Functional Modifications and Electronic Influences on Macrocyclic Tetra-aza Copper (II) Complexes

Brian P. Niebuhr, Marianne E. Burnett, and Kayla N. Green, Ph.D.
Green Research Group, Department of Chemistry and Biochemistry at Texas Christian University, Fort Worth, TX USA

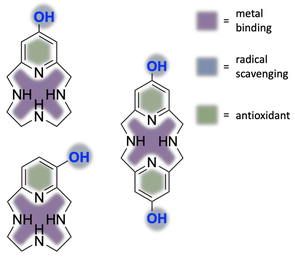
ABSTRACT

A library of novel pyridinophane tetra-aza macrocyclic molecules derived from 1,4,7,10-tetraaza-2,6-pyridinophane (pyclen) capable of chelating biologically relevant metal ions have been synthesized. Applications of these types of molecules currently being pursued are 1) therapeutic, focusing on radical scavenging and metal chelation and 2) diagnostic, focusing on magnetic resonance imaging (MRI) contrast agents when complexed with specific metal ions. Despite wide interest in these molecules, a full study of the electronic effects imparted by substitution to the pyridyl moiety and the subsequent impact on the metal center has not yet been conducted. The objective of the present study is to characterize metal complexes of four, new tetra-aza macrocyclic metal chelating molecules. The pyridyl functional groups studied include: **A**) unmodified pyridyl (**L1**), **B**) *14*-hydroxyl (**L2**), **C**) *14*-nitrile (**L3**), and **D**) *14*-nitro (**L4**) modified pyclen structures. Procedures for metal ion chelation with copper (II) ion, followed by characterization and analysis of the electronic environments of each are presented.

INTRODUCTION

Current study

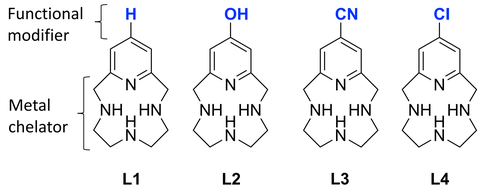
- Development of ligand series (organic synthesis)
- Metal-binding promiscuity
- Pyridine backbone features



Research question

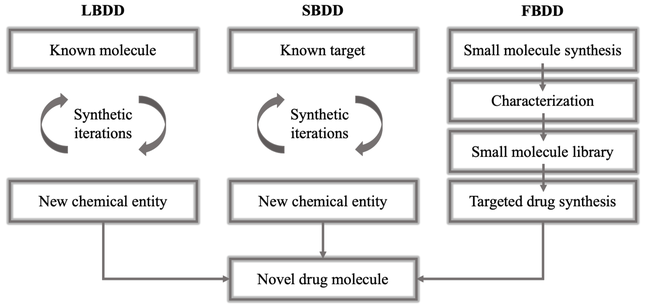
> If small **chemical modifications** are introduced to the pyridine backbone, then a **change** in the **electronic environments** of the free macrocycle and the metal complex should be measurable using fundamental chemical techniques.

Ligand library for analysis

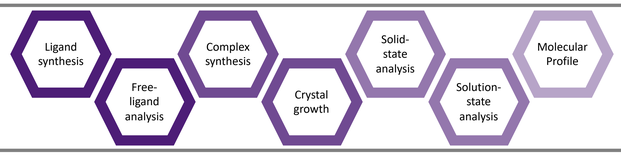


Significance to new-molecule development

Ligand- (LBDD), structure- (SBDD), & fragment- (FBDD) based approaches to drug design.



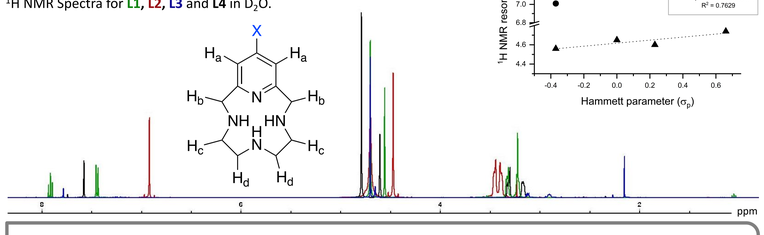
EXPERIMENTAL APPROACH

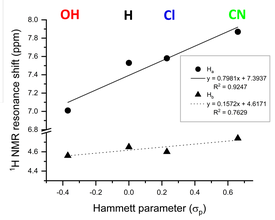


LIGAND ANALYSIS: ^{1}H NMR

^{1}H NMR	X	H_a	H_b	H_c	H_d
L1	8.00 (1H)	7.53 (2H)	4.65 (4H)	3.41 (4H)	3.32 (4H)
L2	OH	7.01 (2H)	4.56 (4H)	3.51 (8H)	
L3	CN	7.87 (2H)	4.74 (4H)	3.16 (8H)	
L4	NO_2	7.58 (2H)	4.60 (4H)	3.30 (4H)	3.16 (4H)

