

3.2.1.6 Choice of Metal

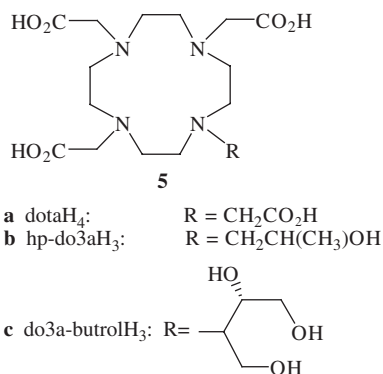
As indicated in the preceding discussion the metal ions of particular interest for MRI contrast agent applications include high spin d^5 Fe^{3+} , high spin d^5 Mn^{2+} , f^7 Gd^{3+} and f^5 Dy^{3+} (Table 1). The high magnetic moment and long electronic relaxation time of Gd^{3+} make it the most widely used ion in MRI applications. Compared to Gd^{3+} the smaller ionic radius of Mn^{2+} leads to a shorter metal-proton distance for coordinated water which to some extent offsets the smaller magnetic moment of Mn^{2+} . The long electronic relaxation time of Mn^{2+} is also an attractive feature but this metal ion shows cardiovascular toxicity at low doses limiting its utility in MRI applications. Iron, in the form of Fe^{3+} , is a d^5 ion like Mn^{2+} but without the cardiovascular toxicity. In MRI applications Fe^{3+} is typically used in the form of insoluble iron oxide particles which are neither coordination compounds in the usual sense nor solution species. There has been some interest in Dy^{3+} as a T_2 agent since its very short electronic relaxation time leads to its having a negligible effect on T_1 but the high magnetic moment is effective in reducing signal intensity from its effect on T_2 . A Dy^{3+} complex has been tested in humans for identifying ischemic regions in heart and kidney. However, although the use of Dy^{3+} complexes offers interesting possibilities, in general they may not prove competitive with more familiar and medically established Gd^{3+} agents.

3.2.1.7 Choice of Ligand

The ability to provide very high thermodynamic stability, access of water to an inner sphere binding site and allow rapid exchange without compromising stability are important factors in the choice of ligand for MRI applications. Since lanthanide ions, particularly Gd^{3+} , are the metal ions most commonly used in MRI applications anionic hard donor ligands represent an obvious choice. In particular the polyaminepolycarboxylic acid proligand diethylenetriamine pentaacetic acid (**3a**, $dtpaH_5$ or $DTPA^1$) and its derivatives (**3b–e**) show strong binding to Ln^{3+} ions through having ‘hard’ oxygen donor atoms, being polydentate (so stabilising the complexes through the chelate effect) and being able to achieve the high coordination numbers required by Ln^{3+} ions in a 1:1 ligand/metal complex. The well-known proligand $edtaH_4$ (**4**) is less well suited than $dtpaH_5$ for Ln^{3+} binding since it offers a maximum coordination number of only 6 in a 1:1 ligand/metal complex. Thus $edta^{4-}$ alone cannot saturate the coordination sphere of a lanthanide ion which might typically

¹Very often ligand abbreviations are written in upper case ignoring acidic hydrogen atoms so that ethylenediamine tetra-acetic acid is often referred to as EDTA. However, this can create problems in accurately writing formulae. Under this definition, to be accurate, the formula of the dicalcium salt of ethylenediamine tetra-acetic acid has to be written $Ca_2(EDTA-4H)$ because four H^+ ions have been lost in forming the complex. To avoid this situation, in this book a lower case text abbreviation is also used which includes ionisable hydrogen in the formula of the proligand, hence $edtaH_4$ and $Ca_2(edta)$ for the compound containing $2Ca^{2+}$ and $edta^{4-}$. The abbreviation $edta$ simply represents the core of the molecule with hydrogen removed as neutral H atoms. The upper case acronyms are also used in the usual less formal manner often seen in literature, but not in the construction of formulae representing the actual composition of compounds.

exhibit 8- or 9-coordination. Another structural motif used in lanthanide ion sequestering agents involves a cyclic polyamine core as found in dotaH₄ (**5a**) and its derivatives (**5b,c**). Here additional stability is achieved as a result of the rigid structure of the cyclic polyamine core which preorganises the carboxylate groups into an arrangement better adapted to coordinate to the metal ion (Figure 8). The cyclic polyamine structure also provides an element of steric protection inhibiting the approach of competitor ligands to the metal and slowing down any ligand dissociation.



