SOME PHYSICOCHEMICAL PROPERTIES OF THE GADOLINIUM-DTPA COMPLEX, A CONTRAST AGENT FOR MRI

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• *The physicochemical characteristics of a good contrast agent for NMR are met by the gadolinium-DTPA complex. Measurements of density, viscosity and osmotic pressure of solutions to be injected are reported. A short survey of the results of X-ray analysis of the di-sodium-Gd-DTPA is given.*

In clinical imaging using ^{1}H-NMR the registered signal is generated mainly by protons of the H_2O molecules in body fluids and tissues. The signal intensity depends on the spin-lattice relaxation time (T1) and the spin-spin relaxation time (T2), on the hydrogen density in a particular region, and on flow. Paramagnetic substances injected intravenously into animals shorten T1 of the nuclei and act as signal enhancers. They have the potential to improve the specific identification of pathological tissue and to provide a measurement of organ function. The utilization of paramagnetic compounds, especially metal ions containing unpaired electrons, has been suggested.[1-5] The contrast effect of a paramagnetic ion is an indirect one resulting from the influence on relaxation of surrounding protons, contrary to the direct effect of iodinated radiographic contrast agents in X-ray imaging. A good intravenous contrast agent for NMR would have the following characteristics:

1. An optimum magnetic moment, μ_B, increasing the relaxation rate, expressed as

$$\frac{1}{T1} \sim \mu_B{}^2 ,$$

with an effect even in low concentrations.

2. A low toxicity and a sufficient solubility in water. The solutions must be neutral and stable with a low viscosity and an acceptable osmolality.

3. A useful correlation time constant, τ_C, of $10^{-7} - 10^{-8}$ (s) would be convenient. The higher the molecular volume of the paramagnetic compound, the slower its tumbling motion.

4. An optimal number of water molecules in the surrounding sphere of the paramagnetic center. Proton relaxation enhancement is directly proportional to the number of available coordination proton ligands per paramagnetic ion.

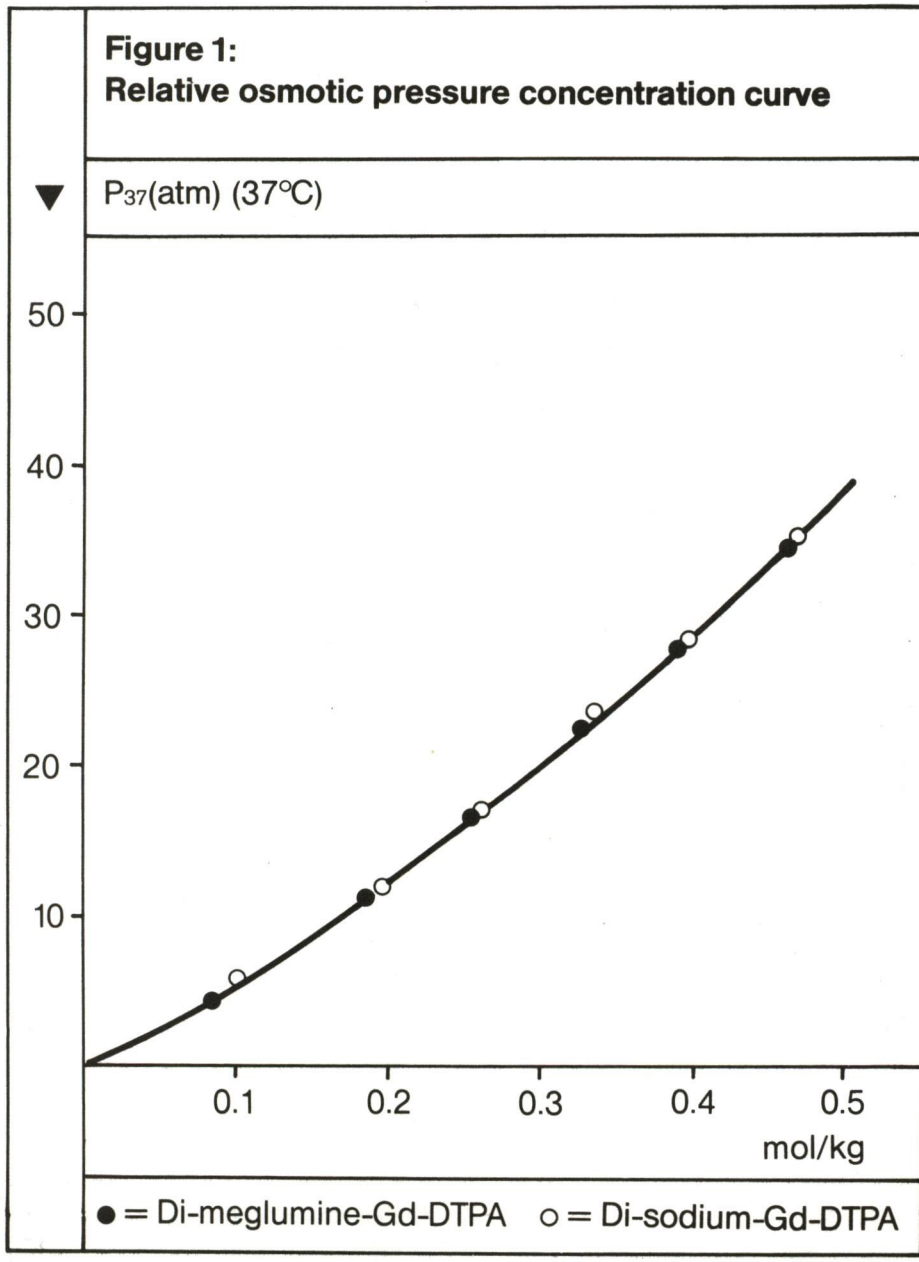
5. A sufficiently low ion-to-nucleus distance r. This can be expressed as

