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Phenylamino Derivatives of Tris(2-pyridylmethyl)amine: Hydrogen-Bonded Peroxodicopper Complexes

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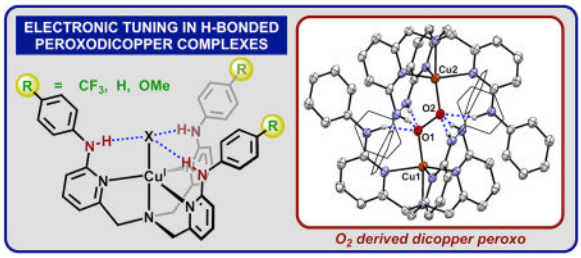
Abstract

A series of copper complexes bearing new 6-substituted tris(2-pyridylmethyl)amine ligands (L^R) appended with NH(*p*-R-C_6H_4) groups (R=H, CF_3, OMe) were prepared. These ligands are electronically tunable ($\Delta E_{1/2}$ = 160 mV) and $Cu^I(L^R)^+$ complexes react with oxygen to form hydrogen bonded (*trans*-1,2-peroxo)dicopper species.

Graphical abstract



Copper-containing oxygenase and oxidase enzymes are an important class of metalloenzymes whose diverse O_2 activation pathways facilitate a wide variety of biological functions.[1] Although challenging to study in the native enzymes, the study of O_2 binding and activation by copper within easily modifiable synthetic systems has greatly expanded our understanding of these metalloenzymes,[2] and the first crystallized Cu-O_2 adduct was the (*trans*-1,2-peroxo)dicopper complex of the tris(2-pyridylmethyl)amine (tpa) ligand.[3] In the nearly 30 years since that structure, modifications to tpa and similar ligand frameworks have been targeted to elucidate the key factors responsible for O_2 binding and activation. Although critical to the function of many metalloenzymes,[4] the impact of secondary coordination sphere hydrogen bonding (H-bonding) interactions on copper-oxygen species is not well understood.[5] For example, H-bonding interactions have been demonstrated to either stabilize[6] or destabilize[7] Cu-O_2(H) adducts. For this reason, synthetic systems bearing tunable second sphere H-bonding groups provide a facile means to study their influence on Cu-O_2 binding and activation.

†Electronic Supplementary Information (ESI) available: Synthetic and experimental procedures and spectral data. CCDC 1584330 and 1584331. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx000

Our lab recently introduced the tris(6-hydroxyl-2-pyridylmethyl)amine (H_3thpa) ligand that incorporates three –OH groups within the secondary sphere of tpa (Fig. 1A).[8] The pendent –OH groups are potent H-bond donors to metal-coordinated substrates and facilitate proton and electron transfer reactions.[9] However, these complexes underwent facile formation of dinuclear copper species in the presence of weak bases, which limited investigations of subsequent reactivity. To overcome this limitation, we targeted pendent phenylamino groups as less acidic, sterically protected H-bond donors (Fig 1A).[10] In contrast to previously reported –NHCO^{t}Bu substituted tpa variants, the phenylamino group provides both steric and electronic flexibility that allows them to act as highly tunable H-bond donors. In this communication we present a series of aniline-appended tripodal ligands that feature highly directed H-bonding interactions of varied acidity and highlight the design concept by demonstrating H-bond dictated O_2 reactivity.

The ligand tris(6-phenylamino-2-pyridylmethyl)amine (L^H) was prepared via a Buchwald-Hartwig coupling of tris(6-bromo-2-pyridylmethyl)amine (Br_3tpa) with aniline, $Pd(OAc)_2$, and *rac*-BINAP. The addition of CuCl to L^H in THF afforded the yellow complex Cu(L^H)Cl (**1^H**) in 59% yield after 48 h. A crystal of **1^H** suitable for X-ray diffraction was grown by layering pentane over a concentrated toluene solution at −30°C (Fig 1C). The solid-state structure revealed C_3-symmetry (R-3 space group) with directed H-bonds from the pendent –NHPh units to the Cl ligand (N–Cl: 3.311(4) Å). These H-bonds are significantly longer than the previous Cu(H_3thpa)Cl complex bearing pendent –OH groups (N_{avg}–Cl: 3.048 Å) consistent with weaker H-bond interactions.[8] In addition, the Cu–N_{axial} and Cu–Cl bonds in **1^H**, at 2.252(4) Å and 2.3398(14) Å respectively, are shortened compared to Cu(H_3thpa)Cl (2.283(2) Å and 2.5661(6) Å respectively). Overall, the phenylamino groups in **1^H** provide a sterically protected pocket for the Cl ligand while allowing for further electronic tuning by modifying the identity of the aniline.

