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Transition Metal Scaffolds as MRI Contrast Agents

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Ruthenium Transition Metal Scaffolds with Gadolinium Chelates as MRI Contrast Agents

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Introduction

Magnetic resonance imaging (MRI) is an important technique used throughout the medical field to gain improved clinical diagnostic ability. Often, different tissues can be weighted within the images if MRI contrast agents are used. Common clinical contrast agents use gadolinium to alter the T_1 relaxation times of protons within surrounding tissues. Gadolinium(III), a lanthanide cation, has a grand seven unpaired electrons with its electronic configuration [Xe] $4f^7$. There are already a plethora of gadolinium chelate contrast agents available for medical use and for research. However the sensitivity of these agents may be improved by increasing the rotational correlation time, τ_r. The goal of slower tumbling rates can be achieved by increasing their molecular weight. Thus, we propose attaching multiple gadolinium chelates to a central transition metal scaffold. The increase in molecular weight will alter the τ_r and improve the relaxation efficiency of the agent. These metal scaffolds will most likely include a Ru_3O core.

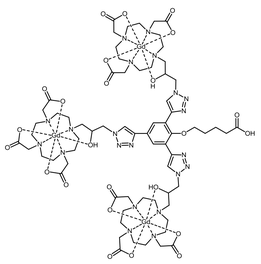
Background

Clinical MRI Contrast Agents

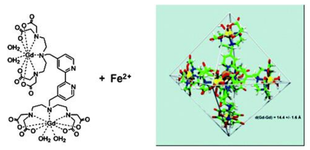
Advantages	Disadvantages
• Provides differentiation between tissues	• Limited contrast efficiency
• Improves MRI sensitivity and contrast	• Lack of multi-modal capability

Previous Work

- Longer relaxation time achieved by Meade et al. with a multiplexed probe with three separate gadolinium chelates attached to a core scaffold via click chemistry. Observed τ_r of 0.74 ns compared to 0.067 ns for the lone chelate at 298 K.[1]



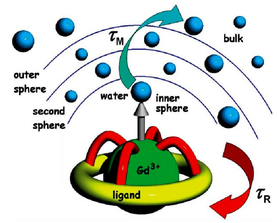
- Metallostars with six Gd(III) centers successfully used for in vivo tests in mice by Livramento et al. The metallostar contrast agent proved useful for high-field applications (9.4 T). Results were compared to a commercial agent, GdDOTA; this comparison showed improved relaxivity of up to four times the commercial agent with an external 4.7 T field.[2]



Caravan, P., et. al., *Chem. Soc. Rev.*, **2006**, 35, 512-523

MRI Contrast Agent Variables

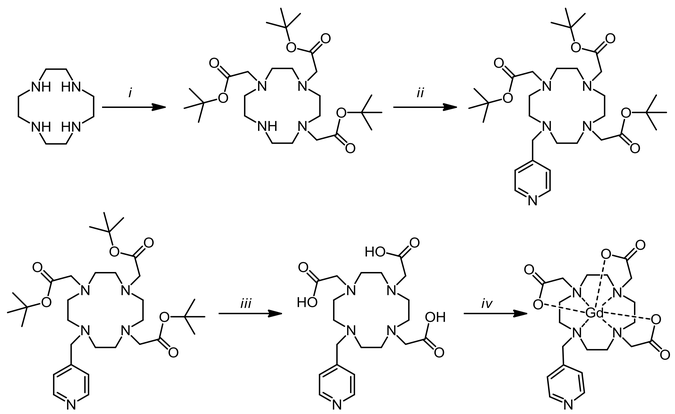
- **Residence Time(τ_m)** – The time that a given water molecule spends in direct interaction with the Gd(III) ion.
- **Tumbling Rate(τ_R)** – Describes period of the molecular Brownian motion for the Gd chelate.
- **q** – The average number of water molecules directly interacting with Gd at any given time.
- **Secondary Sphere Interaction** – The interaction with water molecules not directly bound to the Gd center, but oriented in an organized fashion relative to the chelate.



Hermann et. al. *Dalton Trans*, **2008**, 23, 3027-3047

Synthesis of Gadolinium Chelate

The desired ligand 4-(DO3A)MePy was synthesized via the functionalization of cyclen to tBuDO3A, which was further functionalized to 4-(tBuDO3A)MePy. The ligand was then deprotected with TFA. Finally, $GdCl_3$ was used to facilitate the coordination to the complex. Procedures were derived from the literature describing syntheses of similar chelates.[3, 4] This ligand is ideal for a number of reasons, including that it does not allow for the discharge of free Gd(III), which is toxic, and it is potentially capable of attaching to a transition metal scaffold core, allowing for multiple chelates to act in unison.



i – t-butyl bromoacetate, sodium acetate, DMA

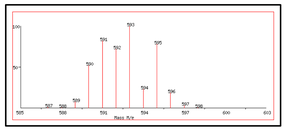
ii – Cs_2CO_3, KI, 4-bromomethyl pyridine

iii – TFA, DCM

iv – $GdCl_3$, pH 6.5

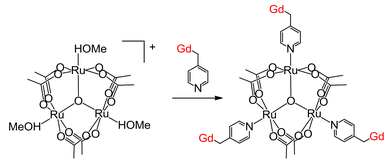
Characterization

Each compound was primarily characterized by ESI mass spectrometry, along with NMR spectroscopy. The final predicted isotopic envelope of the gadolinium chelate is presented. The peaks and intensities matched up with the experimentally observed isotopic envelope. The predicted and experimental isotopic envelopes were thus in good agreement, providing evidence for the synthesis of the chelate.



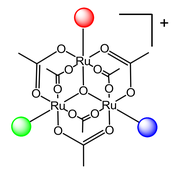
Future Directions

The pyridine arm on the ligand should allow for multiple chelates to be attached to a ruthenium oxide scaffold. The resultant macromolecule should have a slow tumbling rate. The reduction in the tumbling rate should give rise to a longer rotational correlation time τ_r, which should increase the T_1 relaxation time for protons in water molecules.



Theranostic Contrast Agents

- There is a growing need to visualize the efficacy of treatment in many areas of medicine.
- A theranostic agent combines a delivered therapeutic agent with a diagnostic agent.
- Theranostics enable visualization of drug localization and facilitate the development of tailored treatment plans.
- Multimodal imaging allows for the coregistration and validation of delivery.



- MRI contrast agent
- therapeutic molecule
- fluorescent/radioactive

References

[1] Meade, T.J., et al., *J. Am. Chem. Soc.*, **2011**, 133 (14), 5329-5337

[2] Livramento, J.B., et al., *Contrast Med. Mol. Imaging* **1**: 30-39 (2006)

[3] Hermann, et. al., *Dalton Trans*, **2008**, 23, 3027-3047

[4] Faulkner, S., et. al., *Organometallics*, **2012**, 31, 5673-5676

[5] Caravan, P., et. al., *Chem. Soc. Rev.*, **2006**, 35, 512-523

Acknowledgements

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