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Syntheses, characterization, density functional theory calculations, and activity of tridentate SNS zinc pincer complexes based on bis-imidazole or bis-triazole precursors

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ABSTRACT

A series of tridentate pincer ligands, each possessing two sulfur- and one nitrogen-donor functionalities (SNS), based on bis-imidazole or bis-triazole salts were metallated with $ZnCl_2$ to give new tridentate SNS pincer zinc(II) complexes $[(SNS)ZnCl]^+$. The zinc complexes serve as models for the zinc active site in liver alcohol dehydrogenase (LADH) and were characterized with single crystal X-ray diffraction, ^1H, ^{13}C, and HSQC NMR spectroscopies, electrospray mass spectrometry, and elemental analysis. The zinc complexes feature SNS donor atoms and pseudotetrahedral geometry about the zinc center, as is seen for liver alcohol dehydrogenase. The bond lengths and bond angles of the zinc complexes correlate well to those in horse LADH. The SNS ligand precursors were characterized with ^1H, ^{13}C, and HSQC NMR spectroscopies, elemental analysis, and cyclic voltammetry, and were found to be redox active. Gaussian calculations were performed and agree with the experimentally observed oxidation potentials for the pincer ligand precursors. The zinc complexes were screened for the reduction of electron-poor aldehydes in the presence of a hydrogen donor, 1-benzyl-1,4-dihydronicotinamide (BNAH), and it was determined that they enhance the reduction of electron-poor aldehydes. The SNS zinc pincer complexes with bis-triazole ligand precursors exhibit higher activity for the reduction of 4-nitrobenzaldehyde than do SNS zinc pincer complexes with bis-imidazole ligand precursors. Quantitative stoichiometric conversion was seen for the reduction of pyridine-2-carboxaldehyde via SNS zinc pincer complexes with either bis-imidazole or bis-triazole ligand precursors.

1. Introduction

The synthesis and characterization of complexes that attempt to mimic natural catalytic behavior have furthered the understanding of the enzymatic activity of metalloenzyme sites [1]. Model complexes are low molecular mass systems that replicate the metalloenzyme in terms of structures, ligand donor atoms, and oxidation states [2]. Nature is used as a model for the design of highly active and efficient catalysts, and is also the inspiration behind the synthesis of each model complex in order to investigate structures and functions of enzymes.

Liver alcohol dehydrogenase (LADH) is a zinc metalloenzyme that catalyzes the oxidation of alcohols to aldehydes and ketones, and also catalyzes the reverse reaction, which is the reduction of a ketone or an aldehyde to an alcohol [1,3]. The crystal structure of horse LADH has been solved [4]. The resting enzyme includes one zinc(II) metal center, which is pseudo-tetrahedrally ligated with a labile water molecule and so-called "SNS" ligand environment containing one N-histidine and two S-cysteine side chains. The nitrogen and sulfur atoms are provided by the histidine and cysteine residues of a single polypeptide chain [5]. Several LADH models have been previously reported with the same electron donor atoms as the metalloenzyme [6–13]. However, reactivity data was either not reported in some cases [14a–e] or it was determined for zinc LADH model complexes possessing donor atoms that are different than those within the enzyme's active site [15].

In a continuous effort to understand the catalytic activity of metalloenzymes, we have chosen to model the structure and reactivity of the zinc active site in LADH using a new and unique family

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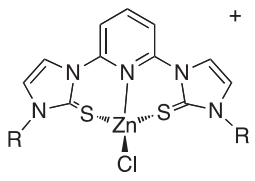
of robust SNS pincer ligands. First published in 1976, tridentate pincer ligands offer several advantages over monodentate ligands [16]. Primarily, tridentate pincer ligands offer favored metallation due to a less negative delta entropy of formation in comparison to monodentate ligands, which makes their metal complexes more stable [16]. Secondly, tridentate pincer ligands have been shown to inhibit dimerization of the metal complexes as a whole, a process that could possibly slow or inhibit catalytic activity [16,17]. Thirdly, the conformational and electronic properties of tridentate ligands can be tuned by using different starting materials in their syntheses. Depending largely on the electron count of the metal center, tridentate pincer ligands can coordinate the metal atom in either a facial or meridional fashion [16,17].

Pincer ligands have been utilized successfully in organometallic chemistry to prepare highly catalytically active and robust complexes [17]. The pincer ligand is an excellent system for use in modeling biological activity since the N-atom of pyridine, is sp^2-hybridized like that of histidine, and the thioimidazolyl S-donors have been reported by Parkin and Vahrenkamp to model thiol-derived ligands in bio-inspired zinc chemistry [18,15].

