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Designing new MRI contrast agents: a coordination chemistry challenge

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Contents

Abstract

Gadolinium(III) polyacetic macrocyclic complexes featuring cycloalkyl groups directly grafted onto 1,4,7,10-tetra-azacyclododecane feature interesting properties such as higher rigidity, better kinetic inertness and faster water exchange times. The solution structures of the paramagnetic Yb(III) complexes are deduced from the NMR spectra and the effect of the Gd(III) chelates on the T_1 relaxation times of water is interpreted by measuring independently parameters such as the water exchange times and the diffusion coefficients. Substituting the tetra-aza ring with a coordinating unit such as 1,10-phenanthroline leads to ditopic

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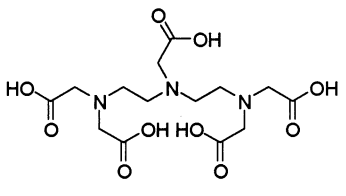
ligands that spontaneously form heteropolymetallic Gd(III)-Fe(II) complexes of well-defined stoichiometry with a marked effect on relaxivity.

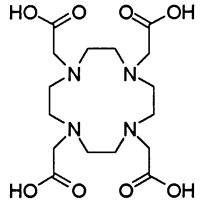
Keywords: Contrast agents; Lanthanides; Macrocycle; Magnetic resonance imaging; Nuclear magnetic resonance; Paramagnetic

1. Introduction

Contrast agents for magnetic resonance imaging (MRI) have become familiar in hospitals around the world. Despite the remarkable quality of unenhanced magnetic resonance images, better morphological and functional information is usually obtained with gadolinium chelates, manganese(II) complexes or superparamagnetic particles [1]. So far, the gadolinium complexes have attracted the most attention and have found the most widespread practical applications. Most of these complexes are derived from either DTPA or DOTA although other lanthanide complexes are promising [2].



DTPA



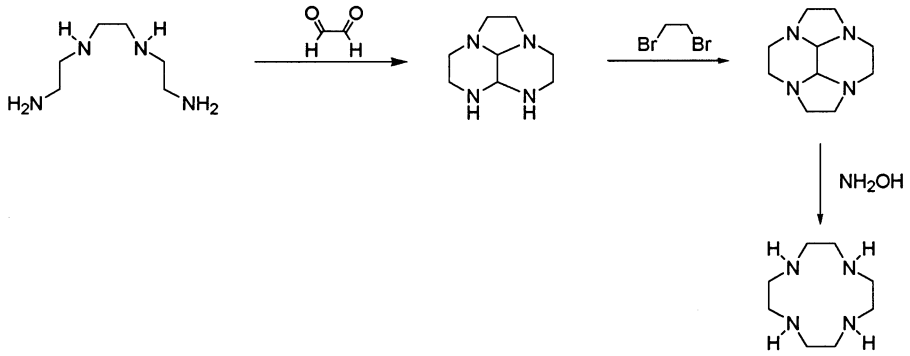
DOTA

As the authors of the present paper are mostly interested in lanthanide chelates of the DOTA-type, the results reported here will be concerned with macrocyclic ligands only [1]. These complexes must be thermodynamically highly stable and kinetically inert and they should feature as many water molecules as possible in the first coordination sphere of their metal ions. Furthermore, thorough analyses of the solution behavior of the complexes should be carried out so that subtle changes can be brought to the structure of these compounds in order to achieve the highest possible decrease in relaxation times.

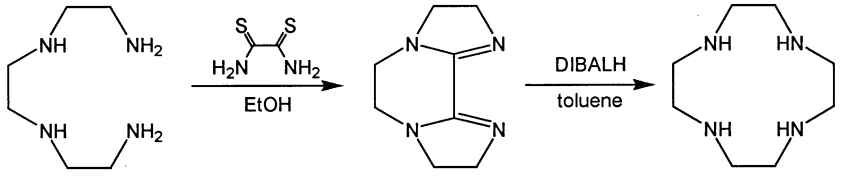
2. Syntheses

The gadolinium(III) ion is too toxic at the levels used in MRI imaging and it cannot be injected as such. The choice of DTPA as a ligand that forms a stable Gd^{3+} chelate and facilitates renal excretion was rather obvious since the properties of this ligand were quite well known. It was also commercially available, although not necessarily in a state of purity suitable for pharmacological applications. Despite its interesting coordination properties, the choice of DOTA was less obvious because of the time-consuming preparation of 1,4,7,10-tetra-azacyclododе-

cane, cyclen. The Richman and Atkins procedure [3] has been the most preferred synthetic method for years but it has now been superseded by more direct and more efficient techniques [4,5]. For instance, the following reaction scheme allows one to obtain cyclen on the industrial scale for 1000 US $ per kg [6].



Another procedure was suggested by Weisman and Reed [7] and we found that this procedure is particularly easy to implement in the laboratory even if it uses rather expensive starting materials and reactants.



Cyclen is also available now at a more reasonable price than in the past [8]. These efforts and many others in organic synthesis probably yielded more new chelating agents during the last few years than since the discovery of DTPA. New macrocycles derived from DOTA and substituted in the tetra-aza cycle or on the acetate arms have been prepared either for linking chelates to a macromolecule or for achieving a higher hydrophobicity. We have added new members to this family of compounds by grafting aliphatic and partially reduced aromatic groups directly onto the cyclen ring [9]. As illustrated in Fig. 1, a 'crab-like' approach allows the synthesis of DOTA derivatives substituted by one or two aliphatic groups. The resulting increased hydrophobicity favors an hepatobiliary uptake and excretion and leads to better imaging of the liver [10].

There is only one water molecule in the first coordination sphere of the Gd(III) ion complexed with the tetra-acetic ligands derived from cyclen and syntheses have been conducted to obtain chelates with a higher degree of hydration even if this leads to a decrease in the stability of the complexes. For that purpose, cyclen has been selectively substituted on one, two or three nitrogen atoms in nearly all possible stereochemical arrangements. The preparation of 1,7-disubstituted cyclen proved surprisingly easy [11]. Ligands such as DO2A are

thus readily obtained and the trade-off between a higher hydration number because of a more open structure and a lower stability because of a smaller number of coordinating groups might not be too unfavorable since DO2A has been claimed to form stable lanthanide chelates [12].

