Synthesis and Cyclic Voltammetry Studies of Copper Complexes of Bromo- and Alkoxyphenyl-Substituted Derivatives of Tris(2-pyridylmethyl)amine: Influence of Cation−Alkoxy Interactions on Copper Redox Potentials

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A combination of host−guest chemistry and coordination chemistry in the design of electrochemical sensors for alkali metal and ammonium ions is described. The sensor molecules are coordination complexes between a copper ion and a functionalized tripodal ligand. Upon presentation of the ion to the sensor molecule, a shift in the redox potential of the copper ion occurs. In the course of the study, three new alkoxyphenyl-substituted derivatives of the ligand tris(2-pyridylmethyl)amine (TPA) were prepared and characterized. The synthesis of the new ligands involved the preparation of bromopyridyl−TPA derivatives followed by Suzuki coupling with substituted phenylboronic acids. Cyclic voltammetry studies of copper complexes of the ligands indicated that steric effects played a dominant role in the overall determination of the copper redox couple. Studies of the alkoxyphenyl ligands indicated that small but reproducible changes in the copper redox couple occurred upon presentation of a guest cation that would be expected to form a complex with the copper−ligand complex.

Introduction

Microsensors for analysis of gases and liquids are a topic of interest because of their potential for monitoring intracellular components, pollutants, and other analytes.[1,2] The two requirements for a chemical sensor are (1) selective interaction with the target substance and (2) generation of a detectable spectroscopic[3] or electrochemical signal.[4] An attractive approach is to devise sensors that act at the single-molecule level, due to the increased potential for fine tuning of selectivity. Several studies in the field of host−guest or supramolecular chemistry have sought to devise molecular-level units capable of selective binding and signaling.[5] In particular, macrocyclic polyether systems[6] have provided an important testing ground for a variety of approaches. Electrochemical sensors have been designed by conjugation of a crown ether with a redox-active organic moiety[7−22] or a transition metal.[23−35] Crown ethers and calixarenes have been attached to polythiophenes to create sensors[36−38] for alkali metal cations[39] and viologen.[40] In these studies, the formation of a host−guest complex was detected by a change in the electrochemical behavior of the redox-active moiety. In some cases, a new peak appeared in the cyclic voltammogram of the complex; in other cases, no new peak appeared but a shift occurred in the half-point potential. In

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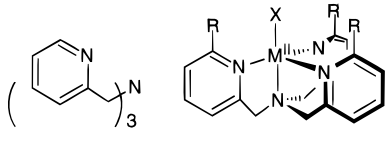


1 (TPA) $[M(R_3TPA)X]^{2+}$

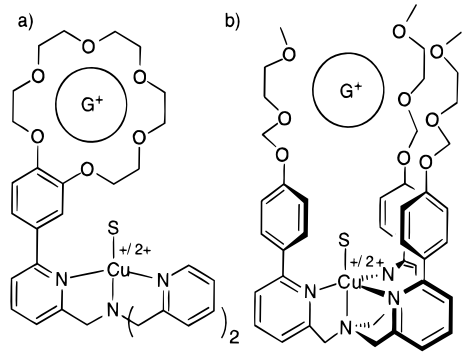
Figure 1. Geometry of Cu^{II} complexes of TPA and its derivatives.

certain instances, only a shift in one of the two peaks of the cyclic voltammogram was reported. In cases demonstrating reversible electrochemical behavior, the difference between the half-point potentials for the host coordination complex in the presence and absence of guest, ΔE, is determined (eq 1). In

$$\Delta E = E_{1/2}\{[H^{ox}(G)]/[H^{red}(G)]\} - E_{1/2}\{[H^{ox}]/[H^{red}]\} \quad (1)$$

equation 1, H^{ox} represents the oxidized form of the host, H^{red} the reduced form of the host, $H^{ox}(G)$ the oxidized form of the host−guest complex, and $H^{red}(G)$ the reduced form of the host−guest complex.

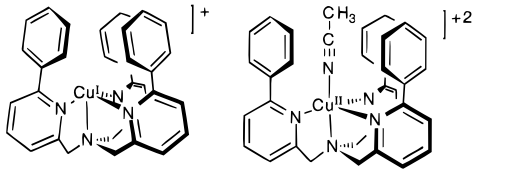
We have utilized the ligand tris(2-pyridylmethyl)amine (TPA, **1**; Figure 1) as a scaffold for the design of metallohost−guest complexes.[41] Our efforts have focused on this robust ligand because of the many interesting studies that have been reported with TPA complexes of a wide variety of metal ions.[42−50] Karlin and co-workers reported that, among these, various Cu^{I} and Cu^{II} complexes of TPA demonstrated reversible electrochemistry in solution.[51] A variety of crystallographic structures of Cu^{I} and Cu^{II} complexes of TPA[52] and related compounds[53,54] have been reported, as have solution studies of structures and reactions of various complexes.[55−57] Copper(II) complexed with TPA in solution can be expected to adopt a trigonal bipyramidal geometry with the N_4 ligand occupying the equatorial site and one apical site, with solvent or a counterion coordinated in the remaining apical position. The solution structures of TPA complexes of Cu^{I} are not as well established, but several lines of evidence suggest that in acetonitrile solution the structure is very similar to that for the Cu^{II} complex, with an elongated $Cu-N_{sp^3}$ bond.[53]



$[Cu(\mathbf{4})(S)G]^{+2/3}$ $[Cu(\mathbf{5})(S)G]^{+2/3}$

Figure 2. (a) A complex with an N_4 binding site for a redox-active metal ion such as copper and a second binding site for cations (G = guest, S = solvent). Binding of cations in one site would be expected to influence binding at the other site by electrostatic repulsion. (b) A complex with two cations but with potentially both electrostatic and geometric information transfer between the sites.

