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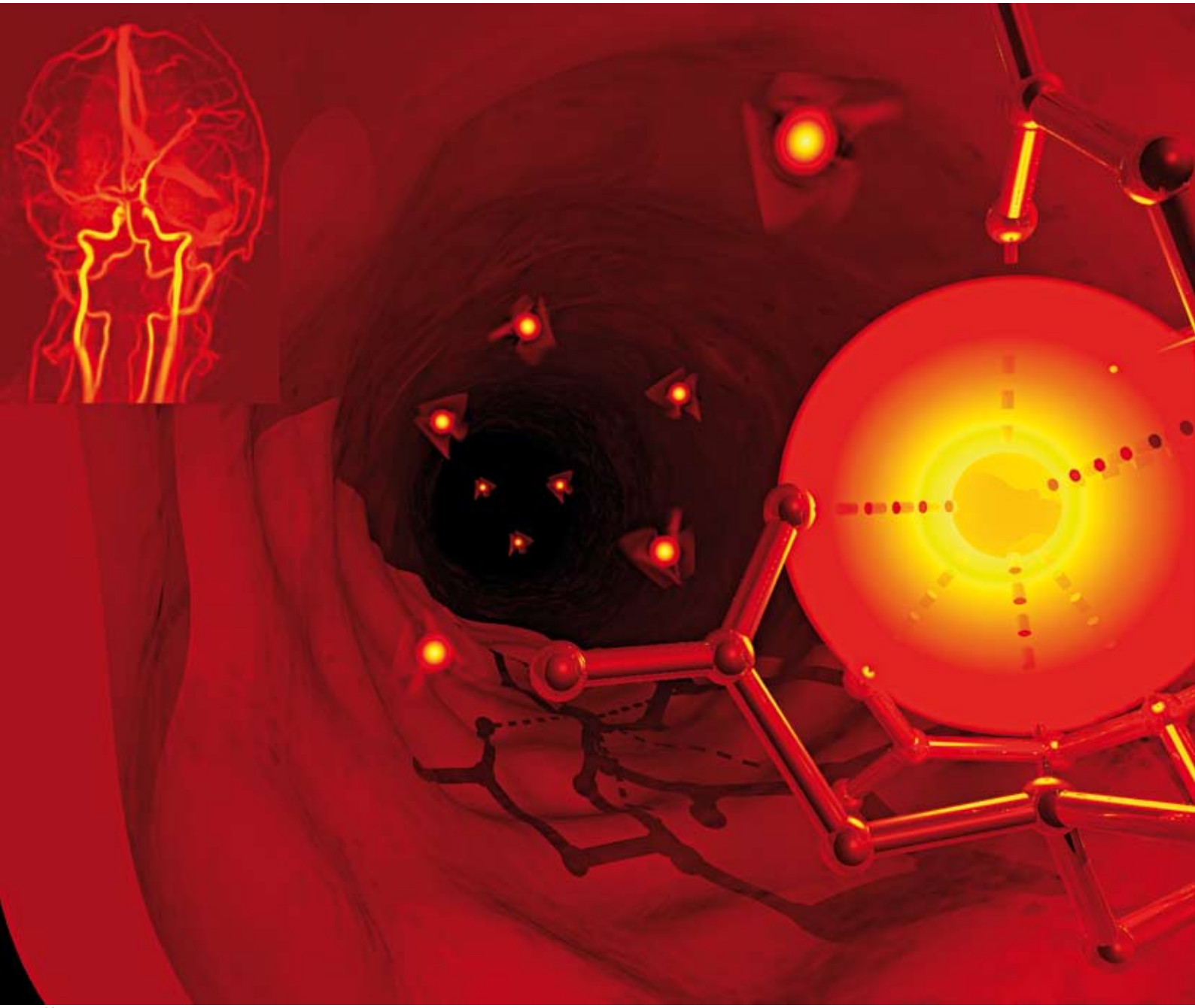

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Gadolinium(III) complexes as MRI contrast agents: ligand design and properties of the complexes

Petr Hermann, Jan Kotek, Vojtěch Kubíček and Ivan Lukeš*

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Magnetic resonance imaging is a commonly used diagnostic method in medicinal practice as well as in biological and preclinical research. Contrast agents (CAs), which are often applied are mostly based on Gd(III) complexes. In this paper, the ligand types and structures of their complexes on one side and a set of the physico-chemical parameters governing properties of the CAs on the other side are discussed. The solid-state structures of lanthanide(III) complexes of open-chain and macrocyclic ligands and their structural features are compared. Examples of tuning of ligand structures to alter the relaxometric properties of gadolinium(III) complexes as a number of coordinated water molecules, their residence time (exchange rate) or reorientation time of the complexes are given. Influence of the structural changes of the ligands on thermodynamic stability and kinetic inertness/lability of their lanthanide(III) complexes is discussed.