We recently attempted to obtain more rigid chelates of the DO2A type by bridging the tetra-aza ring with an ethylene or a propylene group [13,14]. The synthesis of

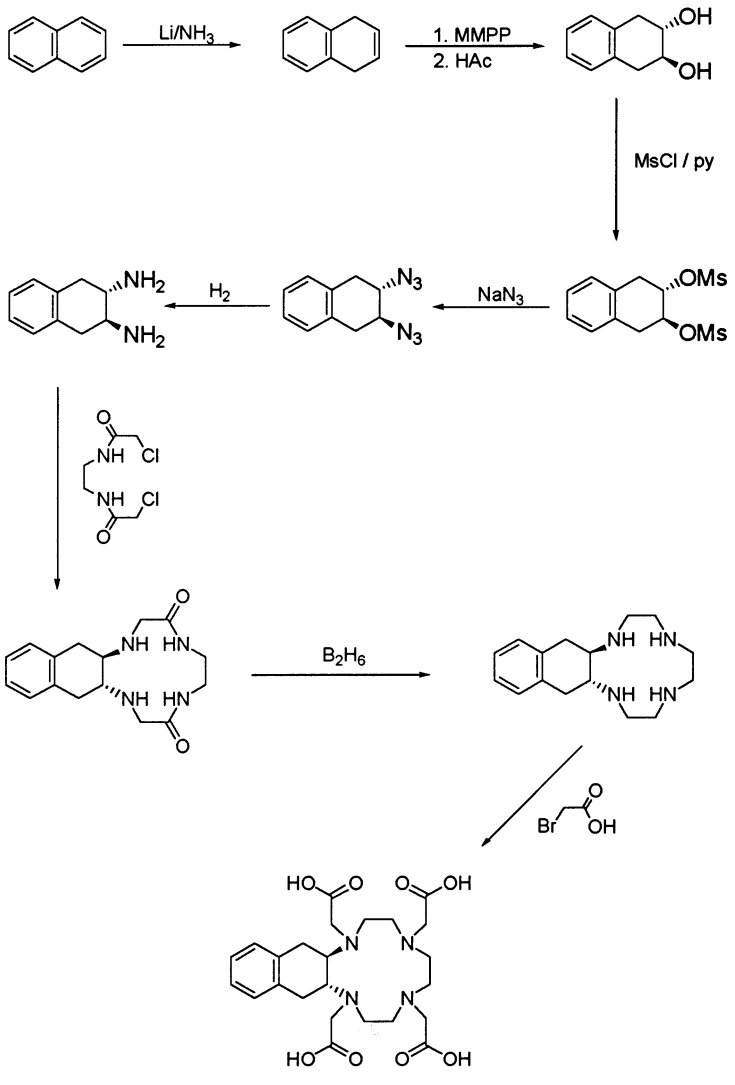


Fig. 1. Synthesis of (TE)DOTA.

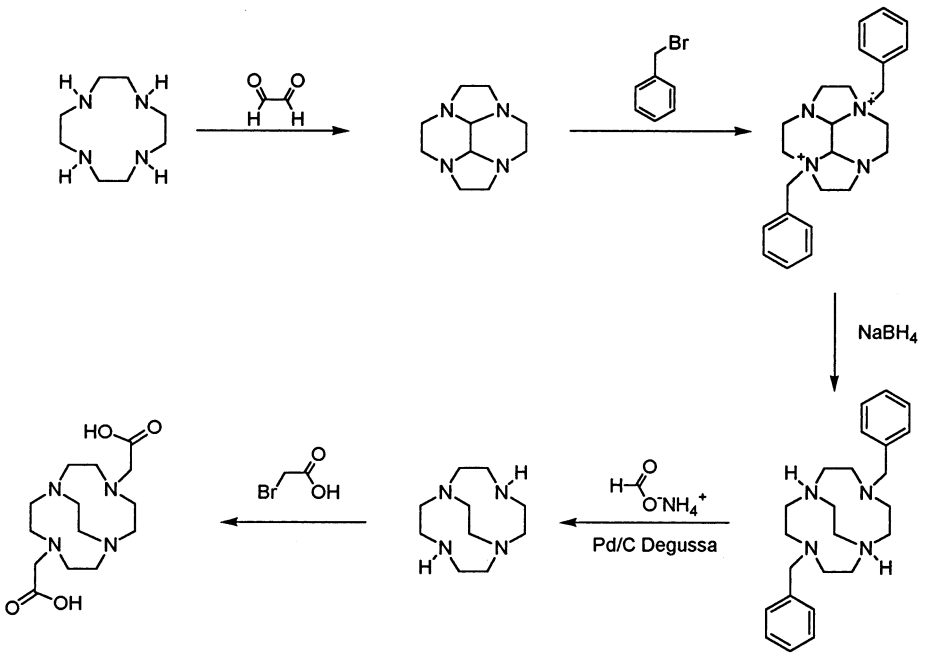
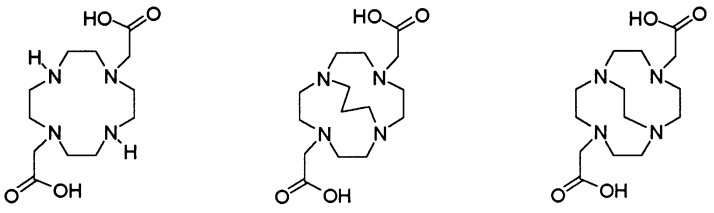


Fig. 2. Synthesis of DO(EN)2A.



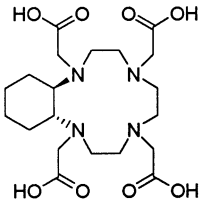
DO2A DO(PR)2A DO(EN)2A

DO(EN)2A is shown in Fig. 2, it is one among many examples that illustrate the remarkable flexibility that has been achieved recently when modifying the structure of cyclen.

3. Kinetic and thermodynamic studies

The kinetic inertness and the thermodynamic stability of the new DOTA ligands are of utmost importance since stability affects directly the toxicity of the Gd(III) chelates. DOTA itself forms exceedingly stable lanthanide chelates presumably because the tetra-aza cycle is able to adopt its most stable conformation, a square

conformation in which all lone electronic pairs of the nitrogen are directed toward the metal ion [15]. The kinetics of formation and even more remarkably, of dissociation are extremely slow [16], a quite unusual feature in the coordination chemistry of the 4*f* elements. The complex formation proceeds through an intermediate that is sufficiently long lived to be observed by NMR [16]. Force field calculations suggest that the metal ion is incompletely encapsulated in this intermediate [17]. The dissociation is hampered by the tight packing of the macrocyclic cage that inhibits the protonation of the nitrogen atoms and the resulting dissociation of the metal complexes. The kinetics become even slower if the rigid forming groups are directly grafted onto the tetra-aza ring. For instance, the half-life of GdDOTA and Gd(CY)DOTA are 23 h and 50 h, respectively, in 1 M HCl [18].



(CY)DOTA

Such a difference ensures an even lower toxicity of the contrast agents and could be of importance if the chelates are to be linked to biological macromolecules since their residence time in the body becomes longer. A higher kinetic inertness is also highly desirable in nuclear medicine. Surprisingly, we also observed very slow kinetics of formation with the diacetic ligands despite the more open structure of these compounds. Because the complexation kinetics of the DOTA derivatives with lanthanides are so slow, the determination of stability constants is fraught with difficulties and the results must be taken with reservation. As an illustration, the stability constants of $GdDOTA^-$ published in the literature are plotted versus their date of publication in Fig. 3. However, fast kinetics are sometimes also observed, as in the case of DO(PR)2A which form poorly stable lanthanide chelates as can be expected because of the steric crowding brought about by the propylene bridge: $\log K_{ML} = 5.7$ for La(III) to 7.9 for Yb(III).

