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Monosaccharide Interactions with Rh(III) cis-Bipyridine Complexes

BY SARAH M. LANE

Sarah Lane, is a senior majoring in Bio-chemistry/Biomed. She received an ATP summer research grant and produced this piece under the mentorship of Dr. Steven Haefner. Her future plans include more research and graduate school. Her research will also be presented at the American Chemical Society meeting in Atlanta in 2006.

Abstract

Carbohydrates are extensively involved in a variety of cell-cell interactions, including cell-cell recognition communication, adhesi,on, and signaling. The ability to manipulate these carbohydrate activities could have numerous medical applications, such as treatments for cancer or infectious diseases. We are currently examining the ability of metal complexes to selectively bind to the specific saccharides, d-glucose and d-mannose. In particular we are interested in preparing solvated cis-bis-chelates of Rh(III). Reaction of $[Rh(bpy)_2Cl_2]PF_6$ with two equivalents of $AgBF_4$ does not give the expected disubstituted species, $[Rh(bpy)_2(DMF)_2]^{3+}$. Instead, the monosubstituted complex, $[Rh(bpy)_2(DMF)Cl]BF_4$ was obtained in a 34% yield. The ^1H NMR spectrum of $[Rh(bpy)_2(DMF)Cl]^{2+}$ confirmed the adjacent position of the DMF and Cl⁻ groups. Likewise, reaction of $[Rh(bpy)_2Cl_2]PF_6$ with neat triflic acid produces cis-$[Rh(bpy)_2(OTf)Cl]OTf$ instead of the expected bis-chelate complex. ^1H NMR of the product reveals a mixture of isomers. Both cis-$[Rh(bpy)_2(DMF)Cl]^{2+}$ and cis-$[Rh(bpy)_2(OTf)Cl]^+$ react with glucose in basic solutions. Preliminary titrations studies of these compounds with simple monosaccharides reveal that complexation between rhodium and monosaccharides occur as evidenced by Uv-vis spectral changes.

The interactions between metals and carbohydrates have been a subject of recent notice in chemistry.1 This is due to the important roles metals carry out in the biochemical processes of oligosaccharides. These processes are carried out by the binding of oligosaccharides to specific proteins called lectins. Lectins

are involved in cell-cell interaction, including binding of glycoproteins, which take part in viral replication, cell recognition, and cell growth.1 The association of lectins and saccharides is primarily via hydrogen bonding; consequently, such interactions tend to be weak.2·3 Therefore, interfering with the functions of oligosaccharides, by replacing its hydrogen bonding with lectins for a more stable metal-saccharide bond, could lead to the ability to control the physiological processes of cellular interactions.

There are a limited number of well characterized metal-sugar complexes; therefore it is crucial to establish the conditions needed to bind simple monosaccharides to a metal.

The circumstances under which this takes place can then be applied to a future goal of building a polymetalic system capable of targeting specific carbohydrates. Of relevance to this goal is studying simple monometallic-saccharide interactions, in an effort to provide information on the binding sites of the sugar and the affinity of various sugars to a metal (figure 1).4 The binding sites on a monosaccharide are hard to predict because their fixed orientation limits the ways in which the hydroxyl groups on the sugar can coordinate to a metal.4 In addition, monosaccharides change conformation in solution, which hinders their interactions with metals.5
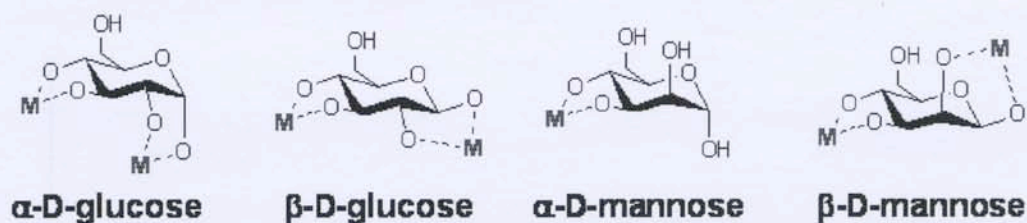

Figure 1. Possible binding sites of monosaccharides to metal.