$$\text{dipolar interaction} \sim \frac{1}{r^n} .$$

The increase of relaxation decreases as the n^{th} power of the distance between the proton and the paramagnetic center.

Regarding this catalogue of characteristics, we have chosen the Gadolinium-DTPA complex as a contrast agent for MRI, for the following reasons: The Gd^{3+}-ion contains seven unpaired electrons in the well protected 4f-electron orbitals, its magnetic moment is as high as 8.0 Bohr magnetons[3] and it reveals

an unusually strong hydrogen-proton spin-lattice relaxation effect.[6] However, it was anticipated that the well known serious toxicity of the rare earth element Gadolinium would prevent its application as a versatile contrast agent to human beings.[2] This problem was solved by complexation of the Gd^{3+}-ion with diethylenetriaminepentaacetic acid (DTPA). The very stable Gd-DTPA complex (log K1 = 22-23)[7] has a LD_{50} in rats after intravenous injection of 10 mmol/kg, while the LD_{50} of gadolinium chloride was only 0.3 mmol/kg.[5] This complex is freely soluble in water as its salt with sodium and/or with N-methyl-glucamine. In addition, the neutral aqueous solutions are well suited for an

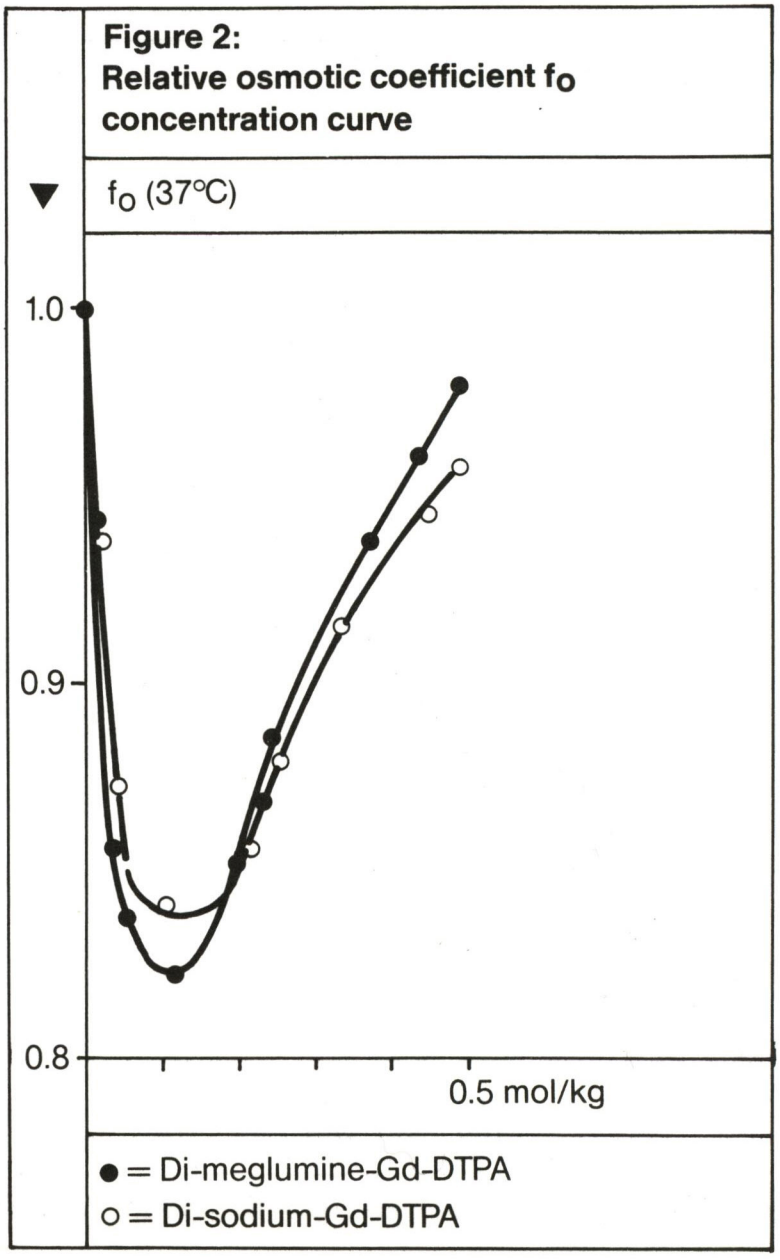


intravenous application in view of their low viscosity (see below). Gd-DTPA is qualified as a contrast enhancer producing distinct effects on the relaxation of protons in aqueous solutions.[5]

Measurements were performed of osmotic pressure, density and viscosity of solutions of both salts of Gd-DTPA to determine these properties at clinically useful concentrations. The coordination sphere of the complex was investigated by X-ray analysis.