Two ligand derivatives featuring electronically distinct, yet sterically similar H-bond donors were prepared. 4-Trifluoromethylaniline and 4-methoxyaniline afforded ligands L^{CF3} and L^{OMe} respectively, which were metalated with CuCl to provide Cu(L^{CF3})Cl (**1^{CF3}**) and Cu(L^{OMe})Cl (**1^{OMe}**). The electronic influence of each ligand variant was interrogated by analysis of the $Cu^{I/II}$ redox couple (Fig 1B). Complex **1^H** exhibits a reversible $Cu^{I/II}$ redox couple at −470 mV vs Fc (CH_2Cl_2; 0.1 M NBu_4PF_6). This value is shifted to more negative potentials relative to the –OH complex Cu(H_3thpa)Cl (−365 mV vs Fc), consistent with increased electron releasing properties of L^H than H_3thpa. The $Cu^{I/II}$ redox couple in **1^{OMe}** features the most reducing Cu center at −510 mV vs Fc. The electronically deficient **1^{CF3}**, however, exhibits a $Cu^{I/II}$ redox couple at −350 mV vs Fc, which highlights the electronic tunability of the L^R ligands with simple substitution on the parent aniline. To contextualize these electrochemically obtained values with a well-defined metric, the potential difference of **1^{CF3}** (120 mV) and **1^{OMe}** (−40 mV) from the parent aniline (**1^H**) were plotted against Hammett values (*p*-substitution) of 0.54 and −0.27 respectively (see SI). The electrochemical shifts show a good correlation (R^2 = 0.98) with these Hammett values, indicating that they may be used to provide a predictive measure ligand field effects within the tpa scaffold.

The electronic variability in the L^R ligand series was also evident by ^{1}H NMR and IR spectroscopy. All three complexes are C_3-symmetric by ^{1}H NMR spectroscopy (CD_2Cl_2) and show a significantly downfield shifted –NH resonance consistent with H-bonding interactions between the –NH and the Cl ligand. The –NH peak appears at δ=9.88 in **1^{H}** whereas it shifts downfield (δ=10.17) in **1^{CF3}** and upfield (δ=9.72) in **1^{OMe}**. The magnitude of the two shifts, +0.29 and −0.16 respectively, are again consistent with the expected proportion based on Hammett parameters (R^2 = 0.99, see SI). The weakening of the –NH bond upon H-bonding is also evident by infrared spectroscopy (CH_2Cl_2) where the –NH stretching frequency shifts from 3431 cm^{-1} for L^H to 3223 cm^{-1} in **1^{H}**. However, the value of the –NH stretch for **1^{CF3}** and **1^{OMe}** does correlate directly with the Hammett value. The –NH stretch in **1^{OMe}** shifts to lower energy (3220 cm^{-1}) consistent with a stronger H-bond interaction, while the –NH stretch in **1^{CF3}** falls between **1^{H}** and **1^{OMe}** at 3221 cm^{-1}. The IR data demonstrate the difficulty of assigning trends in a complex system where electronic character of the metal and M-X unit is highly coupled to both H-bond donor strength and H-bond acceptor strength.