Nevertheless, some researchers have been successful in complexing monosaccharides to metals, including sodium, calcium, and lanthanide compounds.6 Palladium, a second row transition metal, has been successfully bonded to a series of five carbon sugar rings and six carbon sugar rings.4 There are, however, a limited numbers of second and third row transition metal-monosaccharide complexes, and no known rhodium-monosaccharide complexes. Herein we report on our efforts to examine the ability of rhodium bis-bipyridine complexes to bind simple monosaccharides.

Results and Discussion

Our initial efforts have focused on the synthesis of cis-[Rh(bpy)$_2$(DMF)$_2$]$^{3+}$ where bpy = 2,2-bipyridine and DMF = dimethylformamide. Bipyridine complexes of rhodium were selected as starting materials because of the stability such chelating ligands afforded. The cis-orientation of the bipyridine ligands will create two adjacent coordination sites that may accommodate the hydroxyl groups of a monosaccharide (figure 2).
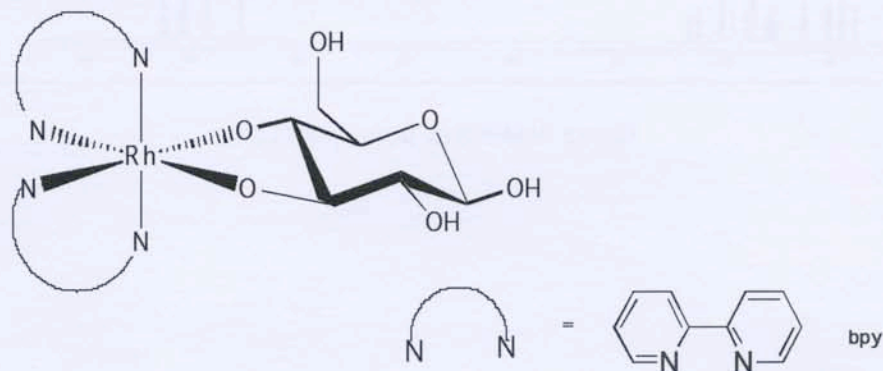
Figure 2. Rhodium-glucose complex.

The coordinated solvent molecules are expected to be weakly held and therefore readily replaced by an incoming sugar. In addition the overall 3+ charge of the complex should further promote sugar complexation.

To prepare the target compound we chose cis-$[Rh(bpy)_2Cl_2]PF_6$ as our starting point. In 2001, Kim et. al. successfully displaced the chloride ions of $[Rh(bpy)_2Cl_2]PF_6$ with bipyridine and H_2O using Ag^+ under thermal conditions. The Ag^+ ion reacts with the coordinated Cl^- ions to produce

AgCl which precipitated from the solution. Accordingly we reacted $[Rh(bpy)_2Cl_2]PF_6$ with two equivalents of $AgBF_4$ in DMF. Stirring at room temperature for 24 hours provides an orange/yellow solution and a grey precipitate. Filtration of the solution followed by slow addition of toluene yields a pale colored solid.