4. Nuclear magnetic resonance investigations

The relaxivity of Gd(III) chelates, i.e. their ability to reduce the relaxation times T_1 and T_2 of water, depends on a number of factors such as the symmetry of the complexes or the distance between the paramagnetic center and the protons of the hydration water molecules [19,20]. Interpreting relaxivity data requires a detailed knowledge of the chelate solution structures and it is well known that these are not necessarily correlated with solid state geometries because of the lability of the lanthanide complexes. The NMR spectroscopy of dia- and paramagnetic lanthanide complexes of DOTA and its derivatives proved to be a very useful tool for

investigating the solution behavior of these compounds. Of particular relevance here is the extensive use in the past of paramagnetic lanthanide chelates as NMR shift reagents because these compounds induce large shifts of dipolar origin [20]. However, it rapidly appeared that the high lability of these complexes does not allow quantitative structural inferences. Indeed, the paramagnetic shifts induced by these compounds originate from several species of different geometries that are in fast exchange on the NMR time scale. Separating the contributions of each species proved to be an impossible task [21]. Solution structural studies are thus feasible only if a rigid ligand is able to form highly stable lanthanide chelates to which it can impose at least part of its steric requirements. It is only in that case that the calculated paramagnetic shifts can be reliably compared with experimental induced shifts. The paramagnetic shifts δ_i induced by the Yb(III) ion are essentially dipolar in origin and are calculated with the dipolar equation [20] on the basis of a structural model from which the geometric factors can be computed. Crystallographic structures, if available, or models calculated by a molecular mechanics approach can be used for this purpose. There have recently been new efforts in this field and the results seem promising despite the difficulties encountered when dealing with high coordination numbers. In our hands, the approach reported by Hay [22] and Cundari [23] yielded structures that seemed to be in agreement with the NMR spectra. Whatever the model used, the problem of orienting the magnetic susceptibility axes in the absence of any symmetry elements still remains and one then has to resort to suboptimal best fit mathematical approaches.

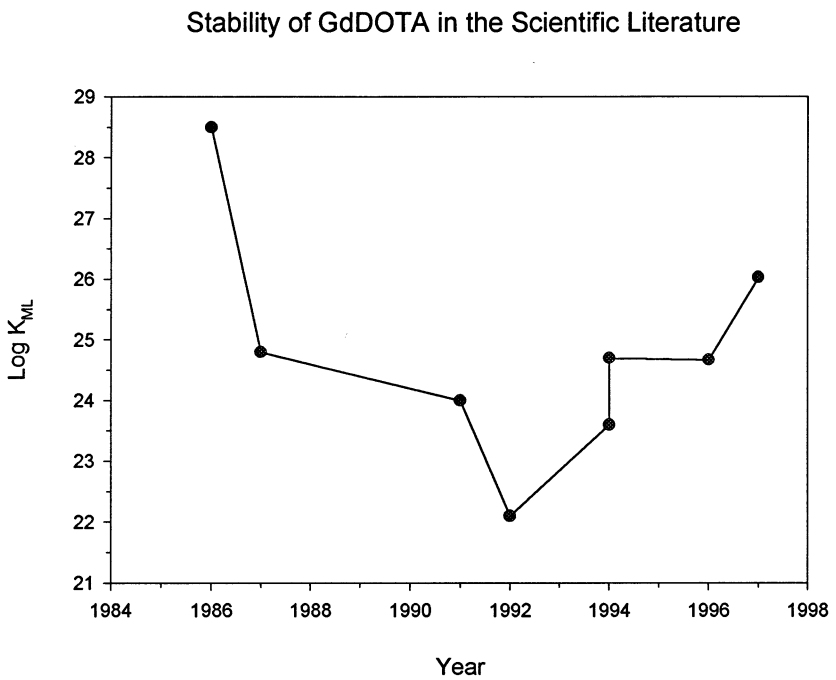
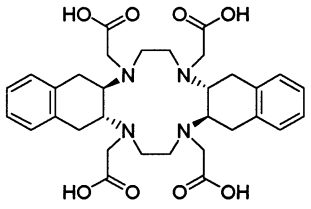
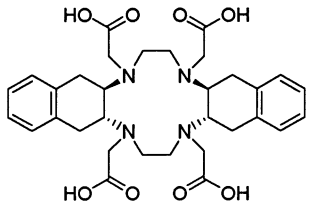


Fig. 3. Stability of $GdDOTA^-$ as a function of the publication year.

NMR spectroscopy can of course be used on a purely qualitative basis to assess the rigidity of lanthanide macrocyclic chelates. The spectra of the two isomers of $Yb(TE)_2DOTA$ are presented in Fig. 4 [24].

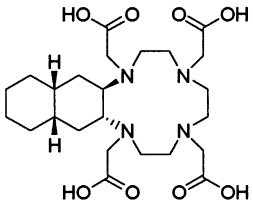


trans-anti-trans

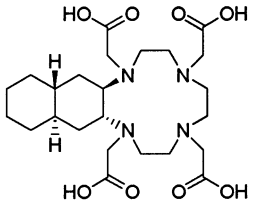


trans-syn-trans

The stereochemical arrangement of the nitrogen atoms of the *trans-anti-trans* isomer favors the square [3.3.3.3] conformation also found in DOTA [25] and a highly rigid chelate is obtained as shown by the numerous highly shifted and relatively sharp NMR peaks. On the contrary, the geometry of the *trans-syn-trans* isomer totally prevents the ligand from adopting this stable conformation and a flexible complex is obtained resulting in broad NMR peaks. Another unusual feature of these chelates is also observed in Fig. 4: the rigid species adopts two different conformations in solution as indicated by a total number of NMR peaks that is twice what is expected. This phenomenon has already been reported in the case of DOTA [26,27] and has been assigned to a slow exchange between two conformational isomers that differ by the relative arrangements of the tetra-aza cycle and of the acetate groups that can be either in a clockwise or a counter-clockwise propeller-like arrangement. Another example of a qualitative NMR analysis is illustrated in Fig. 5 in which are shown parts of the NMR spectra of the Yb(III) complexes with (*cis*-DE)DOTA and (*trans*-DE)DOTA.