To the best of our knowledge, such tridentate pincer ligand systems have rarely been used in bio-inspired modeling chemistry. Our group has already had success in preparing tridentate SNS ligands that incorporate thione-substituted based imidazole functionalities as well as zinc model complexes that contain these ligands [19]. The tridentate ligands used in these systems were relatively rigid as the pyridine and the imidazoles were directly bound to each other. Further, in an effort to understand the presence and sterics of ancillary alkyl groups on the ability of this model system to reduce aldehydes, the ligands were prepared with imidazolyl rings having R groups of various sizes as shown in Fig. 1.

In our current work, we seek to further our understanding of the catalytic nature of the zinc complexes by tuning the structure of tridentate SNS-pincer ligands. Previously, we prepared somewhat rigid ligand systems through the use of 2,6-dibromopyridine as a ligand precursor. Here, we use the starting material 2,6-(dibromomethyl)pyridine to introduce a methylene linker into the pincer ligand, thereby allowing us to examine the effect of ligand flexibility on substrate binding toward the goal of better understanding the catalytic activity of LADH. In a similar vein, Crabtree and coworkers have shown that such a modification in Pd CNC-pincer complexes leads to improved catalytic activity in carbon-carbon bond formation reactions [20]. We expect to fine-tune further the electronic environment imparted by our ligand set through the use of imidazole- and triazole-based precursors in the preparation of the pincer ligand precursor as has been shown previously by Crabtree and Miecznikowski [21]. Furthermore, sulfur-substituted triazoline systems(1,2,4-triazolinethiones) have been prepared by others, so we have adapted their synthetic protocol for use in our current work [22].

We therefore present here the syntheses, spectroscopic and electrochemical characterization, computational study, and activity screening of various tridentate SNS-pincer complexes of zinc in which the ligand set is modified through the placement of a methylene linker between its pyridinyl and imidazolyl or triazolyl segments.



R = *i*Pr, neopentyl, *n*-butyl

Fig. 1. Zinc-based SNS model complexes previously prepared by Miecznikowski et al. [20].

2. Experimental

2.1. General procedures

All reagents used are commercially available and were used as received. Isopropyl imidazole, neopentyl imidazole, 1-isopropyl triazole, 1-*n*-butyl triazole, 1-neopentyl triazole, 2,6-bis{[(*n*-butyl)-N′-methylene]imidazole}pyridine bromide, were prepared as reported previously [23–26]. BNA^+ and BNAH were prepared as reported previously [27].

NMR spectra were recorded at 25 °C on a BrukerAvance 300 MHz NMR spectrometer. Spectra were referred to the solvent residual peak. Electrospray mass spectrometry was performed on a Micromass ZQ instrument or a Varian LC–MS instrument using nitrogen as the drying and nebulizing gas. Cyclic voltammetry experiments were performed using a Cypress Electroanalytical System with a silver wire reference electrode, a glassy carbon working electrode, and a platinum counter electrode. The supporting electrolyte for the cyclic voltammetry experiments was tetra-N-butylammonium tetrafluoroborate. The ferrocenium/ferrocene couple was used as an internal reference; reduction potential values were corrected by assigning the ferrocenium/ferrocene couple to 0.40 V versus SCE. When an inert atmosphere was needed, a M-Braun inert atmosphere glove box and standard Schlenk techniques were used with thoroughly degassed solvents. IR spectra were collected using a Thermo Nicolet AVATAR 380-FT-IR with a SMART SPECULATR reflectance adaptor. C, H, N elemental analyses were performed by Atlantic Microlab Inc. (Norcross, GA).

2.2. Crystallographic analyses

Crystals of **1**, **3**, **5b**, and **6** were mounted on a glass fiber or loop and placed in a −80 °C nitrogen stream on a Bruker diffractometer equipped with a Smart CCD at Boston College (Chestnut Hill, MA). Crystallographic data were collected using graphite monochromated 0.71073 Å Mo Kα radiation and integrated and corrected for absorption using the Bruker SAINTPLUS software package [28]. The structures were solved using direct methods and refined using least-square methods on F-squared [29]. All other pertinent crystallographic details such as *h*, *k*, *l* ranges, 2θ ranges, and R-factors can be found in Table 1.

2.3. Reactivity

In a typical reaction, 0.1 mmol of 4-nitrobenzaldehyde (or pyridine 2-carboxaldehyde), 0.2 mmol of BNAH, and 0.1 mmol of the zinc complex or 0.2 mmol $ZnCl_2$ were dissolved in 3 mL of $CDCl_3$. The reaction was heated at reflux. Aliquots of the reaction were taken at certain times and analyzed using ^1H NMR spectroscopy. All data are averages of at least two runs.

2.4. Gaussian calculations

GAUSSIAN 03 was used to perform single-point calculations and DFT geometry optimizations using the B3LYP hybrid functional with 6-31G* basis sets as provided with the software [30]. Calculations were performed on the ligands alone with R = Me in all cases. The structures of the ligands were first optimized in the gas phase as neutral and as cationic species under the C_s and C_2 point groups. Frequency analysis was performed on the optimized structures to determine whether or not they represented true minima. Small