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Redox Active Macrocyclic Receptors for Neutral Guests

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A novel series of triazine-appended macrocyclic complexes has been investigated as potential hydrogen bonding receptors for complementarily disposed heterocycles. Cocrystallization of a melamine-appended azacyclam complex of Cu^{II} has been achieved with barbitone, the barbiturate anion and thymine. In each case, a complementary DAD/ADA hydrogen bonding motif between the melamine group and the heterocycle has been identified by X-ray crystallography. Electrochemical studies of the copper macrocycles in both nonaqueous and aqueous solution show anodic shifts of the $Cu^{II/I}$ redox couple of more than 60 mV upon addition of guest molecules with matching H-bonding motifs. The Zn^{II} analogues have been synthesized via transmetalation of the Cu^{II} complex, and their guest binding properties investigated by NMR spectroscopy. ^{1}H NMR shifts of up to 0.8 ppm were observed upon addition of guest, and stability constants are similar to those obtained electrochemically.

Introduction

A redox active receptor traditionally consists of two components, a redox active center in close proximity to a binding site.[1] Cations and anions, being charged entities, create an electrostatic field around themselves. When bound to a receptor, this electrostatic field exerts an effect on the redox subunit, altering its redox potential. So in effect, this electrostatic field is the means by which communication between subunits of a receptor occurs. A more challenging problem is the design of redox active receptors for neutral molecules. Electrostatic host−guest attractive forces cannot be utilized for guest binding.[2] However, noncovalent interactions such as hydrogen bonding and $\pi-\pi$ stacking are strongly direction-dependent and may be useful for binding neutral guests. The interaction between host and guest must produce a measurable change in the redox potential of the host through either a guest-induced conformational change or polarization of a nearby functional group. Several notable examples of redox active neutral molecule receptors exist. Diederich and co-workers synthesized one of the first redox active molecular receptors in 1990,[3] using an isoalloxazine moiety incorporated into a cyclophane. Electron-deficient 4,4′-bipyridinium residues (viologens) are effective redox active receptors[4] as are other organic redox receptors such as 9,10-phenanthrenequinone and 1,8-naphthalimide.[5] Beer and co-workers have attached the redox active ferrocene subunit to both calixarenes[6] and cavitands[7] to produce receptors capable of binding small solvent molecules such as DMF, DMSO, or EtOH. Tucker and co-workers have also used the ferrocene subunit to produce redox active neutral molecule receptors that are complementary to carboxylic acids.[8] The same group has reported a nucleobase receptor comprising a Zn^{II}−cyclen complex attached to a redox active anthraquinone moiety.[9] This molecule binds thymidine and uridine selectively. The ferrocenylboronic acid derivatives of Shinkai and co-workers detect the presence of saccharides,[10] although these rely on covalent modification of host and guest, rather than noncovalent interactions.

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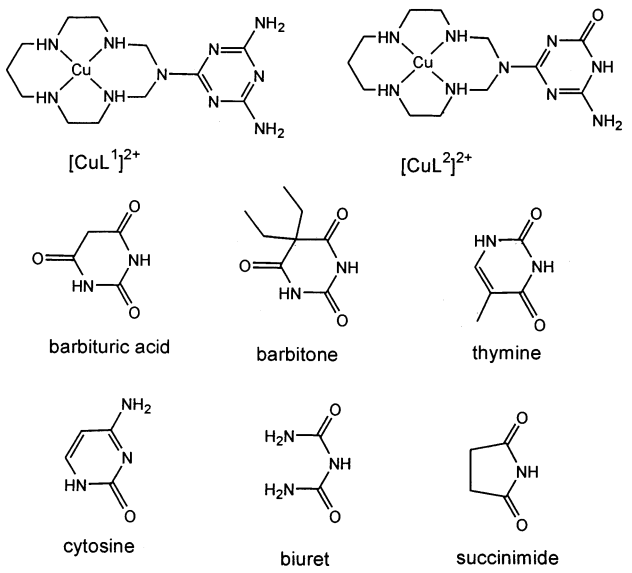
Chart 1



Previously, we reported syntheses and characterization of azacyclam Cu^{II} complexes appended with melamine (L^1) and ammeline (L^2) triazine rings (Chart 1).[11] Triazines have well-documented H-bonding properties. For example, the melamine ring in L^1 presents a three-point donor/acceptor/donor (DAD) H-bonding edge comprising the apical ring N-atom flanked by the two NH_2 groups. There are many biologically active heterocycles (barbiturates, nucleic bases) that offer a complementary (ADA) H-bonding pattern to melamine,[12] and as such, they are ideal targets for receptors such as L^1. The redox active metal ion (Cu^{II}) bound within the macrocyclic ring offers an electrochemical signal that is sensitive to H-bonding host−guest interactions. In this work, we will show that complexes such as $[CuL^1]^{2+}$ are both sensitive and selective redox active receptors for a range of biologically important neutral guest molecules. The corresponding diamagnetic Zn^{II} complexes have also been prepared, and their guest binding has been investigated by NMR spectroscopy.