Previous work from this laboratory resulted in the synthesis and characterization of Cu^{I} and Cu^{II} complexes of the ligand, tris((6-phenyl-2-pyridyl)methyl)amine (TPPA).[68] The complexes $[Cu^{I}(TPPA)]BPh_4$ (**2**) and $[Cu^{II}(TPPA)(MeCN)](ClO_4)_2$ (**3**) were



$[Cu^{I}(TPPA)]^{+}$ $[Cu^{II}(TPPA)(MeCN)]^{+2}$

2 **3**

prepared, and their X-ray crystal structures and electrochemical behavior were determined. In the copper(I) complex **2**, two phenyl rings stack in a "T" configuration; space-filling models indicate that the copper(I) is completely encapsulated by the TPPA ligand. In **3**, the ligand contains a cavity in which a MeCN solvent molecule is bound. To create the cavity, the ligand undergoes a helical "twist". The complexes also displayed well-behaved electrochemistry as determined by cyclic voltammetry.

These data suggested that molecular recognition-based sensors might be derived from phenyl-substituted TPA complexes by making use of the one-electron redox chemistry and the synthetic flexibility of the ligand system. Two initial sensor designs were envisioned and are discussed in this paper. The first case involved covalent attachment of a benzo-18-crown-6 moiety to a TPA ligand, **4**. Such a system would present binding sites for copper ions (the N_4 site) as well as for hard cations such as alkali metals or ammonium ions (the O_6 site). Binding at the O_6 site should be detectable by a change in the Cu^{I}/Cu^{II} couple at the N_4 site. The ligand holds the two sites apart from one another such that only electrostatic interaction would be expected to play a role in the change in redox potential. Thus, the binding of a positively charged guest would be expected to result in a shift of redox potential in the positive direction.

A second system was envisioned with an O_6 site lacking a macrocyclic structure. Thus, binding at the O_6 site would be expected to depend to some degree upon preorganization provided by the binding of a copper ion at the N_4 site. Conversely, the copper atom should "feel" the binding of a guest at the O_6 site through the covalent scaffolding that connects

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the two sites, e.g., as in $[Cu(\mathbf{5})(MeCN)G]^{(2/3)+}$. Thus, the inner coordination sphere of the copper atom would be influenced by guest binding, which would be expected to influence the electrochemistry of the copper atom in addition to the electrostatic effects. The strategy of using a metal ion to preorganize a ligand to create a second binding site has been utilized in several interesting systems.[41,58−61]

Experimental Section

All reagents and solvents were purchased from commercial sources and used as received unless noted otherwise. The following were distilled under nitrogen before use: THF and ether from sodium benzophenone ketyl; methanol from $Mg(OMe)_2$; DMF from BaO; MeCN from CaH_2. Melting points were obtained with a MEL-TEMP II apparatus and are uncorrected. Analytical glassware was soaked in a concentrated H_2SO_4 bath and rinsed with deionized water before use. UV−vis spectra were obtained on a Perkin-Elmer Lambda 5. NMR spectra were acquired on a Varian Gemini 200. ESI-MS experiments were performed on a Vestec Model 201 single-quadrupole electrospray mass spectrometer. Reactions were generally carried out under nitrogen atmosphere.

6-Bromo-2-(bromomethyl)pyridine, 7. Compound **6** (59.6 mmol, 11.2 g) was added to 100 mL of 48% hydrobromic acid, and the reaction mixture was heated in an oil bath (bath temperature 120 °C) for 12 h. The solution was neutralized carefully with sodium hydroxide and then extracted with CH_2Cl_2. The combined organic fractions were dried over Na_2SO_4. After removal of the solvent, the desired product (11.9 g, 35.8 mmol, 60%) was obtained. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.5 (dd, 1H), 7.3 (m, 2H), 4.4 (s, 2H). ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 158.3, 141.7, 140.0, 128.0, 123.0, 33.1.

6-Bromo-2-(aminomethyl)pyridine, 8. Compound **7** (7.04 g, 29.7 mmol) in 50 mL of DMF was reacted with potassium phthalimide (11.8 g, 63.9 mmol) and $NaHCO_3$ (6.38 g, 73.7 mmol). The mixture was heated to reflux for 3 h and then cooled to room temperature. The white solid that formed was removed by suction filtration. The solvent from the filtrate was removed by rotary evaporation. Water was added until a white precipitate formed, followed by vacuum filtration, giving the phthalimide derivative. Without further purification, this was redissolved in 150 mL of HBr (48%), and the mixture was heated to reflux for 15 h. The resulting solution was cooled to obtain a precipitate of phthalic acid, which was removed by filtration. The solution was cooled in an ice bath, basified with 10 M sodium hydroxide to pH >10, and extracted several times with ether. The combined solutions were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The residue was dried under vacuum. A yield of 3.04 g of **8** was obtained (58%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.6 (dd, 1H), 7.3−7.1 (m, 2H), 4.0 (s, 2H), 2.0 (br s). ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 164.2, 142.1, 139.3, 126.5, 120.4, 47.9.

