Derivable High Spin Fe(III) and Mn(II) Phosphonate Scaffolds for Molecular MRI

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Target audience
Molecular imagers and developers of novel MRI contrast materials

Purpose
Although Gd(III) complexes have proven invaluable for blood pool and interstitial contrast, their use as targeted intracellular paramagnetic reporters has been less successful, with low molecular weight (<1kDa) lanthanide complexes showing resistance to diffusion across biological barriers. To achieve high intracellular accumulations in target tissues, paramagnetic ligands must not only maintain low molecular weight but also possess favorable chemical properties enabling optimal biodistribution. To meet this challenge, we have investigated a new class of low molecular weight, high spin Fe(III) and Mn(II) chelate complexes based on pyrophosphate and bisphosphonate ligands that demonstrate excellent chemical stability, strong T₁ relaxivity, and broad potential for derivatization and paramagnetic labeling.

Methods and Results
Iron(III) pyrophosphate
P₂O₇, a known chelator of Fe(III), is also a bridging molecule for several current drug/prodrug and radionuclear coordination complexes. We have developed a facile protocol for synthesizing a paramagnetic scaffold incorporating two P₂O₇ anions with one Fe(III), yielding a high spin, octahedral Fe(III) complex coordinating two inner sphere waters (q = 2) (Fig. 1A). At 7T field strength, r₁ for this low molecular weight complex is 5.2 mM⁻¹ s⁻¹, equivalent to relaxivity of the Gd(III) agent Gadobutrol at identical field strength. The estimated stability constant (log Kₛ) for the Fe(P₂O₇)₂ complex is > 22 at neutral pH and room temperature based on competition experiments with EDTA (log Kₛ = 26). Animal experiments reveal rapid renal clearance of the Fe(P₂O₇)₂ complex, evidence that the complex remains intact in vivo. With the Fe:pyrophosphate moiety linked to various ligands, the capacity to form the paramagnetic Fe(P₂O₇)₂ scaffold is retained with first pass. Thus thiamine, inosine, and guanine pyrophosphate derivatives, for example, are all capable of forming analogous Fe(P₂O₇)₂ paramagnetic complexes.

Mn(II) bisphosphonate
Bisphosphonates with R1 OH groups off the bridging carbon form stable tridentate 1:1 complexes with Mn(II) (Fig. 2A). Mn(II):etidronate, as a prototype, produces relaxivity at 7T in excess of 9 mM⁻¹ sec⁻¹ (Fig. 2B). Pilot experiments in normal mice show stability of the Mn:etidronate prototype in vivo. In comparison to free Mn(II), which rapidly enhances myocardium and is otherwise quickly taken up by liver hepatocytes, sequential MRI after intravenous Mn(II):etidronate reveals no evidence of cardiac enhancement, but instead a striking initial arterial blood pool phase, followed by elimination through kidneys and gallbladder/small bowel (Fig. 2C).

Discussion and Conclusion
The development of new Fe(III) and Mn(II)-based paramagnetic scaffolds offer potential for intracellular biodistribution, drug labeling, and strong T₁ contrast enhancement properties necessary for molecular MR imaging. The marked contrast enhancement of the Fe(P₂O₇)₂ complex and Mn bisphosphonate analogues is due in part to stable coordination of two coordinating inner waters, as well as significant outer sphere contributions mediated through phosphate groups. r₁ values > 20-30 mM⁻¹ sec⁻¹ at 1.5T, easily achieved with these paramagnetic complexes, will readily enable detection of novel drug complexes at micromolar concentrations using quantitative T₁ mapping techniques.

Fig. 1. A. the Fe(P₂O₇)₂ paramagnetic scaffold. B. ESI-MS of the Fe(P₂O₇)₂ scaffold

Fig. 2. A. bisphosphonate and pyrophosphate. B. etidronate. C. in vivo MRI of Mn:Etidronate, at 1, 10, and 30 min.