The ^1H NMR of the solid shows a series of resonances from 7.70 ppm to 9.91 ppm that corresponds to the aromatic bipyridine protons (Figure 3).
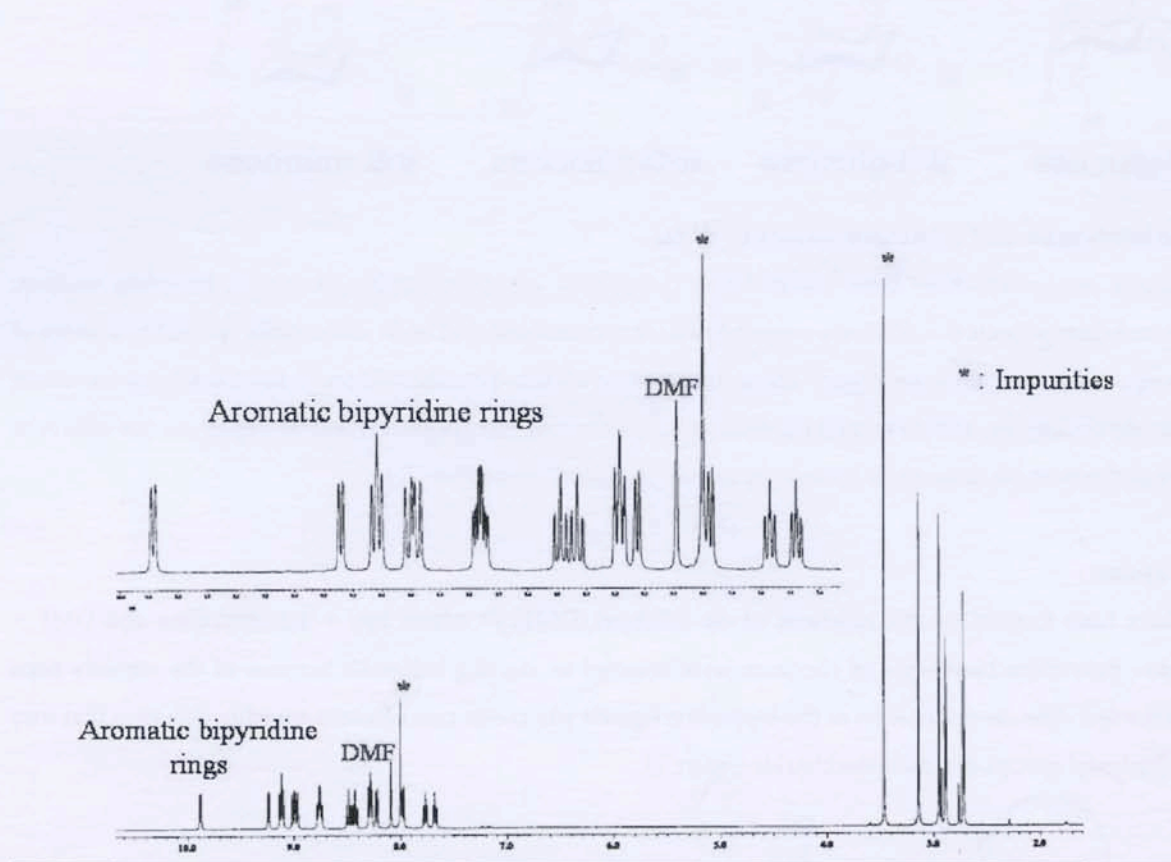

Figure 3. ^1H NMR of cis-$[Rh(bpy)_2(DMF)Cl]^{2+}$.

Integration of this region indicates that there are a total of 16 magnetically inequivalent protons. Based upon its symmetry a ^{1}H NMR spectrum of the compound cis-[Rh(bpy)$_2$(DMF)$_2$]$^{3+}$ is expected to have eight signals from the bipyridine protons in the aromatic region. Each bipyridine has a total of eight protons, with four protons on each ring. A cis conformation of the DMF ligands would create two sets of inequivalent bipyridine rings. One bipyridine ring would be trans to the coordinated DMF while the second ring is cis to the DMF. Such an arrangement would produce a total of eight inequivalent protons. However, the presence of sixteen protons signals indicates that two different groups occupy the remaining coordination sites. In other words the spectrum suggests that only partial substitution occurred to give the monosubstituted DMF complex, cis-[Rh(bpy)$_2$(DMF)Cl]$^{2+}$. This would cause the two bipyridines to become inequivalent, with one bipyridine ring trans to a chloride and the second bipyiridine ring trans to the DMF group. The presence of coordinated DMF is readily evident from the ^{1}H NMR spectrum and appears as 3 signals at 2.98 ppm and 3.17 ppm for the inequivalent methyl groups,

and 8.12 ppm for the formyl protons. Integration of these resonances confirms that there is only one DMF complexed. The IR spectrum of cis-[Rh(bpy)$_2$(DMF)Cl]$^{2+}$ further supports the presence of coordinated DMF. A strong carbon oxygen double bond appears at 1651cm^{-1} corresponding to the carbonyl group of the DMF. This absorption appears at lower energy than in free DMF and is indicative of oxygen bound DMF. A strong broad band attributed to the B-F stretch of a BF$_4$ counter ion appears at 1060 cm^{-1}, confirming the formation of Rh(III) cationic species. The UV-vis spectrum of cis-[Rh(bpy)$_2$(DMF)Cl]$^{2+}$ shows a single band at 314 nm that gradually tails into the visible spectrum.