Bis(2-pyridylmethyl)((6-bromo-2-pyridyl)methyl)amine, 9 (BrTPA). Compound **8** (1.2 mmol, 0.23 g) was added to a solution of picolyl chloride hydrochloride (2.4 mmol, 0.4 g) in 1.5 of mL water. A solution of 10 M NaOH (0.47 mL) was added slowly, and the mixture was heated (70 °C) for 3 h. The mixture was cooled and extracted with $CHCl_3$ (3 × 5 mL). The combined extracts were dried over $MgSO_4$, and the $CHCl_3$ was removed on a rotary evaporator. The residue was purified by passing through a short silica column with ethyl acetate as eluant. A yield of 265 mg of BrTPA was obtained (0.72 mmol, 60%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.6 (d, 2H), 7.7−7.4 (m, 6H), 7.3−7.1 (m, 3H), 3.87 (br s, 6H). ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 159.5, 149.65, 149.58, 141.7, 139.2, 136.9, 126.7, 123.6, 122.5, 122.1, 60.8, 60.0. Mp: 58−60 °C. ESI-MS, *m*/*e*: 407 (M + K^+), 391 (M + Na^+), 369 (M + H). CI-MS (NH_3), *m*/*e*: 369 (100%), 371 (90%). Anal. Calcd for $C_{18}H_{17}N_4Br$: C, 58.55; H, 4.64; N, 15.17. Found: C, 58.38; H, 4.50; N, 14.97.

Tris((6-bromo-2-pyridyl)methyl)amine, 10 (Br_3TPA). Compound **8** (1.52 mmol, 0.285 g) was added to a solution of **11** (3.05 mmol, 0.7415 g) in 1.2 mL of water containing a few drops of methanol. A solution of 10 M NaOH (0.6 mL) was slowly added, and the mixture was heated (70 °C) for 30 min. The resulting mixture was cooled and extracted with $CHCl_3$. The combined extracts were dried, and the $CHCl_3$ was removed on a rotary evaporator. The residue (0.85 g) was recrystallized from ether, giving 0.50 g of Br_3TPA (0.95 mmol, 62.5%). (Substitution of compound **7** for **11** resulted in a lower yield (50%).) ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.6−7.4 (m, 6H), 7.4−7.3 (m, 3H), 3.9 (s, 6H). ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 161.0, 141.9, 139.1, 126.8, 122.3, 60.0. Mp: 132−134 °C. ESI-MS, *m*/*e*: 565 (M + K^+), 549 (M + Na^+), 529 (M + H^+). Anal. Calcd for $C_{18}H_{15}N_4Br_3 \cdot H_2O$: C, 39.66; H, 3.14; N, 10.28. Found: C, 39.62; H, 2.79; N, 10.03. High-resolution MS (Gly, FAB):, *m*/*e*: calcd (MH^+, tallest peak in isotope packet), 526.8903; found, 526.8906.

6-Bromo-2-(chloromethyl)pyridine Hydrochloride, 11. To compound **6**[62] (60.00 mmol, 11.28 g) was added 18 mL of $SOCl_2$, the reaction mixture was heated for 10 min, and Excess $SOCl_2$ was removed by careful evaporation on a rotary evaporator. A 100-mL portion of pentane was added to the residue and then removed by rotary evaporation to facilitate complete removal of $SOCl_2$. The residue was washed with pentane and then dried under vacuum to give pure **11** (11.38 g). Additional crystals could be obtained by concentration of the filtrate, giving an additional 1.20 g of product (51.77 mmol, 86% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.6 (1H), 7.45 (2H), 4.6 (2H).

If the reaction time was too long or if the temperature was too high during evaporation of solvent, the compound 6-chloro-2-(chloromethyl)-pyridine was obtained which was indistinguishable from the 6-bromo compound by ^{1}H NMR. This side reaction was generally revealed by examination of mass spectra of subsequent synthetic intermediates.

Bis((6-bromo-2-pyridyl)methyl)(2-pyridylmethyl)amine, 12 (Br_2-TPA). Picolylamine (1.2 mmol, 0.124 mL) was added to a solution of **11** (2.4 mmol, 0.58 g) in 1.5 mL of water. A solution of 10 M NaOH (0.47 mL) was slowly added, and the mixture was heated (70 °C) for 30 min, after which it was cooled and extracted with chloroform (3 × 5 mL). The combined extracts were dried over Na_2SO_4, and the chloroform was removed on a rotary evaporator. The residue was purified by recrystallization from ether to obtain 0.37 g of Br_2TPA as a white solid (0.83 mmol, 69%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.6 (d, 2H), 7.8−7.1 (m, 8H), 3.89 (s, 2H), 3.88 (s, 4H). ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 161.3, 149.6, 141.8, 139.1, 136.9, 126.8, 123.6, 122.6, 122.2, 122.8, 60.0 (the 60.7 ppm peak was not observed). Mp: 60−62 °C. Anal. Calcd for $C_{18}H_{16}N_4Br_2$: C, 48.24; H, 3.60; N, 12.50. Found: C, 48.33; H, 3.53; N, 12.40.