(*cis*-DE)DOTA



(*trans*-DE)DOTA

The NMR peaks in Fig. 5 are assigned to protons in the axial positions of the tetra-aza cycle by comparison with the spectra of $YbDOTA^-$. Two conformational isomers in nearly identical proportion are observed for Yb(*trans*-DE)$DOTA^-$ with four peaks each as expected because the ligand is asymmetrical. However, each isomer of Yb(*cis*-DE)$DOTA^-$ displays up to eight NMR peaks. The conformations of the decalin substituents in the two Yb(III) complexes are depicted in Fig. 5 and the differences between the NMR spectra is attributed to the two different arrangements that the *cis*-decalin group can adopt. It should also be noted that these stereochemical differences have a profound effect on the relative populations of the conformational isomers.

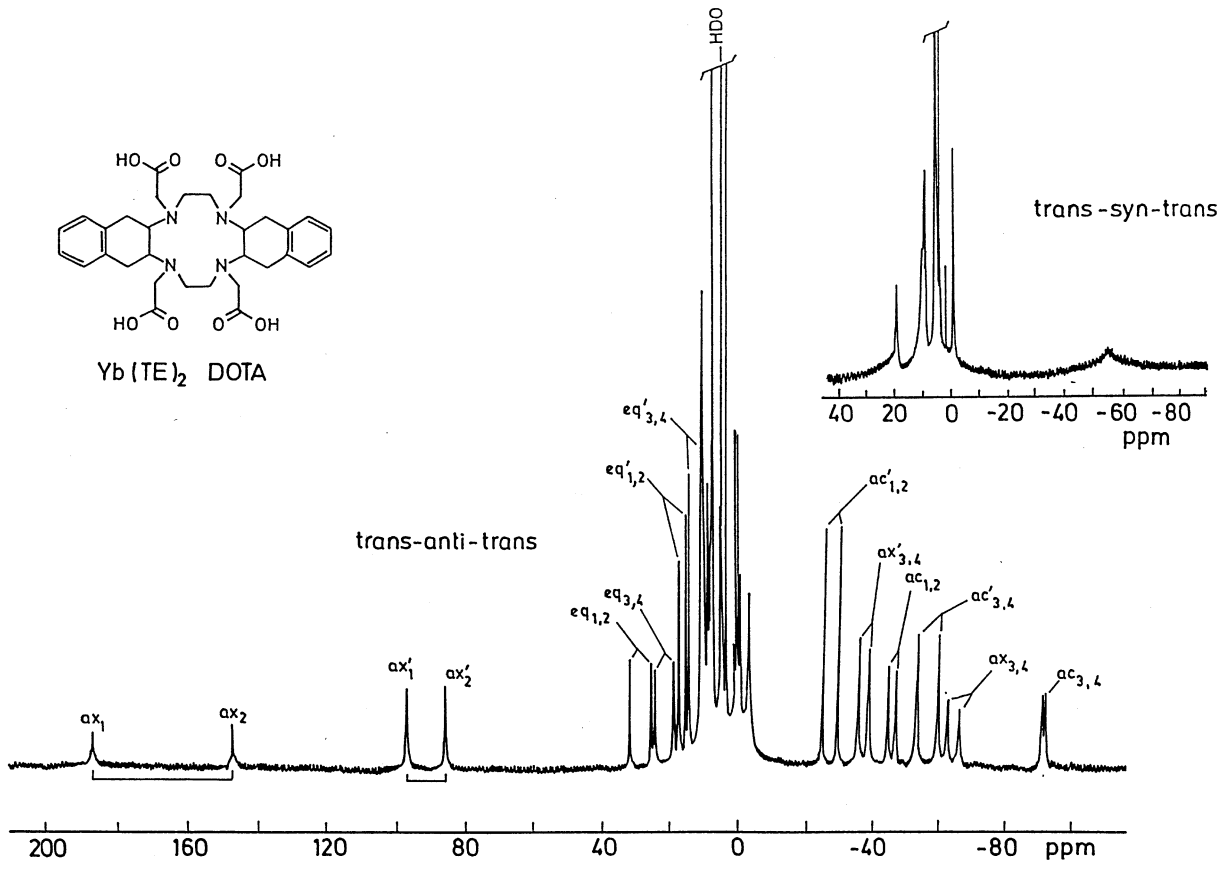


Fig. 4. ^{1}H-NMR spectra of the *trans-anti-trans* and the *trans-syn-trans* stereoisomers of $Yb(TE)_2DOTA^-$.

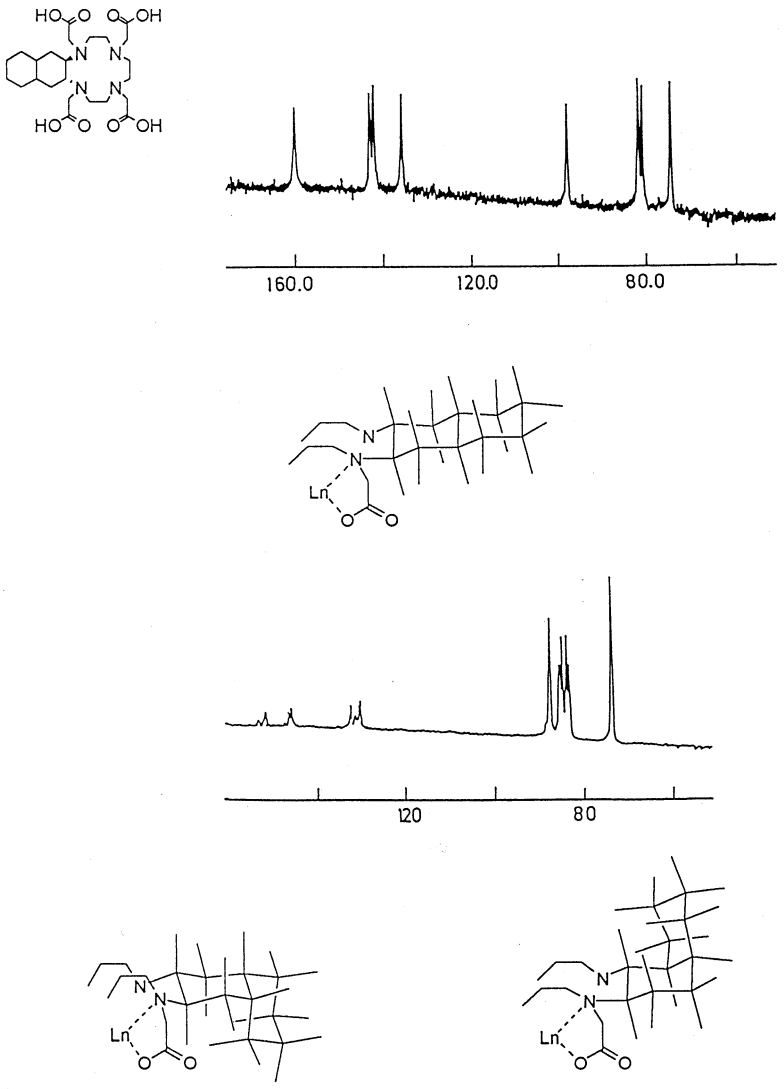


Fig. 5. ^{1}H-NMR spectra of the stereoisomers of Yb(DE)DOTA^{-} with a schematic presentation of their decaline substituent in the *trans* (top) or *cis* (bottom) conformation.

