Synthesis and Characterization of Pyridine and Pyrazine-Derived Tripodal Ligands for Use in Novel Mn(II)-Based MRI Contrast Agents

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Introduction

Molecular resonance imaging (MRI) is a powerful technique for visualizing structures inside the body. In approximately 40% of MRI scans, a contrast agent is used to improve the definition of soft tissues in the scan. After injection into the bloodstream, contrast agents can increase the visibility of blood vessels, areas of inflammation, and tumors (Figure 1).

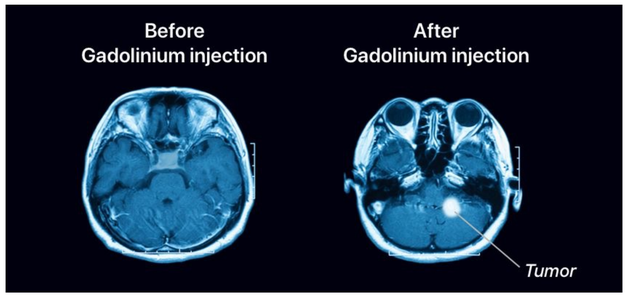
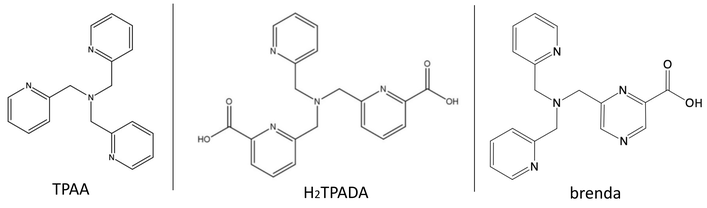


Figure 1. Images from MRI scans before and after the use of a gadolinium-based contrast agent.[1]

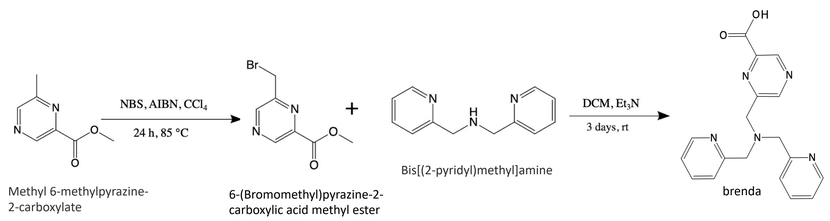
The most common MRI contrast agents are gadolinium chelates, meaning that the ligands in the complex are coordinated to a central gadolinium(III) ion. Unfortunately, in patients with renal insufficiencies, repeated use of gadolinium-based contrast agents (GBCAs) have been shown to result in severe ailments like gadolinium toxicity and nephrogenic systemic fibrosis. When kidneys fail to quickly remove GBCAs, transmetalation can occur and result in the release of free gadolinium(III), which is toxic in the body. To avoid transmetalation, stability of the chelate is an important factor to consider.[2] Thus, it is important to research alternative contrast agents that are safer and still effective.

Pyridine and Pyrazine-Based Ligands of Interest

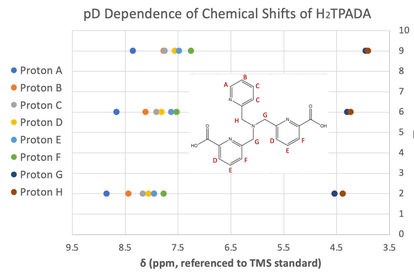
As determined in previous research, ligands that are small, water-soluble, and polydentate are more favorable for creating metal-ligand chelates.[3,4] The ligands explored here contain nitrogen and oxygen atoms that can effectively coordinate to metal ions.[5] Manganese is being examined as a potential central metal ion because it is present in the human body, is not highly susceptible to oxidation, and can form stable paramagnetic complexes.[6,7] The present research explores the syntheses and characterizations of three different tripodal ligands, including tris(2-pyridylmethyl)amine (TPAA), 6,6'-[((pyridin-2-ylmethyl)azanediyl) bis(methylene)] dipicolinic acid (H_2TPADA), and 6-[[bis(2-pyridinylmethyl)amino]methyl]-2-pyrazinecarboxylic acid (brenda). The differences between the pyrazine and pyridine rings in the ligands are compared using titration data that provides information about the conditions under which the ligands are protonated.



