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Hydrogen Bonding Cavities Regulating Redox Behavior and Binding of Metal-Bound Ligands

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Binding of 3,5-di-*tert*-butyl-1,2-benzochatechol (H_2DTBC) at Zn^{II} complexes of a tetradentate, tripodal ligand L is significantly enhanced (36–4.6 × 10^4 fold), and its reduction potential shifted (90–270 mV) to more positive values by introducing one to three amino hydrogen bond donors. The structure of one of the [(L)Zn(DTBC)] complexes is reported and shows intramolecular N–H···O hydrogen bonding between the ligand-based amino group and the Zn^{II}-bound chatecholate, which provides an explanation for the observed behavior.

Several metalloenzymes involved in important redox processes such as respiration, photosynthesis, and activation of dioxygen have highly conserved hydrogen bonds in their active sites.[1] Some of these interactions feature a metal-bound redox-active molecule and protein residues or solvent molecules. In some cases, these hydrogen bonds appear to be linked to the site function because, without them, the reactivity is greatly reduced or altered; consummate examples are cytochromes P450.[2] Metal complexes with hydrogen bonding features have been the subject of considerable current interest in connection with modeling of the chemistry of these redox metalloenzymes.[1a,3−10] These metal complexes have elucidated several important roles associated with the hydrogen bonding environments. These include the ability to tune the reduction potentials of the metal center(s)[3−5] and the stability of catalytically important intermediates.[1a,6−9] The incorporation of noncoordinated groups close to the metal binding site has also proved to be a powerful approach to significantly improving the functional properties of synthetic complexes for O_2 activation[10] and other chemistry.[11,12] Synthetic molecules featuring hydrogen bonding groups and recognition of their complementary redox-active partners have been receiving considerable attention also in connection with supramolecular chemistry and understanding biological electron-transfer processes.[13]

It is difficult to dissect hydrogen bond effects from other ligand effects and from the charge-transfer processes between the redox-active metal and substrate. Thus, the extent to which hydrogen bonding environments affect the electrochemical behavior of metal-bound redox-active ligands, which is fundamental to this diverse chemistry, is not known.

We assess here this aspect by using structurally homologous Zn^{II} complexes **0**−**3** with 6-aminopyridyl hydrogen

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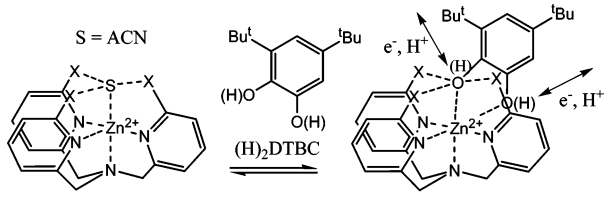
Scheme 1



X = 3H, $[(TPA)Zn(S)]^{2+}$ **0**
X = 2H, NH_2, $[(L^{Am1})Zn(S)]^{2+}$ **1**
X = H, $2NH_2$; $[(L^{Am2})Zn(S)]^{2+}$ **2**
X = $3NH_2$; $[(L^{Am3})Zn(S)]^{2+}$ **3**

bond donors rigidly preorganized to interact with an electroactive substrate coordinated to the Zn^{II} center (Scheme 1). Because Zn^{II} ions are redox-inactive for the relevant experimental conditions, their use simplifies the interpretation of electrochemical data. The substrate we selected was 3,5-di-*tert*-butyl-1,2-benzocatechol (H_2DTBC) because it possesses a biologically important catechol moiety that can undergo two one-electron-oxidation processes to produce 3,5-di-*tert*-butyl-1,2-benzosemiquinone (DTBSQ) and 3,5-di-*tert*-butyl-1,2-benzoquinone (DTBQ) and binds strongly to metal ions, including Zn^{II}.