The –NHPh appended tpa derivatives provide a tunable framework for studying O_2 binding to Cu and the resulting H-bonded (*trans*-1,2-peroxo)dicopper complexes. The complex $[Cu^I(L^H)]BAr'$ (BAr'= $[B(C_6F_5)_4]^-$) was prepared by mixing L^H and $Cu(MeCN)_4BAr'$ in CH_2Cl_2 under an inert atmosphere. ^{1}H NMR spectroscopy was used to verify formation of a C_3-symmetric Cu(I) complex. Cooling a CH_2Cl_2 solution of $[Cu^I(L^H)]BAr'$ to −70°C and introducing dry O_2 afforded the (*trans*-1,2-peroxo)dicopper complex $[(Cu(L^H))_2(O_2)][BAr']_2$ (**2^{H}**). The reaction was confirmed by a color change in solution (colorless to brown) and the appearance of a band at 457 nm (ε= 3000 $M^{-1}cm^{-1}$) in the electronic absorption spectrum, assigned as the oxygen to copper ligand-to-metal charge transfer (LMCT) band. This contrasts with the unsubstituted complex $[(Cu(tpa))_2(O_2)][PF_6]_2$ which exhibits a primary LMCT band at 525 nm (ε= 11500 $M^{-1}cm^{-1}$) and a shoulder at 590 nm (ε= 7600 $M^{-1}cm^{-1}$).[3] In **2^{H}** we propose that the directed H-bonding interactions to the peroxide unit reduces peroxide electron donation into Cu. This effect weakens the Cu–O bond and results in a hypsochromic shift of the LMCT. Furthermore, the hypochromic shift and loss of the shoulder band in **2^{H}** was also observed by Masuda and co-workers in a similar H-bonded system and was postulated to be due to decreased rotational freedom of the peroxo unit.[5f] Complex **2^{H}** was subjected to additional spectroscopic characterization.[11] The EPR (X-band) spectrum for **2^{H}** is silent, consistent with other S=1 integer spin (*trans*-1,2-peroxo)dicopper complexes. Upon warming to room temperature, solutions of **2^{H}** convert to a green, EPR active species, suggesting decomposition to monomeric Cu(II) byproducts. The UV-Vis and EPR data were corroborated by solid-state characterization of **2^{H}**.

A crystal of **2^{H}** suitable for X-ray diffraction was grown in CH_2Cl_2 in a −80° freezer under an atmosphere of oxygen over 3 days (Fig 2B), constituting the first crystallographically characterized H-bonded (*trans*-1,2-peroxo)dicopper complex. For each 'Cu(L^H)' in **2^{H}** only one –NHPh group engages in H-bonding with the proximal oxygen of the peroxo unit (N5–O1: 2.723(7) Å) while the other two –NHPh groups engage the distal oxygen (N6–O2: 2.859(7) Å and N7–O2: 2.851(7) Å). Previous examples of H-bonded Cu-O_2 species have shown that H-bonding to the proximal oxygen generally increases stability of the species

while H-bonding to the distal oxygen decreases stability.[5g] **2^{H}** contains both proximal and distal H-bonds and stable in solution at −70°C for at least 8 hours, consistent with a net stabilizing effect to the O–O unit. The weakening of the Cu–O bond covalency in **2^{H}**, observed by UV-Vis, was also corroborated by the solid-state data. The Cu–O bond at 1.902(3) Å is elongated compared to the unsubstituted complex $[(Cu(tpa))_2(O_2)][PF_6]_2$ (1.852(4) Å). The O–O bond in **2^{H}** (1.477(5) Å) is also elongated compared to the parent tpa complex (1.433(9) Å). Although the O–O bond might be expected to shorten as a result of H-bonding interactions with the peroxide,[5e, 5f] additional structural factors may be responsible for the bond elongation. The steric profile provided by the –NHPh groups on L^H limit the possible interatomic distance between Cu centers. The Cu···Cu distance in **2^{H}** (4.691(1) Å) is 0.3 Å longer than that observed for $[(Cu(tpa))_2(O_2)][PF_6]_2$ (4.358(3) Å). Despite these steric considerations, stability may also be augmented by **π-π** interactions between the pendent –NHPh groups and the opposing pyridine rings (**π-π** distance: 3.4–3.6 Å).

