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Rhenium Bipyridine Complexes for the Recognition of Glucose

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Bipyridine ligands containing pendant methyl, amino, and amino-boronic acid groups were synthesized. Coordination complexes of these ligands with rhenium were prepared straightforwardly and in good yield. The fluorescence behavior of the Re complexes was studied as a function of pH and exposure to various concentrations of glucose. The methyl bipyridine complex showed no change in fluorescence with pH, the amino derivative showed a rapid decrease from low pH to neutral, and the amino-boronate derivative showed little change from pH 4 to 10. Fluorescence quenching was observed at high pH as expected on the basis of a photoinduced electron transfer (PET) signaling mechanism. This behavior can be explained on the basis of the first oxidation and reduction potentials of these complexes. Glucose testing showed a significant dependence on the solvent system used. In pure methanol, the rhenium boronate complex exhibited a 55% fluorescence intensity increase upon increasing glucose concentration from 0 to 400 mg/dL. However, in 50 vol % methanol/phosphate buffered saline, none of the complexes showed significant response in the glucose range of physiological interest.

Introduction

The development of sensors for the continuous determination of blood glucose levels in vivo remains an important goal in the treatment of diabetes.[1,2] Current therapy for insulin-dependent diabetics requires the sampling of blood at discrete intervals throughout the day. This is both unpleasant for the patient and fails to give an accurate signal of the continually changing glucose levels in the blood stream with time. The continuous measurement of glucose concentrations is crucial in providing feedback to insulin delivery devices. Small insulin pumps are now commercially available for the precisely controlled injection of insulin. When combined with a continuous sensor, these systems could then be used to mimic the glucose detection and insulin secretion functions of the pancreas.

Because of the importance of developing a continuous in vivo glucose sensor, a number of research groups are attempting to address this problem using different approaches.[2−5] The overwhelming majority of sensors reported in the literature and available commercially are based on the electrochemical detection of hydrogen peroxide produced by the reaction of glucose oxidase with glucose. By comparison, there are relatively few studies of systems using optical detection, some of which rely on proteins for sensing.[4,6−8] Designs based on large proteins, such as glucose oxidase or Concanavalin A show promise[9,10] but have the limitation of

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(1) For recent information on glucose sensors, insulin pumps, and diabetes research in general, see the following web sites for example: American Diabetes Association Home Page, http://www.diabetes.org; Children with Diabetes Home Page, http://www.childrenwithdiabetes.com; The Diabetes Mall, http://www.diabetesnet.com.
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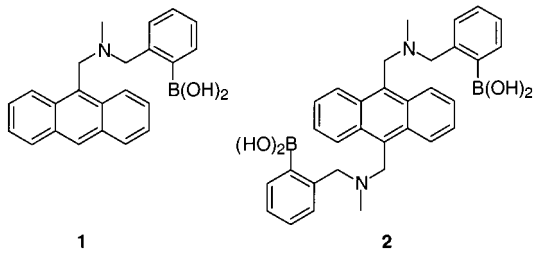
Chart 1



using molecules that can potentially denature. Denaturing of the protein typically occurs because of hydrogen peroxide produced as a byproduct of the enzymatic reaction.

Thus, we are designing new glucose detection systems based on more robust, small molecule transducers that respond by fluorescence. The goal is to develop such complexes for attachment to membranes and implant these materials subcutaneously. Once implanted, the membranes will be expected to remain in place for long periods in time, with glucose measured through the skin by optical excitation and detection. In terms of chemistry, a key to this design is the synthesis of small molecule transducers for glucose. A number of systems have been published previously which primarily involve detection by colorimetry and circular dichroism spectroscopy.[11−13] A smaller set of compounds makes use of fluorescence detection,[14−16] the most promising of these being boronic acid derivatives of anthracene, compounds **1** and **2**.[17] Compound **1** shows an impressive 120% increase in fluorescence upon increasing glucose, with the glucose concentration of a solution increasing from 0 to 300 mg/dL in 33% MeOH/phosphate buffered saline (PBS, pH 7.4). The main factors limiting the utility of this compound for use in a commercial sensor are low water solubility and short wavelength excitation and emission. Water solubility is clearly needed for operation in vivo; fluorescence at long wavelengths is important because of greater transmission of visible light through the skin toward the red end of the spectrum.[4] New molecules need to be developed that overcome these limiting properties. A recent study by Kukrer and Akkaya has used this approach to create a squaraine dye with an appended boronic acid group that shows modest increases in fluorescence with increasing glucose concentration.[15]

To design new molecular transducers, it is important to understand the mechanism by which signaling occurs. In the case of **1**, fluorescence switching occurs by photoinduced electron transfer (PET), a common mechanism for such

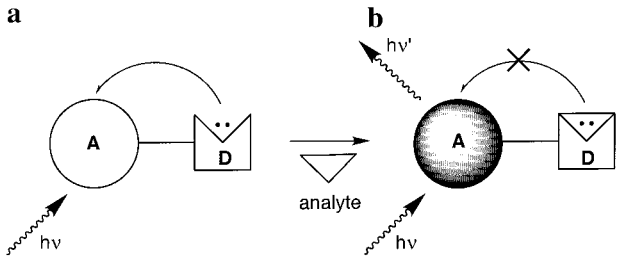


Figure 1. Schematic drawing of PET sensors: (a) in the absence of analyte, the electron donor (**D**) quenches the fluorescence of the electron acceptor/fluorophore (**A**). (b) In the presence of analyte, electron transfer does not occur, and **A** fluoresces.

chemical transduction.[11,18−23] A schematic of a PET sensor is shown in Figure 1. An electron donor (D), such as an amine, quenches the fluorescence of an electron acceptor (A) in the absence of an analyte. When the analyte is present, the oxidation potential of D is raised, and electron transfer does not occur, giving an increase in fluorescence. Other detection systems are known to operate by PET, such as the ruthenium and rhenium bipyridine complexes reported by Meyer et al.,[24,25] Murtaza et al.,[26] and Ziessel et al.,[27] the naphthalimide and perylene systems reported by de Silva et al.,[28,29] a variety of molecular sensors reported by Beer,[30] and visible wavelength lanthanide calix[4]arene complexes.[31] In these systems, the most common recognition elements are pendant amines, calixarenes, or crown ethers used for measuring pH or alkali metal concentration. Such systems are limited to the relatively few types of recognition elements available. Yam and Kai[32] have reported a rhenium bipyridyl complex for the transduction of saccharides by absorbance, and Mizuno et al. have previously synthesized other types of organic and inorganic bipyridyl boronic acids.[33,34] In this paper, we report the synthesis and fluorescence studies of new boronic acid derivatives of rhenium bipyridine complexes for potential use as glucose sensing molecules.