Experimental Section

Safety Note. Perchlorate salts are potentially explosive. Although no problems were experienced with the compounds synthesized, they should only be handled in small quantities, never scraped from sintered glass frits, nor heated in the solid state.

Syntheses. $[CuL^1](ClO_4)_2\cdot 2H_2O$ and $[CuL^2](ClO_4)_2$ were synthesized according to published methods.[11]

Transmetalations. (6-(4′,6′-Diamino-1′3′5′-triazinyl)-1,4,6,8,-11-pentaazacyclotetradecane)zinc(II) Perchlorate Dihydrate, $[ZnL^1](ClO_4)_2\cdot 2H_2O$. The zinc analogue was prepared using a modified transmetalation procedure.[13] $[CuL^1](ClO_4)_2\cdot 2H_2O$ (0.32 g, 0.5 mmol) was dissolved in 25 mL CH_3CN, and the solution was purged with N_2 for 10 min. Approximately 1.6 g of 2% Zn(Hg) was added, and the mixture refluxed for 1 h, to afford a colorless solution. The mixture was filtered and then concentrated to give a colorless solid (0.31 g, 97% yield). Calcd for $C_{12}H_{30}Cl_2N_{10}O_{10}Zn$: C, 23.67; H, 4.97; N, 23.01. Found: C, 23.60; H, 4.63; N, 22.95. ^{1}H NMR (200 MHz, CD_3CN): 1.6−2.0 (m), 2.4−3.3 (m), 3.49 (broad s), 3.8−4.1 (m), 5.32 (d), and 5.95 ppm (broad s). ^{13}C NMR (200 MHz, CD_3CN): 28.6, 44.5, 48.0, 50.1, 63.2, 167.0, 168.6 ppm. Infrared: 3443, 3215, 2946, 2865, 1667, 1623, 1556, 1486, 1454, 1414, 1339, 1288, 1113, 1085, 980, 952, 883, 813, 627 cm^{-1}.

(6-(6′-Amino-1′*H*-1′3′5′-triazine-4′-one)-1,4,6,8,11-pentaazacyclotetradecane)zinc(II) Perchlorate Trihydrate, $[ZnL^2](ClO_4)_2\cdot 3H_2O$. The zinc complex of L^2 was prepared in a manner similar to the melamine analogue $[ZnL^1](ClO_4)_2$, in 88% yield. Calcd for $C_{12}H_{31}Cl_2N_9O_{12}Zn$: C, 22.96; H, 4.98; N, 20.08. Found: C, 23.18; H, 4.43; N, 19.99. ^{1}H NMR (200 MHz, CD_3CN): 1.78 (m), 2.6−3.2 (m), 3.48 (m, broad), 4.08 (m), 5.05 (m), 5.46 (dd), 6.56 (s, broad). ^{13}C NMR (200 MHz, CD_3CN): 28.7, 44.6, 45.7, 47.8, 47.9, 49.9, 50.3, 63.2, 63.4, 159.2, 161.5, 166.7 ppm. Infrared: 3216, 2935, 2867, 1674, 1652, 1628, 1558, 1506, 1472, 1423, 1404, 1338, 1287, 1146, 1113, 1080, 998, 947, 928, 885, 796, 625 cm^{-1}.

Cocrystals. (6-(4′,6′-Diamino-1′3′5′-triazinyl)-1,4,6,8,11-pentaazacyclotetradecane)copper(II) Barbiturate Hydrogencarbonate Heptahydrate, $[CuL^1](HCO_3)\cdot(C_4H_3N_2O_3)\cdot 7H_2O$. Vapor diffusion of EtOH into a concentrated aqueous solution of $[CuL^1](ClO_4)_2$, barbituric acid, and Na_2CO_3 (1:2:1 molar ratio) afforded crystals suitable for X-ray diffraction.

(6-(4′,6′-Diamino-1′3′5′-triazinyl)-1,4,6,8,11-pentaazacyclotetradecane)copper(II) Sesquiperchlorate Hemiiodide 5,5-Diethylbarbituric acid, $[CuL^1](ClO_4)_{1.5}I_{0.5}\cdot(C_8H_{12}N_2O_3)$. Vapor diffusion of 2-propanol into a concentrated aqueous solution of $[CuL^1](ClO_4)_2$ (1 equiv), barbitone (2 equiv), and a trace of NaI gave crystals suitable for X-ray diffraction.

