Click Chemistry Towards Allyl-Polymer MRI Contrast Agents: Solubility, Kinetics, And Magnetic Responses

Mingrui (Lily) Gong, Bryan Beckingham, and Michael Minkler

The general principle of Magnetic Resonance Imaging (MRI) is that it exerts a strong external magnetic field to force protons in the body to align with the magnetic field. The MRI sensor then captures the energy released by the proton and records the T1 relaxation time, or the time that the proton takes to recover from the "excited" state to the equilibrium state. Water protons in different tissue structures provide different T1 values, which allow MRI to generate the scan or images. However, sometimes more detail or contrast between different tissues is required to evaluate the area of interest. In this situation, a MRI contrast agent is introduced to enhance the contrast between nearby water protons, typically by shortening the T1 relaxation time. Most of the current MRI contrast agents are gadolinium-based. Unfortunately, studies have shown that gadolinium can deposit in the body and potentially lead to severe side-effects, especially for patients with renal problems. To reduce this potential risk, a low-toxicitiy and biocompatible MRI contrast agent is sought to investigate as a possible replacement for gadolinium-based contrast agents. Here, we investigate poly (allyl glycidyl ether) (PAGE)-based materials due to its biocompatible polyethylene glycol (PEG) backbone and pendant allyl, which is amenable for click chemistry (thiol-ene coupling) as shown in Figure 1.

This pendant allyl group can incorportate magneto-responsive groups that can impact the T1 relaxation time. The experimental approach is to functionalize PAGE with various content of a magneto-responsive groups and examine its impact on the T1 relaxation time. As an initial test of this chemistry, a small molecule was synthesized by the reaction of histamine and *y*-thiobutyrolactone. This molecule contains a thiol group for reacting the PAGE-pendant allyl groups and a histamine residue for later quaternization. Once isolated, this small molecule was used to functionalize PAGE through click chemistry and quaternize it with iron(III) chloride ($FeCl_3$) to introduce the magneto-responsive character. ^1H Nuclear Magnetic Resonance (NMR) was used to stimulate the general condition in MRI and to determine its impact on T1 relaxation time. This synthesis process was successfully completed to obtain a 20 mol% functionalized PAGE that was used to investigate the T1 relaxation time in dimethyl sulfoxide (DMSO). The ratio between functionalized PAGE and DMSO was varied from 5 mg/mL to 50.1 mg/mL. Overall, T1 relaxation times decrease as the content of functionalized PAGE increases in the solution.

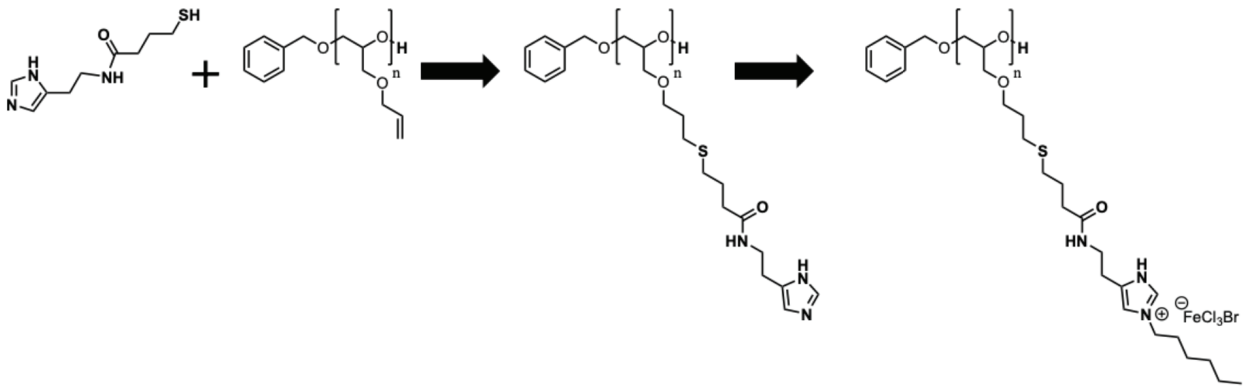

Figure 1. Reaction scheme for the synthesis of magneto-responsive PAGE.

There are still many questions that remain unanswered. For instance, we wish to understand how this T1 relaxation time compares with common Gadolinium-based contrast agents, investigate how functionalized PAGE behaves when placed in water, and possibly test it with actual cells or tissues. This experiment successfully investigated an alternative materials approach to low-toxicity and biocompatible MRI contrast agents.

Statement of Research Advisor

Lily has been very productive in learning new chemistry and techniques for synthesizing new materials for next-generation bio-compatible MRI contrast agents. Her work has laid the foundation for future work in this area and I am greatly looking forward to her future research contributions.
-Bryan Beckingham, Chemical Engineering