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Experimental Section

General. All reactions were performed under an atmosphere of N_2, followed by workup in air. Protected boronate esters were stored under vacuum to prevent hydrolysis during storage. Toluene and THF were distilled from sodium/benzophenone under N_2; dichloromethane and acetonitrile were distilled from calcium hydride under N_2. 4,4′-Dimethyl-2,2′-bipyridine (bpyMe) was purchased from Aldrich or GFS Chemicals. The compounds 4-(bromomethyl)-4′-methyl-2,2′-bipyridine (bpyCH_2Br)[35−37] and 2,2-dimethylpropane-1,3-diyl[*o*-(bromomethyl)phenyl]boronate (**3**)[5] were prepared by literature methods. Samples for FTIR spectroscopy were prepared as solutions in $CHCl_3$, and only the C═O stretches are reported. Unless otherwise stated, all NMR spectra were recorded at 500 MHz for ^{1}H and 125 MHz for ^{13}C at 20−25 °C using $CDCl_3$ as the solvent. Unless stated otherwise, mass spectra were obtained using electrospray ionization (50 V) with a 50% methanol/water solvent mixture with 1% acetic acid added. Electrochemical experiments were carried out in argon-purged acetonitrile solutions with a BAS 100 multipurpose instrument interfaced to a personal computer, using cyclic voltammetry (CV) techniques. The working electrode was a glassy carbon electrode; its surface was polished with a 0.05 mm alumina−water slurry on a felt surface immediately prior to use. The counter electrode was a Pt wire, and the reference electrode was Ag/AgCl. The concentration of the examined compounds was typically 5.0×10^{-4} M; 0.1 M tetrabutylammonium perchlorate was added as supporting electrolyte. XPS samples were prepared as solids on cellulose tape using C 1s at 284.6 eV as reference and were analyzed as described elsewhere.[38]

Fluorescence Measurements. To avoid the dilution corrections necessary for pH and glucose titrations, stock solutions of known pH, solvent composition, and glucose concentration for each data point to be collected were prepared. A 30.0 μL aliquot of a 1.00 mM solution of the fluorophore in the chosen solvent was added to 3.00 mL of an appropriate stock solution using the same solvent. For pH studies, the solvent system consisted of 0.05 M aqueous NaCl adjusted to the appropriate pH with 0.5 M HCl or 0.5 M NaOH and then mixed in a 1:1 ratio with methanol (50 vol % saline/methanol solvent). For glucose studies, the solvent consisted of glucose dissolved in either methanol or 50 vol % methanol/PBS (phosphate buffered saline, pH 7.4). Fluorescence experiments were performed in dilute ($\sim 10^{-5}$ M) solutions at room temperature by using an ISA SPEX FluoroMax-2 spectrofluorimeter equipped with a Hamamatsu 1527 photomultiplier. Luminescence maxima reported are uncorrected for photomultiplier response. Excitation spectra were performed on all luminescent compounds, obtaining a good match with the respective absorption spectra. Absorption spectra were recorded with an HP 8453 UV−vis spectrophotometer. Fluorescence measurements were made as a function of pH and glucose concentration by exciting the fluorophore at its peak excitation wavelength and measuring fluorescence intensity at the peak emission wavelength. Excitation and emission peak maxima are reported for each of these compounds in 50% methanol/PBS solution. The samples were run in the signal to reference mode, with slit widths between 1 and 5 mm, in polystyrene cells. The fluorimeter was calibrated on quartz-distilled water. We used the protected boronate ester [(bpyNB)Re$(CO)_3$(py)](OTf) for our spectroscopic studies, rather than isolating and using the unprotected compound, because of ease of synthesis. Control experiments were carried out by NMR and fluorescence spectroscopy to demonstrate that the presence of even small amounts of water in methanolic solution resulted in immediate and quantitative removal of the neopentyl glycol protecting group. This is in accordance with results by James et al. indicating extremely weak binding constants for simple diols compared to saccharides for other boronate systems[17] and NMR studies by Bielecki et al. in which trace amounts of water affect the binding mode of saccharides and boronates.[39]

Compound Synthesis. 4-(Methylaminomethyl)-4′-methylbipyridine (bpyCH_2NHMe). A stream of $MeNH_2$ gas was bubbled through a solution of bpyCH_2Br (1.52 g, 5.76 mmol) in 75 mL of THF at 0 °C for 15 min to give a cloudy colorless solution. The solution was allowed to warm to ambient temperature, and stirring continued for 16 h. The solvent was removed to give an oily white solid. A pale yellow solution was extracted from a white powder with diethyl ether and the solvent removed under vacuum to give bpyCH_2NMeH (1.20 g, 98%) as a pale yellow liquid. ^{1}H NMR: δ 8.52 (d, 1H, J = 5.0 Hz), 8.44 (d, 1H, J = 5.0 Hz), 8.24 (s, 1H), 8.14 (s, 1H), 7.20 (d, 1H, J = 4.9 Hz), 7.02 (d, 1H, J = 4.9 Hz), 3.74 (s, 2H), 2.36 (s, 3H), 2.32 (s, 3H), 1.65 (br s, 1H).^{13}C{^{1}H} NMR: δ 156.3, 155.9, 150.3, 149.2, 148.9, 148.1, 124.7, 122.9, 122.0, 120.4, 54.9, 36.1, 21.2. GC/EIMS: m/z 212 $(M - H)^+$, 184 $(bpyMe)^+$.

4-(*N*−Benzylmethylaminomethyl)-4′-methylbipyridine (bpyN). A solution of HNMe(CH_2Ph) (0.680 mL, 5.27 mmol) in 5 mL of CH_2Cl_2 was added dropwise to a solution of bpyCH_2Br (0.693 g, 2.63 mmol) in 30 mL of CH_2Cl_2 over a few minutes to gradually give a golden solution. Stirring was continued for 2 h and the solvent removed under vacuum. The crude product was dissolved in 40 mL of $CHCl_3$ and then 30 mL of H_2O were added. A saturated solution of sodium carbonate was added to adjust the pH to 8. The layers were separated, followed by washing of the organic layer with 2 × 30 mL H_2O. The solvent was removed to give an oily white solid. A pale yellow solution was extracted from a white powder with diethyl ether and the solvent removed under vacuum to give bpyN (1.20 g, 98%) as a pale yellow liquid. ^{1}H NMR: δ 8.63 (d, 1H, J = 5.0 Hz), 8.55 (d, 1H, J = 5.0 Hz), 8.35 (s, 1H), 8.23 (s, 1H), 7.41 (d, 1H, J = 4.9 Hz), 7.38 (d, 2H, J = 7.3 Hz), 7.32 (t, 2H, J = 7.5 Hz), 7.24 (m, 1H), 7.12 (d, 1H, J = 4.9 Hz), 3.60 (s, 2H), 3.57 (s, 2H), 2.42 (s, 3H), 2.21 (s, 3H).^{13}C{^{1}H} NMR: δ 156.9, 156.6, 150.4, 149.8, 149.6, 148.7, 139.4, 129.5, 128.9, 127.7, 125.3, 124.4, 122.7, 121.9, 62.8, 61.4, 43.0, 21.8. GC/EIMS: m/z 302 $(M - H)^+$, 184 $(M - NMeCH_2Ph)^+$.