(6-(4′,6′-Diamino-1′3′5′-triazinyl)-1,4,6,8,11-pentaazacyclotetradecane)copper(II) Diperchlorate Thymine Trihydrate, $[CuL^1](ClO_4)_2\cdot(C_5H_6N_2O_2)\cdot 3H_2O$. Vapor diffusion of 2-propanol into a concentrated aqueous solution of $[CuL^1](ClO_4)_2$ and thymine in 1:2 ratio gave crystals suitable for X-ray work.

Physical Methods. Cyclic voltammetry was performed using a BAS 100B/W analyzer employing a glassy carbon working electrode, a platinum auxiliary electrode, and a nonaqueous Ag/$AgNO_3$ reference electrode. Cyclic voltammetry was also performed on a hanging mercury drop electrode, using a Princeton Applied Research 303 SMDE, with a Ag/AgCl reference electrode and a platinum wire counter electrode. Differential pulse polarography was performed on the same instrument. All solutions were 0.1 M in Et_4NClO_4 and were purged with N_2 before measurement. The stoichiometry of each electron-transfer process was established by wave-height comparisons with known one-electron redox processes. Infrared spectra of compounds dispersed as KBr disks were measured on a Perkin-Elmer series 1600 FT-IR instrument. NMR spectra were measured on Bruker AC200 FT and Bruker AMX400 instruments. All chemical shifts are cited versus the methyl resonance of sodium 3-(trimethylsilyl)-propane sulfonate.

X-ray Crystallography. Cell constants were determined by a least-squares fit to the setting parameters of 25 independent reflections measured on an Enraf-Nonius CAD4 four-circle diffractometer employing graphite-monochromated Mo Kα radiation (0.71073 Å) and operating in the $\omega-2\theta$ scan mode within the range $2° < 2\theta < 50°$. Data reduction was performed with XCAD4[14]

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Table 1. Crystal Data

	$[CuL^1](HCO_3)\cdot(C_4H_3N_2O_3)\cdot 7H_2O$	$[CuL^1](ClO_4)_{1.5}I_{0.5}\cdot(C_8H_{12}N_2O_3)$	$[CuL^1](ClO_4)_2\cdot(C_5H_6N_2O_2)\cdot 3H_2O$
formula	$C_{17}H_{44}CuN_{12}O_{13}$	$C_{20}H_{38}Cl_{1.5}CuI_{0.5}N_{12}O_9$	$C_{17}H_{38}Cl_2CuN_{12}O_{13}$
fw	688.18	770.79	753.03
space group	$P\bar{1}$ (No. 2)	$P\bar{1}$ (No. 2)	$P2_1/n$ (No. 14)[a]
a, Å	8.6441(7)	11.715(1)	7.275(2)
b, Å	9.097(1)	12.108(1)	25.739(4)
c, Å	20.291(2)	13.423(2)	16.352(3)
α, deg	79.122(8)	93.58(1)	
β, deg	79.505(7)	108.33(1)	95.50(1)
γ, deg	71.063(8)	108.82(1)	
V, Å^3	1469.5(2)	1682.1(3)	3048(1)
Z	2	2	4
T, °C	23	23	23
λ, C	0.71073	0.71073	0.71073
μ, cm^{-1}	8.25	12.89	9.73
ρ_{calcd}, g cm^{-3}	1.555	1.522	1.641
$R(F_o)$[b]	0.0514	0.0945	0.0727
$wR2(F_o^2)$[c]	0.1041	0.2315	0.1902

[a] Variant of $P2_1/c$. [b] $R(F_o) = \sum||F_o| - |F_c||/\sum|F_o|$. [c] $wR2(F_o^2) = (\sum w(F_o^2 - F_c^2)/\sum wF_o^2)^{1/2}$.

within the WINGX suite of programs. Structures were solved by direct methods with SHELXS86[15] and refined by full-matrix least-squares analysis with SHELXL97.[16] All calculations were done within the WINGX package of programs.[17] Drawings of molecules were produced with ORTEP3.[18] Crystal data appear in Table 1. Specific refinement details for each structure follow.

$[CuL^1](HCO_3)\cdot(C_4H_3N_2O_3)\cdot 7H_2O$. All non-H atoms were refined with anisotropic thermal parameters. Ligand and barbiturate H-atoms were constrained at calculated positions using a riding model. Water and bicarbonate H-atoms were located from difference maps and then restrained at those positions.

$[CuL^1](ClO_4)_{1.5}I_{0.5}\cdot(C_8H_{12}N_2O_3)$. The relatively low number of observed reflections could not support anisotropic refinement of all non-H atoms. Atoms C1−C5, C11, and C15−C18 were refined isotropically. One of the barbitone ethyl groups was rotationally disordered, and the two contributors C20A and C20B were refined at 50% occupancy. The axially bound perchlorate (Cl2, O8−O11) was restrained to 50% occupancy.

