The f-Block Metals in Radiotherapy and Imaging: Tuning Size Selectivity and Chemical Inertness of Extended Macrocycles

Jenelle Weaver Literature Seminar October 29, 2019

The lanthanides, comprising the first 15 elements in the f-block, have played a central role in both diagnostic and therapeutic medicine.[1] The lanthanides have many interesting optical and magnetic properties suited for a wide-range of biomedical applications.[2] Many of the lanthanides also possess radioisotopes with desirable properties for radiotherapy and imaging as shown in **Figure 1**.[1,2,3] In general, radioisotopes of the lanthanides are produced through finely tuned nuclear reactions between neutrons or protons and a stable target.[4] As a consequence of the lanthanides similar chemical properties, chemists have relied on size differences in their ionic radii for their selective binding. [3,5] However, many of the lanthanides have not been used in a clinical setting due to a lack of suitable chelating agents.[1,4]

Isotopes	Decay Mode	Application
^{134}La, ^{135}La	β^+/Electron Capture	Therapy/Imaging
^{134}Ce	Electron Capture	Therapy
^{149}Pm	β^-	Therapy
^{153}Sm	β^-	Therapy
^{149}Tb, ^{152}Tb, ^{155}Tb, ^{162}Tb	α/β^+	Therapy/Imaging
^{166}Ho	β^+/Electron Capture/β^-	Therapy
^{170}Tm	β^-	Therapy
^{177}Lu	β^-	Therapy

Figure 1. Relevant radiolanthanides of interest for medical applications.

In order to leverage the distinct properties of the lanthanides for medical applications, they need to be administered in a chelated form *in vivo*.[1] Chelating agents must form a highly stable and inert complex with the metal ion, as decomplexation results in bone and liver uptake which is toxic to the human body.[1,3,6] For use in radiotherapy and imaging, chelators are conjugated to a biological targeting vector, such as a peptide or antibody, that can deliver the lanthanide radioisotope to its desired location.[1,2,7] Fast complexation is essential for applications that employ short-lived radioactive lanthanides, which can undergo considerable decay during the preparation of the radiopharmaceutical agent.[1] Polyaminocarboxylate macrocycles have been preferred as biological chelation agents for the lanthanides over their acyclic counterparts since acyclic agents tend to decomplex more readily under physiological conditions.[1,3,6] Macrocyclic ligands generally incorporate hard bases for complexation of lanthanides, can be easily functionalized with pendant arms, and bear pre-organized binding pockets.[6]

DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) (**Figure 2**), one of the most widely used macrocyclic chelator in nuclear medicine,[2] often requires elevated temperature and extended reaction times to achieve quantitative radiolabeling,[8] and the stability of its complexes decreases dramatically for larger ions.[1] In many instances, studies of DOTA complexes lack consideration of ionic radius, which dominates the nature of the ligand-metal interaction.[2] Recently, the design of new chelation systems have focused on variations in

macrocycle ligand design. Efforts to improve macrocycles have been directed at altering ring size, rigidity, and the functional groups of pendant arms.

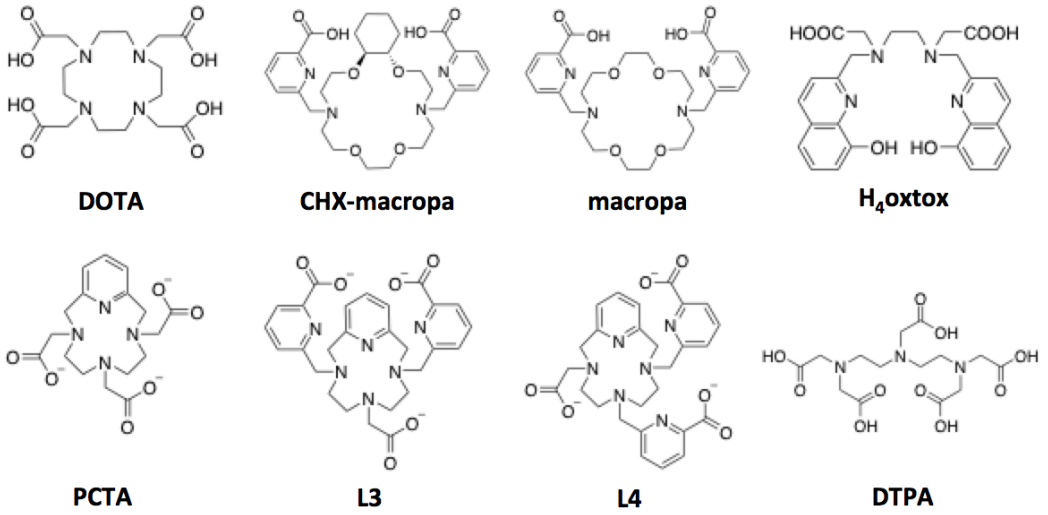

Figure 2. Structures of relevant chelators discussed.

