 5.

Synthesis of Ru(II) MeCN complexes **12–14** by solution phase methods.

Table 1

Conditions and Ru(II) sources examined for conversion of resin-bound ligand **8a** to Ru(II) complexes [Ru(**9a**)(DMSO)Cl]Cl (**10a**) and [Ru(**9a**)(MeCN)₂]X₂ (**11a**, X = OTf, O₂CCF₃)

Condition ^{a,b}	Ru(II) source (equiv) ^c	Solvent	Temperature (°C) ^{d,e}	Time (h)	% Yield ^{f,g}
1 ^a	A (2)	DMF	50 ^d	18	24 ^f
2 ^a	A (2)	MeOH	50 ^d	18	35 ^f
3 ^a	B (2)	MeCN	50 ^d	18	<5 ^g
4 ^a	B (4)	MeCN	80 ^e	0.5	<5 ^g
5 ^a	B (4)	EtOH	80 ^e	0.5	<5 ^g
6 ^a	A (4)	EtOH	80 ^d	18	70 ^f
7 ^a	A (4)	EtOH	80 ^e	0.5	57 ^f
8 ^b	A (4)	EtOH	80 ^e	0.5	68 ^f
9 ^a	A (10)	EtOH	120 ^e	1	51 ^f
10 ^a	C (4)	EtOH, then MeCN:H ₂ O	80 ^e	0.5 × 2	81 ^g

^a **8a** derived from polystyrene resin (0.75 mmol/g);

^b **8a** derived from Tenta-Gel resin (0.23 mmol/g);

^c Ruthenium(II) sources are *cis*-[Ru(DMSO)₄Cl₂] (A), [Ru(COD)(MeCN)₄](OTf)₂ (B) and *fac*-[Ru(DMSO)₃(O₂CCF₃)₂(H₂O)] (C);

^d conventional heating;

^e microwave heating (50 W);

^f % yield of [Ru(**9a**)(DMSO)Cl]⁺ as determined by absorbance at λ_{max} = 345 nm (ε = 10,500 M⁻¹ cm⁻¹) after cleavage from resin with 95% TFA in H₂O;

^g % yield of [Ru(**9a**)(MeCN)₂]²⁺ as determined by absorbance at λ_{max} = 348 nm (ε = 9040 M⁻¹ cm⁻¹) after cleavage from resin with 95% TFA in H₂O.

Table 2

ESMS data for compounds **11a–j** showing major m/z values observed and molecular formulas for dications consistent with the data

Compound ^b	m/z (obs)	Formula (calcd) ^c
11a	337	[Ru(11a)(MeCN) ₂] ²⁺
11b	340	[Ru(11b)(MeCN) ₃] ²⁺
11c	344	[Ru(11c)(MeCN) ₂] ²⁺
11d	351	[Ru(11d)(MeCN) ₂] ²⁺
11e	389	[Ru(11e)(MeCN) ₂] ²⁺
11f	355	[Ru(11f)(MeCN)] ²⁺
11g	355	[Ru(11g)(MeCN)] ²⁺
11h	382	[Ru(11h)(MeCN)] ²⁺
11i	nd ^a	nd ^a
11j	387	[Ru(11j)(MeCN) ₂] ²⁺

^aRuthenium complex with suitable isotope pattern was not detected by ESMS.