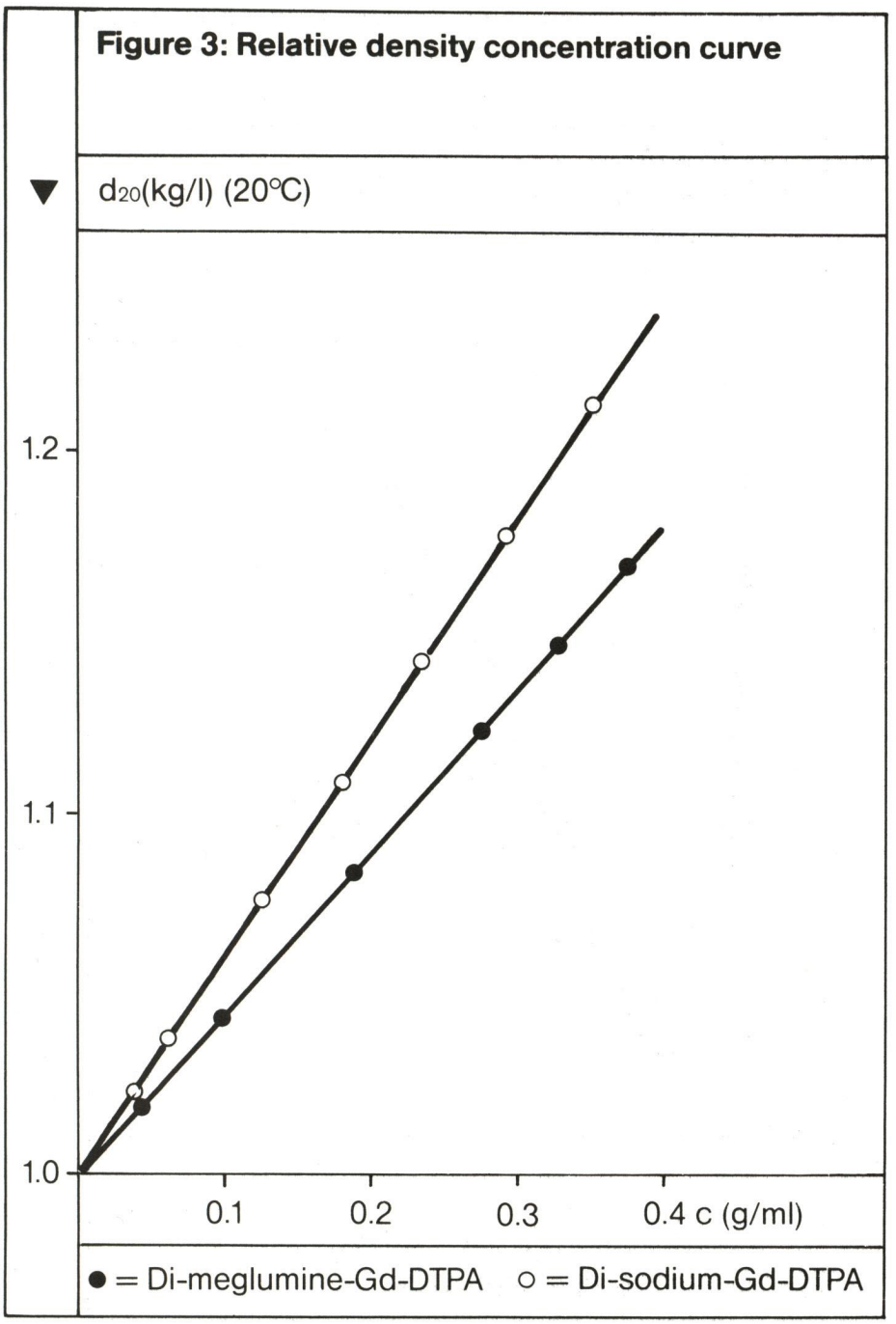
MATERIALS AND METHODS

The Gd-DTPA complex and its salts were synthesized as described earlier.[8] For mea-



surements the following apparatus was used: Vapour pressure osmometer (Knauer GmbH, Berlin), digital precision densitometer DMA 10 (A. Paar KG, Graz), and automated Ubbelohde viscosimeter (Schott Geräte GmbH). The osmotic coefficients were determined by an isopiestic method with sucrose as the reference substance.[9,10]

