The contrast in an MRI image arises from the differing signal intensities (*SI*) arising from the different volume elements. These SI are related to the concentrations of water protons, [H], in the different tissues in the body so that muscle, fat and bone, for example, might produce signals of differing intensities. However, signal intensity is not only dependent on the concentration of water, it also depends upon the rate at which the protons concerned relax from the excited state to the ground state as a result of interactions with their surroundings and with other protons. A 'longitudinal' relaxation time, T_1, is associated with the transfer of energy from the excited protons to their surroundings and a 'transverse' relaxation time, T_2, is associated with the exchange of energy between ground state and excited state protons. The reciprocals of these times are the relaxation rates for the two processes. One further complication in the measurement is the need to allow for the movement of water into or out of the volume element during the time the measurement is being made. This is expressed in a parameter H_v. The MRI machine operator can optimise the image produced by varying two operator defined parameters. These are *PR* and *SE,* which respectively represent the applied radiofrequency pulse repetition time and the time during which the emitted radiation is detected, *i.e.* the spin echo time. Taking these various parameters into account an approximate expression for the signal intensity from a given volume element is given by Equation (1).

$$SI = [\mathrm{H}]Hv[\exp(-SE/T_2)\{1-(-PR/T_1)\}] \quad (1)$$

Signal intensity tends to increase with increasing $1/T_1$ and decrease with increasing $1/T_2$ but, for most tissues, the average T_2 values are only a fraction of the corresponding T_1 values. As an example values of 747 ms for T_1 and 71 ms for T_2 were found in Putamen tissue in the brain. In a magnetic field of 1.4 T (corresponding with a frequency of 60 MHz) values for T_1 typically lie in the range 200–500 ms for different tissue types. The operator can select radiofrequency pulse sequences to emphasise the effect of changes in $1/T_1$ compared to $1/T_2$ (T_1 weighted) or, conversely, to emphasise $1/T_2$ compared to $1/T_1$ (T_2 weighted).

3.2.1.2 Contrast Agents for Magnetic Resonance Imaging

In clinical applications of MRI it is often useful if the contrast between regions in the image can be altered beyond that possible using adjustments of the scanning equipment. A simple way to do this would be to change the relative signal intensity by changing the concentration of water in one region compared to another. As an example, attempts to displace liquid containing water from the GI tract using $C_8F_{17}Br$ (Imagent®), an inert liquid free of water protons, showed the procedure to be possible. However, the approach was impracticable because of the cost and side effects of the treatment. Similarly replacement of water by deuterium oxide (heavy water) is precluded by the toxicity and quantity of heavy water required. Fortunately there is another way in which image contrast might be manipulated. The magnitude of *SI* depends, not only upon [H], but also upon T_1 and T_2 so that compounds capable of modifying

relaxation times could be used to modify *SI* and hence image contrast. Dissolved or colloidal paramagnetic materials can have a profound effect on the values of T_1 and T_2 and so can change the signal intensity in an MRI scan. If a paramagnetic compound is introduced into the subject and enters one region or tissue type in preference to another, contrast enhancement should result. Materials which can produce this effect are known as MRI contrast agents.

Contrast agents can increase $1/T_1$ and $1/T_2$ to varying degrees depending on the applied magnetic field and the nature of the agent. As examples, contrast agents containing Gd^{3+} complexes tend to increase $1/T_1$ and $1/T_2$ by broadly similar amounts and T_1 weighting typically gives the best images with these because of the dominance of the $1/T_1$ term in determining the magnitude of the signal intensity. In contrast iron oxide particles tend to have a much larger effect on the/T_2 term and so are usually best used with T_2 weighted imaging.

Paramagnetic materials are those in which the atoms contain unpaired electrons. Some non-metal compounds of this type (known as radicals) can be obtained but they tend to be highly reactive and toxic. The nitroxide radical provides an example of one of the more stable groups which may appear in non-metal compounds of this type (*e.g.* **1**). Apart from the problems of reactivity associated with non-metal radicals, such compounds tend to have only one unpaired electron. In contrast compounds of transition metals or lanthanides often contain more than one unpaired electron and do not normally show the reactivity associated with radicals. As examples Cr^{3+} contains 3 unpaired electrons, Mn^{2+} and Fe^{3+} in their high spin states contain 5 unpaired electrons and Gd^{3+} contains 7 unpaired electrons (Figure 5). Complexes of such metal ions, which also show suitable biodistribution and pharmokinetic behaviour, have potential for use as MRI contrast agents through their effects on T_1 and T_2. However, the design of the ligands used to complex the metals is crucial if the necessary combination of stability and *in vivo* behaviour is to be obtained. The choice of ligand also has an important effect on the ways in which the complex can influence T_1 and T_2.

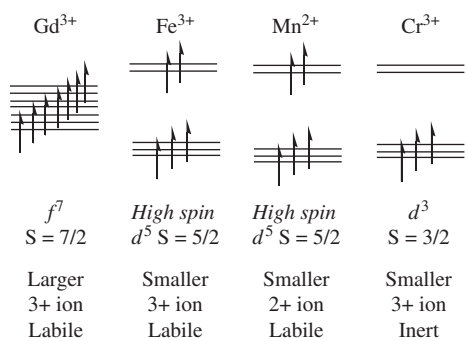
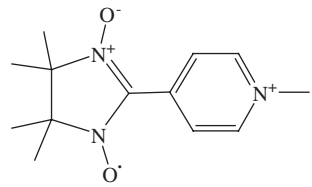


Figure 5 *Crystal field splitting diagrams to show the number of unpaired electrons in Gd^{3+}, high spin Fe^{3+}, high spin Mn^{3+} and Cr^{3+}*