The electronic tuning provided by L^{CF3} and L^{OMe} regulates the energy of the O to Cu LMCT. $[Cu(L^{CF3})]BAr'$ and $[Cu(L^{OMe})]BAr'$ readily bind O_2 at −70°C to form the analogous (*trans*-1,2-peroxo)dicopper complexes $[(Cu(L^{CF3}))_2(O_2)][BAr']_2$ (**2^{CF3}**) and $[(Cu(L^{OMe}))_2(O_2)][BAr']_2$ (**2^{OMe}**). While the series of complexes (**2^{R}**) are all brown in solution, the LMCT band shifts as a function of the electronic character at the metal.[12] **2^{CF3}** features a 7 nm hypsochromic shift of the LMCT, while **2^{OMe}** features a 3 nm bathochromic shift from the parent **2^{H}**. The observed shifting of the LMCT contrasts with previously reported substituted tpa ligands, where the addition of 4-OMe groups to the pyridine backbone had *no* effect on the LMCT.[13] In **2^{R}**, the shift of the LMCT bands is in accordance with the ligands' respective electronic (Hammett) parameter ($R^2 = 0.99$, see SI) and may be a product of both the Cu effective charge *and* H-bond donor strength. The oxidation potential of the halide-free $[Cu^I(L^R)]BAr'$ complexes, obtained by square-wave voltammetry, provided an additional description of the electronic character at Cu. $[Cu(L^H)]BAr'$ in MeCN (0.1M NBu_4PF_6) exhibits an irreversible oxidation event at +110 mV vs Fc. The associated L^{CF3} and L^{OMe} Cu(I) complexes feature redox potentials shifted by +90 mV and −20 mV from L^H, respectively. Importantly, these values are significantly more positive than $[Cu(tpa)]PF_6$ (E_{ox} = −386 mV vs Fc, see SI). O_2 binding to $[Cu(L^{CF3})]BAr'$ at potentials as high as +200 mV vs Fc contrasts with most known Cu(I)-tpa variants that exhibit diminished O_2 reactivity at more positive potentials.[14] These data indicate that the Cu(I) centers in $[Cu(L^R)]BAr'$ are only modestly reducing and might be anticipated to engage in very weak binding to O_2. To account for the facile O_2 reactivity, we propose that the H-bonding groups on L^R provide additional stabilizing interactions for O_2 binding.

A sterically identical ligand to L^H with no H-bond donors was prepared in order to determine the role of H-bonding on the formation of the (*trans*-1,2-peroxo)dicopper complexes. The ligand tris(6-phenoxy-2-pyridylmethyl)amine (tpa^{OPh}) containing pendent phenylether groups was prepared via an Ullmann coupling of phenol and Br_3tpa. When tpa^{OPh} and $Cu(MeCN)_4BAr'$ were dissolved in CH_2Cl_2 and cooled to −70°C the resulting complex $[Cu(tpa^{OPh})]BAr'$ did not react with O_2. ^{1}H NMR spectra of $[Cu(L^H)]BAr'$ and

[Cu(tpa^{OPh})]BAr' in CD_2Cl_2 revealed an almost identical chemical shift of the methylene protons, at δ=4.07 and 4.05 respectively, consistent with a similar electronic environment at copper.[15] ^{1}H NMR spectra of [Cu(L^H)]BAr' and [Cu(tpa^{OPh})]BAr' exhibit C_3-symmetry at both 25°C and −80°C, however, at −80°C the methylene proton peak on [Cu(tpa^{OPh})]BAr' broadens by 16.8 Hz, consistent with a fluxional process. This observation of dynamic ligand binding may further contribute to the lack of O_2 reactivity with tpa^{OPh}.[16] Although steric and electronic properties of [Cu(L^R)]BAr' would suggest that formation of **2^R** is unfavorable, these hindrances were overcome by introducing favorable hydrogen bonding interactions.

In conclusion, we have introduced a new variation on the tpa framework that incorporates highly tunable –NHPh groups in the secondary sphere. These groups act as H-bond donors while providing steric protection that can be used to isolate H-bonded Cu^{I}Cl complexes. Cu(I) complexes bearing the new ligands react with O_2 to form H-bonded (*trans*-1,2-peroxo)dicopper complexes whose spectroscopic characteristics are dictated by the ligand electronics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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11. Resonance Raman spectroscopy was also used to interrogate the O–O and Cu–O stretching frequencies in $\mathbf{2^{H}}$; however no ^{18}O active modes were defined.
12. Complex $\mathbf{2^{CF3}}$ precipitates from CH_2Cl_2 at −70°C over 30 sec. Therefore UV-Vis spectra of $\mathbf{2^{R}}$ were collected in a 1:1 CH_2Cl_2:acetone solution by first forming the complexes in pure CH_2Cl_2 followed by addition of cold acetone.
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15. The chemical shift of the methylene protons is highly sensitive to the electronic environment. For instance, the methylene protons shift from +0.04 ppm in $\mathbf{1^{CF3}}$ to −0.04 ppm in $\mathbf{1^{OMe}}$ compared to $\mathbf{1^{H}}$. Voltammetry was uninformative (see ref 16).
16. No discernable redox events could be obtained for [Cu(tpa^{OPh})]BAr'. We propose that a fluxional ligand dissociation process (shown from VT NMR studies) is responsible for the observed poor voltammetry response on the timescale of the electrochemical measurements.