When carried out in the case of Yb(III) DOTA complexes bearing aliphatic substituents on the tetra-aza cycle, quantitative structural analyses based on the dipolar equations yield very good agreement between experimental and paramagnetic shifts provided the best fit procedure takes into account the orientation of the axes of the magnetic susceptibility tensor. As an example, Fig. 6 shows that very good agreement is obtained in the case of Yb(TE)DOTA^{-} assuming that the z axis of the magnetic susceptibility tensor makes an angle of 3.1° with the perpendicular

to the N_4 plane (conformational isomer with the most shifted peaks). The reliability of these calculations can be checked by recording the EXSY and COSY spectra of the complexes. Two-dimensional NMR spectroscopy of diamagnetic chelates is commonplace but recording such spectra for Yb complexes is less straightforward because of the shortening of the relaxation times and of the very large chemical shift range (up to 400 ppm.). However, provided appropriate precautions are taken, very informative 2D spectra can be obtained and used to fully assign the NMR spectra as shown previously in the case of DOTA and as demonstrated in Fig. 7 for Yb(*trans-anti-trans* CY)$_2$DOTA.

5. Relaxometric studies

NMR dispersion curves, i.e. the dependence of the relaxation rate or relaxivity $1/T_1$ of water with the observation frequency, afford information that is important both practically and theoretically [19,28]. For small rapidly rotating chelates such as GdDOTA$^-$, the dispersion curves have a simple 'S' shape, the relaxivity being essentially dominated by the electronic relaxation time τ_s at low fields and by the rotational correlation time τ_r at high fields. As medical imaging is mainly carried out at 20 MHz, many efforts have been made at increasing the relaxivity at this frequency. This can be accomplished by increasing the molecular weight of the complex that will then rotate more slowly. The molecular weight increase brought about by grafting aliphatic groups on the DOTA ligand remains modest and no

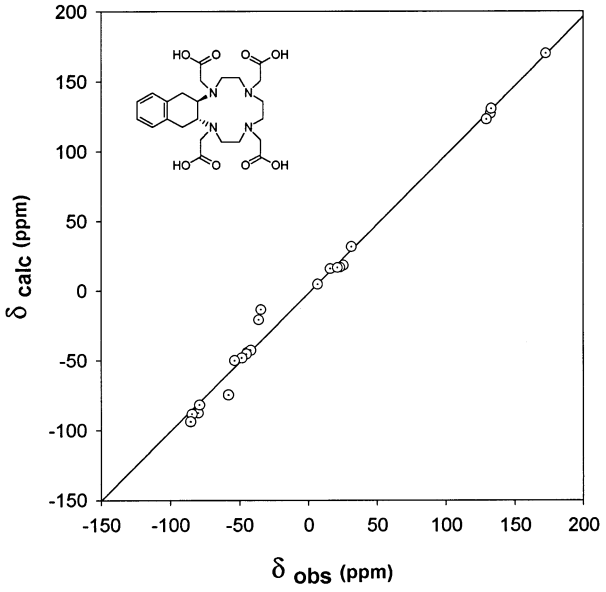


Fig. 6. Calculated and experimental paramagnetic shifts of Yb(TE)DOTA$^-$.

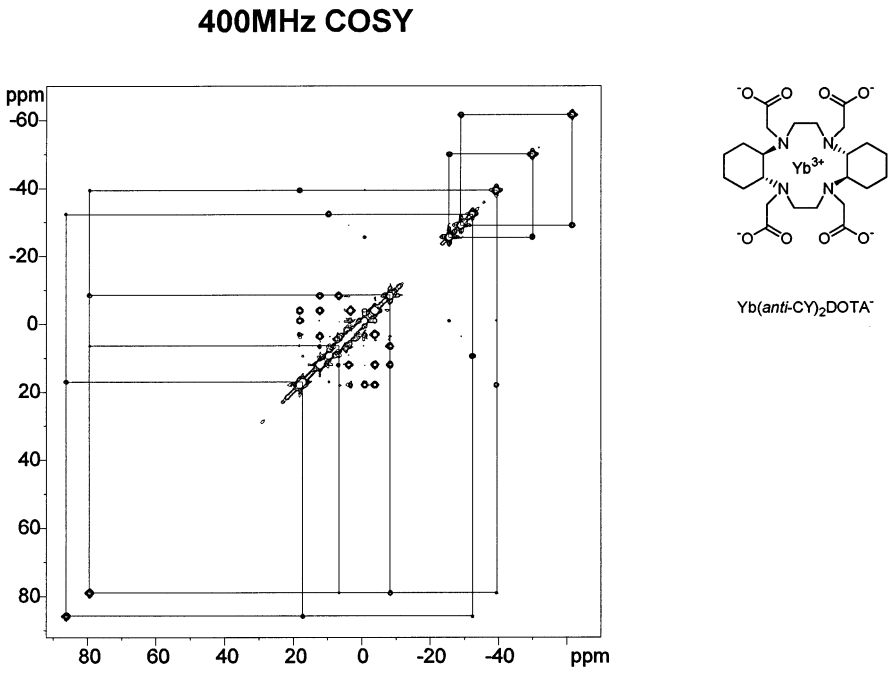


Fig. 7. COSY-NMR spectrum of Yb(*trans-anti-trans* CY)$_2$DOTA$^-$.

large improvements in relaxivity can be expected. Indeed, a small increase is observed with many substituted ligands as shown in Fig. 8 in the case of (TE)$_2$DOTA chelates. The most interesting practical feature of these ligands thus remains their better kinetic stability.

A lot of efforts have been devoted to the interpretation of the NMRD curves of Gd(III) complexes. The experimental data are fitted by the classical Solomon–Bloembergen–Morgan equations that account for the dependence of the relaxation rate $1/T_1$ on the field of measurement.A quantitative analysis of the NMRD curves requires the best fit adjustment of no less than nine parameters in these equations and even more if the temperature dependence of some of them is taken into account. One thus has to assign values to some of the parameters, for instance the proton-metal distances r and a for the water molecules in the first and second coordination spheres, the number of associated water molecules q_w and/or the diffusion coefficient D of the complex. The calculated NMRD curves reproduced in Fig. 8 were obtained with the following parameters: rotational correlation time $\tau_r = 70 \pm 5$ ps, correlation time for the modulation of the zero field splitting $\tau_v = 5 \pm 5$ ps, zero field electronic relaxation time $\tau_{S0} = 510 \pm 132$ ps, water exchange time $\tau_m = 61 \pm 4$ ns (vide infra) and assuming $r = 3.1$ Å and $a = 3.8$ Å. These parameters are in the range usually obtained by best fit for small Gd(III) chelates. Deducing so many parameters from a few simple S shape curves with a limited number of data points is prone to errors. Thus, it comes as no surprise that

several authors have attempted to determine several parameters independently by appropriate techniques. For instance, the fluorescence life times of free or complexed Eu(III) and Tb(III) in H_2O and D_2O can be correlated with the number of water molecules in the first coordination sphere of these ions [29]. It is then no longer needed to treat the q_w parameter as adjustable although the fluorescence method is thwarted by rather large experimental errors and could lead to spurious results because of differences in the lanthanide–water distance between various complexes [30]. However, measurements performed in a systematic manner appear to yield a reliable hydration scale and it seems that the substitution of the DOTA ligand by bulky groups leads to a reduction in q_w. For instance, we found that this parameter decreases from 0.89 for $TbDOTA^-$ to 0.80 for $Tb(TE)DOTA^-$ to 0.47 for Tb(*trans-syn-trans*-$CY)_2DOTMA^-$, a ligand derived from $(CY)_2DOTA$ and featuring α-methyl acetate groups.

