Dy$^{3+}$ ion has 5 unpaired electrons but because of a large orbital contribution its effective magnetic moment is 10.5 BM, substantially higher than the spin only value of 5.9 BM. The very short electronic relaxation time of Dy$^{3+}$ means that it has little effect on $T_1$ but can act as an effective $T_2$ agent. Advantages over iron oxide particles include improved tolerance and more rapid injection with the prospect of differentiating ischemic tissue from that with normal perfusion. However, similar diagnostic information might be obtained using cheaper, more well established Gd$^{3+}$ complexes.

3.2.1.5 **Coordination Compounds as Paramagnetic MRI Contrast Agents**

The design of coordination compounds for use as paramagnetic MRI contrast agents presents a particular challenge to the coordination chemist. In order to develop a successful agent it is necessary to reconcile several conflicting requirements. The biological requirement is for a compound with low toxicity combined with suitable biodistribution and pharmokinetic behaviour. Toxicity is a particular issue since relatively large doses are required for an MRI contrast agent to be effective, typically in the range 0.1–0.3 mmol kg$^{-1}$. This makes it particularly important that the metal is not readily released from the ligand as this would allow binding to serum proteins or other in vivo complexing agents. Transfer of the metal in this way would result in a loss of control over metal ion toxicity and biodistribution. Rather the complex should remain intact and be excreted completely and rapidly following the imaging procedure. This requires the complex to be thermodynamically stable and kinetically inert. Suitable modification of ligand structure might then be used to optimise biodistribution and pharmokinetic behaviour.

The basic requirements for an effective contrast agent are that it should have a high magnetic moment, accommodate at least one water molecule in the first coordination sphere of the metal ion and that the coordinated water should undergo rapid exchange with bulk water. In order to attain a high magnetic moment it is necessary to choose high spin metal ions with a large number of unpaired electrons. Such complexes have little or no crystal field stabilisation energy, a property typically resulting in labile behaviour. This labile behaviour is useful in being associated with rapid water exchange. However, the presence of a vacant binding site for water in the complex provides a potential pathway for initiating ligand dissociation. Complexes in which the metal coordination sphere is completely saturated by the ligand so that aquation is blocked would be more inert. Thus the requirements for an effective contrast agent appear to be at odds with those of a complex with suitable in vivo properties. Since complex stability in vivo cannot be attained by using kinetically inert metal ions, stability must be attained largely through the thermodynamics of complex formation. Complexes with very high stability constants are needed. This in turn implies polydentate ligands of suitable structure and with donor atom types chemically well matched to the metal ion. In the case of lanthanide ions such as Gd$^{3+}$, for example, hard oxygen donor atoms would be preferred for
compatibility with the hard metal centre. The ligand also needs to be anionic as this will promote binding to the metal cation and, if an anionic complex is formed, interactions with outer sphere water will be increased, improving relaxivity. However, charged complexes may be less acceptable in terms of their \textit{in vivo} effects as mentioned in Section 3.2.1.9. Careful selection of the ligand structure can allow the stability of the metal ligand complex to be improved without reducing the lability of coordinated water. As an example a relatively rigid backbone, which requires the ligand donor atoms to occupy locations close to those which will be occupied in the complex, should give a more stable complex than a corresponding ligand with a non-rigid backbone. The more rigid ligand is said to be ‘preorganised’ in that the structural arrangement of the ligand atoms needs to change little in forming the complex (Figure 8). This reduces the energy penalty associated with complex formation which arises from necessary changes in ligand structure.

![Diagram of preorganised ligand structure](image)

**Figure 8** A schematic representation of how a preorganised ligand can offer higher complex stability compared to a non-preorganised counterpart. Both complex types contain labile water. (a) Little structural change is needed in the ligand during complex formation and the rigid backbone offers protection of one side of the metal ion from attack by other ligands. (b) Energy is required to change the ligand structure to that present in the complex making complex formation less thermodynamically favourable. The ligand structure is less well suited to preventing attack by competitor ligands.
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 d⁵ Fe³⁺, high spin d⁵ Mn²⁺, f⁷ Gd³⁺ and f⁵ Dy³⁺ (Table 1). The high magnetic moment and long electronic relaxation time of Gd³⁺ make it the most widely used ion in MRI applications. Compared to Gd³⁺ the smaller ionic radius of Mn²⁺ leads to a shorter metal-proton distance for coordinated water which to some extent offsets the smaller magnetic moment of Mn²⁺. The long electronic relaxation time of Mn²⁺ 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 Fe³⁺, is a d⁵ ion like Mn²⁺ but without the cardiovascular toxicity. In MRI applications Fe³⁺ 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 Dy³⁺ as a T₂ agent since its very short electronic relaxation time leads to its having a negligible effect on T₁ but the high magnetic moment is effective in reducing signal intensity from its effect on T₂. A Dy³⁺ complex has been tested in humans for identifying ischemic regions in heart and kidney. However, although the use of Dy³⁺ complexes offers interesting possibilities, in general they may not prove competitive with more familiar and medically established Gd³⁺ 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 Gd³⁺, 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, dtpaH₅ or DTPA¹) and its derivatives (3b–e) show strong binding to Ln³⁺ 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 Ln³⁺ ions in a 1:1 ligand/metal complex. The well-known proligand edtaH₄ (4) is less well suited than dtpaH₅ for Ln³⁺ binding since it offers a maximum coordination number of only 6 in a 1:1 ligand/metal complex. Thus edta⁴⁻ alone cannot saturate the coordination sphere of a lanthanide ion which might typically

¹ Very 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 Ca₂(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 edtaH₄ and Ca₂(edta) for the compound containing 2Ca²⁺ and edta⁴⁻. 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.

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