From the slope of the function $d_2 = d_1 + (1 - \bar{v}_2 \cdot d_1)\, c$ (d_1 = density of pure water, d_2 =



density of the solution, c = concentration of the solution in g/ml) the partial specific volume $\bar{v}_2$ (ml/g) is obtained.[11-13] With the aid of density and viscosity studies the number of bound water molecules per molecule of complex salt was calculated from the hydration coefficient, δ, (g water per g substance) based on the equation

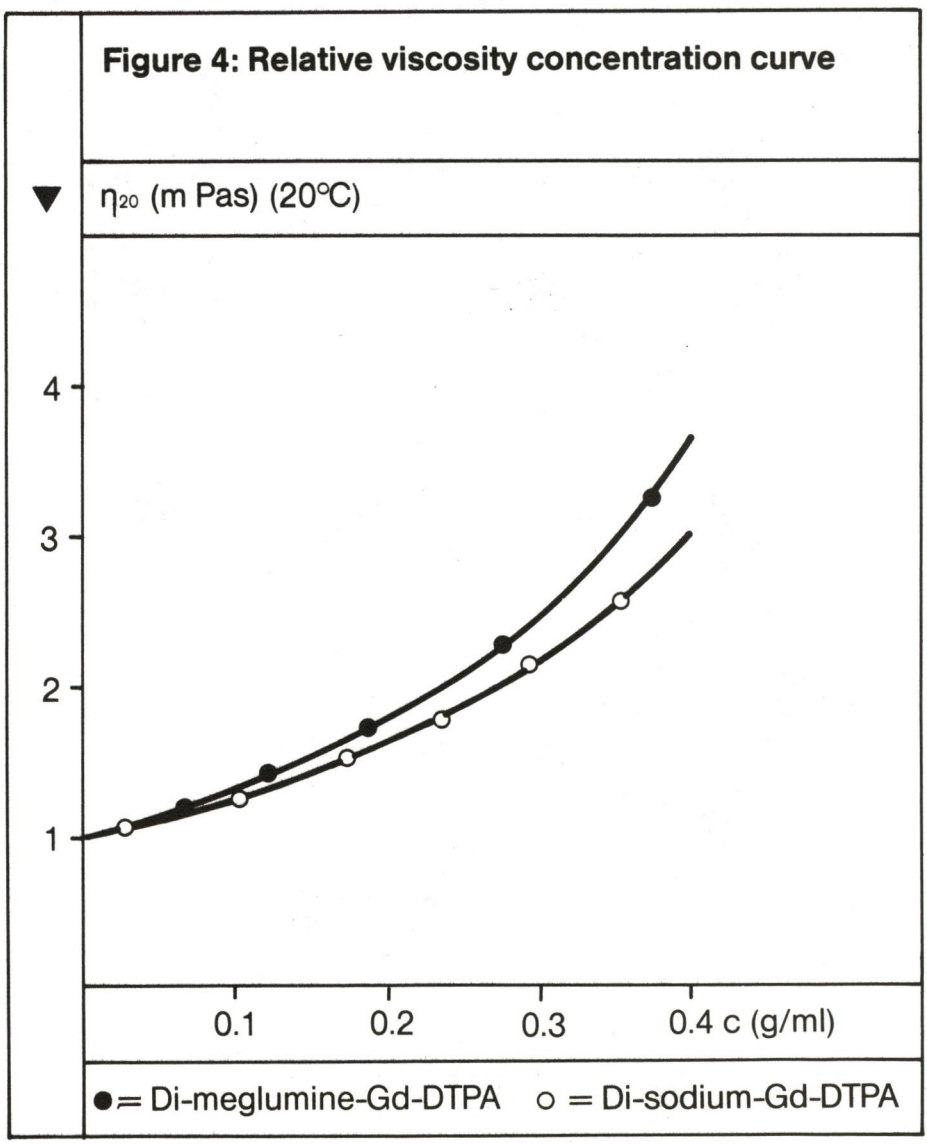
$$\delta = \bar{v}_2 \, d_1 \left(\frac{\bar{\eta}}{2.5 \cdot \bar{v}_2} - 1\right),$$