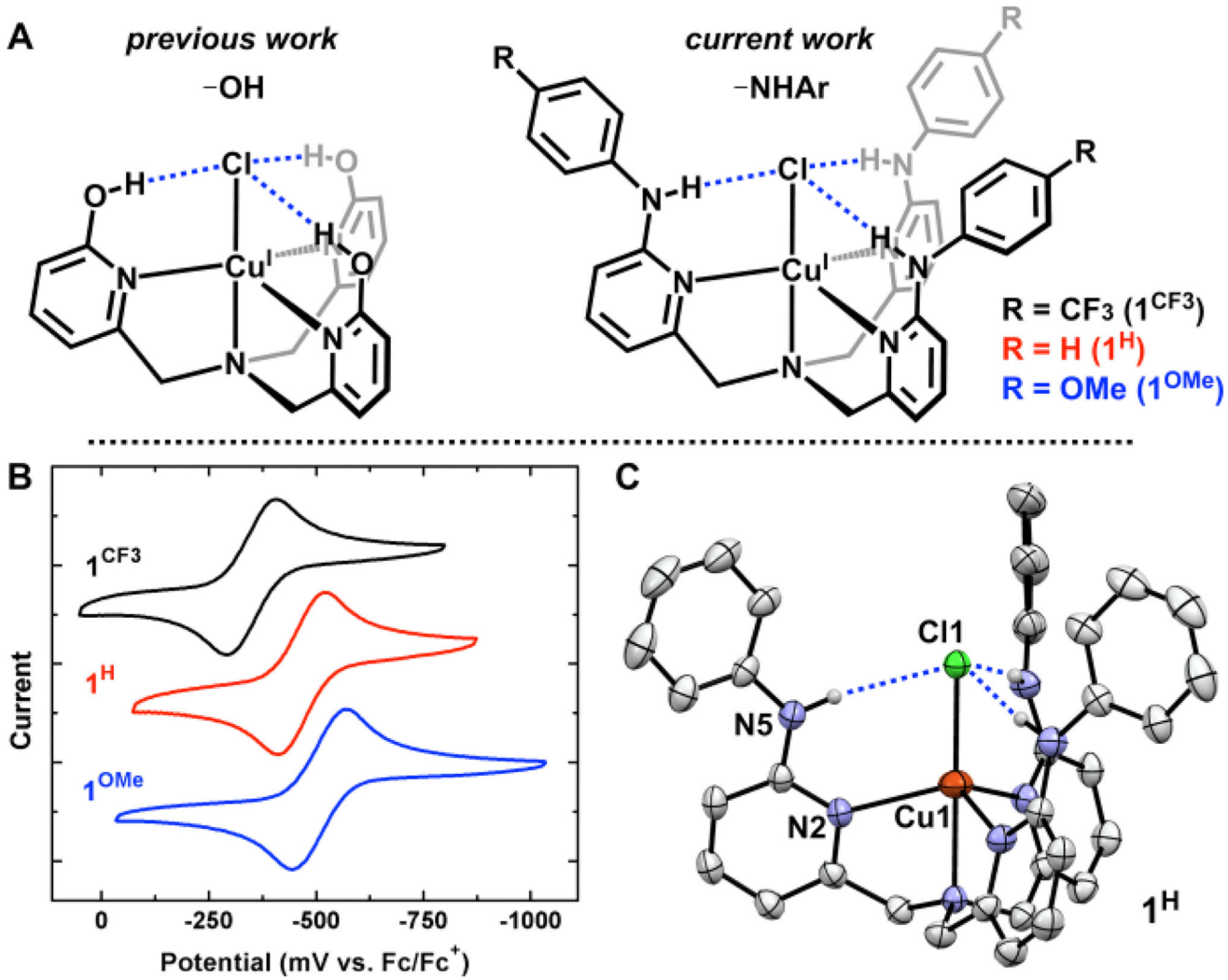

Figure 1.

