Synthesis, Characterization, and Reactivity of Schiff Base Transition Metal Complexes

Isabella R. Demyan[1], Jason G. Marmorstein[1], Joseph Tanski[2], Prof. Laurie A. Tyler[1]

[1] Department of Chemistry, Union College, Schenectady, NY 12308
[2] Department of Chemistry, Vassar College, Poughkeepsie, NY 12604

Abstract

Research in the Tyler Lab has been focused on determining the reaction conditions which promote full or partial hydrolysis of Schiff base imine ligands while ligated to either Cu(II) or Ni(II) metal centers, and if that hydrolysis can be controlled. Biological studies are also conducted on these compounds to determine their possible utility. Specifically, antibacterial research has been of interest due to increased antibiotic resistance. Schiff bases have been central to this effort, as their presence in nature and functionality have been used in many medicinal applications, such as antifungal and antimalarial medicines. The research presented here includes the synthesis and characterization of novel imine ligands and the corresponding metal complexes. The ligands are synthesized by reacting two equivalents of a substituted pyridine aldehyde (R = H, OMe, Me) with ethylenediamine in ethanol, and were characterized by ^{1}H NMR and IR spectroscopies. Complex formation reactions were carried out in a 1:1 ligand to metal molar ratio with several different Cu(II) and Ni(II) salts. The Cu(II) complexes have been characterized with ^{1}H NMR, IR, elemental analysis, and X-Ray crystallography. The ligands and metal complexes will be assessed for antibacterial activity using several different methods.

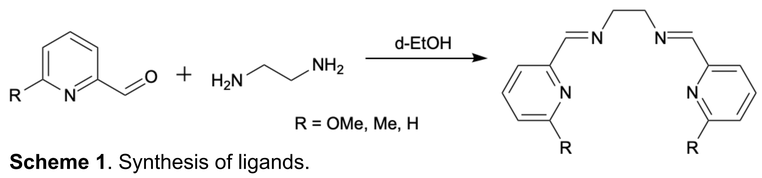
Introduction

The chemistry and reactivity of imines, particularly Schiff base imines, have been the subject of research across many disciplines of chemistry. Schiff bases are specific types of imines which contain only alkyl or aryl functional groups and are considered “privileged ligands” due to the ease in which they are made, via a condensation reaction of a primary amine with an aldehyde or ketone.[1] Further, Schiff base-containing compounds are widely used in biological applications, such as antifungals and antivirals, in which the imine moiety has been key to their function.[1]

Researchers such as Rathelot *et al.* have studied Schiff-base functionalized isoquinolines for antimalarial applications, where the Schiff base has shown to be integral in the function of the drug.[2] Furthermore, biological reactivity can be modulated by ligation of the Schiff base to a metal center. There are several studies regarding the effect of chelation of imine ligands to metal centers. Festus *et al.* researched a series of pyrimidine-based Schiff base ligands, in which the chelation effect and stabilization of the metal-organic framework improved the compounds’ biological activity.[3] Schiff base ligands are also subject to hydrolysis, and it is believed that the identity of the metal salt plays a role in the full or partial hydrolysis of the imine bond.[4-5]

Ligand Synthesis and Characterization

The ligands were synthesized by reacting two equivalents of a substituted pyridine aldehyde with ethylenediamine in EtOH and refluxing for 1 h. The solid $PyOMe_2(en)$ ligand was isolated by cooling the solution to 0℃ for 24 h. $PyMe_2(en)$ and $Py_2(en)$ were isolated as solids by concentrating the mother liquor. Each derivative was characterized by ^{1}H NMR and IR spectroscopies.



Scheme 1. Synthesis of ligands.

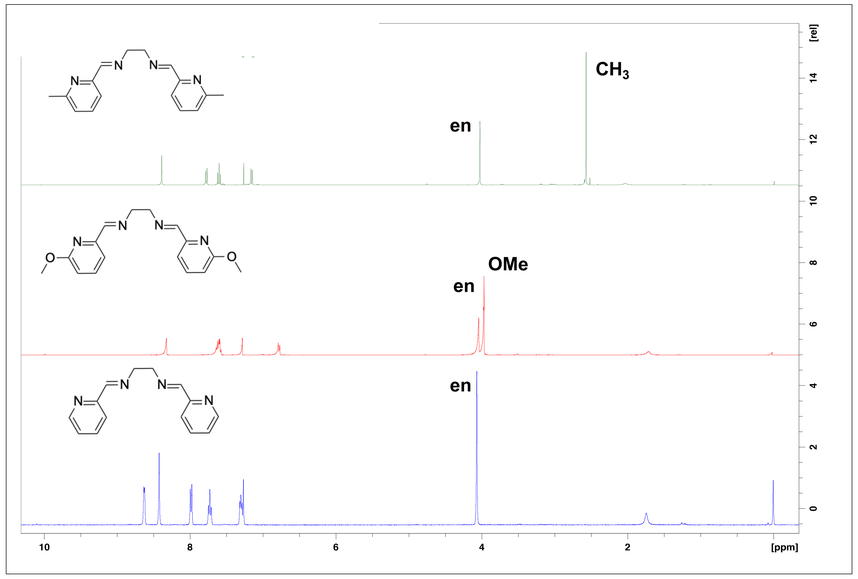


Figure 1. ^{1}H NMR spectra of pyridine substituted ligands in $CDCl_3$.

Table 1. Selected ligand IR Data.