$[CuL^1](ClO_4)_2\cdot(C_5H_6N_2O_2)\cdot 3H_2O$. Non-H atoms were refined with anisotropic thermal parameters, except for disordered perchlorate O-atoms (O8A−O11A/O8B−O11B), which were refined with complementary occupancies and isotropic thermal parameters.

Results and Discussion

Cocrystals of $[CuL^1]^{2+}$. The H-bonding capabilities of the complex $[CuL^1]^{2+}$ are now well-established.[11,19] The DAD H-bonding array of the melamine moiety may be satisfied by a three-point H-bonding structure (Etter motif $R^3_3(12)$[20]) when coupled with heterocycles bearing the complementary ADA pattern. The protonated form of the macrocycle $[Cu(HL^1)]^{3+}$ bears a DDD H-bond array; this disrupts the resulting H-bonding, as shown in Scheme 1 (structure A) where a zwitterionic adduct forms when the

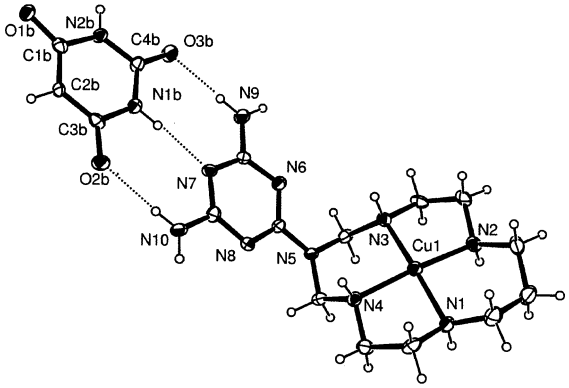
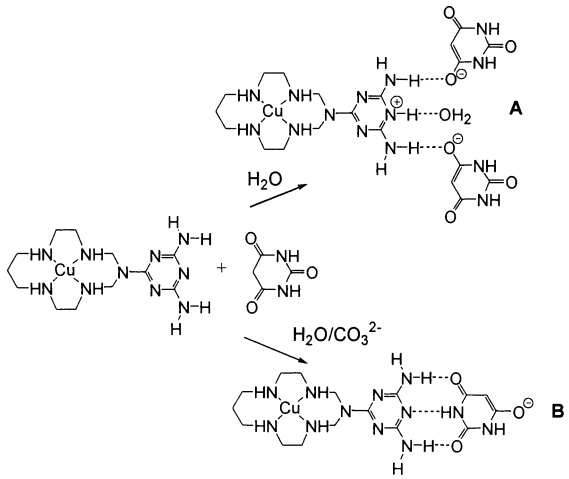


Figure 1. ORTEP plot of the $[CuL^1]^{2+}$/barbiturate adduct (30% probability ellipsoids). Counterions and water molecules omitted. Selected H-bonding contacts: N1B−H1B1···N7 2.04 Å, 174.9° (N1B···N7 2.90 Å); N9−H9A···O3B 2.03 Å, 177.8° (N9···O3B 2.89 Å); N10−H10A···O2B 2.09 Å, 177.2° (N10···O2B 2.95 Å).

Scheme 1



complex is protonated by barbituric acid.[19] We reasoned that if 1 equiv of a weak base was added to a mixture of $[CuL^1]^{2+}$ and barbituric acid, then the DAD/ADA H-bonded adduct (structure B in Scheme 1) should be accessible.

Figure 1 shows the resulting structure where the anticipated three-point H-bonded adduct between $[CuL^1]^{2+}$ and the barbiturate anion has been achieved. The H-bonding distances (N···H and O···H) within this motif lie in the range 2.0−2.1 Å, and the N−H···A angles are close to linear. The melamine and barbiturate rings are essentially coplanar.

This three-pronged H-bonding motif is omnipotent in solid state structural chemistry. A survey of the Cambridge Crystallographic Database revealed that the same DAD/ADA H-bonding motif is found in 97% of all structures where both H-bonding components are present.[21] The protonation sites of the barbiturate anion were identified from difference maps during refinement. As can be seen, the methylene group (C2B) of the parent acid has been singly deprotonated, and a pseudoaromatic heterocyclic ring is formed. The C1B−O1B bond (1.283(7) Å) is somewhat longer than the remaining C−O bonds (C3B−O2B 1.258(7) Å, C4B−O3B 1.226(7) Å) suggesting that most of the negative charge

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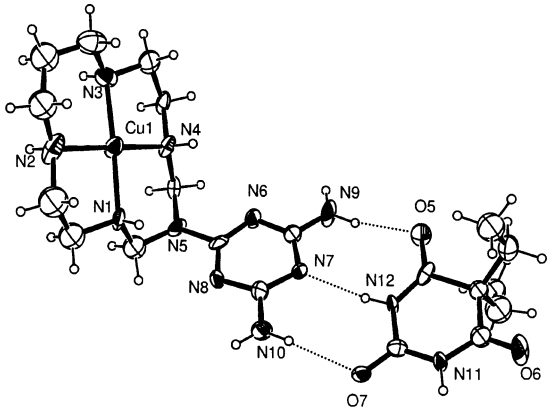