Bis(2-pyridylmethyl)((6-chloro-2-pyridyl)methyl)amine, 15 (ClTPA). The procedure described for the synthesis of BrTPA was followed with compound **14** (0.480 g, 3.37 mmol) and picolyl chloride hydrochloride (0.843 g, 5.17 mmol), affording the product in 74% yield (0.621 g, 1.91 mmol). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.5 (d, 2H), 7.7−7.5 (m, 6H), 7.2−7.1 (m, 3H), 3.88 (s, 4H), 3.86 (s, 2H). ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 161.1, 159.5, 149.6, 139.4, 136.9, 136.8, 123.5, 122.9, 122.5, 121.7, 60.7, 60.1. Mp: 50−52 °C. ESI-MS, *m*/*e*: 326 (M + H). Anal. Calcd for $C_{18}H_{17}ClN_4$: C, 66.56; H, 5.28; N, 17.25. Found: C, 66.85; H, 5.32; N, 17.08.

Bis((6-bromo-2-pyridyl)methyl)((6-chloro-2-pyridyl)methyl)-amine, 16 (Br_2ClTPA). The compound was prepared from ((6-chloro-2-pyridyl)methyl)amine in a manner similar to that described for Br_3TPA (43% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.6−7.4 (m, 6H), 7.4−7.3 (m, 3H), 3.9 (s, 6H). ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 161.0, 160.5, 151.1, 141.9, 139.5, 139.2, 126.9, 123.1, 122.3, 121.9, 60.0. Mp: 120 °C. ESI-MS, *m*/*e*: 505 (M + Na^+). Anal. Calcd for $C_{18}H_{15}N_4ClBr_2$: C, 44.80; H, 3.13; N, 11.60. Found: C, 44.67; H, 2.94; N, 11.43.

4-((2-Methoxyethoxy)methoxy)bromobenzene, 17. 4-Bromophenol (20 mmol, 3.46 g) in 50 mL of THF or ether was cooled to 0 °C before adding 2 N *n*-butyllithium (20 mmol, 10 mL). The compound

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(2-methoxyethoxy)methyl chloride (24 mmol, 2.74 mL) was added, and stirring was continued for 2 h. Water (20 mL) was added, and the solution was extracted with ether. After removal of the solvent by rotary evaporation and purification by vacuum distillation, the yield of **17** was 4.65 g (17.8 mmol, 89% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.4 (d, 2H), 7.0 (d, 2H), 5.2 (s, 2H), 3.8 (t, 2H), 3.6 (t, 2H), 3.4 (s, 3H). ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 132.7, 118.6, 116.6, 114.7, 94.1, 72.1, 68.3, 59.5.

Bis(2-pyridylmethyl)((6-(4-((2-methoxyethoxy)methoxy)phenyl)-2-pyridyl)methyl)amine, 19. Compound **17** (2.6 g, 10 mmol) was added to 20 mL of dry THF or ether, and the mixture was cooled to −80 °C; then 2 M *n*-butyllithium (10 mmol, 5.0 mL) was added. The reaction mixture was warmed to -45 °C for 15 min and then cooled to −80 °C. Trimethyl borate (1.7 mL, 15 mmol) in 2 mL of ether was added, and the mixture was allowed to warm to ambient temperature overnight. Water (50 mL) was added, and the solution was stirred for 2 h. The THF was removed by evaporation, and the residue was extracted with three 75-mL portions of ether. The solvent was removed by rotary evaporation to yield 1.78 g (7.90 mmol, 79%) of **18**.

To a stirred solution of **9** (1.0 mmol, 0.37 g) and $Pd(PPh_3)_4$ (0.030 mmol, 35 mg) in 2 mL of dry toluene under nitrogen were added 1 mL of 2 M Na_2CO_3 and **18** (1.2 mmol, 0.28 g) in 0.5 mL of methanol. The vigorously stirred mixture was heated at reflux temperature for 12 h and then cooled and partitioned between 50 mL of CH_2Cl_2 and 25 mL of 2 M Na_2CO_3 containing 2.5 mL of concentrated NH_3. The organic layer was dried (Na_2SO_4) and then concentrated to dryness under reduced pressure. Flash chromatography on alumina afforded the 36.4 mg of **19** (0.775 mmol, 77.5%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.5 (d, 2H), 8.0−7.9 (d, 2H), 7.7−7.4 (m, 7H), 7.2−7.0 (m, 4H), 5.3 (s, 2H), 4.0−3.8 (m, overlapping peaks, 8H), 3.6 (m, 2H), 3.4 (s, 3H). ESI-MS, *m*/*e*: 493 ($M + Na^+$), 471 ($M + H^+$). Anal. Calcd for $C_{28}H_{30}N_4O_3$: C, 71.47; H, 6.43; N, 11.91. Found: C, 71.37; H, 6.65; N, 11.68.