$Cu^{I}Cl$ complexes derived from H_3thpa and L^R (A). Cyclic voltammetry of **1^{H}**, **1^{CF3}** and **1^{OMe}** ((B) 0.1 M NBu_4PF_6 CH_2Cl_2). Crystal structure of **1^{H}** ((C) 30% ellipsoids, H atoms not involved in H-bonding omitted for clarity).

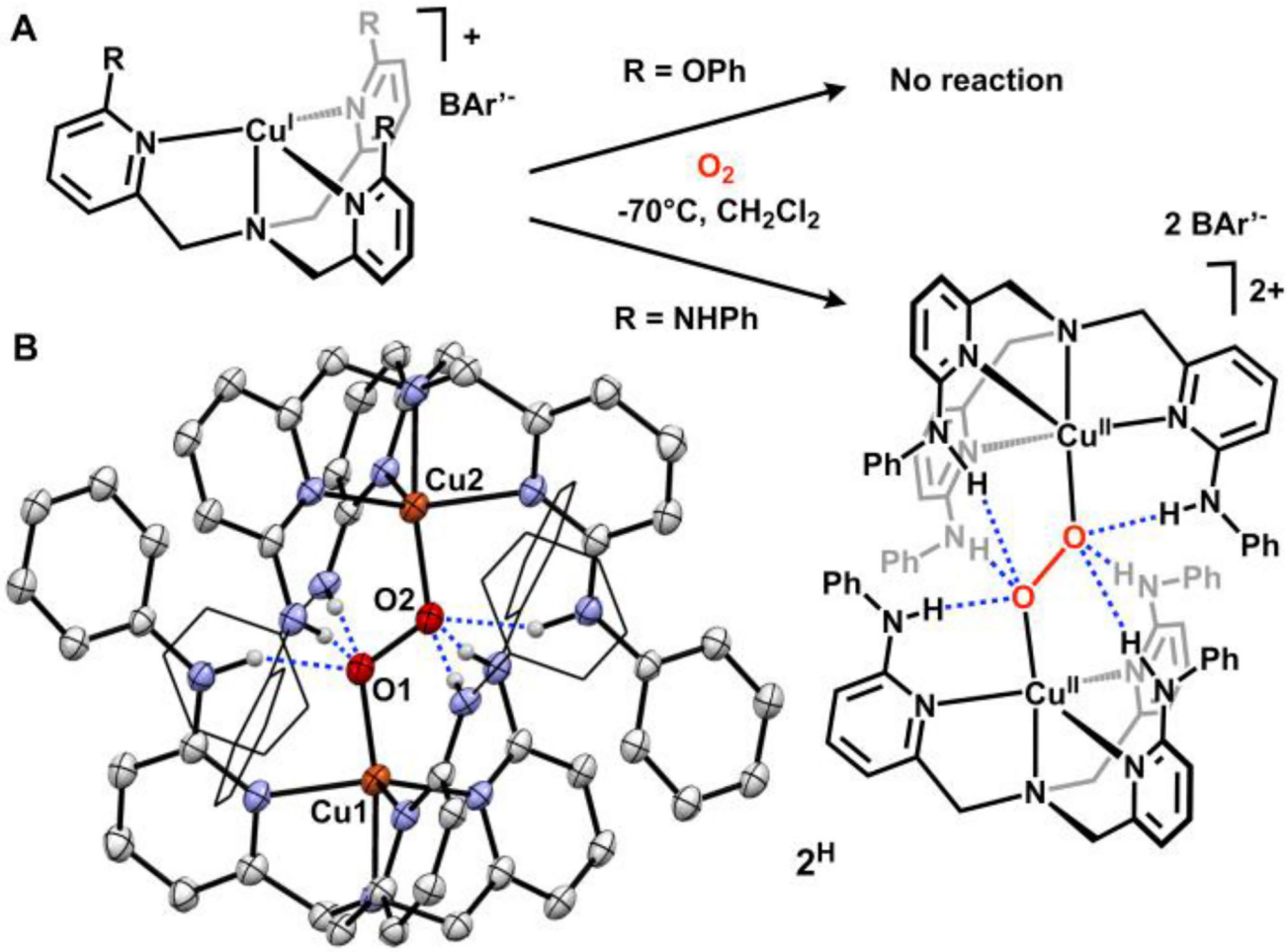

Figure 2.

Reactivity of Cu(I) complexes toward O_2 (A). Crystal structure of $\mathbf{2^H}$ ((B) 30% ellipsoids, some atoms represented in wireframe, H atoms not involved in H-bonding and BAr' counteranions omitted for clarity).