2,2-Dimethylpropane-1,3-diyl[*o*-(methylaminomethyl)phenyl]-boronate (4). A stream of $MeNH_2$ gas was bubbled through a solution of **3** (7.02 g, 24.8 mmol) in 150 mL of CH_3CN at 0 °C for 20 min to give a yellow solution. Stirring was continued for 3 h and the reaction allowed to warm to room temperature. The solvent was removed under vacuum to give a yellow powder. A yellow solution was extracted from a white powder with chloroform and the solvent removed under vacuum to give **4** (5.48 g, 95%) as a pale yellow powder. ^{1}H NMR: δ 7.54 (d, 2H, J = 6.8 Hz), 7.19 (m, 2H), 6.98 (d, 2H, J = 7.2 Hz), 3.82 (s, 2H), 3.53 (s, 4H), 1.01 (s, 6H).^{13}C{^{1}H} NMR: δ 140.8, 130.0, 127.7, 127.3, 123.0, 72.5, 55.8, 35.2, 32.4, 22.5. ESIMS: m/z 234.1 $(M + H)^+$.

4-{*N*-[*o*-(5,5-Dimethylborinan-2-yl)benzyl]-*N*-[methylamino]-methyl}-4′-methylbipyridine (bpyNB). Method A. A solution of

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3 (1.60 g, 5.64 mmol) in 60 mL of THF was added dropwise over 1 h to a solution of bpyCH_2NMeH (1.204 g, 5.65 mmol) and NEt_3 (0.787 mL, 5.65 mmol) in 60 mL of THF to give a cloudy white mixture by the end of addition. Stirring was continued for 1 h and then the solvent removed under vacuum. The crude solid was extracted with diethyl ether and the solvent removed to give pure bpyNB (1.91 g, 82%) as a cream colored to white powder. Method B. A mixture of bpyCH_2Br (0.525 g, 2.00 mmol) and **4** (0.927 g, 3.99 mmol) was dissolved in 40 mL of THF to immediately give a cloudy white mixture. The reaction was stirred for 1 h and then the solvent removed under vacuum. The crude solid was extracted with diethyl ether and the solvent removed under vacuum to give pure bpyNB (0.424 g, 51%) as a pale yellow solid. ^{1}H NMR: δ 8.64 (d, 1H, J = 5.0 Hz), 8.54 (d, 1H, J = 5.0 Hz), 8.32 (s, 1H), 8.24 (s, 1H), 7.64 (d, 1H, J = 7.0 Hz), 7.34−7.23 (m, 4 H), 7.14 (d, 1H, J = 4.9 Hz), 3.79 (br, 2H), 3.77 (s, 4H), 3.73 (br s, 2H), 2.44 (s, 3H), 2.29 (s, 3H), 1.05 (s, 6H).^{13}C{^{1}H} NMR: d 156.5, 156.0, 149. 5, 149.3, 149.2, 148.3, 133.2, 129.0, 127.7, 125.0, 124.9, 123.9, 122.4, 122.2, 121.5, 72.5, 61.3, 59.9, 42.1, 32.1, 22.2, 21.4. ESIMS: m/z 348.0 (unprotected M + H)$^+$.

(bpyMe)Re(CO)$_3$Cl. A mixture of $Re(CO)_5Cl$ (774 mg, 2.14 mmol) and bpyMe (394 mg, 2.14 mmol) in 40 mL of CH_2Cl_2 and 120 mL of toluene was heated at reflux for 2 h to give a bright yellow-orange solution. The solvent was removed under vacuum and the crude material recrystallized from CH_2Cl_2/hexanes to give (bpyMe)Re(CO)$_3$Cl as a pure yellow powder (1.00 g, 95%). ^{1}H NMR: δ 8.89 (d, 2H, J = 5.6 Hz), 7.98 (s, 2H), 7.34 (d, 2H, J = 5.6 Hz), 2.58 (s, 6H).^{13}C{^{1}H} NMR: δ 197.5, 155.6, 152.8, 151.4, 128.1, 123.9, 21.9. ESIMS: m/z 454.8 (M − Cl)$^+$. IR: ν_{CO} = 2022, 1917, 1895 cm^{-1}. Anal. (wt %) Calcd for $ReC_{15}O_3H_{12}N_2Cl$: C, 36.77; H, 2.47; N, 5.74. Found: C, 36.44; H, 2.59; N, 5.65.

(bpyN)Re(CO)$_3$Cl. The procedure used was analogous to that for (bpyMe)Re(CO)$_3$Cl. The reaction of $Re(CO)_5Cl$ (299 mg, 0.827 mmol) and bpyN (251 mg, 0.827 mmol) gave (bpyN)Re(CO)$_3$Cl as a yellow powder (486 mg, 96%). ^{1}H NMR: δ 8.91 (d, 1H, J = 5.6 Hz), 8.86 (d, 1H, J = 5.6 Hz), 8.19 (s, 1H), 7.98 (s, 1H), 7.50 (d, 1H, J = 5.6 Hz), 7.38 (m, 4H), 7.31 (m, 2H), 3.66 (br s, 4H), 2.57 (s, 3H), 2.32 (s, 3H).^{13}C{^{1}H} NMR: δ 197.5, 190.0, 155.8, 155.6, 153.7, 152.9, 152.7, 151.5, 138.2, 129.1, 128.8, 128.1, 127.8, 126.8, 124.1, 122.6, 62.5, 60.0, 43.1, 21.9. ESIMS: m/z 574.0 (M)$^+$. IR: ν_{CO} = 2022, 1917, 1895 cm^{-1}. Anal. (wt %) Calcd for $ReC_{23}H_{21}O_3N_3Cl$: C, 45.35; H, 3.48; N, 6.90. Found: C, 43.58; H, 3.58; N, 6.55.