Tris((6-(4-((2-methoxyethoxy)methoxy)phenyl)-2-pyridyl)methyl)amine, 5. To a stirred solution of **10** (1 mmol, 0.52 g) and $Pd(PPh_3)_4$ (0.1 mmol, 0.12 g) in 6 mL of dry toluene under nitrogen were added 3 mL of 2 M Na_2CO_3 and **18** (10 mmol, 2.25 g) in 1.5 mL of methanol. The vigorously stirred mixture was heated at reflux temperature for 12 h and then cooled and partitioned between 50 mL of CH_2Cl_2 and 25 mL of 2 M Na_2CO_3 containing 2.5 mL of saturated aqueous NH_3. The organic layer was dried (Na_2SO_4) and then concentrated under reduced pressure. Flash chromatography on silica afforded **5** (0.24 g, 0.28 mmol, 28%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.0 (d, 6H), 7.8−7.5 (m, 9H), 7.2−7.0 (d, 6H), 5.3 (s, 6H), 4.1 (s, 6H), 3.9 (t, 6H), 3.6 (t, 6H), 3.4 (s, 9H). ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 160.0, 158.4, 156.6, 137.4, 133.8, 128.7, 121.1, 118.4, 116.8, 93.9, 72.2, 68.2, 61.0, 59.6. ESI-MS, *m*/*e*: 853 ($M + Na^+$), 831 ($M + H^+$). Anal. Calcd for $C_{18}H_{17}N_4O$: C, 69.21; H, 6.78; N, 6.73. Found: C, 68.98; H, 7.05; N, 6.53.

Compound 4. To a stirred solution of 4-bromobenzo-18-crown-6 (420 mg, 1.07 mmol) in 6 mL of THF at −78 °C was added 1.3 mL of *n*-butyllithium (2.1 mmol, 1.6 M in hexane). After 1 h of stirring at −78 °C, 1.0 mL of $B(OMe)_3$ was added quickly in one portion. The resulting solution was stirred at −78 °C for 45 min. Methanol (0.5 mL) was added, and the mixture was allowed to warm to room temperature. The solvent was removed by evaporation below room temperature, and several portions of methanol were repeatedly (three times) added and removed to eliminate the excess $B(OMe)_3$. To the crude residue were added a 2 M solution of Na_2CO_3 (4 mL), 2 mL of methanol, 8 mL of toluene, BrTPA (160 mg, 0.93 mmol), and $Pd(PPh_3)_4$ (60 mg, 0.06 mmol). This mixture was heated to 65−70 °C overnight. After cooling, the mixture was partitioned between 40 mL of CH_2Cl_2 and 40 mL of water. The organic layer was removed, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, and the CH_2Cl_2 was removed on a rotary evaporator. The residue was chromatographed on alumina (9:1/$CHCl_3$−ether) to give 234 mg (90%) of product. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.5 (m, 2H), 7.7−6.9 (m, 12H), 4.3−4.2 (m, 4H), 4.0 (s, 9H), 3.8−3.7 (m, 13H). ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 160.1, 159.4, 156.6, 150.6, 150.4, 149.5, 137.4, 136.8, 133.4, 123.3, 122.4, 121.1, 120.5, 118.4, 114.3, 113.5, 71.3, 70.2, 69.81, 69.75, 69.70. MS (FAB), *m*/*e*: 601.46 ($M + H^+$). Anal. Calcd for $C_{34}H_{40}N_4O_6 \cdot H_2O$: C, 66.00; H, 6.84; N, 9.06. Found: C, 65.72; H, 6.79; N, 8.67. High-resolution MS (Gly, NBA, FAB), *m*/*e*: calcd (MH^+), 601.3026; found, 601.3019.

[Cu(4)NaCl](ClO$_4$)$_2$. The salt $Cu(ClO_4)_2 \cdot 6H_2O$ (37 mg, 0.1 mmol) [***Note**: Perchlorate salts of metal complexes with organic ligands can be explosive and should be handled in small quantities and with great caution.*[63]] was dissolved in 0.4 mL of methanol. The crown ether compound **4** (60 mg, 0.1 mmol) was dissolved in 0.4 mL of methanol. The two solutions were combined, giving a blue precipitate. A solution of 6 mg of NaCl (0.1 mmol) in water was added. Upon mixing, the solution became homogeneous briefly, followed by formation of another precipitate, which was collected and dried under vacuum overnight. Anal. Calcd for $C_{34}H_{40}N_4O_6 \cdot CuCl_2 \cdot NaClO_4 \cdot H_2O$: C, 46.64; H, 4.83; N, 6.40. Found: C, 46.28; H, 4.68; N, 6.36.

Recrystallization from 50% methanol−water gave crystals from which a low-quality data set was collected. A model was obtained but could not be refined satisfactorily.

Electrochemistry. Electroanalytical measurements were performed using an EG&G Model 273 potentiostat. Data were processed on EG&G M250 Research Electrochemistry Software. Cyclic voltammetric data were recorded using a glassy carbon working electrode (0.082 cm^2), a platinum counter electrode, and a Ag/Ag^+ reference electrode consisting of silver wire immersed in an MeCN solution of $AgNO_3$ (0.1 M). Glassy carbon electrode surfaces were polished with 0.05-mm alumina, sonicated in water, and air-dried immediately before use. The complexes all underwent reversible one-electron oxidations. The electrochemical experiments were repeated, and the positions of the waves were compared to the potential of the ferrocenium/ferrocene (Fc^+/Fc, $E° = 0.4$ V vs NHE) couple. The MeCN solution (containing 0.1 M $(n\text{-}Bu)_4NPF_6$, as supporting electrolyte, 0.8−1.0 mM each of the ligand copper salt, and variable concentrations of metal salts) was placed in a single-compartment electrochemical cell and degassed by bubbling with N_2(g) saturated with MeCN. A N_2 atmosphere was continuously maintained above the solution while the experiments were in progress. Solutions were equimolar (within <5%) in ligand and $Cu(ClO_4)_2$ (ligands **5** and **19**) or $Cu(OSO_2CF_3)_2$ (anhydrous, ligand **4**), unless otherwise specified. Concentrations of Cu solutions were determined by titration with standard EDTA (Aldrich).