^{1}H NMR Spectra for **L1**, **L2**, **L3** and **L4** in D_2O.

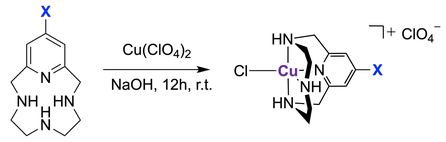




SOLID-STATE ANALYSIS

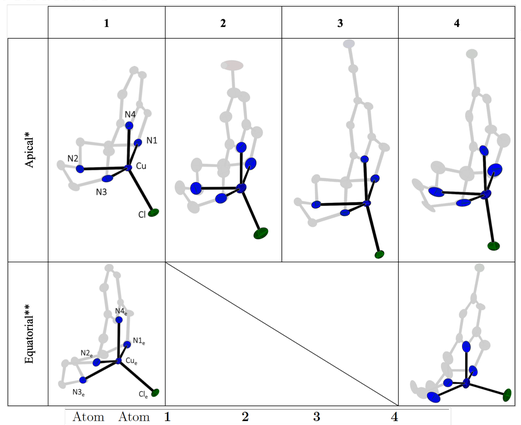
X-RAY DIFFRACTION

Synthesis



Crystalline sample of **3** grown by slow evaporation in water.

Crystal Structures



Solid state structures of complexes **1**, **2**, **3**, and **4** highlighting the metal coordination sphere. The carbon scaffold is represented in light grey. The perchlorate counter ions were omitted for clarity. *Apical chlorine (Cl_a) was determined by an N4-Cu-Cl bond angle greater than 135˚. **Equatorial chlorine (Cl_e) was determined by an N4-Cu-Cl bond angle less than 135˚.

Atom	Atom	**1**	**2**	**3**	**4**
Cu1	Cl1	2.2394 (10)	2.226 (9)	2.2705 (12)	2.262 (3)
Cu1	N1	2.060 (2)	2.082 (16)	2.078 (2)	2.086 (7)
Cu1	N2	2.144 (2)	2.173 (19)	2.213 (2)	2.232 (7)
Cu1	N3	2.076 (2)	2.079 (16)	2.084 (2)	2.083 (6)
Cu1	N4	1.947 (2)	1.939 (16)	1.9600 (19)	1.977 (6)

Selected bond lengths (Å) for the five-coordinate complexes **1**, **2**, **3**, and **4**. Bond lengths for the equatorial complexes **1** and **4** are omitted for clarity.

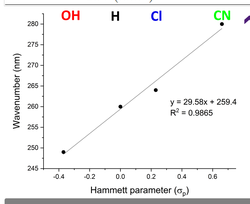
Atom	Atom	Atom	**1**	**2**	**3**	**4**
N4	Cu1	Cl1	148.69 (7)	154.20 (5)	167.81 (5)	172.50 (19)
N2	Cu1	Cl1	110.77 (7)	106.91 (5)	96.37 (6)	95.00 (18)
N4	Cu1	N2	100.49 (9)	98.89 (6)	95.72 (8)	92.4 (2)
N1	Cu1	Cl1	98.76 (7)	100.69 (5)	101.12 (6)	102.4 (2)
N3	Cu1	Cl1	102.05 (7)	100.07 (5)	99.21 (5)	98.09 (18)
N1	Cu1	N3	158.99 (9)	158.57 (6)	156.86 (7)	155.8 (3)
C3	C12	N5	-	-	178.5 (3)	-
		τ	0.17	0.07	0.18	0.28

Selected bond angles (˚) for the five-coordinate complexes **1**, **2**, **3**, and **4**. τ-values were calculated according to literature, where τ=(β-α)/60 where β is the greater basal angle and α is the lesser of the basal angles. Bond angles for the equatorial complexes **1** and **4** are omitted for clarity.