(bpyNB)Re(CO)$_3$Cl. The procedure used was analogous to that for (bpyMe)Re(CO)$_3$Cl. The reaction of $Re(CO)_5Cl$ (310 mg, 0.857 mmol) and **6** (357 mg, 0.860 mmol) gave **7** as a yellow powder (560 mg, quantitative yield). ^{1}H NMR: δ 8.84 (d, 1H, J = 5.4 Hz), 8.83 (d, 1H, J = 5.4 Hz), 8.10 (s, 1H), 8.02 (s, 1H), 7.70 (d, 1H, J = 7.0 Hz), 7.35−7.22 (m, 5H), 3.87 (d, 1H, J = 12.2 Hz), 3.77 (d, 1H, 12.2 Hz), 3.72 (s, 4H), 3.46 (br s, 2H), 2.58 (s, 3H), 2.35 (s, 3H), 1.00 (s, 6H).^{13}C{^{1}H} NMR: δ 197.5, 190.1, 155.7, 155.6, 153.4, 152.6, 152.5, 151.3, 144.1, 134.2, 129.7, 129.2, 127.9, 127.2, 127.0, 124.4, 124.0, 72.5, 62.5, 59.2, 44.0, 32.0, 22.0, 21.7. ESIMS: m/z 654.0 (unprotected M + H)$^+$, 618.0 (unprotected M − Cl)$^+$. IR: ν_{CO} = 2021, 1917, 1895 cm^{-1}. Anal. (wt %) Calcd for $ReC_{27}H_{30}O_5N_3BCl$: C, 45.74; H, 4.27; N, 5.93. Found: C, 45.35; H, 4.40; N, 5.59.

[**(bpyMe)Re(CO)$_3$(py)](OTf).** A solution of AgOTf (263 mg, 1.02 mmol) in 5 mL of THF was added to a solution of (bpyMe)-Re(CO)$_3$Cl (499 mg, 1.02 mmol) in 50 mL of CH_2Cl_2 to immediately give a cloudy yellow mixture. After stirring for 2 h, the precipitate was removed by filtration, and 100 mL of ethanol and 10.0 mL of pyridine were added to the yellow solution. This was heated at 50 °C for 17 h and exhibited no visual change. The solvent was removed under vacuum to give a bright yellow powder. Chromatography on silica with acetonitrile gave pure [(bpyMe)-Re(CO)$_3$(py)](OTf) as a yellow powder (555 mg, 80%). ^{1}H NMR: δ 8.91 (d, 2H, J = 5.7 Hz), 8.59 (s, 2H), 8.18 (d, 2H, J = 5.7 Hz), 7.83 (t, 1H, 7.7 Hz), 7.54 (d, 2H, 5.5 Hz), 7.37 (t, 2H, 7.0 Hz), 2.62 (s, 6H). ^{13}C{^{1}H} NMR: δ 196.0, 191.5, 155.6, 154.9, 152.1, 151.8, 140.0, 129.7, 127.3, 126.7, 21.8. ESIMS: m/z 533.9 (M)$^+$. IR: ν_{CO} = 2034, 1932 cm^{-1}. Anal. (wt %) Calcd for $ReC_{21}H_{17}N_3O_6SF_3$: C, 36.95; H, 2.51; N, 6.16. Found: C, 36.62; H, 2.79; N, 5.75.

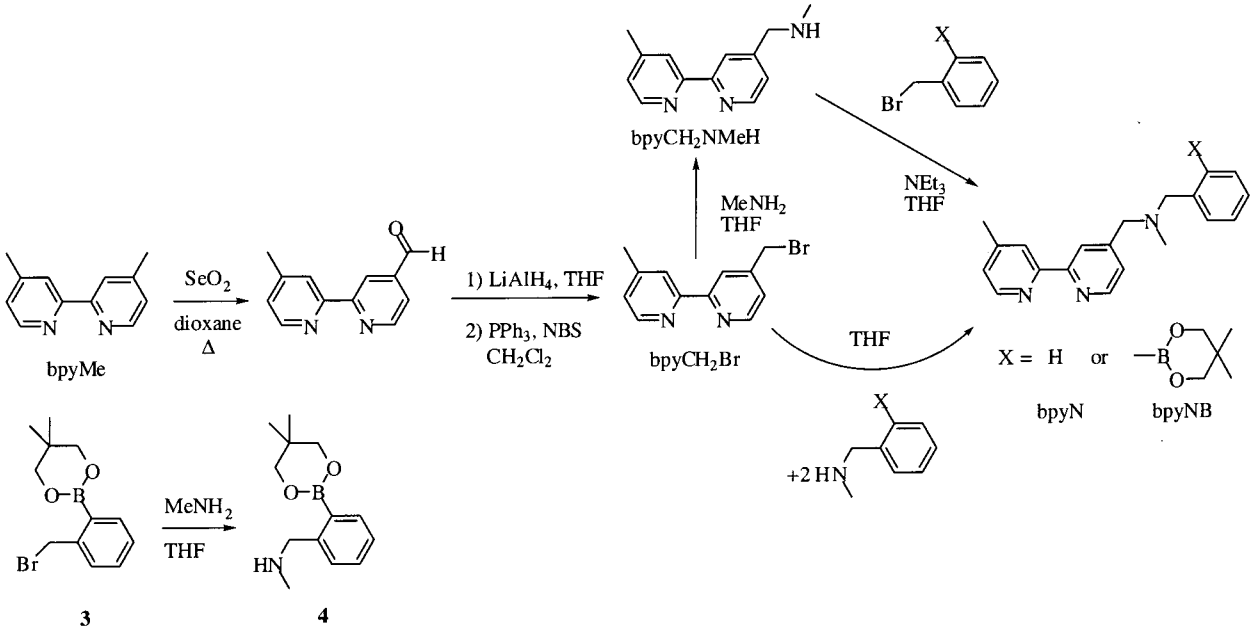
[**(bpyN)Re(CO)$_3$(py)](OTf).** The procedure used was analogous to that for [(bpyMe)Re(CO)$_3$(py)](OTf). The reaction of AgOTf (154 mg, 0.599 mmol) and (bpyN)Re(CO)$_3$Cl (363 mg, 0.596 mmol), followed by chromatography on silica with 1:2 toluene/acetonitrile gave pure [(bpyN)Re(CO)$_3$(py)](OTf) as a yellow powder (260 mg, 54%). ^{1}H NMR: δ 8.96 (d, 1H, J = 5.7 Hz), 8.90 (d, 1H, J = 5.7 Hz), 8.61 (s, 1H), 8.52 (s, 1H), 8.18 (d, 2H, J = 5.2 Hz), 7.84 (d, 1H, J = 5.6 Hz), 7.81 (t, 1H, J = 7.5 Hz), 7.54 (d, 1H, J = 5.6 Hz), 7.36 (t, 4H, J = 7.2 Hz), 7.32 (t, 2H, J = 7.5 Hz), 7.24 (t, 1H, J = 7.2 Hz), 3.85 (s, 2H), 3.66 (s, 2H), 2.65 (s, 3H), 2.31 (s, 3H). ^{13}C{^{1}H} NMR: δ 196.0, 195.9, 191.3, 156.7, 155.8, 155.5, 154.9, 152.4, 152.2, 151.8, 140.0, 138.5, 129.8, 129.2, 128.6, 128.3, 127.6, 127.3, 126.8, 125.4, 62.5, 59.9, 43.0, 21.9. ESIMS: m/z 652.9 (M)$^+$. IR: ν_{CO} = 2034, 1931 cm^{-1}. Anal. (wt %) Calcd for $ReC_{29}H_{26}N_4O_6SF_3$: C, 43.44; H, 3.27; N, 6.99. Found: C, 40.50; H, 3.52; N, 6.56.