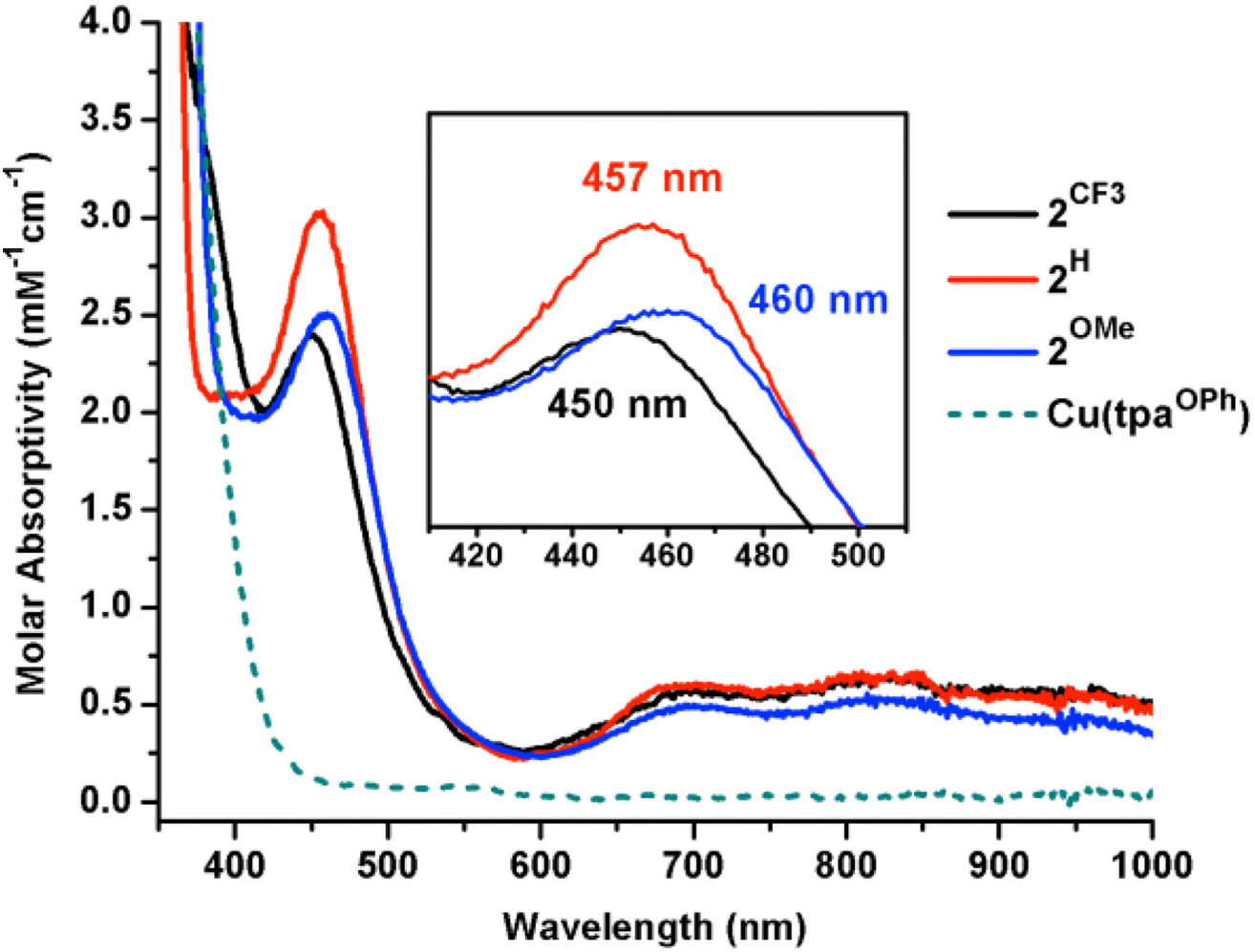

Figure 3.

UV-Vis overlay of **2^{H}**, **2^{CF3}**, **2^{OMe}** (1:1 CH_2Cl_2/acetone, −70°C), and the reaction of [Cu(tpa^{OPh})]BAr' with O_2 at −70°C. Inlay shows λ_{max} of O to Cu LMCT in **2^{R}**.