Magnetic resonance imaging (MRI) is indispensable for diagnostic clinical medicine and biomedical research.\(^1\) By enhancing specific features of an image, contrast agents improve the sensitivity and therefore utility of MR images. Poly(aminocarboxylate)-based Gd\(^{III}\) chelates are currently the only agents used clinically. Recently, Raymond and co-workers developed hydroxypyridonate (HOPO)-based Gd\(^{III}\) chelates that are more effective at enhancing the contrast of MR images.\(^2,3\) This attribute of HOPO complexes encourages the development of even more effective chelates. Here, we describe oligomeric HOPO-based Gd\(^{III}\) chelates generated by using ring-opening metathesis polymerization (ROMP). This approach provides contrast agents with extraordinary sensitivity and versatility.

The strength of Gd\(^{III}\)-based contrast agents can be improved by increasing the number of coordinated water molecules, optimizing the water exchange rate between bound and bulk water molecules, increasing the rotational correlation time, or increasing the number of Gd\(^{III}\) ions per molecule.\(^4\) The HOPO-based agents have an increased number of water molecules in the intramolecular environment and a near optimal water exchange rate; together, these features lead to a higher relaxivity.\(^5\) Increasing the rotational correlation time can further improve these agents as well as poly-(aminocarboxylate)-based systems involving proteins, linear polymers, dendrimers, and micellar aggregates.\(^1,5\) We reasoned that highly sensitive and tunable contrast agents could be made through incorporation of multiple HOPO-based Gd\(^{III}\) chelates into an easily functionalizable macromolecule.

Our strategy for generating contrast agents with the desired attributes relies on ROMP. We envisioned that this synthetic strategy could afford the first multivalent HOPO-based agents. ROMP is an ideal polymerization method for this purpose because it can give rise to polymers with multiple sites that can be functionalized.\(^7\) Such flexibility is beneficial because the utility of contrast agents can be increased by equipping them with targeting moieties or fluorescent probes. Moreover, the use of ROMP is advantageous because it can yield polymers of well-defined length.\(^6\) Thus, our strategy allows for multiple Gd\(^{III}\) ions to be incorporated into polymers of varying lengths, which should yield a series of agents with controlled relaxivities. We embedded a HOPO-based chelating moiety within a benzonorbornadiene unit that constitutes the backbone of the polymer upon ROMP. We integrated the chelator into the backbone to increase the rotational correlation time of the resulting macromolecules.

Polymeric contrast agents 10a and 10b were generated via a modular synthesis from benzonorbornadiene monomer 3 and HOPO-chelator 7 (Scheme 1). This strategy utilizes the novel attributes of the new monomer 3: a lanthanide binding catechol and a reactive site from which a complete chelate can be generated. This convergent strategy provides a means to use the succinimidyl esters to conjugate other groups, for example, for targeting or fluorescence imaging.
significant increase in per GdIII ion relaxivity was not observed upon transition from the monomeric agent to the shorter oligomeric agent; however, an increase in relaxivity of 1.4-fold per GdIII ion was observed for the longer polymer. Not only is the GdIII relaxivity (light bars) increased by 1.4-fold but also the molecular relaxivity (dark bars) increases 10.6-fold upon incorporation of multiple GdIII chelates. Polymer 10b has a molecular relaxivity of 111 ± 1.5 mM⁻¹ s⁻¹ (Figure 1); when compared with agents used in the clinic, this value is nearly 30-fold greater.

Our approach of incorporating multiple HOPO-type GdIII chelates using ROMP yields polymers with extremely large molecular relaxivities. These large relaxivity values are proportional to rotational correlation times estimated from the molecular weights of linear polymers of GdIII diethylenetriaminepentaacetic acid.¹⁻¹² The features of ROMP-derived polymers allow for functionalization of the monomer units and termini through orthogonal chemistry to yield multivalent, target-specific contrast agents. We envision that this strategy can be optimized to create hypersensitive, targeted imaging agents.

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Supporting Information Available: Synthetic methods and experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

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