The formation of LZn/DTBC adducts (L = TPA, L^{Am1-3}) was studied by UV−vis in acetonitrile (ACN) solutions containing 0.1 M tetrabutylammonium tetrafluoroborate ($TBABF_4$), the supporting electrolyte used in the electrochemical studies (see below). The spectrum of H_2DTBC treated with $Me_4NOH{\cdot}6H_2O$ to give $HDTBC^-$ [14] changes in the presence of 1 equiv of $[(L)Zn(ACN)](ClO_4)_2$, with no further changes observed in the presence of more LZn^{II} indicating the formation of 1:1 adducts. Definitive proof for the formation of 1:1 LZn/DTBC adducts was obtained by X-ray crystallography. The structure of $[(L^{Am1})Zn(DTBC)]$ shows two crystallographically independent molecules where the Zn^{II} center is in a distorted octahedral geometry and $DTBC^{2-}$ acts as a bidentate ligand. The average C−O distance of 1.33 Å is characteristic of DTBC complexes.[15] Importantly, the structure shows the formation of intramolecular N−H···O hydrogen bonding between the ligand aminopyridyl unit and the Zn^{II}-bound DTBC [N···O distances of 3.059 Å for molecule 1 (not shown) and 3.002 Å for molecule 2 (Figure 1) are essentially identical with those found in several redox metalloenzymes[1]]. It is interesting to note that the O atom involved in intramolecular hydrogen bonding is the O2 oxygen [O(24) in the structure], which is more basic than O1[16] [O(14) in the structure].

The cyclic voltammograms (CVs) were carried out under N_2 in ACN in the presence of 0.1 M $TBABF_4$. The complexes were formed in situ by reacting equimolar amounts of the appropriate tripodal ligand L,[17] $Zn(ClO_4)_2{\cdot}6H_2O$, and $(Me_4N)HDTBC$ in ACN. The CVs of

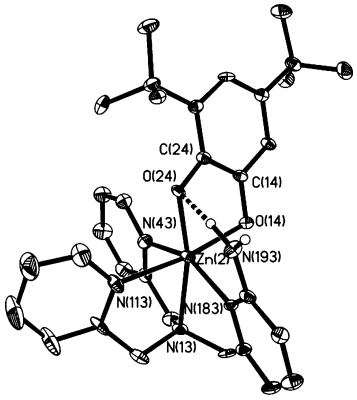


Figure 1. Thermal ellipsoid plot (30% probability) showing the Zn^{II} coordination environment of $[(L^{Am1})Zn(DTBC)]$. C-bound H atoms and solvent molecules are omitted for clarity. Selected bond lengths (Å): Zn(2)−N(13) 2.257(5), Zn(2)−N(43) 2.216(4), Zn(2)−N(113) 2.221(5), Zn(2)−N(183) 2.136(6), Zn(2)−O(14) 2.047(3), Zn(2)−O(24) 1.966(4).

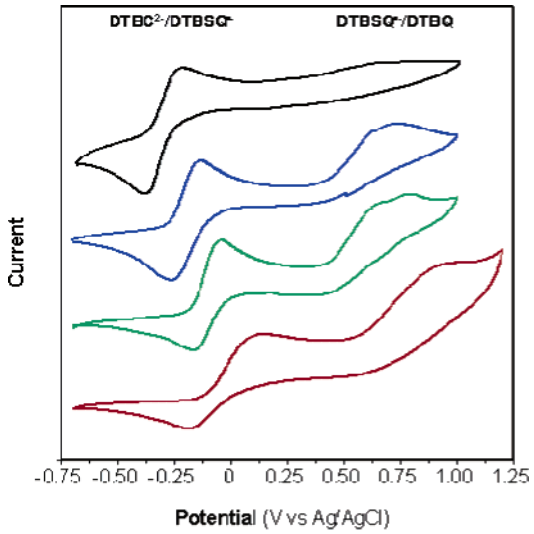


Figure 2. CVs of [(TPA)Zn(DTBC)] (black), $[(L^{Am1})Zn(DTBC)]$ (blue), $[(L^{Am2})Zn(DTBC)]$ (green), and $[(L^{Am3})Zn(DTBC)]$ (red) in an ACN solution containing 0.1 M $TBABF_4$. Scan rate = 100 mV s^{-1}.

the LZn/DTBC (1:1) adducts show a quasi-reversible wave at −0.29 (L = TPA), −0.20 (L^{Am1}), −0.11 (L^{Am2}), and −0.02 V (L^{Am3}) vs Ag/AgCl corresponding to the Zn^{II}-bound catecholate ($DTBC^{2-}$) to semiquinone ($DTBSQ^{\bullet-}$) couple (Figure 2). A second irreversible oxidation occurs at 0.64 (TPA), 0.73 (L^{Am1}), 0.78 (L^{Am2}), and 0.94 V (L^{Am3}), which can be assigned to the semiquinone to quinone redox process.[18a] As previously suggested in complexes of these and other dioxolene ligands, the nonreversible nature of this couple can be ascribed to the instability of the LZn/DTBQ adduct.[18] The $DTBC^{2-}/DTBSQ^{\bullet-}$ redox couple is shifted by 90 mV to more positive potentials even in the presence of only one amino hydrogen bond donor and by as much as 270 mV in the presence of three. The combined effect of Zn^{II} binding and hydrogen bonding is a remarkable 1.15−1.33 V shift to more positive potentials (metal-free redox behavior is reported in ref 14), presumably due to synergistic effects because similar, but less pronounced, effects have