where $\bar{\eta}$ = initial slope of the relative viscosity-concentration curve y.

RESULTS AND DISCUSSION

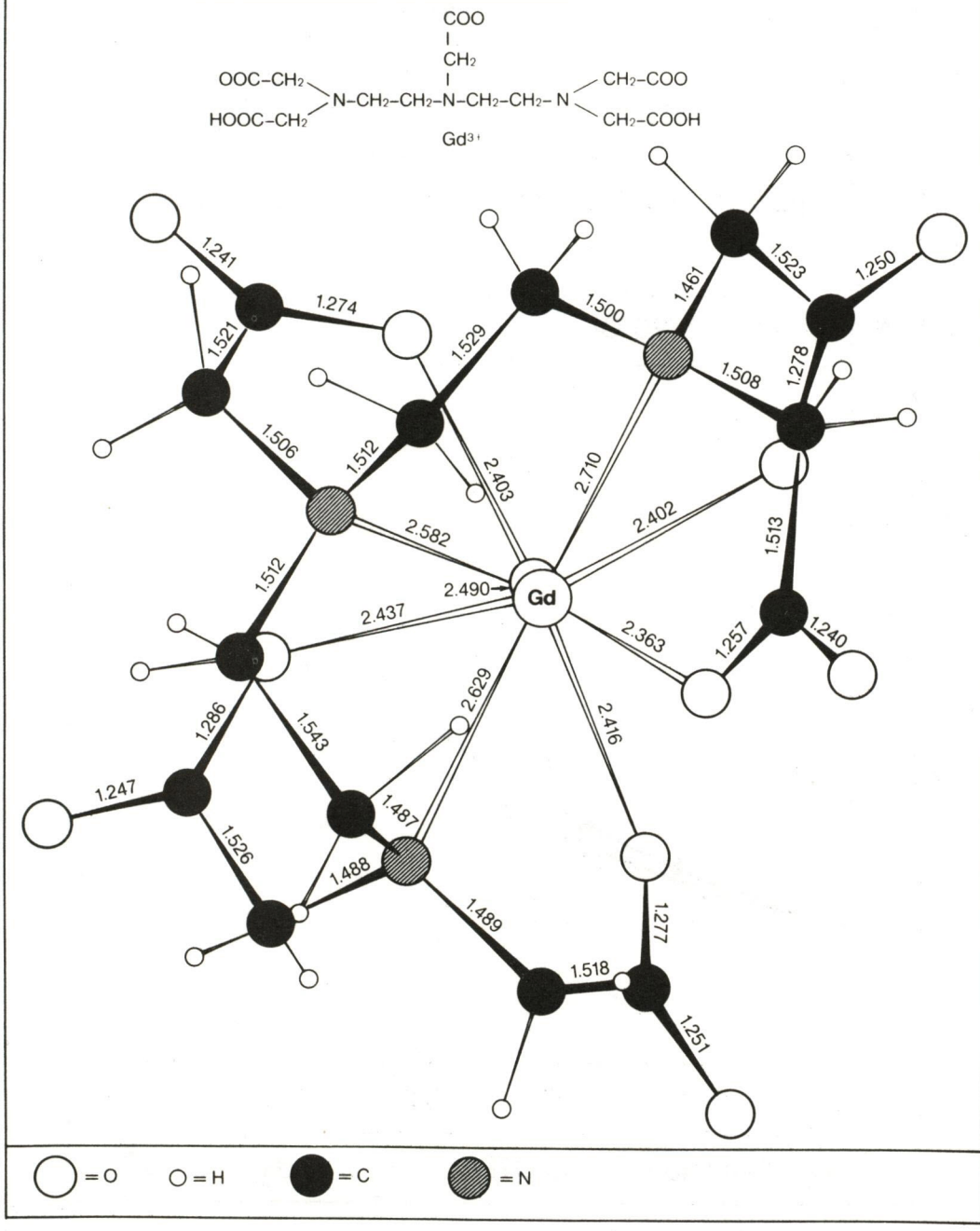
In the range of concentration of < 0.5 mol/kg the osmotic pressures of the solutions of both the salts are rather similar at 37°C (Figure 1). Regarding the osmotic coefficients, the minima of the curves can be explained by the superposition of molecular interaction and hydration. In this range of