When the synthesis of cis-[Rh(bpy)$_2$(DMF)$_2$]$^{3+}$ proved to be problematic, the focus was turned to the compound [Rh(bpy)$_2$(OTf)$_2$]OTf.[7] Triflate ($^-$OTf = CF$_3$SO$_3^-$) is a very labile ligand, and is readily displaced in favor of other ligands. Synthesis of the triflate complex [Rh(bpy)$_2$(OTf)$_2$]OTf was attempted by reacting two equivalents of triflic acid with [Rh(bpy)$_2$Cl$_2$]PF$_6$ in ortho-dichlorobenzene, and heating just below reflux (figure 4).[7]
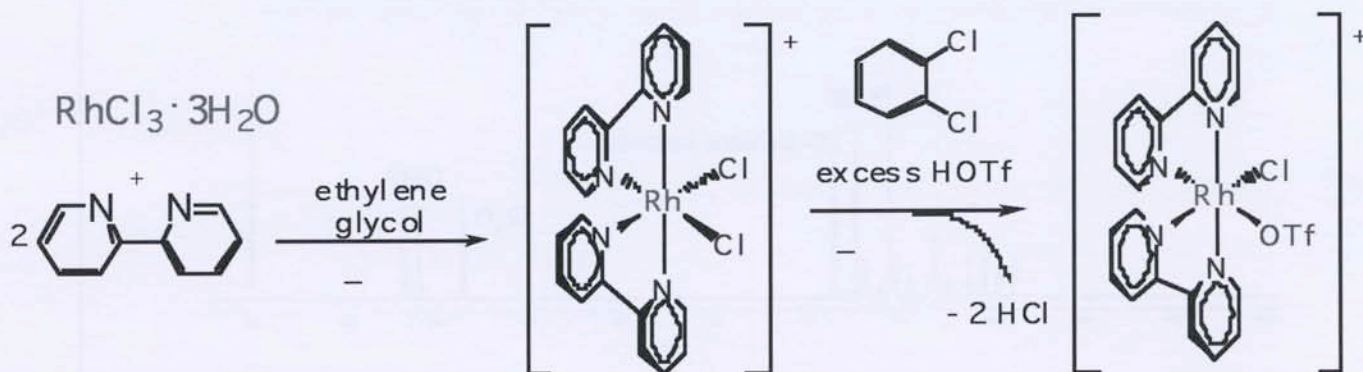
Figure 4. Synthesis of cis-[Rh(bpy)$_2$(OTf)Cl]$^+$.[7]

During the course of the reaction, the neat triflic acid protonates the chloride ion producing HCl. The HCl then escapes as a gas from the solution. After heating the reaction for a total of five hours an off white solid was precipitated by addition of diethyl ether. The ^{1}H NMR spectrum of the solid, shown in figure 5, clearly indicates that the solid is composed of two components.

A resonances: [Rh(bpy)$_2$(OTf)(Cl)]$^+$; 16 protons indicate this complex is present.