Introduction

Tomography of magnetic resonance (Magnetic Resonance Imaging, MRI) has gained great importance in the last three decades in medicinal diagnostics as an imaging technique with a superior spatial resolution and contrast.[1] The most important advantage of MRI over the competing radio-diagnostic methods such as X-Ray Computer Tomography (CT), Single-Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET) is definitely no use of harmful high-energy radiation. Moreover, MRI often represents the only reliable diagnostic method for, *e.g.* cranial abnormalities or multiple sclerosis. The resolution reached is close to 1 mm^3 with contemporary MRI clinical scanners, and the resolution on the cellular level was demonstrated in a laboratory experimental setup. Consequently, the diagnostic potential of MRI seems to be still enormous. In addition to the assessment of anatomical changes, MRI can be utilized for monitoring of organ functions. For instance, MRI has been used to follow functions of the human brain on a real time-scale by a method called functional-MRI or fMRI.[2]

Physical principles of MRI rely on the monitoring of the different distribution and properties of water in the examined tissue and also on a spatial variation of its proton longitudinal (T_1) and transversal (T_2) magnetic relaxation times.[1] Thus, an MRI scanner is able to generate several types of images. A significant benefit of MRI to medicinal diagnostics arises from a contrast produced by local differences in healthy and pathologically changed parts of the same tissue. In particular, T_1 and T_2 were proved to be rather sensitive to biochemical conditions (such as water concentration, temperature, pH, salt or fat concentration *etc.*) of the tissue under study.

Department of Inorganic Chemistry, Faculty of Science, Universita Karlova (Charles University), Hlavova 2030, 128 40, Prague 2, Czech Republic. E-mail: lukes@natur.cuni.cz; Fax: +420-221951253; Tel: +420-221951259

In the course of time, it was found that in some examinations of, *e.g.* the gastrointestinal tract (GIT) or cerebral area, the information obtained from a simple MRI image might not be sufficient. In these cases, the administration of a suitable contrast-enhancing agent (CA) proved to be extremely useful. Quite soon, it was demonstrated that the most promising class of CAs could be compounds comprising paramagnetic metal ions. The first CA tested *in vivo* was the Cr(III) complex of EDTA (EDTA = ethylenediaminetetraacetic acid).[3] Unfortunately, this candidate suffered from a lack of long-term stability and has never been used clinically. The first example of a modern MRI CA is considered to be the gadolinium(III) complex of DTPA (DTPA = diethylenetriaminepentaacetic acid) approved for clinical usage in 1988.[4]

From the physical point of view, there are two major families of CAs classified according to the relaxation process they predominantly accelerate, *i.e.* T_1-CAs (paramagnetic) and T_2-CAs (superparamagnetic).[1] Whereas T_1-CAs induce a positive contrast, *i.e.* a ^{1}H NMR signal of the affected tissue increases, compounds affecting the T_2 relaxation cause lowering of a local proton signal and, thus, they show a "negative enhancement" pattern.[5]

Besides this classification, all CAs can be divided (according to the site of action) into extracellular, organ-specific and blood pool agents. Historically, the chemistry of the T_1-CAs has been explored more extensively as the T_1 relaxation time of diamagnetic water solutions is typically five-times longer than T_2 and, consequently easier to shorten.[1] From the chemical point of view, T_1-CAs are complexes of paramagnetic metal ions, such as Fe(III), Mn(II) or Gd(III), with suitable organic ligands.

On the other hand, T_2-CAs, developed slightly later, are conceptually microcrystalline iron oxide nanoparticles (MION), called also small superparamagnetic iron oxides (SPIO) or ultrasmall superparamagnetic iron oxides (USPIO).[1,6] In addition to their effect on T_2, these agents also induce faster T_1-relaxation;

Petr Hermann

Petr Hermann started graduate studies with Prof. Lukeš in 1988 and graduated in 1993. He was a postdoctoral fellow at University of Massachusetts (Amherst) with Prof. L. D. Quin (1993–1995). At his alma mater*, he became a lecturer (1993) and docent (2004). His current research is focused on synthesis and investigations of complexing ability of polyazamacrocycles with phosphorous acid pendant arms.*

Jan Kotek

Jan Kotek is a former student Prof. I. Lukeš and Dr. P. Hermann. He received his PhD degree in 2004. He was then a postdoctoral fellow in Leuven (Belgium) under the supervision of Prof. K. Binnemans. He has been a lecturer in the department since 2000 and is a member of Prof. Lukeš' team involved mostly in the synthesis, potentiometry and X-ray studies of macrocyclic ligands and their complexes.