Figure 2. ORTEP plot of the $[CuL^1]^{2+}$/barbitone adduct (30% probability ellipsoids). Counterions and water molecules omitted. Selected H-bonding contacts: N12−H12B···N7 2.05 Å, 160.9° (N1B···N7 2.88 Å); N9−H9D···O5 2.12 Å, 167.6° (N9···O3B 2.96 Å); N10−H10A···O2B 2.22 Å, 157.3° (N10···O2B 3.03 Å).

resides on O1B. The coordination environment of the metal center is tetragonally elongated octahedral with Cu−N bond lengths in the expected range (2.004(5)−2.041(5) Å). Weakly bound aqua ligands (Cu−O 2.357(4) and 2.621(5) Å) occupy the axial coordination sites, with the axial elongation arising from Jahn−Teller distortion of the d^9 electronic ground state. The macrocyclic ring itself adopts the common *trans*-III (*RRSS*) configuration of its N-donors, with two secondary amine protons pointing up and the other two down.[22] This is the most commonly encountered coordination mode in cyclam complexes, and it allows the two six-membered chelate rings to adopt the energetically favorable chair conformation, although one of these rings is distinctly flattened due to the presence of the trigonal planar N-atom (N5). All structures of $[CuL^1]^{2+}$ determined to date possess this conformation. The melamine ring and the CuN_4 plane approach orthogonality (Cu1···N5···N7 113.1°) as a consequence of the steric requirements of the substituted six-membered chelate ring.

Cocrystallization of the charge neutral barbitone with $[CuL^1]^{2+}$ was also achieved. Figure 2 shows the structure of the H-bonded adduct. The three-point H-bonding motif is once again apparent, and the H-bond distances are similar to those in the barbiturate structure. The angles subtended at each H-atom are distorted by about 20° from linearity. This distortion is related to a twisting of the nominally coplanar melamine and barbitone rings (dihedral angle N9−N7−N12−O5 14.9°). Given that the barbiturate anion and barbitone rings present identical H-bonding patterns, the ruffled H-bonding motif identified in this structure is most likely attributable to packing effects. The Cu^{II} environment comprises four macrocyclic Cu−N bonds (2.00(2)−2.01(2) Å) and axially bound iodo (Cu−I 3.121(3) Å) and perchlorate anions (Cu−O 2.72(2) Å), each at half-occupancy.

The thymine cocrystal of $[CuL^1]^{2+}$ was isolated, and its structure is illustrated in Figure 3. In this case, the melamine and thymine rings are close to coplanarity, and the H-bond contacts within the three-point motif are in the range 2.06−2.18 Å. The Cu^{II} environment comprises the four macrocyclic Cu−N bonds (2.004(7)−2.025(7) Å) and axially bound perchlorate ligands (Cu−O3 2.513(7) Å; Cu−O4′ ($x-1$, y, z) 2.597(6) Å). The perchlorate ligand bridges adjacent Cu^{II} centers to form a chain parallel with the *a* axis.

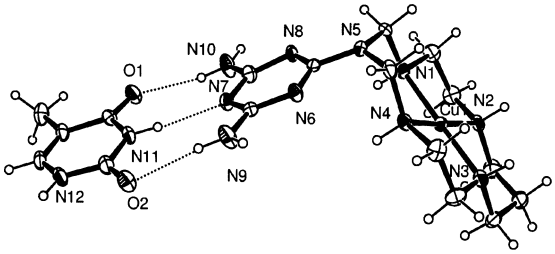

Figure 3. ORTEP plot of the $[CuL^1]^{2+}$/thymine adduct (30% probability ellipsoids). Counterions and water molecules omitted. Selected H-bonding contacts: N11−H11···N7 2.08 Å, 176.1° (N11···N7 2.94 Å); N9−H9C···O2 2.18 Å, 176.0° (N9···O3B 3.03 Å); N10−H10A···O1 2.06 Å, 169.2° (N10···O2B 2.91 Å).