B resonances: *trans*-[Rh(bpy)$_2$(Cl)$_2$]$^+$ or *trans*-[Rh(bpy)$_2$(OTf)$_2$]$^+$; 4 protons indicate one of these complexes is present.
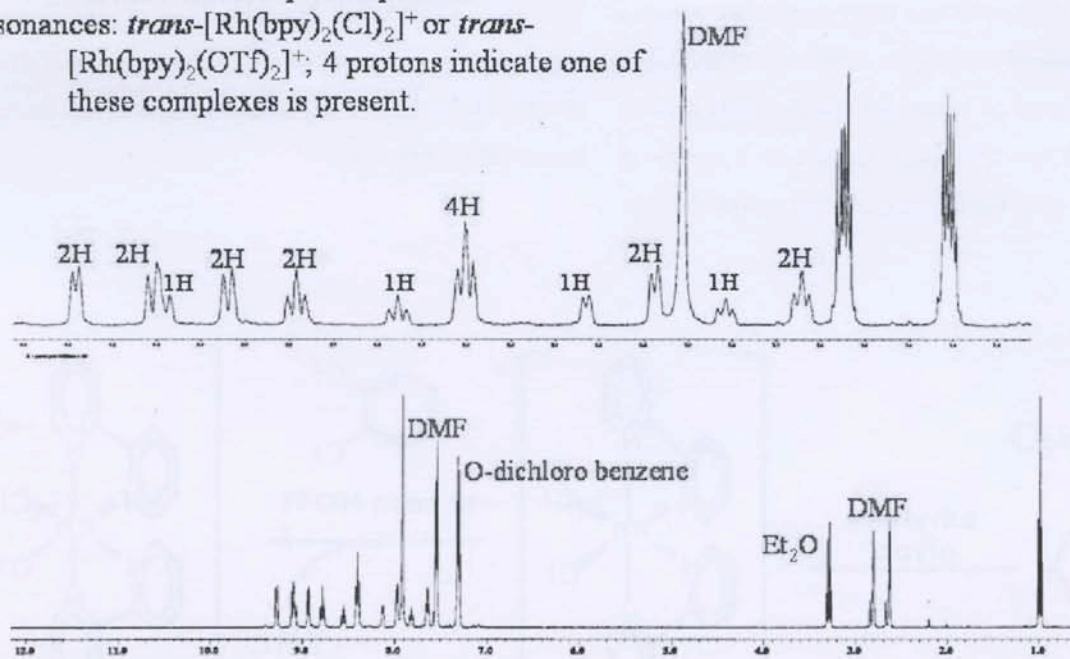
Figure 5. 1H NMR of cis-[Rh(bpy)2(OTf)Cl] +.

The major component (labeled as A resonances) is believed to be the partially substituted triflate complex, $[Rh(bpy)_2(OTf)Cl]^+$. This conclusion is justified by the presence of sixteen inequivalent bipyridine protons in the aromatic region. The second product (labeled as B resonances) is believed to be trans-$[Rh(bpy)_2(L)_2]^+$, where L represents either Cl^- or OTf. Because each ring of the bipyridine is equivalent, only four signals appear in the spectrum corresponding to the four unique protons. The relative intensities for aromatice resonances suggests that 73% of the sample corresponds to the cis-$[Rh(bpy)_2(OTf)Cl]OTf$ isomer.

The Uv vis of the triflate complex in DMF shows a split band in the UV region. Over a period of 12 hours the two bands coalesced into a single absorption at 311nm. This strongly indicates that the triflate ligand was displaced by DMF, but the process is slow. After taking into account the minor impurities the spectrum is identical to that of the cis-$[Rh(bpy)_2(DMF)Cl]^{2+}$ compound. The similarity of these spectra is more evidence that the chloride substitution was incomplete and the major product of the triflate synthesis is cis-$[Rh(bpy)_2(OTf)Cl]^+$.

Reactions of $[Rh(bpy)_2(Cl)L]^{n+}$ (L=DMF, OTf) with Monosaccharides:

The reactivity of the monosubstituted DMF compounds with d-glucose and d-mannose was analyzed through a series of titrations. The titrations were performed in DMF by adding increasing amounts of d-glucose and d-mannose in a strongly basic solution (pH=12). The reactions were monitored by UV-vis spectroscopy (figure 6). The type of spectral change differed between the two rhodium compounds used. For example, upon addition of increasing quantities of sugar to the compound $[Rh(bpy)_2(DMF)Cl]^{2+}$, a split band formed as a downward shift in absorbance occurred (Figure 6).
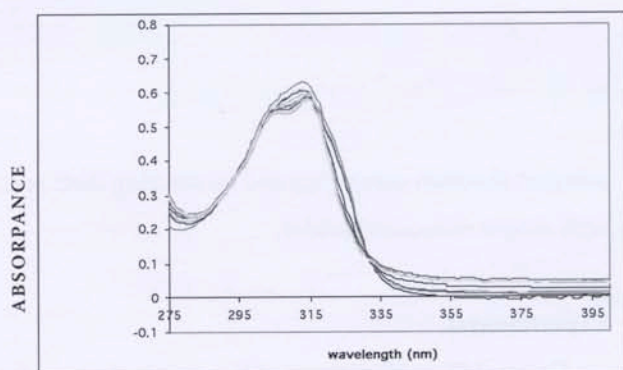
WAVELENGTH (NM)
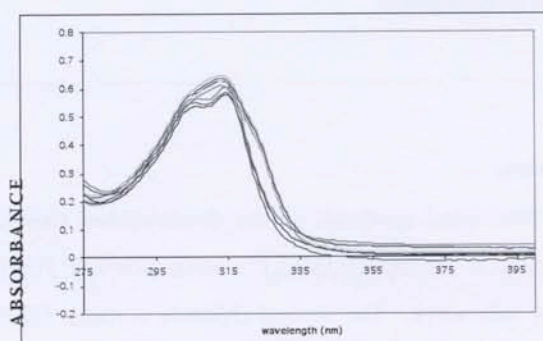
WAVELENGTH (NM)

