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 T_1 relaxivity, and broad potential for derivatization and paramagnetic labeling.

Methods and Results

Iron(III) pyrophosphate

P_2O_7, 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 P_2O_7 anions with one Fe(III), yielding a high spin, octadehedral Fe(III) complex coordinating two inner sphere waters (q = 2) (Fig. 1A). At 7T field strength, r_1 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 K_1) for the $Fe(P_2O_7)_2$ complex is > 22 at neutral pH and room temperature based on competition experiments with EDTA (log K_1 = 26). Animal experiments reveal rapid renal clearance of the $Fe(P_2O_7)_2$ complex, evidence that the complex remains intact *in vivo*. With the Fe:pyrophosphate moiety linked to various ligands, the capacity to form the paramagnetic $Fe(P_2O_7)_2$ scaffold is retained with first pass. Thus thiamine, inosine, and guanine pyrophosphate derivatives, for example, are all capable of forming analogous $Fe(P_2O_7)_2$ paramagnetic complexes.

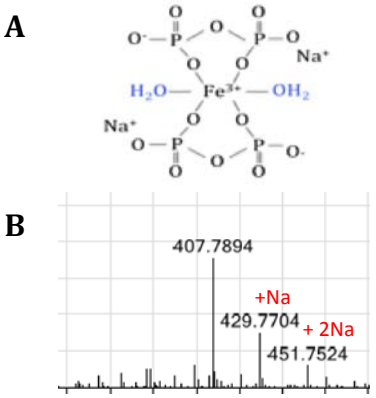

Fig. 1. **A**, the $Fe(P_2O_7)_2$ paramagnetic scaffold. **B**, ESI-MS of the $Fe(P_2O_7)_2$ scaffold

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**).

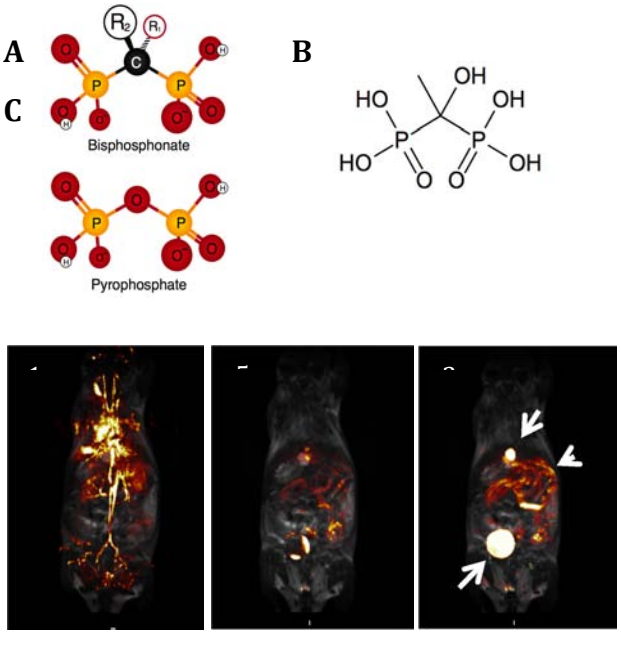

Fig. 2 **A**, bisphosphonate and pyrophosphate. **B**, etidronate. **C**, *in vivo* MRI of Mn:Etidronate, at 1, 10, and 30 min.

Discussion and Conclusion

The development of new Fe(III) and Mn(II)-based paramagnetic scaffolds offer potential for intracellular biodistribution, drug labeling, and strong T_1 contrast enhancement properties necessary for molecular MR imaging. The marked contrast enhancement of the $Fe(P_2O_7)_2$ 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. r_1 values > 20-30 $mM^{-1}s^{-1}$ at 1.5T, easily achieved with these paramagnetic complexes, will readily enable detection of novel drug complexes at micromolar concentrations using quantitative T_1 mapping techniques.