[**(bpyNB)Re(CO)$_3$(py)](OTf).** The procedure used was analogous to that for [(bpyMe)Re(CO)$_3$(py)](OTf). The reaction of AgOTf (115 mg, 0.448 mmol) and (bpyNB)Re(CO)$_3$Cl (292 mg, 0.447 mmol), followed by chromatography on basic alumina with 9:1 acetonitrile/methanol gave pure [(bpyNB)Re(CO)$_3$(py)](OTf) as a yellow powder (182 mg, 45%). ^{1}H NMR: δ 8.94 (d, 1H, J = 5.7 Hz), 8.90 (d, 1H, J = 5.7 Hz), 8.36 (s, 1H), 8.24 (s, 1H), 8.18 (d, 2H, J = 5.1 Hz), 7.79 (t, 1H, J = 7.7 Hz), 7.65 (d, 1H, J = 5.6 Hz), 7.62 (d, 1H, J = 5.6 Hz), 7.53 (d, 1H, J = 7.3 Hz), 7.35 (t, 2H, J = 7.0 Hz), 7.14 (m, 2H), 7.06 (m, 1H), 3.86 (d, 2H, J = 12.8 Hz), 3.73 (s, 4H), 3.63 (q, 2H, J = 15.0 Hz), 2.64 (s, 3H), 2.38 (s, 3H), 0.98 (s, 6H). ^{13}C{^{1}H} NMR: δ 195.7, 195.6, 191.4, 155.9, 155.3, 155.2, 154.3, 152.4, 152.3, 151.8, 144.1, 139.9, 135.9, 133.9, 130.0, 129.4, 129.0, 128.7, 127.2, 126.8, 126.1, 125.4, 72.4, 62.4, 59.6, 44.5, 31.9, 21.9, 21.7. ESIMS: m/z 697.2 (unprotected M)$^+$. IR: ν_{CO} = 2034, 1931 cm^{-1}. Anal. (wt %) Calcd for $ReC_{33}H_{35}O_8BSF_3N_4$: C, 43.95; H, 3.91; N, 6.21. Found: C, 43.69; H, 3.95; N, 6.12.

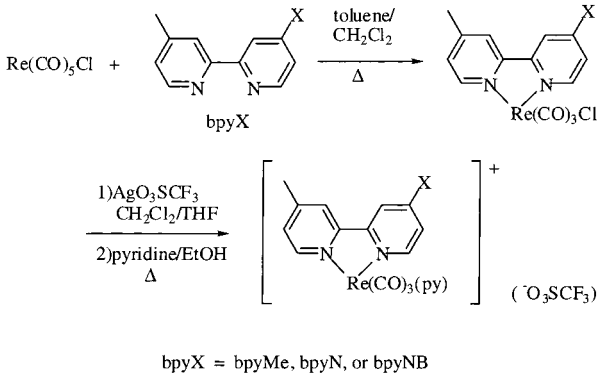
Results

Bipyridine Ligand Synthesis. We have synthesized new boronate and benzyl bipyridine ligands by the routes shown in Scheme 1. Previous work has shown that compound bpyCH_2Br provides the simplest entry into a variety of functionalized bipyridine compounds.[35−37] While the preparation of bpyCH_2Br can only be carried out in moderate yields, the final two alkylation steps generally occur in 70−80% yield, allowing multigram batches of bpyN or bpyNB to be conveniently prepared. Compound **3** was introduced by James et al. as a useful reagent for appending the *o*-tolylboronic acid group to fluorophores such as ArCH_2-NHMe (Ar = phenyl, naphthyl, anthryl).[17] We have prepared the amino boronate reagent **4**, which can also be used in the synthesis of bpyNB. In this case, either the linear or convergent route gives acceptable results, although in other

Scheme 1. Synthesis of Bipyridine Ligands



Scheme 2. Preparation of Rhenium Complexes



systems **3** or **4** were found to be more convenient depending on the transformation required.

Rhenium Complex Synthesis. Rhenium complexes [(bpyX)Re(CO)$_3$Cl] and [(bpyX)Re(CO)$_3$(py)](OTf) (bpyX = bpyMe, bpyN, and bpyNB; py = pyridine; OTf^- = $CF_3SO_3^-$) were prepared as shown in Scheme 2 using the bipyridyl ligands bpyMe, bpyN, and bpyNB. These reactions are analogous to previously reported reactions and can be carried out in high yield.[25,30,40] The three ligand derivatives were prepared for rhenium in order to aid in the interpretation of the fluorescence and electrochemical data discussed later. The ^{1}H and ^{13}C{^{1}H} NMR spectra and MS data clearly confirm the identity of the compounds. In the IR spectra of the three chloro complexes, [(bpyX)Re(CO)$_3$Cl] (bpyX = bpyMe, bpyN, and bpyNB), each exhibit carbonyl stretches at 2022, 1917, at 1895 cm^{-1}; CO resonances are observed at 2034 and 1931 cm^{-1} for each of the pyridinium complexes [(bpyX)Re(CO)$_3$(py)](OTf). These data are in accord with the reported values for [(bpyCH$_2$NEt$_2$)Re(CO)$_3$Cl] (2021, 1915, at 1895 cm^{-1}) and [(bpyCH$_2$NEt$_2$)Re(CO)$_3$(py)](OTf) (2034 and 1931 cm^{-1}).[25] It is worth noting that the carbonyl stretching frequencies are invariant among the set of chloro compounds and among the set of pyridinium complexes. This suggests that the substituent changes on the periphery of the bipyridyl ligands do not substantially alter the electron density at the metal center (see electrochemistry and XPS below). This is further substantiated by the fact that the absorbance spectra between 250 and 500 nm for both [(bpyN)Re(CO)$_3$(py)](OTf) and [(bpyNB)Re(CO)$_3$(py)](OTf) are virtually identical, having maxima at 255, 310, 320, and 345 nm. One compound, [(bpyN)Re(CO)$_3$(py)](OTf), exhibits a C elemental analysis value that is 8% lower than that calculated for the formula $ReC_{29}H_{26}N_4O_6SF_3$. The cause of this difference is probably due, at least in part, to a ligand impurity, but this is not clear and is addressed later.