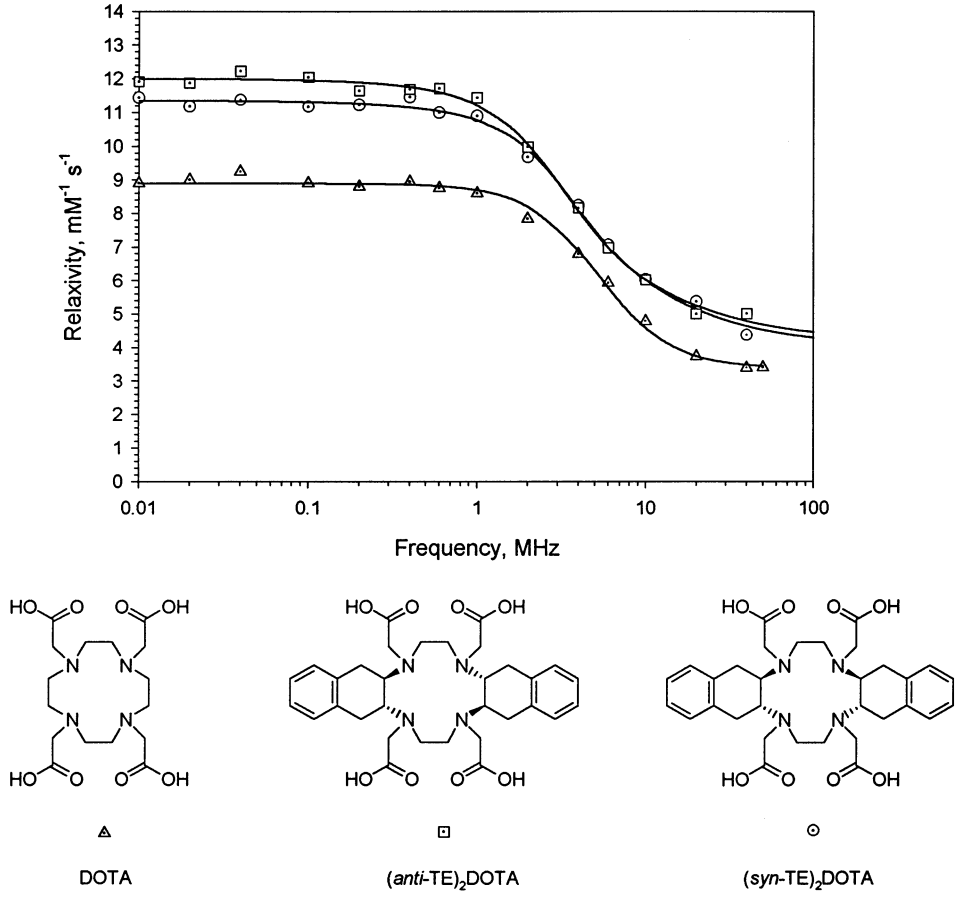


Fig. 8. NMR dispersion curves of $GdDOTA^-$ and the *trans-anti-trans* and the *trans-syn-trans* stereoisomers of $Yb(TE)_2DOTA^-$.

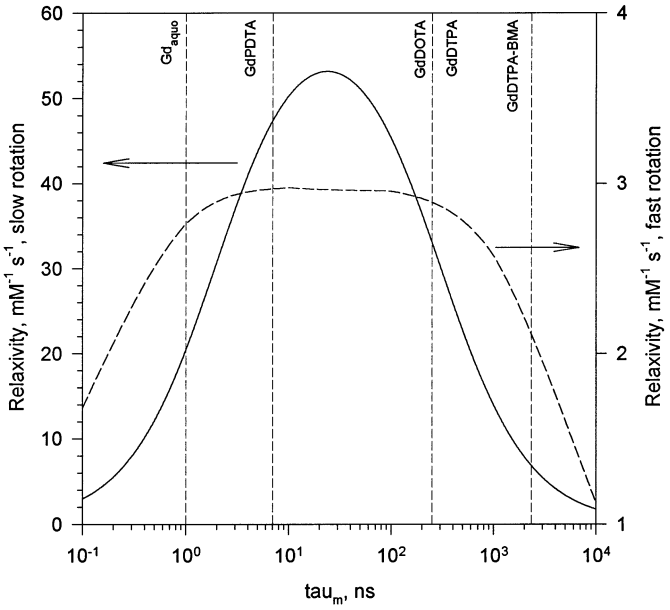
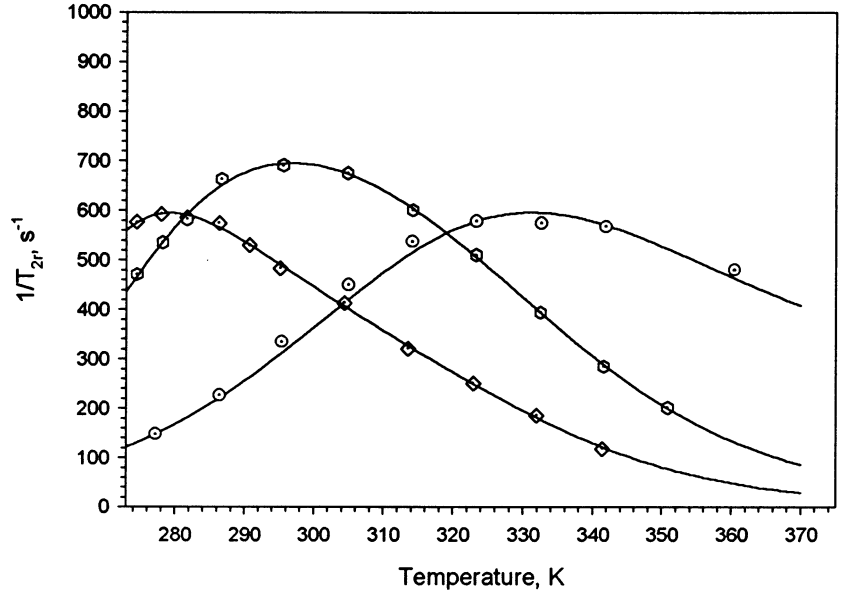
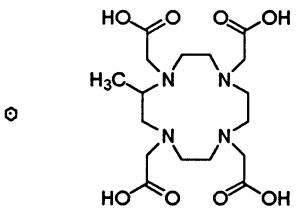


Fig. 9. Influence of the water exchange time τ_m on the relaxivity. The left axis refers to slowly rotating Gd(III) complexes (solid curve) and the right axis refers to rapidly rotating small Gd(III) chelates (dashed curve).

