Rings of Power: Controlling SOD Mimic Activity with Pyridinophane Modifications

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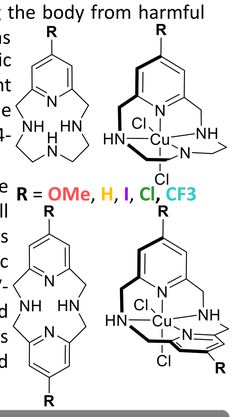
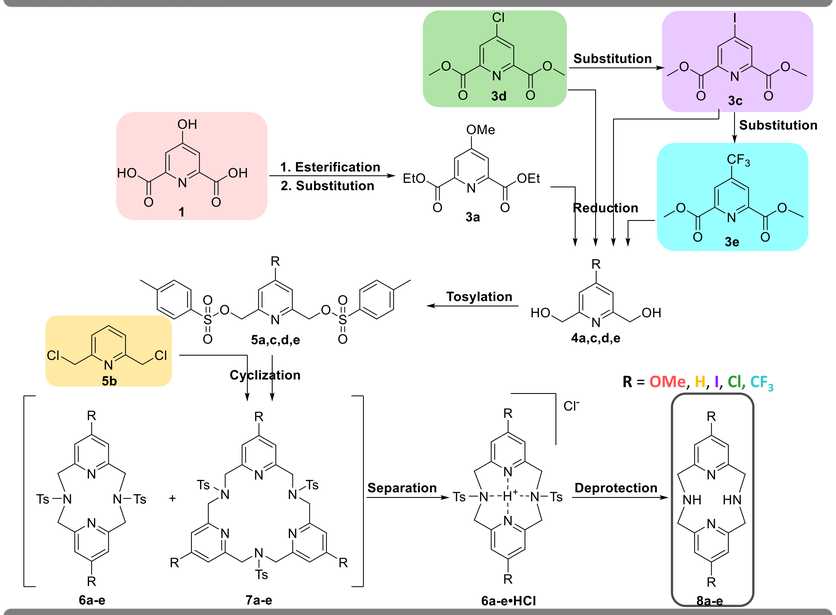
ABSTRACT

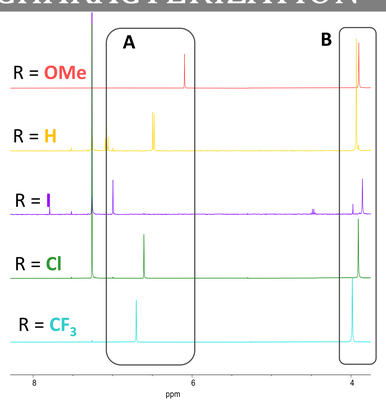
Oxidative stress is the unmitigated accumulation of reactive oxygen species (ROS) in the body and is a key player neurological diseases like Parkinson's and Alzheimer's. Superoxide dismutase (SOD) enzymes are capable of transforming the common ROS molecule superoxide ($O_2^{\cdot-}$) into less toxic species H_2O_2 or O_2, thus protecting the body from harmful reactions of superoxide. Synthetic metal complexes show promise as SOD mimics and could be effective alternatives to therapeutic dosing of SOD enzyme for oxidative stress.[1] In this work, we present a series of 12-membered tetra-aza pyridinophanes ($^{R}Py_2N_2$) and the corresponding copper complexes with substitutions on the 4-position of the pyridine ring.[2,3] Spectroscopic and potentiometric methods were used to (1) explore how the electronic nature of the 4-position substitution affects the electronics of the overall complex, and (2) for comparison to our established $^{R}PyN_3$ series, as structural change affects characterization. The SOD mimic capabilities of the **Cu[$^{R}Py_2N_2$]Cl$_2$** series were explored using a UV-visible spectrophotometric assay. This work is an initial step toward developing these **Cu[$^{R}Py_2N_2$]Cl$_2$** complexes as potential therapeutics for neurological diseases by mimicking SOD's capabilities and protecting the body from oxidative stress.