Table 1. XPS Binding Energies for Selected Re Compounds

compound	Re4f$_{7/2}$, eV	Re4f$_{5/2}$, eV
(bpyMe)Re(CO)$_3$Cl	40.6	42.8
(bpyN)Re(CO)$_3$Cl	40.2	42.6
(bpyNB)Re(CO)$_3$Cl	40.5	42.8
[(bpyMe)Re(CO)$_3$(py)](OTf)	40.8	42.9
[(bpyN)Re(CO)$_3$(py)](OTf)	40.9	43.1
[(bpyNB)Re(CO)$_3$(py)](OTf)	40.8	42.9

The binding energies for Re derived from XPS are shown in Table 1. The positions for all the compounds fall within 40−41 eV for the Re4f$_{7/2}$ and 42.4−43.5 eV for Re4f$_{5/2}$. These data indicate the binding around the metal center is similar in all the complexes, and as seen in the IR and electronic spectral data, the substitutions on the periphery of the bipyridine ligand do not substantially alter the electron density on the metal. Similar behavior is seen in the XPS binding energies for the bipyridyl N atoms. The full XPS analyses of these compounds will be reported elsewhere.

Figure 2 shows the excitation and emission spectra in 50% MeOH/PBS for [(bpyX)Re(CO)$_3$(py)][OTf] where bpyX = bpyMe, bpyN, and bpyNB compounds. The excitation spectra were taken between 280 and 450 nm. Two excitation

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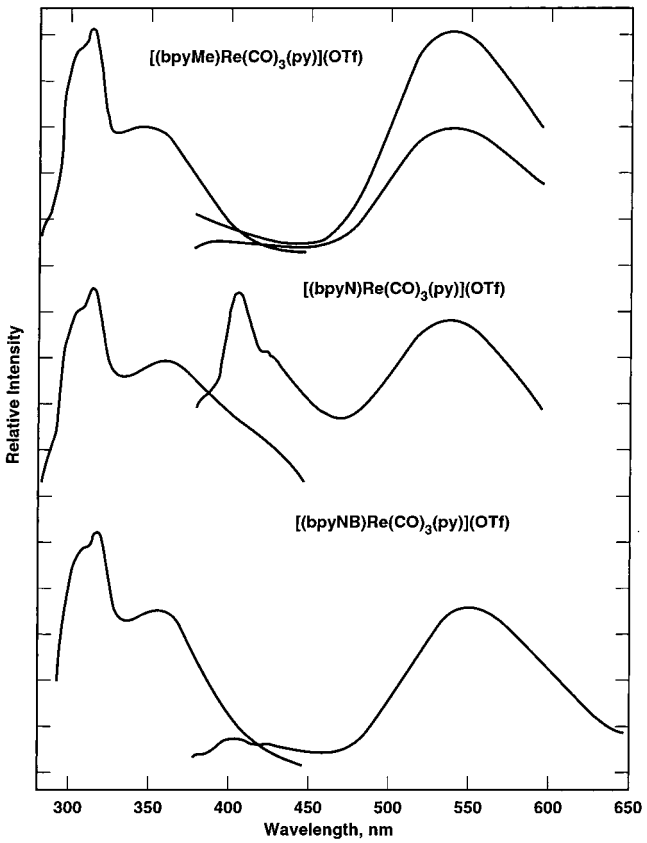

Figure 2. Excitation and emission spectra (intensity vs wavelength) for [(bpyX)Re(CO)$_3$(py)](OTf) (bpyX = bpyMe (top), bpyN (middle), bpyNB (bottom)). Excitation spectra recorded from 280 to 450 nm and emission spectra recorded from 375 to 600 or 650 nm. For emission spectra, λ_{ex} values are the following: bpyMe, 316 and 350 nm (see text); bpyN, 360 nm; bpyNB, 358 nm.

maxima are seen for all three [(bpyX)Re(CO)$_3$(py)][OTf] compounds at the following positions: bpyMe, 316 and 350 nm; bpyN, 316 and 360 nm; bpyNB, 318 and 358 nm.

The emission spectra were taken from 375 to 650 nm. For the emission spectra of [(bpyMe)Re(CO)$_3$(py)][OTf], λ_{ex} = 316 and 350 nm, with the higher intensity spectrum corresponding to the shorter wavelength excitation. The spectra are identical except for relative intensities, having a λ_{em} maximum at 540 nm. For the emission spectrum of [(bpyN)-Re(CO)$_3$(py)][OTf], λ_{ex} = 360 nm, and two emission maxima are seen, at 406 and 540 nm. The emission spectrum from λ_{ex} = 316 nm (not shown) exhibited the same emission spectrum, except for higher intensity. For the emission spectrum of [(bpyNB)Re(CO)$_3$(py)][OTf], λ_{ex} = 358 nm, and only one emission maximum is seen, as in the [(bpyMe)-Re(CO)$_3$(py)][OTf] case. The emission spectrum from λ_{ex} = 318 nm (not shown) exhibited the same emission spectrum, except for higher intensity.

Absorption spectra for [(bpyN)Re(CO)$_3$(py)][OTf] and [(bpyNB)Re(CO)$_3$(py)][OTf] were essentially identical except for relative intensities. The spectra were nearly identical to the excitation spectra having maxima at 253, 306 (sh), 318, and 351 nm.

Table 2 shows the electrochemical potentials of the OTf complexes. The values for the amine oxidation potentials are similar (nonexistent for the Me derivative), as are fluorophore reduction potentials. These values are consistent with the amine oxidation values reported by Ziessel et al. where the rhenium metal oxidation potentials for a series of related compounds are shown to be considerably higher.[27]

Table 2. Electrochemical Data for [(bpyX)Re(CO)$_3$(py)][OTf] where bpyX = bpyMe, bpyN, bpyNB[a]

compound	amine oxidation (V)	fluorophore reduction (V)
bpyMe	nd	−1.3
bpyN	1.3	−1.2
bpyNB	1.25	−1.25

[a] All measurements done using glassy carbon working electrode, Pt counter electrode, and Ag/AgCl reference electrode in 0.1 M TBAP/ACN; nd = none detected.