Electrochemical Binding Studies. Solution electrochemical studies were undertaken to test the effectiveness of complexes such as $[CuL^1]^{2+}$ as redox active receptors. The method of electrochemical detection is based on a shift in the host redox potential (ΔE) as a function of guest concentration according to eq 1

$$\Delta E = \frac{RT}{F}\ln\left[\frac{1 + K_{red}[\text{guest}]}{1 + K_{ox}[\text{guest}]}\right] \qquad (1)$$

where K_{ox} and K_{red} correspond to the 1:1 host/guest complex in the divalent and monovalent forms of the receptor, respectively, and the other terms have their usual meaning.[2] The copper center is sensitive to changes at the melamine moiety, since protonation of a ring N on the melamine results in a positive shift in the $Cu^{II/I}$ potential.[11]

Neutral guest molecules chosen for investigation electrochemically were barbitone, thymine, biuret and cytosine. Although succinimide has an ADA H-bonding edge, it is not suitable for electrochemical studies due to its own redox activity. It is reduced to the succinimide radical anion in acetonitrile or DMF, giving an irreversible response, with a cathodic peak near −1.5 V (vs SCE)[23] (about −1.1 V vs Ag/Ag^+ in our own experiments), which overlaps with the $Cu^{II/I}$ potential in these systems. Potentials were measured using either cyclic voltammetry for reversible systems or square wave voltammetry for quasireversible ones. Binding was measured in CH_3CN, DMF, and a 50% aqueous MeCN solution. Water is a very competitive H-bonding solvent, and its presence inevitably results in a decrease in the observed formation constants. However, the use of water in solvent mixtures allows dissolution of a greater range of guest molecules, and studies in aqueous solution are particularly interesting, since few neutral molecule receptors are effective in this medium. For this reason, all electrochemical data are reported in 50% aqueous MeCN.

The electrochemical reversibility of the $Cu^{II/I}$ couples in 50% aqueous MeCN was a useful feature. Copper(II)

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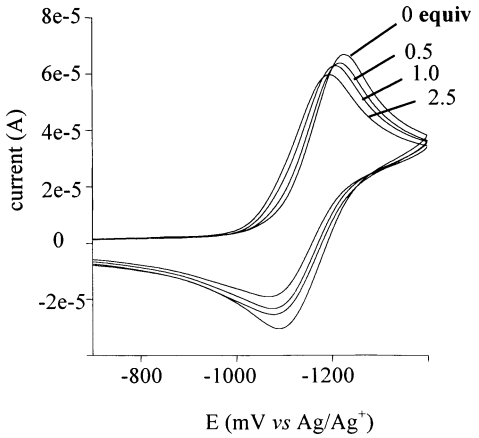

Figure 4. Cyclic voltammograms of $[CuL^1]^{2+}$ upon addition of barbitone (50:50 CH_3CN/H_2O, molar equivalents of barbitone shown).

Table 2. Formation Constants (log K_{ox}/log K_{red}) for 1:1 Adduct Formation with the Oxidized and Reduced Receptor Determined from Electrochemical Titrations (50% Aqueous MeCN)

	$[CuL^1]^{2+}$	$[CuL^2]^{2+}$
	Barbitone	
log K_{red}	2.3(1)	nb
log K_{ox}	1.5(5)	nb
	Thymine	
log K_{red}	2.9(1)	nb
log K_{ox}	nb	nb
	Biuret	
log K_{red}	3.1(2)	nb
log K_{ox}	2.6(2)	nb
	Cytosine	
log K_{red}	nb	2.6(1)
log K_{ox}	nb	2.0(4)

[a] nb indicates no apparent or insignificant binding constant.

tetraaza-macrocyclic complexes invariably exhibit irreversible electrochemistry in aqueous solution. However, as seen in Figure 4, the responses are reversible. It would appear that the acetonitrile present slows disproportionation of the monovalent $[CuL^1]^+$ to a negligible rate on the voltammetric time scale.

The voltammograms show the presence of a single couple that shifts anodically with added guest, which is indicative of weak binding.[2] The guest-induced anodic shifts are consistent with the Cu center being most sensitive to H-bond donation at the apical triazine ring N-atom by the N−H moiety of the guest, akin to protonation.[11] The triazine NH_2 groups, which act as H-bond donors to the guest carbonyl O-atoms, should exert an electron-withdrawing influence on the host and hence a cathodic shift on the $Cu^{II/I}$ potential. The experimental data suggest that this influence is very weak by comparison, presumably due to the remoteness of these groups from the metal center relative to the apical triazine ring N-atom.

Examination of the formation constants presented in Table 2 shows that the systems are indeed bound quite weakly, with values on the order of 10^2 M^{-1} for K_{red} and 10 M^{-1} for K_{ox}. Binding constants are of the same order of magnitude for barbitone in both pure acetonitrile (data not shown) and the 50% acetonitrile/water solvent mixture (Table 2). This is notable, as the competitive nature of water might have removed all H-bonding between the host and guest. Evidently, the three-point H-bonding between the melamine group and barbitone is sufficiently strong that as much as a 50% aqueous solvent mixture does not greatly affect the outcome. Higher concentrations of water led to irreversibility of the $Cu^{II/I}$ couple so this could not be examined in greater detail. Furthermore, this solvent mixture was found to be effective for all the other guest molecules investigated, so other ratios of MeCN to water were not considered. Experiments were also conducted with the guest molecules cytosine and biuret. Biuret, which is effectively a dimer of urea, does possess an ADA pattern, and binding to $[CuL^1]^{2+}$ was indeed apparent. In contrast, cytosine has a DAA H-bonding pattern and as such is incompatible with $[CuL^1]^{2+}$. Indeed, titrations with cytosine gave no significant shifts in the $Cu^{II/I}$ potential, suggesting that no binding is occurring. Similarly, titration of the protonated complex $[Cu(HL^1)]^{3+}$ (DDD) with ADA guests at low pH gave no significant change in the redox potential.