	$Py_2(en)$	$PyOMe_2(en)$	$PyMe_2(en)$
υ_{NC} (cm^{-1})	1645	1651	1648
υ_{CO} (cm^{-1})	n/a	1265	n/a

Complex Formation

Metalation reactions were carried out in a 1:1 ligand to metal molar ratio with Cu(II) and Ni(II) salts. These reactions were completed by slowly adding the desired metal salt to the ligand in solvent and stirred for 24 h at RT. The resultant mixtures were then diffused in one of either THF or diethyl ether (Et_2O) to afford X-Ray quality crystals.

X-Ray Analysis

The 1:1 molar reaction of $PyOMe_2(en)$ with $NiCl_2{\cdot}6H_2O$ resulted in the unexpected dimeric species in **Fig. 2** with the counterion $[NiCl_4]^{2-}$. The recently obtained crystal structure reveals both ligands are fully ligated to the Ni(II) center. Reactions are underway to optimize the product of this reaction by increasing the metal to ligand ratio 3:2.

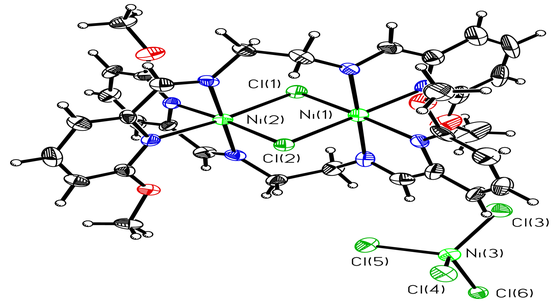
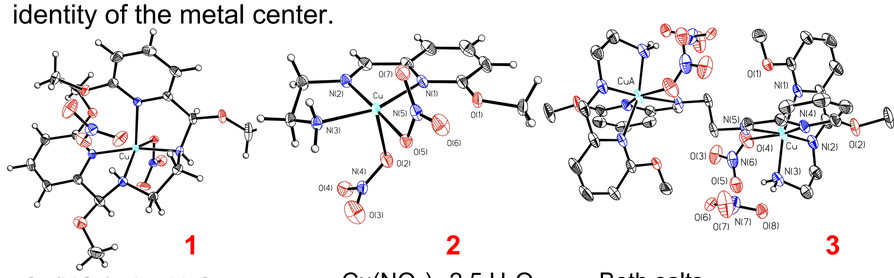


Figure 2. Crystal structure of metal complex $[Ni(PyOMe_2(en))Cl]_2[NiCl_4]$ from reaction with $PyOMe_2(en)$ and $NiCl_2{\cdot}6H_2O$.

Table 2. Selected complex IR Data.

	υ_{NC} (cm^{-1})
Complex	1647

The reactions of $PyOMe_2(en)$ with either $Cu(NO_3)_2{\cdot}2.5\ H_2O$ or $Cu(ClO_4)_2{\cdot}5\ H_2O$ resulted in several different partially hydrolyzed species. There is a clear difference in reactivity and the propensity to hydrolyze between the Cu(II) and Ni(II) complexes that may be modulated by the identity of the metal center.



- $Cu(NO_3)_2{\cdot}2.5\ H_2O$
- Imine hydrolyzed to amine
- Coordination sphere completed by nitrate groups
- MeOH added

- $Cu(NO_3)_2{\cdot}2.5\ H_2O$
- Hydrolyzed half ligand
- Completed by two nitrate ions

- Both salts
- Dimer with 1 full ligand
- Each Cu with hydrolyzed half ligand

Acknowledgements

I would like to thank the Union Chemistry department for my student research grant and the Kane family for the additional funding. I would also like to thank my advisor Prof. Laurie Tyler for her continued support and mentorship, fellow thesis student Jason Marmorstein ‘21, and Prof. Joseph Tanski at Vassar College for solving the crystal structures.

References

1. da Silva, C. M.; da Silva, D. L.; Modolo, L. V.; Alves, R. B.; de Resende, M. A.; Martins, C. V. B.; de Fátima, Â Schiff bases: A short review of their antimicrobial activities. *Journal of advanced research* **2011**, *2*, 1-8
2. Rathelot, P.; Vanelle, P.; Gasquet, M.; Delmas, F.; Crozet, M. P.; Timon-David, P.; Maldonado, J. Synthesis of novel functionalized 5-nitroisoquinolines and evaluation of in vitro antimalarial activity. *European Journal of Medicinal Chemistry* **1995**, *30*, 503-508. .
3. Festus, C.; Okafor, S. N.; Ekennia, A. C. Heteroleptic Metal Complexes of a Pyrimidinyl Based Schiff Base Ligand Incorporating 2,2'-Bipyridine Moiety: Synthesis, Characterization, and Biological Studies. *Frontiers in chemistry* **2019**, *7*, 862.
4. Senthamarai, T.; Chandrashekhar, V. G.; Gawande, M. B.; Kalevaru, N. V.; Zbořil, R.; Kamer, P. C. J.; Jagadeesh, R. V.; Beller, M. Ultra-small cobalt nanoparticles from molecularly-defined Co–salen complexes for catalytic synthesis of amines. *Chemical science (Cambridge)* **2020**, *11*, 2973-2981.
5. Gharamaleki, J. A.; Akbari, F.; Karbalaei, A.; Ghiassi, K. B.; Olmstead, M. M. Synthesis, Characterization and Crystal Structure of a New Schiff Base Ligand from a Bis(Thiazoline) Template and Hydrolytic Cleavage of the Imine Bond Induced by a Co(II) Cation. *Open Journal of Inorganic Chemistry* **2016**, *6*, 76-88.