In 2009, Roco-Sabia and co-workers synthesized macropa (N,N'-bis[(carboxy-2-pyridyl)methyl]-4,13-diaza-18-crown-6) (**Figure 2**), which exhibited unprecedented binding selectivity for the large lanthanide ions.[9] As a result of this study, Thiele and co-workers investigated the ligand CHX-macropa and the effect of increasing structural rigidity on size selectivity (**Figure 2**).[1] CHX-macropa incorporates a rigid cyclohexylene bridge into the polyaminocarboxylic macrocycle framework. Potentiometric titrations of CHX-macropa and macropa lanthanide complexes were carried out in order to determine the stability constants of the metal complexes (log K_{ML}).[1] Relative to macropa, the stability constansts of CHX-macropa decreased across the lanthanide series (**Figure 3**).[1]

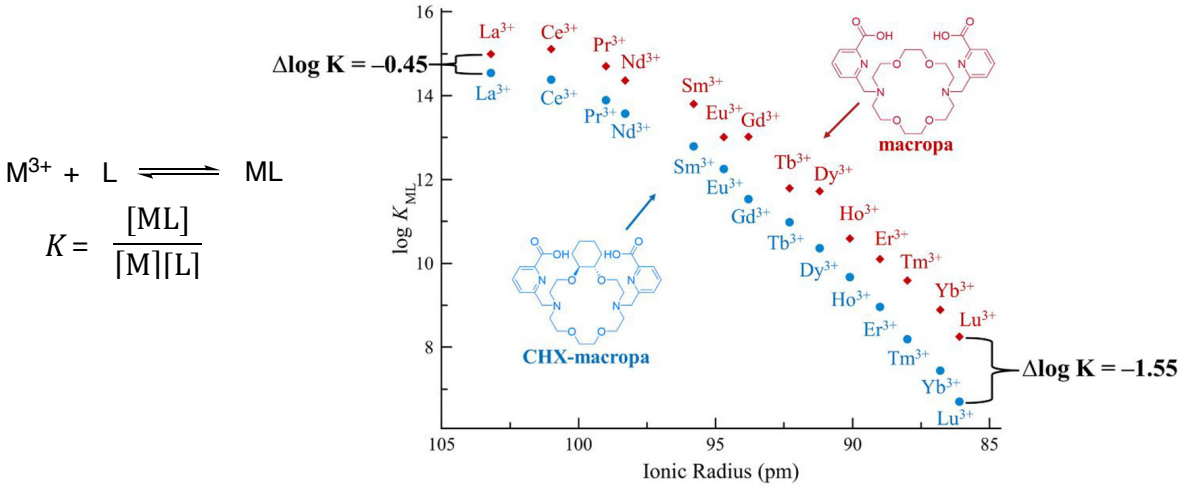

Figure 3. Comparison of stability constants between macropa and CHX-macropa. $\Delta\log K = [\Delta\log K_{\text{macropa}} - \Delta\log K_{\text{CHX-macropa}}]$.

However, upon examining the differences between K_{ML} values in the complexes as a function of lanthanide ionic radius, complexes of CHX-macropa reveal significant destabilization for the smaller lanthanides. This reflects an overall increase in binding selectivity of CHX-macropa for the larger lanthanides. This effect was believed to be a result of enhanced rigidity of the macrocycle backbone, which restricts its conformational freedom and prevents the ligand from attaining an optimal configuration when interacting with small lanthanide ions.[1]

In another study, Le Fur and co-workers sought to investigate variations in the type and position of functional groups on the macrocycle framework and its effect on stability and inertness of the resulting complexes. Expanding upon the previously synthesized PCTA (2,2'2"-3,6,9-triaza-1(2,6)-pyridinacyclodecphane-3,6,9-triyl)triacetate), the macrocycles L3 and L4 incorporate two picolinate pendant arms and a single acetate group (**Figure 2**).[10] In this study, the stability constants for Gd complexes of L3 and L4 were calculated from changes in proton relaxivity due to the dissociation of Gd^{3+} from the resulting complexes at low pH.[10] Compared to PCTA and DOTA, GdL3 and GdL4 were determined to be more stable.[10] Additionally, the dissociation rates of GdL3 and GdL4 were studied by monitoring changes in proton relaxivity over time.[10] Despite their similarity, GdL4 was found to be more inert, demonstrating that subtle changes to the ligand can have a drastic effect on the chemical properties of a chelator-metal complex.

In 2018, Wang and co-workers synthesized and investigated the acyclic chelator H_4oxtox (2,2'-ethane-1,2-diylbis(((8-hydroxyquinolin-2-yl)methyl)azanediyl))diacetic acid) (**Figure 2**) as an alternative to the previously used acyclic chelator DTPA (diethylenetriamine pentaacetic acid) and macrocyclic DOTA.[8] The thermodynamic stability constants of H_4oxtox complexes for a series of trivalent lanthanide ions (Ln^{3+} = La^{3+}, Gd^{3+}, and Lu^{3+}) were determined by UV-potentiometric titrations. In contrast to later work by Thiele and co-workers, the resulting K_{ML} values indicate stable complex formation following $Lu^{3+} > Gd^{3+} > La^{3+}$, in which Lu^{3+} is the most stable.[8] While the stability constants of H_4oxtox are comparable to other macrocyclic chelators, the study lacks definitive data on the kinetic inertness of the resulting complexes. Thus, given the available information, H_4oxtox does not outperform other known macrocyclic chelators.

Variations in the design of macrocyclic chelators have focused on modifications to ligand rigidity and the type and position of functional groups on pendant arms. The result has made relatively small improvements to size selectivity, thermodynamic stability, and the chemical inertness of trivalent lanthanide complexes. Therefore, in order to achieve drastic improvements for *in vivo* radiolanthanide chelators, more creative solutions in ligand design are needed.

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