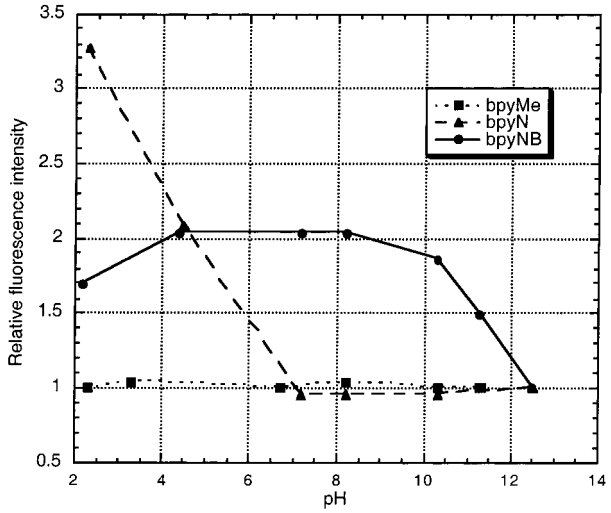

Figure 3. Relative fluorescence intensity at the excitation and emission peak maxima of 10.0 μM [(bpyX)Re(CO)$_3$(py)](OTf) (bpyX = bpyMe, bpyN, bpyNB) in 50% methanol/saline solution vs pH.

pH Dependence of Fluorescence. Figure 3 shows the relative fluorescence intensity of [(bpyX)Re(CO)$_3$(py)](OTf) (bpyX = bpyMe, bpyN, bpyNB) as a function of pH in 50% methanol/saline solution. As expected for compounds without a pendant amine functionality, the relative fluorescence of [(bpyMe)Re(CO)$_3$(py)](OTf) remains constant over the pH range studied; [(bpyN)Re(CO)$_3$(py)](OTf) exhibits a decrease in fluorescence intensity of 71% upon decreasing pH from 2 to 7, with an inflection point at about pH 4.3 (p$K_a \approx 9$ for amines related to bpyN). This discrepancy between the apparent pK_a from fluorescence data and the reported pK_a based on acid−base titrations is well-known.[41] In contrast, [(bpyNB)Re(CO)$_3$(py)]OTf shows a fairly level fluorescence intensity over the pH range 4−10. At pH 11.4, [(bpyNB)-Re(CO)$_3$(py)](OTf) undergoes a single step decrease in intensity of 86%.

Glucose Testing. Figure 4 shows the testing of [(bpyX)-Re(CO)$_3$(py)](OTf) (bpyX = bpyMe, bpyN, and bpyNB) with glucose at various concentrations in 50% methanol/PBS at pH 7.4. All show similar gradual fluorescence responses upon increasing glucose levels in the 10,000−30,000 mg/dL range. At concentrations below 5000 mg/dL, the response of all is complicated and not useful for analytical

(41) Skoog, D. A. *Principles of instrumental analysis*, 3rd ed.; Saunders: Philadelphia, 1985.

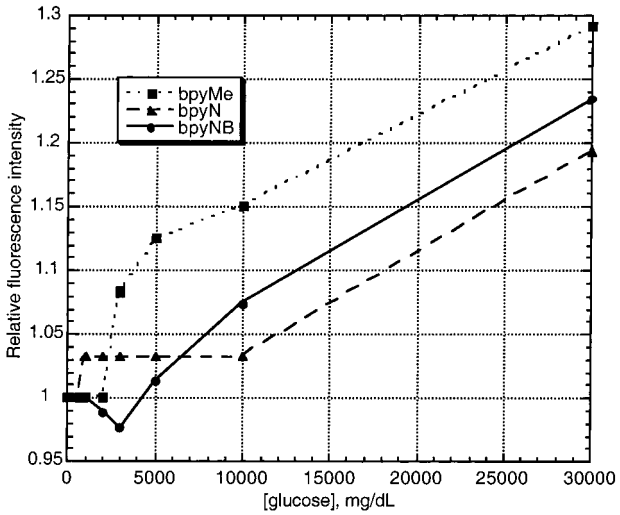

Figure 4. Relative fluorescence intensity at the excitation and emission peak maxima of 10.0 μM [(bpyX)Re(CO)$_3$(py)](OTf) (bpyX = bpyMe, bpyN, bpyNB) in 50% methanol/saline solution vs [glucose].

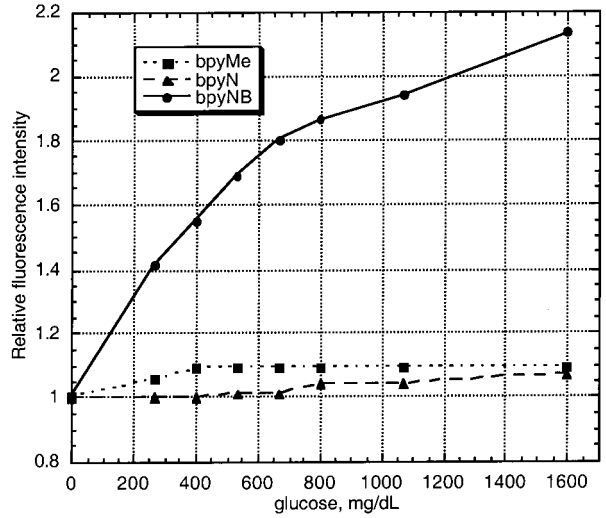

Figure 5. Relative fluorescence intensity at the excitation and emission peak maxima of 10.0 μM [(bpyX)Re(CO)$_3$(py)](OTf) (bpyX = bpyMe, bpyN, bpyNB) in methanol vs [glucose].

purposes. In addition, the bpyNB complex fails to show a large fluorescence increase in the region of physiological interest, 90−300 mg/dL.

Figure 5 shows the effects of changing the solvent system to methanol for glucose testing in the 0−1600 mg/dL range. [(bpyMe)Re(CO)$_3$(py)](OTf) and [(bpyN)Re(CO)$_3$(py)](OTf) show little change in fluorescence intensity with addition of glucose, similar to the behavior seen in Figure 4. [(bpyNB)-Re(CO)$_3$(py)](OTf), however, shows a 55% intensity increase upon increasing glucose concentration from 0 to 400 mg/dL, and ultimately, a 113% increase at 1600 mg/dL.