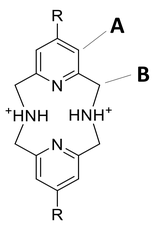


SYNTHESIS



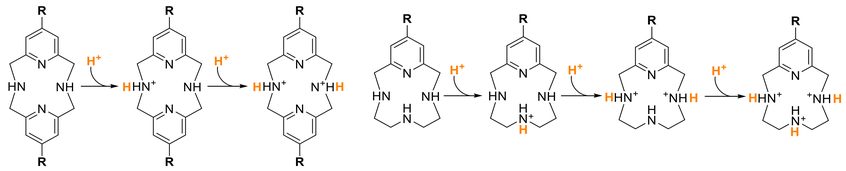
CHARACTERIZATION – ^{1}H NMR





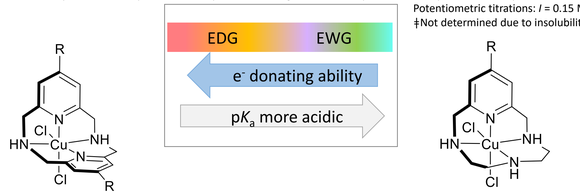
Resonance (**A**) shifts downfield as the group on top changes from electron-donating (**OMe**) to electron-withdrawing (**Cl**, **I**). The difference between the **Cl** and **I** aromatic proton shift can be explained by resonance versus induction effects.

PROTONATION CONSTANTS, METAL BINDING



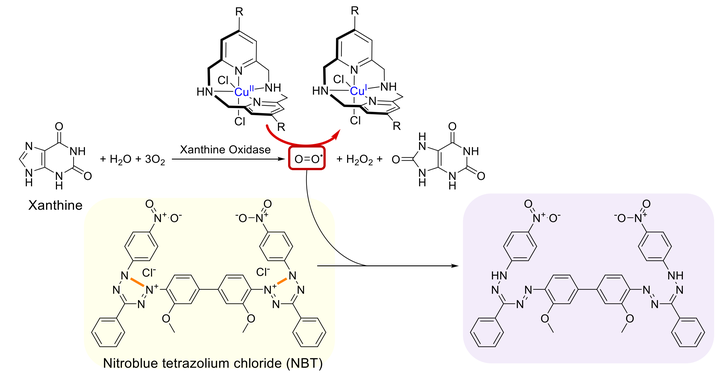
	$^{OMe}Py_2N_2$	$^{H}Py_2N_2$	$^{I}Py_2N_2$	$^{Cl}Py_2N_2$	$^{CF3}Py_2N_2$	$^{OMe}PyN_3$	$^{H}PyN_3$	$^{I}PyN_3$	$^{Cl}PyN_3$	$^{CF3}PyN_3$
log K_1^H	8.05(8)	8.35(2)	‡	7.7(3)	7.5(2)	10.32(2)	11.37(1)	11.20(3)	10.50(2)	11.14(3)
log K_2^H	7.01(7)	7.42(2)	‡	6.2(3)	6.2(1)	8.00(3)	8.22(5)	7.86(9)	7.27(4)	7.47(9)
log K_3^H	-	-	-	-	-	1.75(4)	1.61(5)	0.68(12)	1.37(4)	-
Σ log $K_{N\text{-donors}}$	**15.06**	**15.77**	**‡**	**13.9**	**13.70**	**20.07**	**21.20**	**19.74**	**19.14**	**18.61**

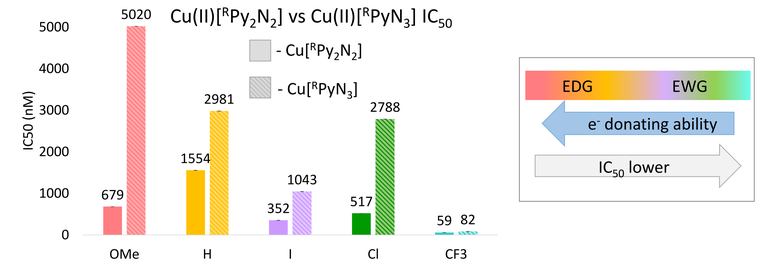
Potentiometric titrations: I = 0.15 M NaCl, T = 298 K.
‡Not determined due to insolubility.