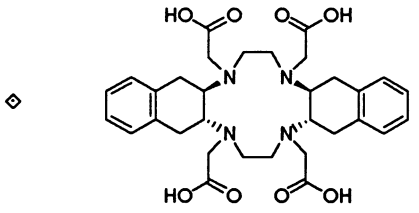
It should be noted here that the exact meaning of this decrease remains open to question and is probably related to the presence in solution of the conformational isomers mentioned above [27]. However, we have not yet found a clear correlation between the relative populations of the conformational isomers and q_w for the CY and TE derivatives. The water exchange time is another parameter that has been investigated in great detail [31]. The measurement of the temperature dependence of the ^{17}O band width of water coordinated to Gd(III) chelates yields values of τ_m and it has been shown that replacing two carboxylic groups by amide functions in the DTPA skeleton leads to a sizeable increase in this parameter [31]. Lengthening the water exchange time is of little importance for rapidly rotating chelates. However, a longer τ_m has a marked effect on relaxivity if a Gd(III) chelate is rigidly linked to a slowly rotating macromolecule and could be detrimental as shown in Fig. 9. Interestingly, measurements carried out in collaboration with Aime and his group at the University of Torino indicate that grafting cycloalkyl groups directly on the DOTA cycle brings about a decrease in the water exchange rates as illustrated in Fig. 10.

The diffusion coefficient D is one of the adjustable parameters in the best fit interpretation of the NMRD curves but it has attracted little attention so far probably because its influence on the relaxivity is not as pronounced as for other factors in Eqs. 3–7. Knowing the exact value of D makes of course the interpretation of NMRD curves more reliable but in addition, there is some uncertainty as to

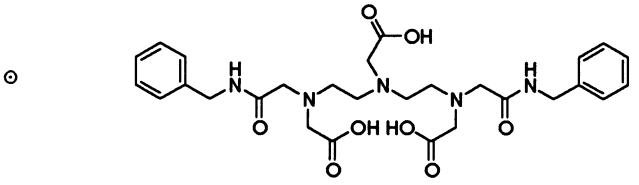




(M)DOTA



(*syn*-TE)$_2$DOTA



DTPA-BBA

Fig. 10. Temperature dependence of the water ^{17}O transverse relaxation time for three Gd(III) chelates. The τ_m values are 2200, 137 and 9.3 ns for the diamide chelate DTPA-BBA [36], (M)DOTA and the *trans-syn-trans* isomer of $(TE)_2DOTA$, respectively.

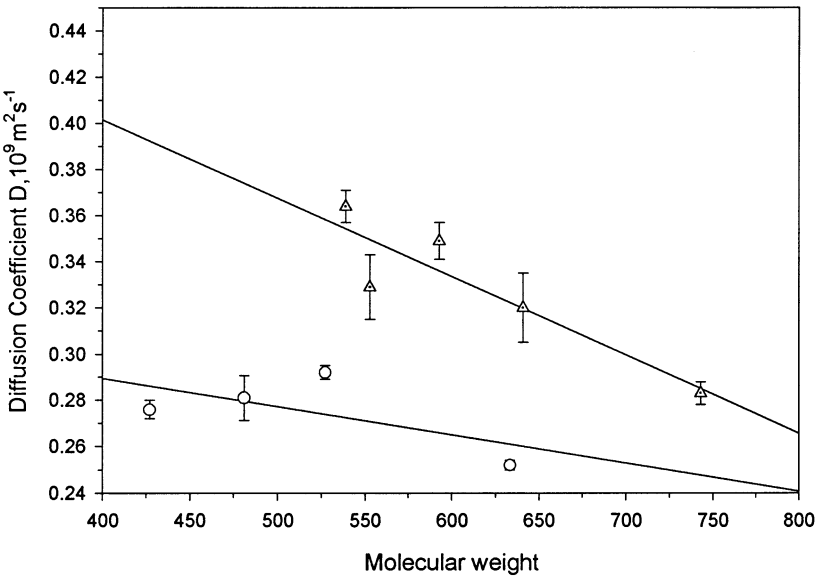
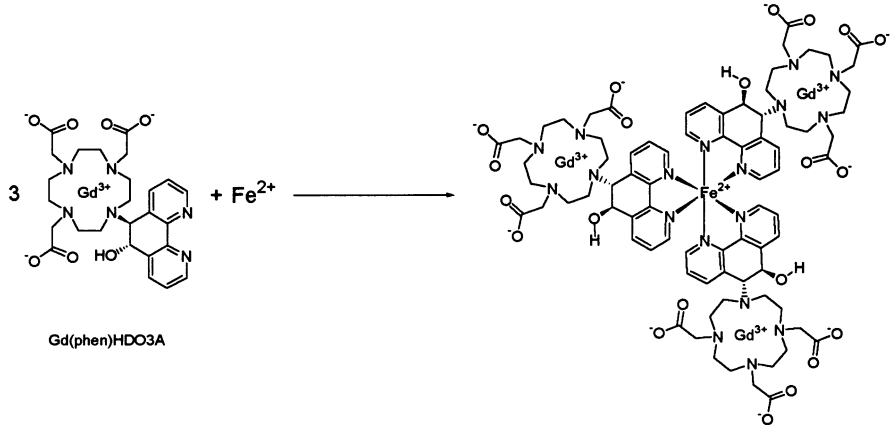


Fig. 11. Diffusion coefficients of macrocyclic (upper data) and non-cyclic (lower data) La(III) chelates.

whether it is better to use Freed's equation (Eq. 7) for computing the outer-sphere relaxivity or if using a non-hydrated chelate such as GdTTHA [3] for that purpose is a better approach. We measured the diffusion coefficients of a series of linear and macrocyclic La(III) chelates by the Stejkal–Tanner pulse gradient spin-echo technique (PGSE) [32]. As shown in Fig. 11, LaDOTA$^-$ and its substituted derivatives diffuse faster than the linear chelates whatever their ionic charge. The macrocyclic complexes are all monoanionic and they all feature a hydrophobic crown that limits the size of their second water coordination sphere. On the contrary, the non-cyclic complexes either possess a higher charge or are more hydrated and we thus postulate that they are surrounded by a larger water shell and diffuse more slowly. Selecting GdTTHA^{3-} as a reference for outer-sphere relaxivity might thus not be the best approach since this complex displays the lowest diffusion coefficient. It is noteworthy that the interaction between lanthanide chelates and macromolecules can also be investigated by measuring diffusion coefficients. If a strong interaction takes place, the diffusion coefficients of the interacting entities become identical and eventually lower than the coefficient of the macromolecule itself. Fig. 12 contains a histogram representing the diffusion coefficients of La(III) chelates, α- and γ-cyclodextrins and their 1:1 mixtures in water. LaDOTA$^-$ interacts very strongly with both cyclodextrins as indicated by the decrease of the diffusion coefficients to values lower than those measured for the free cyclodextrins. By contrast, the diffusion coefficient of La(TE)DOTA$^-$ remains unaltered after the addition of the cyclodextrins and adducts are thus not formed with these compounds. It seems that the substituted tetra-aza crown of La(TE)DOTA$^-$ is unable to penetrate into the cyclodextrin cavities because of its bulkiness [33] [34].