Each $\Delta E_{1/2}$ was determined by measurement of the cyclic voltammogram of the copper complex in the absence and presence of alkali metal or ammonium salt under the same conditions. The potential was first measured using a solution containing ligand, copper salt, and electrolyte. Another solution containing equimolar concentrations of the same species plus alkali metal or ammonium salt was then added, and the cyclic voltammogram was recorded.

Results and Discussion

Synthesis. Syntheses of the halogenated ligands are shown in Scheme 1. Conversion of 6-bromopyridine-2-methanol (**6**)[62] to **7** was effected with concentrated aqueous HBr. Primary amine **8** was then prepared via the phthalimide followed by aqueous HBr hydrolysis.[64] Reaction of **8** with 2 equiv of commercially available picolyl chloride hydrochloride salt and 4 equiv of NaOH provided BrTPA (**9**). Similar alkylation of **8** with **7** provided **10** (Br_3TPA). For Br_2TPA (**12**), the commercially available 2-picolylamine was reacted with 6-bromo-2-(chloromethyl)pyridine (**11**) and NaOH. Compound **11** was prepared from **6** with $SOCl_2$. When too much heat was applied during the workup of **11** (e.g., removal of $SOCl_2$ by distillation at atmospheric pressure), the dichlorinated compound **13** was obtained. The ligand ClTPA was prepared from **1**, and Br_2ClTPA **16** was prepared from **14** and **13**.

The syntheses of the alkoxyphenyl ligands are shown in Scheme 2. Halogen-metal exchange of **17** with *n*-butyllithium (−78 °C), quenching with $B(OMe)_3$, and aqueous workup gave **18**. Suzuki coupling[65,66] of **9** and **18** gave the tripod **5**. The

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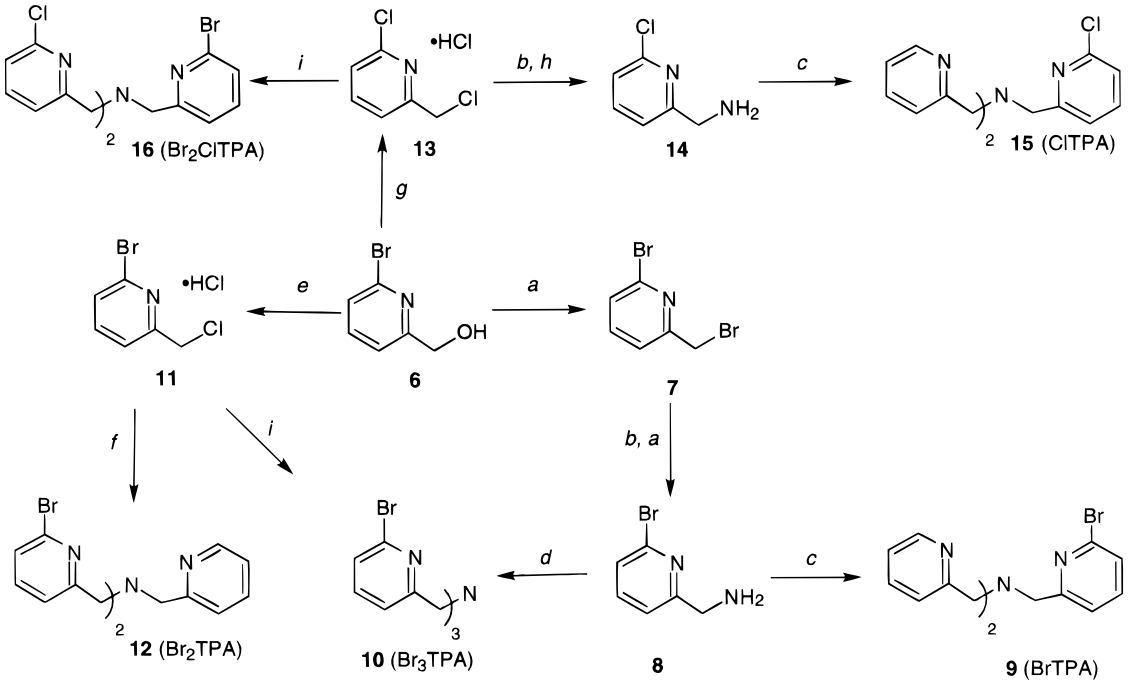
Scheme 1. Synthesis of the Halogenated TPA Derivatives



[a] 48% HBr; base. [b] Potassium phthalimide. [c] 2 equiv of picolyl chloride hydrochloride; NaOH. [d] 2 equiv of **7**; NaOH. [e] $SOCl_2$. [f] 0.5 equiv of picolylamine; NaOH. [g] $SOCl_2$; Δ. [h] 6 N HCl; Δ. [i] 0.5 equiv of **8**; NaOH.

monosubstituted ligand **19** was prepared by coupling of **9** with **18**. Compound **21** was prepared in a manner similar to that for **18**, except that exposure to water or heat was avoided in the workup to avoid deboronation. Suzuki coupling of **9** and **21** formed ligand **4**.