The ammeline appended analogue $[CuL^2]^{2+}$ demonstrated a distinctly different selectivity. If present as the keto tautomer, $[CuL^2]^{2+}$ has an ADD hydrogen bonding pattern. Titration with barbitone (ADA) showed no shift in the $Cu^{II/I}$ redox potential. Titration of $[CuL^2]^{2+}$ with cytosine (DAA) results in a significant anodic shift and measurable formation constants. On this basis, we conclude that $[CuL^2]^{2+}$ is indeed present in its keto form, which was also identified in the X-ray structure of the complex.[11]

Transmetalation. In order to validate the electrochemically determined binding constants, a complementary technique was pursued for the characterization of the H-bonded adducts in solution: in this case, NMR spectroscopy. For this reason, the diamagnetic Zn^{II} complexes of L^1 and L^2 were prepared by reductive transmetalation of their Cu^{II} analogues. Pentaaza macrocycles such as L^1 are unstable in the absence of a bound metal. This is due to the susceptibility of the saturated N−C−N (aminal) linkages within the six-membered chelated ring toward hydrolysis.[24] For this reason, the ligands L^1 and L^2 were originally synthesized via Cu^{II} template reactions and isolated as their ensuing complex. Other metal templates proved problematic, so a diamagnetic metal (Zn^{II}) was introduced via reductive transmetalation. Traditional methods (Zn/HCl, Na_2S) of reduction were too harsh, but the transmetalation procedure of Lampeka and coworkers utilized relatively mild conditions of zinc amalgam in dry acetonitrile under nitrogen.[13]

NMR Titrations. NMR spectroscopy is commonly used for the determination of small binding constants. It may also be used to identify which groups, if any, are actually participating in H-bond formation. In the crossover from the paramagnetic Cu^{II} to the diamagnetic Zn^{II} analogues, we assume that the inductive effect of a complexed Zn^{II} ion should be comparable to that of the Cu^{II} complex, so binding constants determined electrochemically and by NMR should be similar. Both metals are divalent, and of a similar ionic radius (0.72 Å for Cu^{2+}, 0.74 Å for Zn^{2+})[25] so their electronic

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influences on the guest should be quite similar. It is assumed that a similar solution structure is retained upon transmetalation, with solvent molecules occupying the axial coordination sites and the macrocycle encircling the metal. The NMR data are consistent with this, with a mirror plane symmetry element apparent from the ^{13}C NMR spectrum of $[ZnL^1]^{2+}$. Asymmetry of the ammeline ring in $[ZnL^2]^{2+}$ renders all C-atoms magnetically inequivalent. Nevertheless, the positions of the corresponding pairs of ^{13}C resonances match those of higher symmetry $[ZnL^1]^{2+}$, and the *trans* isomer of $[ZnL^2]^{2+}$ is again assigned on this basis.

The melamine proton signals of $[ZnL^1]^{2+}$ appearing at around 6 ppm were used as a signal of H-bonding interactions. This is a relatively broad peak, due to proton exchange processes. Binding was measured in acetonitrile, acetone, and DMSO. The titration procedure was essentially the same as that employed in the electrochemical procedures. The guest molecule was added incrementally and the chemical shift observed. A titration curve was generated plotting guest concentration against chemical shift, and the resulting curve was fitted using a nonlinear least-squares analysis to eq 2[26] to generate the 1:1 complex stability constant:

$$\Delta\delta = \frac{\Delta\delta_{max}}{[R_0]}\left[\frac{[S_0]}{2} + \frac{\Sigma}{2}\left[1 - \sqrt{1 + \frac{[S_0]^2 - 2[S_0]\Psi}{\Sigma^2}}\right]\right] \quad (2)$$

$$\Sigma = [R_0] + \frac{1}{K_a}$$

$$\Psi = [R_0] - \frac{1}{K_a}$$

where $\Delta\delta$ is the observed change in chemical shift, $\Delta\delta_{max}$ is the saturation value, S_0 and R_0 are the total concentrations of guest and receptor, and K_a is the binding constant.

