Effects of a Secondary Pyridine Ring Substitution on Electronics of Pyridinophanes

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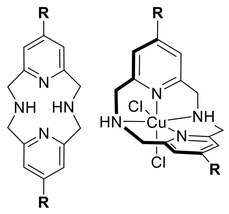
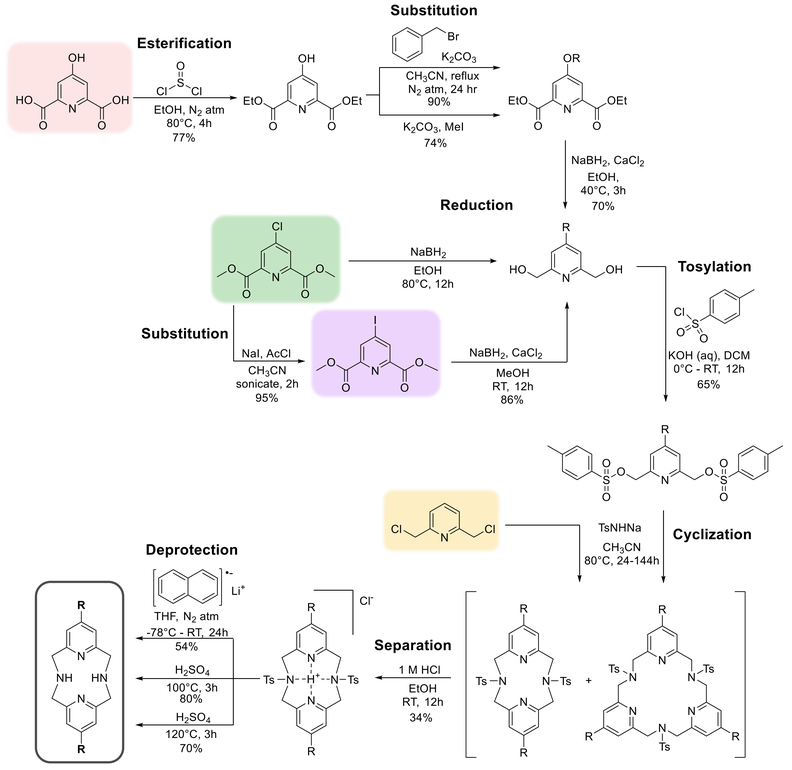
ABSTRACT

Oxidative stress is the unmitigated accumulation of reactive oxygen species (ROS) in the body and is a key player in many maladies, including neurological diseases like Parkinson's and Alzheimer's. Superoxide dismutase (SOD) enzymes are capable of transforming the common ROS molecule superoxide (O_2^-) into less toxic species such as 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 (**Py_2N_2**) and the corresponding copper complexes with substitutions on the 4-position of the pyridine ring. The SOD mimic capabilities of the **$Cu[Py_2N_2]Cl_2$** series were explored using a UV-visible spectrophotometric assay. Spectroscopic, potentiometric, and crystallographic methods were used to explore how the electronic nature of the 4-position substitution affects the electronics of the overall complex, and the complex's activity as a SOD mimic. This work is an initial step toward developing these **$Cu[Py_2N_2]Cl_2$** complexes as potential therapeutics for neurological diseases by mimicking SOD's capabilities and protecting the body from oxidative stress



R = OH, OMe, H, I, Cl

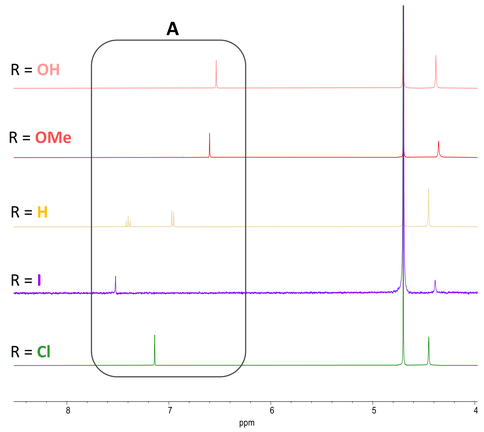
SYNTHESIS



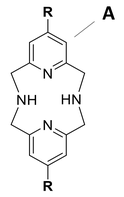
R = OH, OMe, H, I, Cl

	$^{OH}Py_2N_2$	$^{OMe}Py_2N_2$	$^{H}Py_2N_2$	$^{I}Py_2N_2$	$^{Cl}Py_2N_2$
Hammett Parameter (σ)	-0.37	-0.27	0	0.18	0.23

CHARACTERIZATION – ^{1}H NMR



Resonance (**A**) shifts downfield as the group on top changes from electron-donating (OH, OMe) to electron-withdrawing (Cl, I).

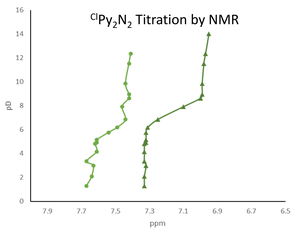


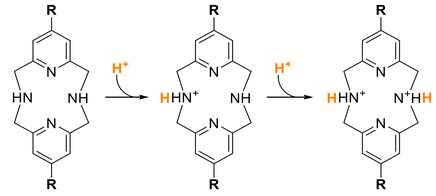
The difference between the Cl and I aromatic proton shift can be explained by resonance versus induction effects.