Electrochemistry. The electrochemical properties of the polyether derivatives were investigated in MeCN (or DMF) using cyclic voltammetry with $(n\text{-Bu})_4NPF_6$ as the supporting electrolyte. All compounds exhibited reversible one-electron oxidation waves. All redox potentials are averages of at least two measurements and are reported vs ferrocene/ferrocenium. The results are listed in Table 1. An earlier study utilized $Cu(ClO_4)_2$ complexes as starting points for the cyclic voltammogram determinations.[67,68] The present work utilized $Cu(MeCN)_4(PF_6)$ as the salt in order to exclude water from the solutions and to avoid the hazard of working with perchlorate salts.[63] Control experiments indicated that half-point potentials were very similar regardless of whether the starting point was the Cu^{I} or the Cu^{II} complex or whether the counterion was ClO_4^- or PF_6^-. Potentials were determined for complexes prepared in situ by mixing the copper salt and the ligand. Stoichiometric ratios of salt and ligand gave half-point potentials identical to those obtained from preformed complexes.

In general, substitution of the 6-position of TPA with bromine atoms has a larger effect on the half-point potentials of the copper complexes than substitution with phenyl substituents. The difference in redox potential between $Cu(TPA)(ClO_4)_2$ and $Cu(PhTPA)(ClO_4)_2$ in MeCN is 90 mV,[67] while that between $Cu(TPA)(PF_6)$ and $Cu(BrTPA)(PF_6)$ is 123 mV. Addition of each additional bromine substituent in the $Cu(Br_nTPA)(PF_6)$ series causes a larger change, similar to the trend for the $Cu(Ph_nTPA)(ClO_4)_2$ in DMF but not in MeCN.[67] The chlorine atom has a smaller effect in ClTPA or Br_2ClTPA complexes than a corresponding bromine atom in the BrTPA or Br_3TPA complexes, opposite to the result that would be expected if the influence of the halogen atoms was due entirely to inductive effects. We conclude that steric effects dominate the influence of the substituents on redox potential in halogenated complexes. The half-point potential for $Cu(Br_3TPA)(PF_6)$ is 653 mV more positive than that of $Cu(TPA)(PF_6)$. The half-point potentials for the alkoxyphenyl-substituted complexes are similar to those previously reported for the analogous Ph_nTPA complexes.[67,68] The similarity of the data for Cu(**19**)(PF_6) and Cu(**4**)$(OTf)_2$ also suggests that inductive effects are of minimal importance.

The electrochemical behavior of the copper complexes of the ligands was examined in the presence of guests capable of binding to the alkoxy groups. Cyclic voltammograms were recorded after progressively adding stoichiometric equivalents of alkali metal ions and ammonium ion to the electrochemical solutions of $[Cu(L)]^{n+}$ complexes. Overall, either small changes in redox potential were observed, or the cyclic voltammogram was not consistent with sufficiently reversible behavior to determine the potential.

The complex $[Cu(\mathbf{4})]^{2+}$ exhibited a positive shift in half-point potential upon addition of various cationic guests: NH_4PF_6 (12 mV), $LiClO_4$ (2 mV), $NaClO_4$ (9 mV), $KClO_4$ (14 mV), $RbClO_4$ (15 mV), $CsClO_4$ (4 mV). A shift in the positive direction is expected if the difference is due to charge−charge repulsion between the guest at the O_6 site and the copper ion (i.e., greater repulsion with the Cu^{2+} making the complex easier to reduce). The largest shifts were observed with NH_4^+, K^+, and Rb^+; addition of other alkali metal perchlorates induced a smaller shift. The overall trend in the values of the redox potentials parallels the expected affinity for the ions for benzo-18-crown-6 from independent measurements under similar conditions.[69] The reproducibility of the measurements was ±3 mV. In most cases, the anodic peak potential shift was larger than that of the cathodic peak. Potentials were measured at a variety of guest concentrations with in an attempt to calculate binding constants, but the changes were too small to obtain satisfactory data.