Figure 4: Relative viscosity concentration curve



concentration the observed osmotic pressures are surprisingly low because of the association of the ions of the complex salts (Figure 2). The relative density of the two salts is shown in Figure 3. The viscosity of solutions to be injected intravenously is very low (Figure 4). The number of bound water molecules per molecule of the di-sodium salt is 22, and per molecule of the di-meglumine salt 35, respectively. This might result in a

Figure 5: X-ray structure analysis of the Gd-DTPA·H_2O complex



slower tumbling motion of the latter. Regarding the x-ray analysis of the di-sodium-Gd-DTPA, which was crystallized from water, the following preliminary results were achieved: The coordination number of the Gd^{3+}-ion is nine which is fairly common for the lanthanide complexes[14] (Figure 5). The ion is coordinated to three amino nitrogens and five carboxylic oxygens from the acetate moieties forming a square antiprism around Gd (III). A water molecule forms the cap above the large square face of the antiprism (Figure 6). Therefore the correct formula of the complex anion is $[Gd \cdot DTPA \cdot H_2O]^{2-}$. The DTPA covers the Gadolinium like a polyp. Further details will be described elsewhere.

The excellent tolerance of the Dimeglumine-Gd-DTPA, as well as a considerable contrast enhancement of NMR-images of cerebral tumours, have already been reported in clinical tests.[15]

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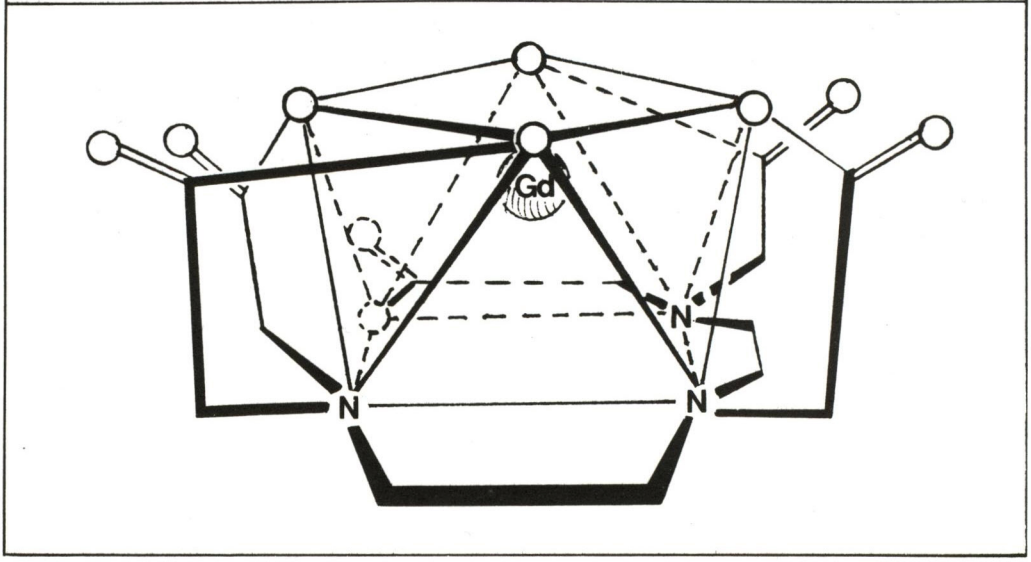
Figure 6: The coordination polyhedron of Gd-DTPA can be described as a distorted capped square antiprism.

○ = O



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