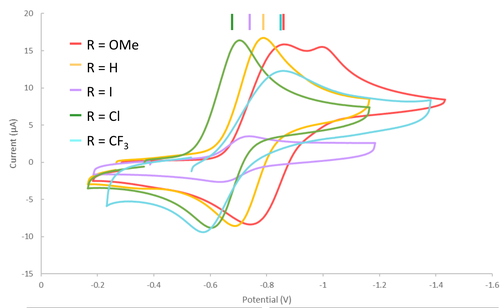
	$^{OMe}Py_2N_2$	$^{H}Py_2N_2$	$^{I}Py_2N_2$	$^{Cl}Py_2N_2$	$^{CF3}Py_2N_2$	$^{OMe}PyN_3$	$^{H}PyN_3$	$^{I}PyN_3$	$^{Cl}PyN_3$	$^{CF3}PyN_3$
Cu(II)	16.25(1)	16.33(2)	--	17.1(2)	14.12(1)	19.38(2)	20.644(3)	19.030(3)	18.611(4)	18.771(7)
Cu(I)	9.44	10.58	--	12.58	8.78	4.34	6.28	11.27	4.56	4.98

EX-VITRO SPECTROPHOTOMETRIC ASSAY



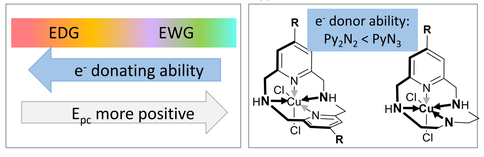


CYCLIC VOLTAMMETRY

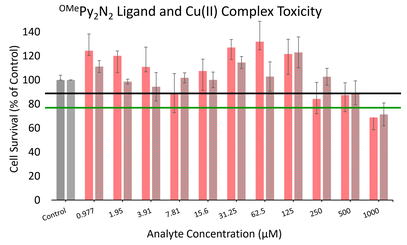


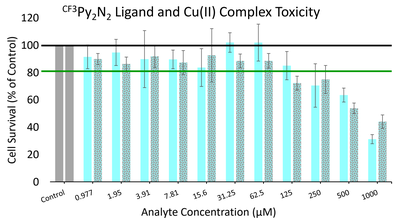
	E_{pc}	$E_{1/2}$
Cu[$^{OMe}Py_2N_2$]	-861	-803
Cu[$^{H}Py_2N_2$]	-789	-740
Cu[$^{I}Py_2N_2$]	-737	-687
Cu[$^{Cl}Py_2N_2$]	-703	-652
Cu[$^{CF3}Py_2N_2$]	-858	-716

	E_{pc}	$E_{1/2}$
Cu[$^{OMe}PyN_3$]	-1071	-988
Cu[$^{H}PyN_3$]	-995	-948
Cu[$^{I}PyN_3$]	-907	-859
Cu[$^{Cl}PyN_3$]	-979	-929
Cu[$^{CF3}PyN_3$]	-1005	-914

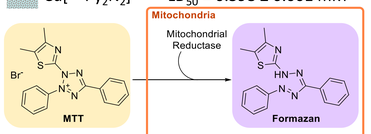


IN-VITRO ASSAY

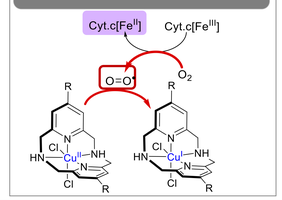




$^{OMe}Py_2N_2$ — LD_{50} = 3.235 ± 0.002 mM
Cu[$^{OMe}Py_2N_2$] — LD_{50} = 4.079 ± 0.001 mM
$^{CF3}Py_2N_2$ — LD_{50} = 0.657 ± 0.001 mM
Cu[$^{CF3}Py_2N_2$] — LD_{50} = 0.598 ± 0.001 mM



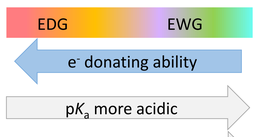
ON-GOING WORK



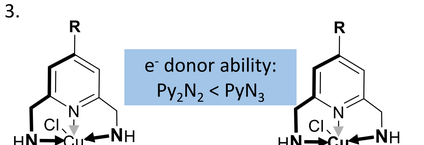
CONCLUSIONS

1. Successful synthesis, purification, and characterization of **Py_2N_2** series, Cu(II) complexes.

2.



3.



Cu(II)[$^{R}Py_2N_2$] weaker complex than Cu(II)[$^{R}PyN_3$]

ACKNOWLEDGEMENTS

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