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The mechanisms through which a paramagnetic metal ion can influence the relaxation times of a proton in a water molecule are quite complicated. At the simplest level it might be expected that the larger the magnetic moment of the metal ion and the closer it is to the proton, the greater will be its effect. Thus Gd^{3+} with 7 unpaired electrons would be expected to be better than high spin Mn^{2+} or Fe^{3+}, each having 5 unpaired electrons, and these ions in turn should be better than Cr^{3+} with only 3 unpaired electrons. It might also be expected that a complex in which a water molecule is directly bonded to the metal ion would give the shortest metal to proton distance. Such a complex should have a greater effect than one in which other ligands saturate the metal ion coordination sphere and prevent any direct water metal interaction. In this context it is important to distinguish between inner sphere water molecules, which are directly bonded to the metal ion, and outer sphere water molecules which are adjacent to the metal complex but not bound to it. There is also the possibility that such outer sphere water molecules may hydrogen bond to a ligand donor atom bound to the metal and so, in effect, become inner sphere (Figure 6). In lanthanide ion complexes water or carboxylate ligands are particularly important in this respect. The situation is further complicated by the effects of

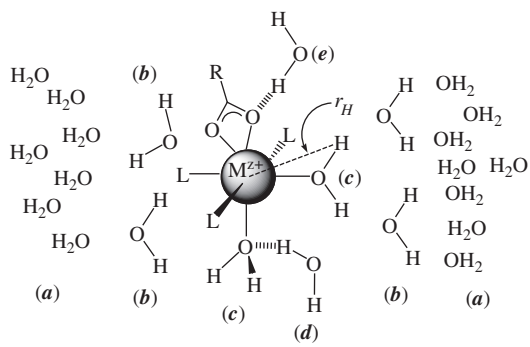

Figure 6 *A schematic representation of the different types of water molecule around a metal ion in a complex* $[ML_3(RCO_2)(H_2O)_2]^{z+}$ *in aqueous media (a) bulk water; (b) 'outer sphere' water; (c) 'inner sphere' water. The distance rH is from the metal ion to a proton in an inner sphere water molecule; (d) an 'outer sphere' water molecule hydrogen bonded to an inner sphere water molecule so that one proton becomes essentially inner sphere; (e) an 'outer sphere' water molecule hydrogen bonded to an inner sphere ligand carboxylate oxygen so that one proton becomes essentially inner sphere*

exchange between the different types of water molecule present. If a water bound to a paramagnetic metal ion exchanges with bulk water in the liquid at a very slow rate compared to the proton relaxation rate, communication of the effect of the paramagnetic ion to the bulk water is very poor. An effective MRI contrast agent will need to show fast exchange of the bound water relative to the relaxation rates. Thus kinetically inert ions such as Cr^{3+} are ineffective compared to labile ions such as Mn^{2+}. The interplay between the proton relaxation times and dynamic processes involving the water molecules in the region of the metal ion is an important contributor to the effectiveness of a metal complex as an MRI contrast agent. In designing metal complexes for use as MRI contrast agents it is necessary to select ligands which not only confer good *in vivo* properties on the complex, but which also optimise the dynamics of the metal water interaction with respect to relaxation times.

3.2.1.3 Relaxivity

The effect of a metal complex $\{ML\}$ on T_1 or T_2 can be conveniently summarised in a parameter known as the relaxivity, r_i ($i = 1$ or 2; r_1 and r_2 being respectively associated with T_1 and T_2). The relaxivity, r_i, is related to the observed reciprocal relaxation time, or relaxation rate, $1/T_{iO}$ ($i = 1$ or 2) and the concentration of the metal complex, $[\{ML\}]$. However, the observed relaxation rate is made up of two components, $1/T_{i\mathrm{P}}$ which is the relaxation rate in the presence of $\{ML\}$ and $1/T_{i\mathrm{D}}$ which is the relaxation rate in the absence of $\{ML\}$, that is the diamagnetic contribution to the relaxation rate, as shown in Equation (2). The relaxivity associated with the complex can be determined from measurements of the observed relaxation rate $1/T_{iO}$ at different concentrations of the metal complex. Since only $1/T_{i\mathrm{P}}$ is dependent on $[\{ML\}]$ a plot of $1/T_{iO}$ against $[\{ML\}]$ gives a line of slope r_i with an intercept of $1/T_{i\mathrm{D}}$ according to Equation (3).

$$1/T_{iO} = (1/T_{i\mathrm{P}}) - (1/T_{i\mathrm{D}}) \quad (i = 1 \text{ or } 2) \tag{2}$$

$$r_i\,[\{ML\}] + (1/T_{i\mathrm{D}}) = 1/T_{iO} \quad (i = 1 \text{ or } 2) \tag{3}$$

The units of $[\{ML\}]$ are mmol l^{-1} for solutions but should be expressed in mmol kg^{-1} for soft tissues which contain significantly less than 100% water. The units of r_i are thus l $mmol^{-1}$ s^{-1} for solutions and kg $mmol^{-1}$ s^{-1} for soft tissues.

Since the relaxivity, r_i associated with a metal ion depends upon $T_{i\mathrm{P}}$ it will be affected by the various factors which contribute to the value of $T_{i\mathrm{P}}$. These include the temperature, the viscosity of the medium, the magnetic field and so the radiofrequency used, the magnetic moment of the metal ion, the number of water molecules attached to the metal ion (q), the distance between the metal ion and the proton of the water molecule (r) and the dynamic behaviour of the system. The dynamics of the system can be described by a group of correlation times which relate to the rotation of the metal complex (τ_R), the residence time for a water molecule bound to the metal (τ_M) and the effect of solute-solvent collisions (τ_v). A further correlation time has to be taken into account which is