PROTONATION CONSTANTS

	$^{OH}Py_2N_2^{\dagger}$	$^{OMe}Py_2N_2$	$^{H}Py_2N_2$	$^{I}Py_2N_2$	$^{Cl}Py_2N_2$
log K_1^H	9.359(2)	8.05(8)	8.35(2)	‡	7.57(6)
log K_2^H	4.21(3)	7.01(7)	7.42(2)	‡	5.14(5)
Σ log $K_{N\text{-donors}}$	13.569	15.06	15.77	‡	12.71

Potentiometric titrations: I = 0.15 M NaCl, T = 298 K.
†The OH moiety has additional protonation events at 11.307(8), 5.25(3), 0.98(2).[1]
‡Not determined due to insolubility.

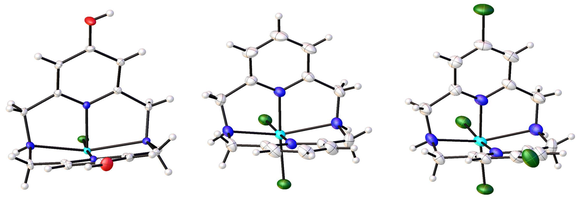


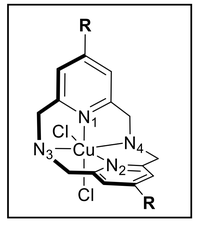


$^{Cl}Py_2N_2$ is more acidic than $^{OH}Py_2N_2$ or $^{OMe}Py_2N_2$

SINGLE CRYSTAL X-RAY DIFFRACTION

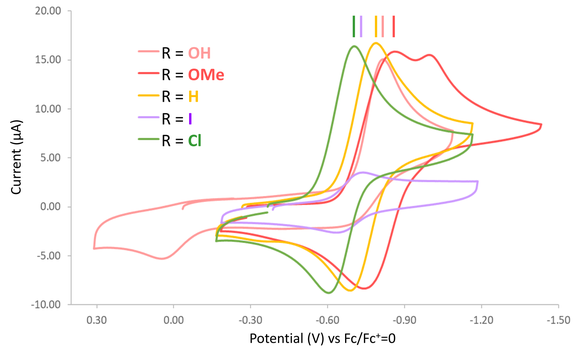
$^{OH}Py_2N_2$[2] $^{H}Py_2N_2$ $^{Cl}Py_2N_2$[3]





	Py_1 N-M (Å)	Py_2 N-M (Å)	N_3-M (Å)	N_4-M (Å)	R-C (Å)	Py-M-Py (°)	Py-Py (Å)
$^{OH}Py_2N_2$	2.007(3)	2.010(2)	2.309(3)	2.313(3)	1.336(3) 1.346(3)	84.45(9)	4.117
$^{H}Py_2N_2$	2.0397(11)	2.0398(11)	2.3405(12)	2.3405(12)	0.950	82.76(6)	4.323
$^{Cl}Py_2N_2$	2.077(4)	2.053(5)	2.379(5)	2.345(5)	1.735(5) 1.742(5)	81.66(17)	4.238

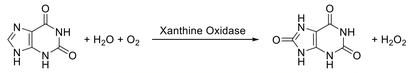
CYCLIC VOLTAMMETRY

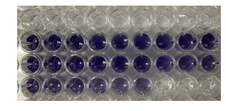


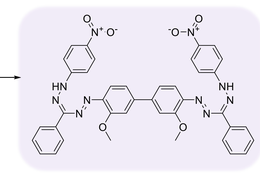
	E_{pc}	$E_{1/2}$
$^{OH}Py_2N_2$ Cu(II/I)	-816	--
$^{OMe}Py_2N_2$ Cu(II/I)	-861	-803
$^{H}Py_2N_2$ Cu(II/I)	-789	-740
$^{I}Py_2N_2$ Cu(II/I)	-737	-687
$^{Cl}Py_2N_2$ Cu(II/I)	-703	-652

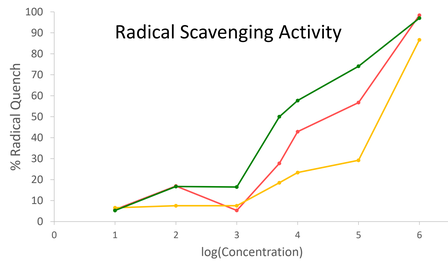
The Cu(II/I) reduction event (E_{pc}):
Electron Withdrawing Groups (Cl, I) > Electron Donating Groups (OH, OMe)

SPECTROPHOTOMETRIC ASSAY









	IC_{50} (µM)
$^{OMe}Py_2N_2CuCl_2$	20.82
$^{H}Py_2N_2CuCl_2$	177.1
$^{Cl}Py_2N_2CuCl_2$	6.306

CONCLUSIONS

- Successful synthesis, purification, and characterization of **Py_2N_2** series.
- Substitution on 4-position tunes the electronics of the Py_2N_2 ligand and the Cu(II) complex. As substitution changes from electron donating (OH, OMe) to electron withdrawing (Cl, I):
  - Downfield shift of aromatic resonance
  - Acidic shift of protonation constants
  - Longer (weaker) N-Cu bond
  - More positive Cu(II/I) reduction potential
- 4-position substitution significantly impacts IC_{50} for radical scavenging

Acknowledgements:

Green Research Group,

Instrumentation provided by Texas Christian University, College of Science & Engineering, Department of Chemistry & Biochemistry.

The Welch Foundation
National Institutes of Health
ACS PRF

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