Stability constant data can provide a basis for comparing complexes and assessing the effect on their properties of structural changes in their ligands. However, it should be noted that the quoted values for the stability constants of a particular complex can show some variability. In part this may reflect differences in the conditions of measurement since the values obtained will often depend upon factors such as solution pH and ionic strength. Provided the stability constant data is obtained under similar conditions they provide a useful means of comparing complexes. The stability constants of some complexes of polyamine-carboxylate ligands are shown in Table 2. These reveal increases in the log *K* values for Gd³⁺ complexes in going from edta⁴⁻ to

Table 2 *Stability constants for some selected 1:1 polymincarboxylate complexes*

Complex ^a	{Gd(edta)} ⁻	{Gd(dtpa)} ²⁻	{Gd(dota)} ⁻	{Gd(dtpa-bma)}	{Gd(hp-do3a)}
log <i>K</i>	17.3	22.4	25.8	16.9	21.8
<i>K</i> _{obs} (10 ³ s ⁻¹) ^b	14 × 10 ³	1.2	0.021	>20	0.064
Complex ^c	{Yb(dtpa)} ²⁻	{Pb(edta)} ²⁻	{Bi(dtpa)} ²⁻	{Gd(do3a)-butrol}	
log <i>K</i>	22.6	18.1	27.8	23.8	

^a Cited with *N*-methylglucammonium (NMG⁺) as the counterion for log*K* values.

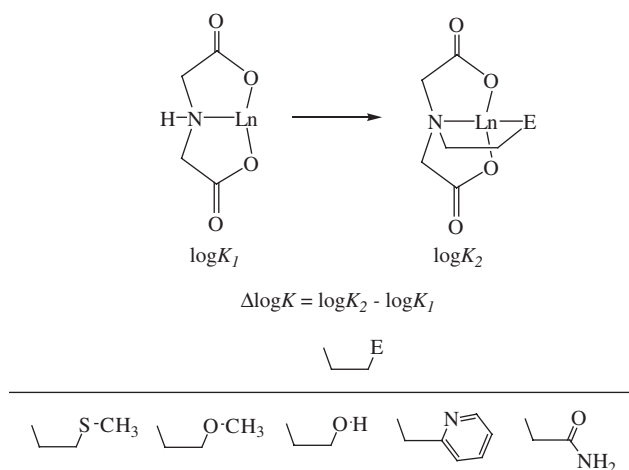
^b Observed rate constant for acid dissociation in 0.1 M acid.

^c Cited with Na⁺ as the counterion.

dtpa⁵⁻ then dota⁴⁻ as might be expected from the discussion above. The values also reveal how changes to the ligand structure can significantly affect the stability of the complex. The stability constant of [Gd(hp-do3a)] is 10,000 times smaller than that of [Gd(dota)]⁻ yet, despite the general similarities between the hp-do3a and do3a-butrol ligands, in the case of [Gd(do3a-butrol)] the reduction is only 100-fold compared to [Gd(dota)]⁻. In part this reduction in stability constant for the substituted dota⁴⁻ ligands reflects the removal of a coordinating carboxylate group from the ligand structure. However the nature of the substituent is also important as shown by 100-fold difference in stability constants between [Gd(hp-do3a)] and [Gd(do3a-butrol)]. Depending upon its structure a substituent might inhibit ligand binding or, conversely, it might improve stability through inhibiting the approach of competitor ligands. If the substituent contains donor atoms in suitable locations for binding to the metal additional stability may be conferred on the complex through chelate formation.



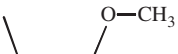

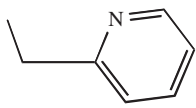
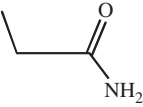
The relative effects of different donor atom types on lanthanide ion complex stability have been measured and the results expressed in terms of a $\Delta\log K$ value. This value is the increase in $\log K$ resulting from the reaction in Scheme 1 in which the hydrogen of the amine dicarboxylate ligand NH group is replaced by an additional chelating group. The results obtained are summarised in Table 3.

The thermodynamic stability of the complex does not provide the complete picture. The rate of ligand dissociation is also important. A kinetically inert complex of low stability might be less prone to release the bound metal ion than a labile complex of high stability. One measure of ligand lability is provided by acid dissociation rates and some examples are provided in Table 2. The edta⁴⁻ ligand, which is unable to saturate the Gd³⁺ coordination sphere, shows a high dissociation rate. Complexes of dtpa⁵⁻ and its derivatives show much smaller dissociation rates but within this group a comparison of $\log K$ values and k_{obs} show that there is no good correlation between kinetic behaviour and



Scheme 1

Table 3 Variation in stability constants for chelating groups in Scheme 1 complexes

logK	
0	
1.6	
2.9	
3.3	
3.38	

thermodynamic stability. The modification of a ligand structure through substitution must be expected to change the stability and kinetic behaviour of its complexes but it cannot be assumed that any particular change will be beneficial.

The nature of the metal ion is also important in determining the stability and kinetic behaviour of the complex. However, within the lanthanide series these effects may be small. The absence of significant crystal field effects means that ionic radius is an important parameter yet, despite the difference in ionic radii, there is little difference in $\log K$ between the closely related lanthanide ions Gd^{3+} (ionic radius 93.8 pm) and Yb^{3+} (ionic radius 86.8 pm) for complexes with dtpa^{5-} (Table 2). Typically it might be expected that the ion with the smaller radius would show the higher binding constant. However, with large polydentate ligands such as dtpa the structure and flexibility of the ligand also plays an important role in determining complex stability since this also reflects the ‘goodness of fit’ between the metal ion and the structural arrangement adopted by the ligand. In the case of the larger p -block ion Bi^{3+} (ionic radius 103 pm) a significantly higher stability constant is found with dtpa^{5-} .