Figure 6. UV-vis spectrum of the compound cis-[Rh(bpy)₂(DMF)Cl]²⁺ titrated with glucose (top) and mannose (bottom).

Whereas the spectrum of the complex [Rh(bpy)₂(OTf)Cl]⁺ showed a downward shift in absorbance (Figure 7), but the spectrum of the complex started off with a split band, which would mask any similar effects as the sugar had on the rhodium-DMF compound. In both instances the addition of increasing amounts of sugar produced spectral changes.
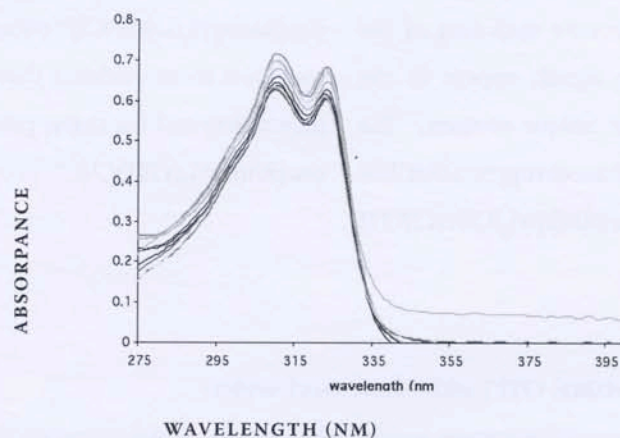

WAVELENGTH (NM)

Figure 7. UV-vis spectrum of the compound cis-[Rh(bpy)₂(OTf)Cl]⁺ titrated with d-glucose.

The cause of the spectral changes will be further analyzed, but based upon the results a hypothesis is formed that the deprotonated hydroxyl groups of the sugar are a strong enough donor to replace both the DMF and Cl⁻ ions. Attempts will also be made to isolate the products in the solution for further characterization. Further reactions between d-glucose and [Rh(bpy)₂(DMF)Cl]⁺ in DMF took place under inert atmosphere. A color change occurred upon heating, but thus far no solid has been isolated.

Conclusion

The attempted synthesis of the disubstituted rhodium compounds cis-[Rh(bpy)₂(DMF)₂]³⁺ and cis-[Rh(bpy)₂(OTf)₂]⁺ did not fully work. The second chloride is more difficult to remove, creating the monosubstituted compounds cis-[Rh(bpy)₂(DMF)Cl]²⁺ and cis-[Rh(bpy)₂(OTf)Cl]⁺. The monosubstituted compounds still showed some reactions with sugar, as evidences by the spectral shifts in the Uv-vis. We are currently trying to isolate any rhodium-monosaccharide complexes that may be present these solutions and characterizing them, using IR and ¹H NMR spectroscopy, and ultimately x-ray diffraction. Concurrently, we are examining additional routs to the disubstituted

solvated rhodium complexes and monitoring their reactions with simple monosaccharides.