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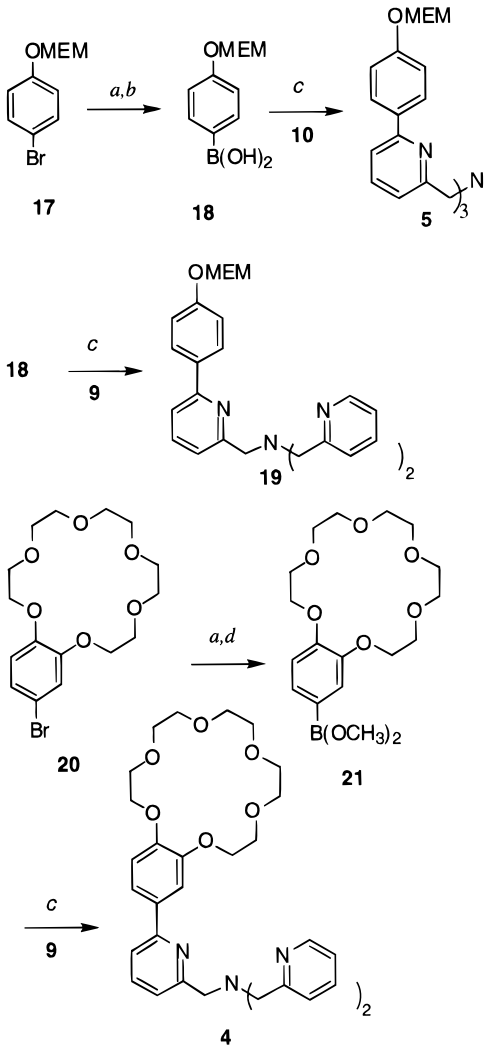
Scheme 2. Synthesis of Alkoxyphenyl−TPA Derivatives



[a] *n*-BuLi; $B(OMe)_3$. [b] H_2O. [c] $Pd(PPh_3)_4$; Na_2CO_3. [d] CH_3OH.

In principle, the complex [Cu(**5**)]PF_6 may also present six oxygen atoms for complexation of cations, although such a binding site would be much less preorganized than that of the 18-crown-6 moiety present in ligand **4**. Cyclic voltammograms of [Cu(**5**)]PF_6 in the presence of Li^+ ions also showed a positive change ($\Delta E_{1/2} = +13$ mV). The redox potential did not change by adding the other alkali metal ions to the same solution, indicating that, for the acyclic complex, Li^+ was the most strongly bound of the alkali metal cations. When NH_4PF_6 was added to the solution, the half-point potential shifted by +30 mV. This value was larger than that observed with [Cu(**4**)]-$(OTf)_2$, possibly due to the closer proximity of the ammonium ion binding site to the copper ion. Smaller changes were observed for the complexes [Cu(**19**)]PF_6 (−8 mV), [Cu-(PhTPA)]PF_6 (+6 mV), and [Cu(TPPA)]PF_6 (−1 mV), suggesting that the presence of the three alkoxyphenyl substituents in proximity to one another results in a larger effect. The effect observed with [Cu(**5**)]PF_6 disappears when the experiment is conducted in DMF, with very little change in potential observed. This is the expected result since DMF should solvate the ammonium ion strongly, preventing any binding to the polyether site of the coordination complex. Attempts to isolate X-ray-quality crystals of complexes of [Cu(**5**)]PF_6 were unsuccessful.

Table 1. Half-Point Potentials (mV, vs Fc/Fc^+) for the Halogen- and Alkoxyphenyl-Substituted TPA−Copper Complexes $[Cu(L)]^{n+}$ in MeCN

complex	$E_{1/2}$	complex	$E_{1/2}$
[Cu(TPA)](PF_6)	−403	[Cu(Br_2ClTPA)](PF_6)	237
[Cu(BrTPA)](PF_6)	−280	[Cu(**19**)](PF_6)	−335
[Cu(ClTPA)](PF_6)	−293	[Cu(**5**)](PF_6)	−125
[Cu(Br_2TPA)](PF_6)	−60	[Cu(TPA)]$(OTf)_2$	−413
[Cu(Br_3TPA)](PF_6)	250	[Cu(**4**)]$(OTf)_2$	−338

The complex [Cu(**4**)] is selective for K^+ and Rb^+, while the nonmacrocyclic compounds are selective for Li^+. This is the expected result in acetonitrile where the inherent binding energy would be expected to be larger due to its greater Lewis acidity deriving from its larger charge:ionic radius ratio. The macrocyclic ring shows greater size and shape selectivity due to the complementarity between the macrocyclic ring and ions of moderate ionic radius and better binding due to increased preorganization.

Overall, the redox potential shifts were small in magnitude for all of the alkali metal or ammonium ions studied. The largest shifts were observed for complexes of **5** in which binding of a guest might be expected to influence the copper ion through both electrostatic and steric interactions. In preliminary experiments,[70] guests capable of binding directly to the copper ion, such as amino acids via carboxylate−copper coordination, were found to induce very large changes in the electrochemical behavior of the copper ion. However, in these cases, the voltammograms obtained indicated irreversible electrochemical behavior, even at reduced temperatures. This is most likely a result of complex redox mechanisms for the copper complexes due to variation of the metal ion coordination number or geometry upon oxidation state change.[71] The complexation of such guests will be studied by other methods and reported in due course.

Summary

The electrochemical results agree with the hypotheses set forth in the design of the ligands. In [Cu(**4**)]$(OTf)_2$, binding of a cation causes a positive shift in the redox potential of the copper(I/II) couple. For [Cu(**5**)]PF_6, a similar result is observed, but the magnitude is somewhat larger for guests that bind to both complexes (e.g., NH_4^+). This may result from the closer proximity of the guest cation to the copper center, and because there may be geometrical communication between the guest and the copper ion through the covalent structure of the scaffold. The reversible redox waves show that the copper complexes act as good redox-active receptors since they display well-defined electrochemical behavior on binding of the guests. However, for many interesting guests, the electrochemical behavior becomes irreversible.

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