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been obtained with either labile metal binding or hydrogen bonding. For example, binding to a more strongly Lewis acidic metal such as Sc^{III} causes a positive shift in the reduction potential of an NAD^+ analogue of ca. 0.6 V.[13d] Reduction of nitrobenzene derivatives in the presence of stronger hydrogen bond donors such as arylureas in solvents where hydrogen bonding between the urea and nitro functionalities takes place results in positive shifts in the potential of the nitrobenzene$^{0/-}$ couple of ca. 0.10−0.20 V.[13a] A similar effect is exerted on the $DTBSQ^{\bullet-}$/DTBQ redox couple. It should be noted that the 6-amino groups are electron-donating and sterically hinder the metal binding site, which presumably should weaken and hinder catecholate binding. Thus, the hydrogen bonds formed with the amino groups must provide a significant stabilization of the reduced catecholate ligand: at least 8.7 (L^{Am1}), 17.4 (L^{Am2}), and 26.0 kJ mol^{-1} (L^{Am3}). Notably, these data also mean that the hydrogen bonding groups of L^{Am1-3} enhance the binding of $DTBC^{2-}$ to the Zn^{II} center by ca. 36-fold (L^{Am1}), 1.3×10^3-fold (L^{Am2}), and 4.6×10^4-fold (L^{Am3}).[19] This result is in excellent agreement with studies carried out on heme metalloproteins in which hydrogen bonding features of the active site are reported to enhance metal−dioxygen binding.[20] It helps to explain why N−H hydrogen bond donors are able to stabilize synthetic metal−peroxo units.[8,9,21,22] Especially relevant is the work by Masuda et al. where the same ligand framework and N−H hydrogen bond donors have been shown to stabilize Cu−peroxo[8,21] and even Zn−peroxo species.[22] Also, it shows that the cooperation of hydrogen bond donors and metal coordination can be exploited to significantly enhance binding of ligands to metal centers, particularly if they are redox active. For comparison, aminopyridyl substituents increase phosphate binding to a mononuclear Co^{III} complex by 33-fold[23a] and to a Zn^{II} complex by 8-fold.[23b]

It is important to note that only mixtures containing equimolar amounts of H_2DTBC and $[(L^{Am2,3})Zn(ACN)]^{2+}$ afford a $DTBC^{2-}$/$DTBSQ^{\bullet-}$ redox couple close to that obtained using $HDTBC^-$. This is consistent with amino hydrogen bond donors progressively increasing the acidity of the protonated catechol.[24] This result is significant because many electron-transfer reactions, including those involved in O_2 activation, are linked to transportation of proton equivalents to the metal-bound species.

In summary, this work has evaluated the extent to which N−H hydrogen bond donors affect redox potentials and binding of electroactive substrates bound to a metal center using synthetic modeling chemistry. For Zn-DTBC and three N−H donors, the effect was a 270-mV shift to more positive reduction potentials and 4.6×10^4-fold enhanced binding. Similar effects may operate in redox metalloproteins; however, they are difficult to quantify because of other ligand effects and charge-transfer processes between the redox-active metal and ligand. This result also suggests that the combination of metal binding and multiple hydrogen bonding to enhance the binding of external molecules to metal centers may be particularly effective for electroactive ligands and stabilizing reactive species.

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Supporting Information Available: X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Obtained from the relationship $K_a(\{(L)Zn\})/K_a(\{(TPA)Zn\}) = \exp[(nF/RT)(E_{1/2}(\{(L)Zn\}) - E_{1/2}(\{(TPA)Zn\}))]$; $T = 293$ K.

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(24) The amino H-bonding groups in $[(L^{Am1-3})Zn(OH_2)]^{2+}$ progressively increase the acidity of the $Zn-OH_2$ unit compared to those in $[(TPA)Zn(OH_2)]^{2+}$.[17]