Discussion

Fluorescence Behavior. All three Re complexes show fluorescence emission maxima at 540−550 nm, consistent with Re diimine complexes in general and bipyridyl complexes specifically,[27,32,42−44] which have been assigned to metal to ligand charge transfer (MLCT). The [(bpyN)Re-(CO)$_3$(py)](OTf) complex also shows a strong emission band at 406 nm, the origin of which is not clear. The bpyN ligand does have fluorescence properties λ_{ex} = 325 nm and λ_{em} = 432 nm. In the middle trace of Figure 2, a shoulder at 432 nm on the maximum at 406 nm can be seen, which is probably due to a ligand impurity (contributing to the discrepancy in the C analysis for [(bpyN)Re(CO)$_3$(py)]-(OTf)). However, the 406 nm maximum in [(bpyN)Re(CO)$_3$-(py)][OTf] may not be due to a ligand impurity. It may be due to a ligand centered excited state involving the lone pair of the N. The same intense emission is seen in [(bpyN(CH$_2$-CH$_3$)$_2$)Re(CO)$_3$(py)][OTf] at λ_{ex} = 365 nm and λ_{em} = 414 and 544 nm. However, the higher energy emission is not seen in either [(bpyNB)(Re(CO)$_3$(py)][OTf] or the bpyNB ligand perhaps because of delocalization of the lone pair with the boron empty orbitals. This is further substantiated by the pH dependence of [(bpyN(CH$_2$CH$_3$)$_2$)Re(CO)$_3$(py)][OTf] which does not exhibit this emission maximum at low pH, probably because of protonation of the amino nitrogen. In addition, the nitrogen XPS data (not shown) indicate only one type of N at N bonded to Re energies.

Electrochemistry. The search for new fluorescent glucose transducers based on PET requires, among other things, an understanding of the electrochemistry of any potential donor−acceptor pair. The free energy of PET (ΔG_{el}) can be calculated using the Rehm−Weller equation shown in eq 1,

$$\Delta G_{el}(\text{kcal mol}^{-1}) = 23.06[E^\circ(D^+/D) - E^\circ(A/A^-)] - w_p - w_r - \Delta G_{00} \quad (1)$$

where $E^\circ(D^+/D)$ is the oxidation potential of the donor, $E^\circ(A/A^-)$ is the reduction potential of the acceptor, and ΔG_{00} is the free energy corresponding to the zero point energy, E_{00}.[21] The quantities w_p and w_r are Coulombic terms for the products and reactants and are found to be small in polar solvents. In this present case, $w_r = 0$ because the reactants are neutral, and to simplify predictions, w_p is assumed to be zero. E_{00} was determined from the overlap of the lowest energy absorbance maximum and the emission maximum spectra (λ_{00}).[21,45]

The measurement of the first reduction potential for the transition metal complexes [(bpyN)Re(CO)$_3$(py)](OTf) and [(bpyNB)Re(CO)$_3$(py)](OTf) and corresponding ligand oxidation potentials, given in Table 2, and the estimated λ_{00} values (458 and 425 nm, respectively) yield calculated ΔG_{el} values of −4.75 and −9.65 kcal/mol, respectively, showing the bpyNB derivative to be more favorable for PET, as observed. In considering the significance of these values, it is worth comparing them to ΔG_{el} for **1**. For **1**, the first oxidation potential and reduction potential are 1.10 and −2.11 V vs Ag/AgCl, respectively, and this compound has a λ_{00} value of 405 nm (using criteria of Kavarnos and Turro[45]). This yields a ΔG_{el} value of 3.47 kcal/mol for **1**,

(42) Caspar, J. V.; Sullivan, B. P.; Meyer, T. J. *Inorg. Chem.* **1984**, *23*, 2104−2109.
(43) Kotch, T. G.; Lees, A. J.; Fuerniss, S. J.; Papthomas, K. I. *Chem. Mater.* **1991**, *3*, 25−26.
(44) Kotch, T. G.; Lees, A. J.; Fuerniss, S. J.; Papthomas, K. I. *Chem. Mater.* **1992**, *4*, 675−683.
(45) Kavarnos, G. J.; Turro, N. J. *Chem. Rev.* **1986**, *86*, 401−449.

suggesting that relative driving force for PET for [(bpyNB)-$Re(CO)_3$(py)](OTf) is approximately 13 kcal mol^{-1} more favorable than that for **1**.[46]

Fluorescence Spectroscopy: pH Dependence. The most direct test of the validity of these calculations is to examine the response of these compounds to pH changes. At high pH, the pendant amino group is expected to quench fluorescence; by protonation of the amine at low pH, quenching should not occur, giving maximum fluorescence. This has been the basis for a number of previous molecular transducers for pH detection, including bipyridine complexes of ruthenium and rhenium.[24,26,28,30] The magnitude of fractional intensity change observed with respect to pH puts an approximate upper bound on the level of response that can be expected with respect to glucose concentration. In [(bpyNB)$Re(CO)_3$(py)](OTf), the modulation of amine quenching by an attached glucose−boronate complex is more complex and more difficult to predict than modulation of this effect by a proton. Understanding the nature of the boron−nitrogen interaction is crucial in the development of a more effective glucose transducer by this approach.

Glucose Response. This level of performance is promising in comparison to known small-molecule glucose transducers. James et al. report a 180% intensity increase from 0 to 1600 mg/dL for **1** in 33% methanol/water,[17] while more moderate increases are observed for the squaraine system (8% increase from 0 to 3000 mg/dL) by Kukrer and Akkaya[15] and the anthracene boronate system (8% decrease from 0 to 3000 mg/dL) by Yoon and Czarnik.[16] By this metric, our compounds exhibit comparable fractional transduction levels and longer wavelengths than many of the currently available systems. The major drawback is that these systems only perform well in nonaqueous solvents, which makes them less useful for operation in the body. Thus, one of our continuing focuses is to develop improved transducers for use in purely aqueous solvents. Most systems reported to date have been studied in organic/aqueous solvent mixtures because of limitations in solubility and performance.

(46) Note: The ΔG_{el} values are meant to be for relative comparison only. The positive ΔG_{el} value in this calculation is probably due to anthracene boronate not having a MLCT and the λ_{00} needing to be estimated by a different method.[45]

Summary

The results obtained from this work are being applied to the development of improved sensors for glucose. For that purpose, it has been worthwhile to demonstrate that a new small molecule transducer for glucose can be designed by a rational approach based on initial studies of electrochemistry and fluorescence properties, thus saving on the time spent synthesizing new saccharide transducers.

Acknowledgment. This work was performed under the auspices of the U.S. Department of Energy by University of California Lawrence Livermore National Laboratory under Contract No. W-7405-Eng-48. Funding for this work was obtained through the U.S. Department of Energy Laboratory Directed Research and Development program, DOC NIST ATP Award 70NANB8H4065, NIH Grant DK-98-008, and MiniMed Inc. We would like to thank Prof. B. Imperiali of Massachusetts Institute of Technology for providing helpful data on the preparation of bipyridine ligands and Robert A. Reibold of LLNL for experimental assistance.

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