SOLUTION-STATE ANALYSIS

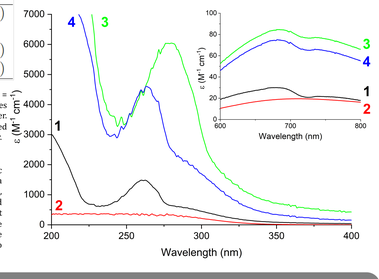
UV-VISIBLE SPECTROSCOPY

Complex	Abs. 1	Abs. 2	Abs. 3	Abs. 4
1	-	260 (1485)	676 (30)	739 (22)
2	249 (8779)	284 (sh)	699 (107)	-
3	221 (sh)	280 (6600)	684 (85)	736 (77)
4	264 (3584)	-	681 (75)	735 (66)



Molar absorption [λ_{max}/nm = (ε/$M^{-1}cm^{-1}$)] values for complexes **1**, **2**, **3**, and **4** measured in water, sh = shoulder, all values reported in table were completed in water.

The electronic absorption spectra for complexes **1**, **2**, **3**, and **4** measured in water at ambient temperature. The inset shows the spectra from 600 to 800 nm in water.



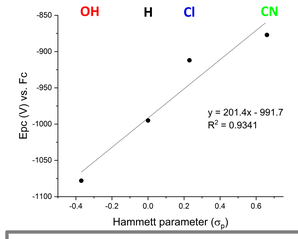
ELECTROCHEMISTRY

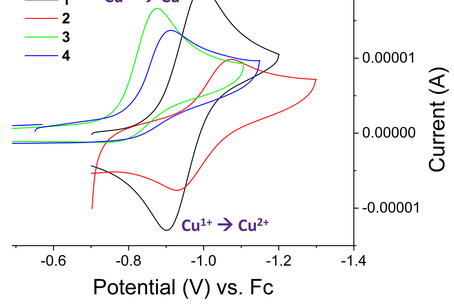
Complex	E_{pa} (mV)	E_{pc} (mV)	I_{pa} (mA)	I_{pc} (mA)	$E_{1/2}$ (mV)	δE	I_{pa}/I_{pc}
1	-902	-995	14.5998	15.6527	-948	93	0.9327
2	-933	-1078	0.00785	0.00936	-1006	145	0.8390
3	-738	-877	1.2055	12.6406	-808	139	0.09537
4	-	-912	-	10.3853	-	-	-

Electrochemical parameters:
Glassy Carbon working electrode
Pt auxiliary electrode
Ag wire reference electrode
DMF/TBAP

Electrochemical data for **1**, **2**, **3**, and **4** using a glassy carbon working electrode, platinum auxiliary electrode, and Ag wire quasi reference electrode (CH_3CN, TBAP, vs. Fc/Fc^+).

Cyclic voltammogram overlays of complexes **1**, **2**, **3**, and **4** at scan rates of 100 mV/s. Experimental conditions: glassy carbon working electrode, platinum auxiliary electrode, Ag wire reference electrode, TBAP in CH_3CN, vs. Fc/Fc^+ (0.00 V).





CONCLUSIONS

- Developed synthetic method for **3** and **4** copper (II) complexes,
  - Significant & observable **change** in the **electronic environment**
  - Beginning to understand **how** the electronics **change**
  - Increasing **control** facilitates **design-to-function**
  - New **approach** to studying these **macrocycles**

ACKNOWLEDGEMENTS

Funding & support provided by the Green Research Group; Akop Yepremyan;
TCU, College of Science & Engineering, Department of Chemistry & Biochemistry;
TCU, Science and Engineering Research Center (SERC) grant.

References*

1. Burnett, M. E. *TCU Digital Repository, Theses and Dissertations*. **2018**. 64-65, 227-230.
2. Johnston, H. *TCU Digital Repository, Theses and Dissertations*. **2018**. 36-40.
3. Lincoln, K. M. *TCU Digital Repository, Theses and Dissertations*. **2015**. 33.
4. Niebuhr, B. IN PREPARATION. **2019**.

* ^{1}H NMR data for **L2**.[2] Crystallographic data, UV-visible, and CV spectrums for **2**.[3] Complex synthesis for **4**.[1]

TCU COLLEGE OF SCIENCE & ENGINEERING
reSEaRCh
Science and Engineering Research Center