As the concentration of guest increased, the melamine proton peak shifted downfield and broadened (Figure S1). Downfield ^1H NMR shifts occur due to electrostatic attraction of the electronegative acceptor, in this case a carbonyl group on the guest molecule.[27] Broadening can be attributed to exchange processes again. A sample titration curve can be seen in Figure 5 with succinimide as the guest, and the formation constant data appear in Table 3. All curves obtained were of a similar shape. It is apparent that there is no leveling off after 1 equiv of guest is added, which can be attributed to the formation of a weakly bound complex. This is typical for H-bonded adducts in strongly polar solvents.[28] The binding constants in acetonitrile and acetone are very similar, particularly for barbitone, reflecting the similar polarity and hydrogen bonding ability of these solvents. When DMSO is the solvent, much reduced binding constants were apparent, reflecting its greater competitiveness as a H-bond acceptor than MeCN or acetone. The binding

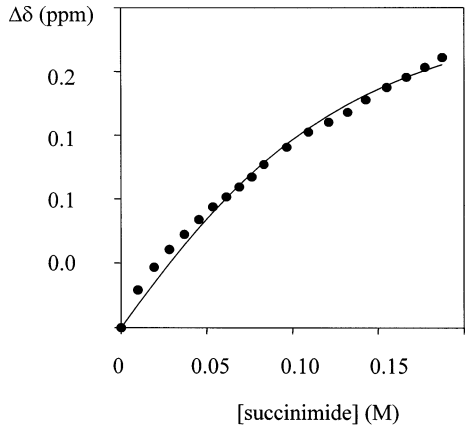

Figure 5. NMR titration curve (melamine ^1H resonance) of $[ZnL^1]^{2+}$ with succinimide in CD_3CN. Curve shows fit to eq 2.

Table 3. Formation Constants (log K_a) for 1:1 Adduct Formation Determined from NMR Titrations of $[ZnL^1]^{2+}$ (0.1 M solutions) with Barbitone and Succinimide

	CD_3CN	acetone-d_6
	Barbitone	
log K_a	1.9(3)	2.0(3)
δ_{max} (ppm)	0.7(1)	0.8(1)
	Succinimide	
log K_a	1.2(1)	1.7(3)
δ_{max} (ppm)	0.3(0.5)	0.4(0.5)

constants obtained from our NMR titrations of the Zn^{II} complexes are comparable to those obtained for the Cu^{II} complexes (K_{ox}) electrochemically. For example, barbitone affords similar stability constants for both techniques, with log K_{ox} of 2.0 being determined for $[CuL^1]^{2+}$ and barbitone in 100% acetonitrile (data not shown), compared with log K 1.9 for the reaction between $[ZnL^1]^{2+}$ and barbitone in the same solvent. The remaining host-guest complexes could not be studied by NMR and electrochemistry in the same solvent system, so no other direct comparisons may be made using these complementary techniques.

The macrocycle $[ZnL^1]^{2+}$ exhibits a slightly larger binding constant for barbitone than succinimide, even though both possess the ADA pattern. The preference may be due to the five-membered ring of succinimide, which is likely to prevent the carbonyl groups from a linear alignment with the melamine primary amines. It was also shown that the protonated complex $[Zn(HL^1)]^{3+}$ (DDD pattern) gave no change in chemical shift upon addition of guest molecules with an ADA H-bonding array.

The ammeline analogue $[ZnL^2]^{2+}$ has also been synthesized, by the same simple method already detailed. Solubility constraints meant that NMR studies of complementary molecules such as cytosine could not be undertaken in the solvents available to us. However, titration of $[ZnL^2]^{2+}$ (ADD H-bonding array) with incompatible guests such as barbitone and succinimide (ADA) gave no significant variation in the triazine ^1H NMR resonances.

Conclusions

The triazine-substituted macrocyclic complexes studied here have been shown to be effective neutral molecule

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receptors. Crystallographic evidence shows the presence of the anticipated DAD/ADA hydrogen bonding motif in the solid state. Solution binding studies by both electrochemistry and NMR spectroscopy have shown that addition of guests with complementary hydrogen bonding patterns leads to a perturbation of the electronic environment of the receptor, even in the presence of highly competitive solvents, including water. Communication between the hydrogen bonding triazine moiety and the macrocyclic redox active center has been demonstrated. Negligible shifts in redox potential or NMR chemical shift are observed for incompatible guest molecules, indicating the selectivity of the receptors. Although these receptors are not sufficiently sensitive to be employed in the detection of submicromolar concentrations, the fact that they remain able to detect the presence of charge neutral guests at millimolar concentrations in mixed aqueous solvents is notable. The selectivity that we have seen may be rationalized on the basis of a match or mismatch between the H-bonding preferences of the host and guest.

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Supporting Information Available: ^{1}H NMR spectra of $[ZnL^{1}]^{2+}$ as a function of added barbitone. Crystallographic information in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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