6. In search of higher relaxivities: self-assembling heterometallic complexes

Higher relaxivities allow one to obtain MRI images with less contrast agents and could allow imaging of receptors if relaxivities of the order of 100–200 $mM^{-1}\ s^{-1}$ were reached as the Solomon–Bloembergen equations predict. The effectiveness of contrast agents can be increased by restricting the motion of Gd(III) chelates by linking them rigidly to macromolecules through covalent or non-covalent bonds, by an improvement of their intrinsic relaxivity or by attaching several paramagnetic entities to biological or synthetic oligomers. A combination of these approaches will probably be needed and numerous laboratory endeavors to find the means of reaching the highest possible relaxivities. We wish to report here preliminary results on a new approach to multimeric Gd(III) chelates. The ligand (phen)HDO3A features two complexing units of totally different nature. The macrocyclic binding site forms highly stable lanthanide chelates while the phenanthroline-like unit is a very good complexing agent of Fe(II). As shown below, the Gd(phen)HDO3A chelate spontaneously associates with Fe(II) to form a tris-complex of high molecular weight as we were able to show by gel permeation chromatography.



An NMRD titration also clearly indicates that a highly stable tris-complex is formed. Fig. 13 presents the NMRD curve for the Gd chelate and its tris-complex with Fe(II). A relaxivity of 12.2 $mM^{-1}\ s^{-1}$ per Gd(III) ion is achieved at 20 MHz and 37°C instead of the 3.7 $mM^{-1}\ s^{-1}$ value obtained for $Gd(phen)DOTA^{-}$. This is still very far from the very high relaxivities that one would like to reach but the self-assembling approach spontaneously yields high-molecular weight slowly rotating multimeric species. It should be noted here that a similar approach has been followed recently by Aime et al. [35] but these authors synthesized ligands that do not form complexes of well-defined stoichiometry and the effect on relaxivity is much smaller than what is reported here. Our work is being pursued along these lines with the synthesis of heterometallic species containing a large number of Gd(III) chelates.

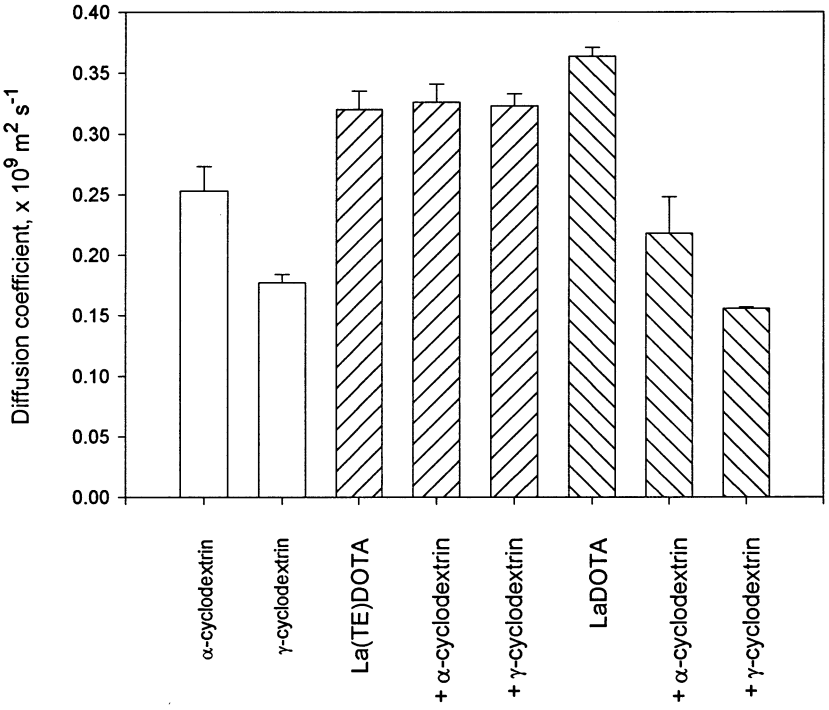


Fig. 12. Diffusion coefficients of α- and β-cyclodextrin, LaDOTA, La(TE)DOTA and their mixtures.

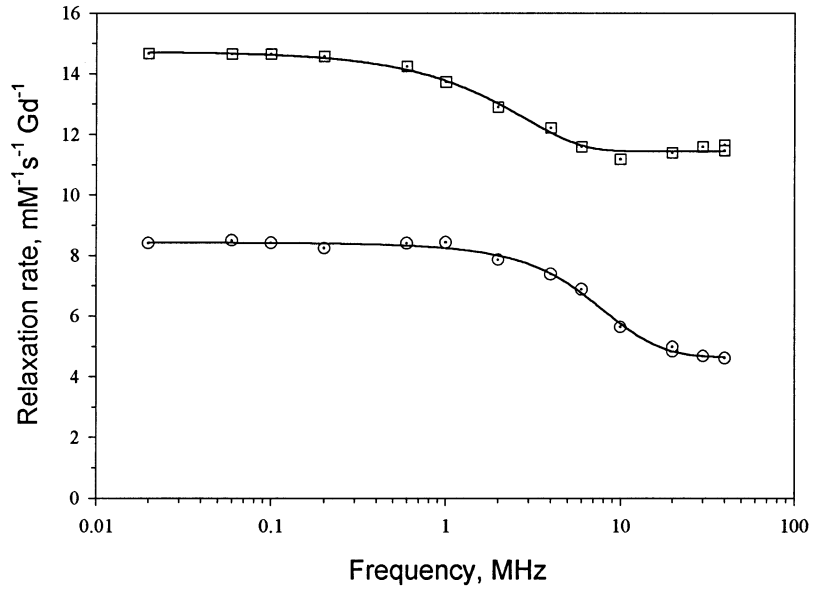


Fig. 13. NMR dispersion curves for Gd(phen)HDO3A and its tris-complex with Fe^{2+}.

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