Experimental

General Considerations: All reactions were preformed under an inert atmosphere in a drybox, or on a double-manifold vacuum line using standard schlenk techniques. All solvents were purchased from commercial sources including DMF, toluene, tetrahydrofuran (THF), diethyl ether, and ortho-dichlorobenzene. In addition the reagents AgBF₄, triflic acid, d-glucose, and d-mannose were also purchased from commercial sources. The starting material [Rh(bpy)₂Cl₂]²⁺ was synthesized according to literature preparation.[7] All UV

visible spectra were collected using a Hewlett-Packard 8543 diode-array spectrophotometer. Infrared spectroscopy was performed as a nujol mull between sodium chloride plates. ^{1}H NMR studies were performed on a 400 MHz JEOL-ECX spectrometer.

Synthesis of *cis*-[Rh(bpy)$_2$(DMF)Cl]: In a 20mL vial, 0.200 g (3.96 x 10^{-4} mol) of [cis-Rh(bpy)$_{2Cl2}$]^2 was reacted with (0.189 g) of AgBF$_4$ in 3mL of DMF. This reaction was left to stir for approximately 24 hours. The resulting dark silver chloride precipitate was removed by filtration. Following filtration, the solution was transferred to a 125 mL Erlenmeyer flask and toluene was slowly added to bring the volume up to 50 mL. The resulting light grey precipitate was isolated by decanting off the colorless solution. The solid was washed twice with 2 mL of tetrahydrofuan (THF). Yield, 34 %. ^{1}H NMR (400 MHz, D$_7$-DMF, ä), 9.91 (d, 1H), 9.27(d, 1H), 9.14(t, 2H), 9.01(q, 2H), 8.79(m, 2H), 8.52(t, 1H), 8.46(t, 1H), 8.31(q, 2H), 8.25(d, 1H), 8.12(s, 1H, HCO), 8.00(d, 2H), 7.80(t, 1H), 7.70(t, 1H), 3.17(s, 3H, -CH$_3$), 2.98(s, 3H, -CH$_3$).

Synthesis of *cis*-[Rh(bpy)$_2$(OTf)Cl]OTf: In a 250mL schlenk flask 0.500g (7.92 x 10^{-4} mol) of the rhodium-dichloride is dissolved in 50mL of ortho-dichlorobenzene. The reaction stirred at room temperature for 25 minutes. Then 2.11 mL of neat triflic acid was syringed in and the reaction was stirred while cooling on ice for 15 minutes. The

reaction was then heated just below reflux for 2.5 hours. Then the reaction was cooled on an ice bath, while stirring, for 20 minutes. Another 2.11mL of triflic acid was syringed in and the reaction continued to stir in the ice bath for 15 minutes. The reaction was then heated below reflux for another 2.5 hours. The reaction was then cooled for 30 minutes on an ice bath, and 80 mL of diethyl ether was added while the reaction continued stirring. An off white solid precipitated and was filtered under argon. The solid was stored under argon in the drybox. 0.83 grams was isolated. ^{1}H NMR (400 MHz, D$_7$-DMF, ä), 9.29 (d, 2H), 9.11 (d, 2H), 9.10 (s, 1H), 8.94 (d, 2H), 8.79 (t, 2H), 8.56 (t, 1H), 8.41 (t, 4H), 8.13 (d, 1H), 7.98 (d, 2H), 7.92 (s, 5H), 7.81 (t, 1H), 7.64 (t, 2H), 7.35 (m, 3H), 7.32 (m, 3H), 3.30 (m, 2H), 2.82 (s, 2H), 2.66 (s, 2H).

Reactions of [Rh(bpy)$_2$(Cl)L]$^{n+}$ (L = DMF, OTf) with d-glucose and d-mannose: Titration studies of [Rh(bpy)$_2$(DMF)Cl]$^{2+}$ and [Rh(bpy)$_2$(OTf)Cl]$^+$ were monitored using Uv-vis spectroscopy. The same cuvette was used the duration of each titration. In the cuvette 200 μL of 4.5x10^{-4} M [Rh(bpy)$_2$(L)Cl]$^{n+}$ (L = DMF or OTf) was added to varying amounts (about 0.3-15 equivalents) of 0.01M d-glucose, and (about 0.3-10 equivalents) 0.01M d-mannose in a 0.01M NaOH solution. DMF was added to bring the total volume to 2 mL. Once prepared the electronic spectrum of each solution was measured immediately.

Endnotes

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