

## Chemistry of Contrast Media

### Small Molecules

#### Chelate Complexes for Imaging

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Learning Objectives:

- How to choose the proper ligand for any given metal ion reporter (largely MR versus nuclear imaging applications)
- Compare and contrast thermodynamic and kinetic principles for metal chelate complexes
- “Hard” versus “soft” metal ions; why does the type of ligand donor atom matter

Metal ions and their complexes play an important role in medical imaging. About 85% of all diagnostic nuclear imaging procedures use a complex of the gamma emitting metastable isotope  $^{99m}\text{Tc}$  and approximately half of all MRI exams are performed using a  $\text{Gd}^{3+}$ -based  $T_1$  contrast agent. Due to their favorable nuclear properties, complexes of  $^{68}\text{Ga}^{3+}$  and  $^{64}\text{Cu}^{2+}$  are emerging as promising new radiopharmaceuticals for PET imaging. To avoid potential toxicity, these ions are always administered in chelated form. In addition to lowering toxicity, the ligand can influence the bio distribution, alter the chemical properties such as relaxivity ( $r_1$ ) or water exchange rates (PARACEST), or have a reactive functional group for covalent attachment of the complex to a targeting vector (e. g. antibody or peptide). Thus, the choice of the ligand is critical in the design of new metal ion-based imaging agents.  $\text{Gd}^{3+}$  and  $\text{Eu}^{3+}$  belong to the lanthanides ( $4f^7$  and  $4f^6$ ) and have an ionic radius of around 0.95Å. They are hard Lewis acids and prefer F, O and N donor atoms. Their preferred coordination number is 8 or 9 and the coordination geometry is typically determined by the ligand. They form highly stable chelate complexes with polyamine polycarboxylate ligands with a matching number of donor atoms. It is therefore not surprising that the macrocyclic ligand DOTA and its derivatives are exceptionally well suited as chelates for these ions. As a result of the rigid, pre-organized nature of the ligand,  $\text{Gd}(\text{DOTA})$  has high thermodynamic stability and kinetic inertness. The complex has one inner sphere water molecule in fast exchange with bulk water molecules, an important consideration for MRI applications. Substitution of glycine amide groups for the carboxylates of DOTA gives rise to a closely related ligand,  $\text{DOTA}(\text{gly})_4$ . The weaker amide oxygen donor atoms in  $\text{EuDOTA}(\text{gly})_4$  lead to a complex with lower stability but, interestingly, higher kinetic inertness than  $\text{GdDOTA}$ .

The aqueous chemistry of  $\text{Ga}^{3+}$  ( $3d^{10}$ ) is governed by its hard Lewis acid character. The  $\text{Ga}^{3+}$  ion has a smaller ionic radius than the  $\text{Ln}^{3+}$  ions and tends to form stable octahedral complexes. For this simple reason, octadentate chelators such as DOTA are not ideal for this ion despite the fact that DOTA derivatives are widely used to chelate  $\text{Ga}^{3+}$  because it is more widely available.  $\text{Ga}^{3+}$  complexes formed with the smaller, hexadentate macrocyclic ligand, NOTA, has exceptionally high kinetic inertness and thermodynamic stability compared to  $\text{GaDOTA}$ .

The chemical properties of  $\text{Cu}^{2+}$  are quite different from the  $\text{Ln}^{3+}$  and  $\text{Ga}^{3+}$  ions. It possesses borderline softness, and therefore, prefers soft donor atoms (N and S) over harder donors such as O. Being a transition metal, there is significant metal-ligand orbital overlap in  $\text{Cu}^{2+}$  complexes. The most common coordination geometry in  $\text{Cu}^{2+}$  complexes is square planar or distorted octahedral.  $\text{Cu}^{2+}$  forms very stable complexes with the rigid cross bridged cyclam derivatives. These complexes have extremely high kinetic inertness and are well suited for nuclear medicine applications.