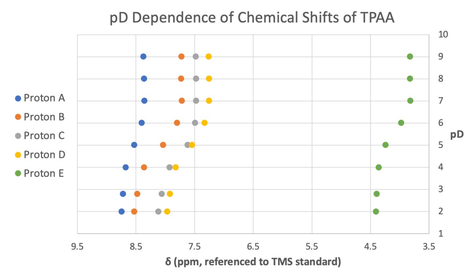
Synthesis of brenda, a Novel Pyrazine Ligand



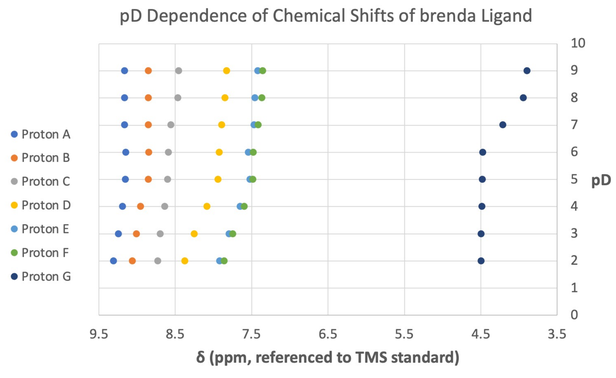
NMR Titrations



For each equivalent hydrogen given above in H2TPADA, the chemical shifts decrease (shielding increases) as the pD increases. However, as with each other NMR titration graph here, no new peaks appear at the lower pD levels where the ligand is protonated. The lack of new peaks for protonated rings demonstrates that the protons are exchanged at a rate that is more rapid than the 400 MHz NMR instrument can detect.

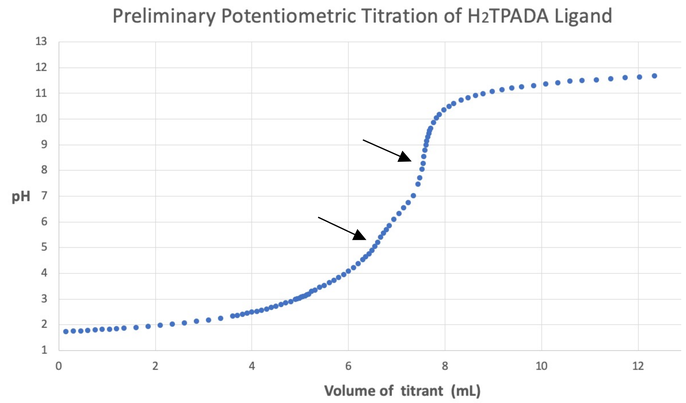


In the TPAA ligand, the four protons on the pyridine rings (Protons A, B, C, and D) experience changes in chemical shifts between pD 4-6, indicating that the ligand was successfully protonated. The increased shielding of the methylene protons (Proton E) between pD 5-7 confirm previously obtained potentiometric data that showed the pKa of the central amine to be 6.97±0.24.[8]



The protons on the pyrazine ring (Protons A and B) undergo a small change in chemical shift between the low and high pD. Comparatively, the aromatic protons on the pyridine rings (Protons C, D, E, and F) experience a greater change in chemical shift over the pD range. This indicates that pyrazine is more difficult to protonate than pyridine in such tripodal ligands. Difficulty in protonating the pyrazine could potentially mean that the presence of pyrazine could increase the stability of a Mn(II) complex due to a greater availability of lone pairs to donate compared to a complex that was made with solely pyridines. The methylene protons (Proton G) undergo a dramatic decrease in chemical shift between pD 6 and 8, which is evidence that the central amine is protonated around pD 7.

Potentiometric Titration



Two different equivalence points appear to be present in the above potentiometric titration of H2TPADA, as shown by the arrows. Since the titrant is the strong base KOH, the equivalence points demonstrate the pH values at which two non-equivalent protons dissociate from the ligand. Further analysis will be conducted on the program Hyperquad to computationally determine the protonation states of this ligand.

Future Directions

- Obtain a complete NMR titration graph for H2TPADA; continue adjusting synthesis procedure to maximize product yield
- Conduct a potentiometric titration of Mn(II)H2TPADA, brenda, and Mn(II)brenda, and analyze using Hyperquad to determine protonation states, pKas, and binding constants of the chemical species
- Explore iron(III) complexes of the tripodal ligands –> electrostatic effects created by charge transfer within the chelates may further stabilize the complexes.

Acknowledgements

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