Nickel (II) Complexes as Paramagnetic Chemical Exchange Saturation Transfer Contrast Agents

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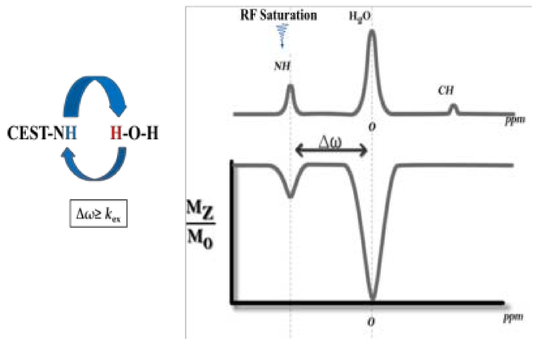
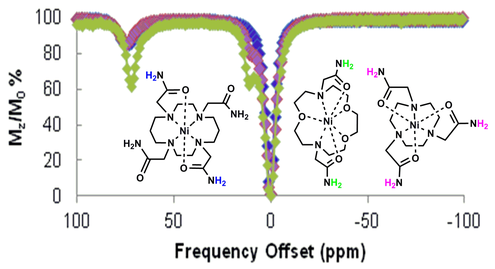
Introduction

Magnetic resonance imaging (MRI) is a powerful imaging tool used for visualizing soft tissues in the body.[1,2]. Recently, there has been an increase in the interest in the development of a new class of MRI contrast agents (CAs) that are known as paramagnetic chemical exchange saturation transfer (paraCEST) contrast agents. ParaCEST requires a paramagnetic complex with exchangeable protons (N**H**, **H**$_2$O, O**H**), which chemically exchange with bulk water in the body. The paramagnetic center of the metal ion creates a large chemical shift difference between the exchangeable protons and bulk water. The irradiation of the peaks associated with exchangeable protons saturate the spin state and, upon chemical exchange between the bulk water and agent, leads to a decrease in the bulk water signal.[1-3]

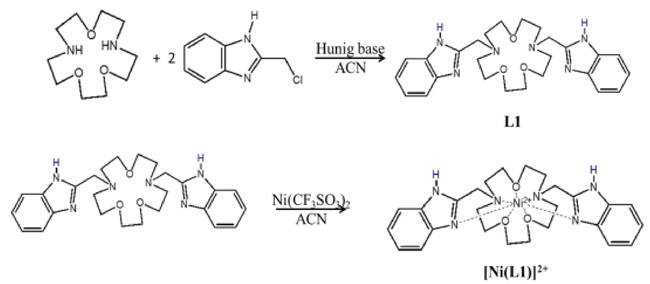


Ni(II) Complexes used as NiCEST Agents

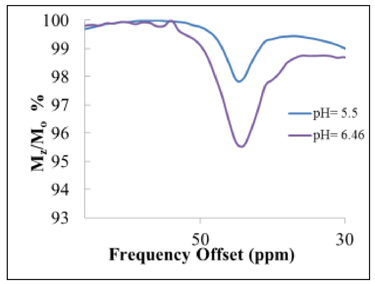


CEST recorded at 500 MHz of solutions containing 10 mM Ni(II) complex, 100 mM NaCl, 20 mM at pH 7.4, RF presaturation pulse applied for 2 seconds B_1=1000 Hz at 37°C

Synthesis of $[Ni(L1)]^{2+}$



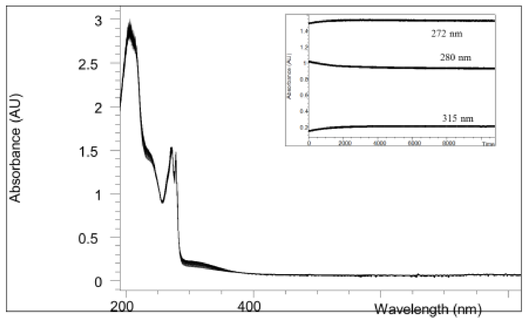
CEST



CEST recorded at 500 MHz of solutions containing 5 mM of $[Ni(L1)]^{2+}$, 20 mM buffer (pH 5.5 and 6.46) at 100 mM NaCl, RF presaturation pulse applied for 2 seconds B_1=1000 Hz at 37 °C

- The exchangeable proton (NH) of $[Ni(L1)]^{2+}$ is shifted downfield 45 ppm away from bulk water

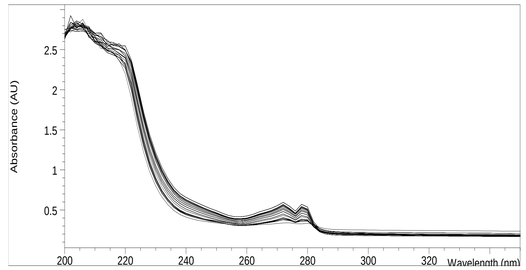
The Effect of Biologically Relevant Cations



The UV-visible spectrum of a solution containing 200 µM $[Ni(L1)]^{2+}$ complex, 10 mM MES at pH 5.5, and with 4 equivalents of $CuCl_2$. The formation of $[Cu(L1)]^{2+}$ was monitored over 3 hours at 315 nm, 280 nm, and 272 nm.

- $[Ni(L1)]^{2+}$ is fairly inert in the presences of biologically relevant cations such as Cu(II) ions.

Binding studies with Iron



The UV-visible spectra of the addition of Fe(II) to a solution containing 50 µM L1, 20 mM HEPES at pH 7.4, and 100 mM NaCl.

- There is an increase in the absorbance at 272 nm as Fe(II) is added to the solution, consistent with binding.

Summary

- The L1 ligand provides increased stability and inertness compared to previously reported of the NiCEST agents[5].
- In the presences of different biologically relevant cations and anions, the complexes were relatively inert towards loss of nickel (II) ion and produced good CEST contrast as monitored by UV-vis and NMR spectroscopy experiments, respectively.

Acknowledgements

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References

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