Vojtěch Kubíček

Vojtěch Kubíček was born in 1978. He obtained his PhD degree in inorganic chemistry in 2007. Now, he works in the group of Coordination and Bioinorganic Chemistry at Charles University in Prague. His scientific interest is focused on the synthesis and coordination chemistry of organophosphorus compounds and on the design of macrocyclic chelators for molecular imaging.

Ivan Lukeš

Ivan Lukeš' studies (PhD 1976) as well as his career are connected with Universita Karlova except stays in Orsted Institute in Copenhagen (1984) and University of Massachusetts at Amherst (1991–92). Through the years his research interest has focused on coordination chemistry and also on phosphorus chemistry. At present, he is concerned with lanthanide complexes and their biomedical application.

nevertheless, they are mostly used as negative CAs. Basically, they consist of nonstoichiometric Fe_3O_4/Fe_2O_3 cores of various sizes (from several nanometers to several tens of nanometers) covered by *e.g.* dextrans or polysiloxanes; hence, their final size reaches several hundred nanometers. In practice, they are used as blood-pool and more recently as organ-specific CAs.

In clinical practice, more than 35% of MRI examinations are performed with the use of CAs. The T_1-CAs based on gadolinium(III) complexes are mostly applied; thus, in this paper, we focus on them and, especially, on the coordination chemistry that controls the properties of such CAs. Utilization of the iron oxide nanoparticles is rather limited, an estimated proportion is less than 10% of all CA administrations.

In this rapidly developing field, a number of reviews on different aspects of the chemistry of complexes associated with CAs developments and usages have been published: monographs,[1,7,8] reviews of general interest,[9–18] reviews on physical aspects,[19] solid-state structures,[20,21] thermodynamic/kinetic stability,[20–24] prototropic exchange,[25] second-sphere effects,[26] quantum chemical calculations,[27] targeted/responsive CAs,[28–31] macromolecular CAs[32,33] or multimodal CAs.[34]

To avoid any ambiguity, fully protonated free ligands (*e.g.* DOTA = H_4dota) and ligand abbreviations used as adjectives are written in capital letters and coordinated ligand anions in the complexes are written, according to the IUPAC nomenclature, in small letters.

Structures of gadolinium(III)-based contrast agents

As highlighted above, the T_1-CAs are mostly based on coordination compounds where the paramagnetic metal ion is wrapped in a multidentate organic ligand. At present, the most widespread family of the T_1-CAs consists of complexes with the Gd(III) ion. Although there are other candidates in the lanthanide series that have a high magnetic moment, the intrinsic relaxation time of the electron-spin state of the cation has to be long enough for efficient transfer of magnetic information to the bulk water. Thus, the prominent position of the Gd(III) ion relies not only in a high magnetic moment (7.9 BM) given by seven unpaired *f*-electrons, but also in a totally symmetric electronic state ($^8S_{7/2}$ ground state), which makes the electronic relaxation time much longer than for other Ln(III) ions, 10^{-8}–10^{-9} s.[5] However, the main problem of the medical utilizations of heavy metal ions like the Gd(III) ion is a significant toxicity of their "free" (aqua-ion) form. Thus, for clinical use of gadolinium(III), it must be bound in a complex of high stability and, even more importantly, it must show a long-term resistance to a transmetallation/transchelation loss of the Gd(III) ion. It was proved that the endogenous metal ions Zn(II)

and Ca(II) are the main competitors and, thus, the candidate ligand has to show a higher complexation selectivity for Gd(III) than for the two cations.[35] The most important toxicological feature of the complex is the rate of decomplexation/transmetallation in comparison with the rate of excretion of the complex from the body. The requirements for *in vivo* stability suggest that kinetic stability, also called kinetic inertness, of the complexes is much more important than their thermodynamic stability.

From the structural point of view, two types of organic ligands have been developed: twelve-membered tetraazamacrocyclic cyclen derivatives (cyclen = 1,4,7,10-tetraazacyclododecane) and acyclic triamines (diethylenetriamine derivatives) with several chelating arms, affording an octadentate fashion of the ligands.[1] The coordination number of the Gd(III) ion in these complexes is nine with the last coordination site occupied by a water molecule, which is crucial for the contrast enhancement mechanism (see below).

The clinically used CAs based on Gd(III) complexes are shown in Chart 1 and their relevant pharmacological characteristics (stability constant, typical application dose, indication and pharmacokinetic data) are summarised in Table 1.

The efficacy of the CA measured as the ability of its 1 mM solution to increase the longitudinal relaxation rate R_1 ($= 1/T_1$) of water protons is called relaxivity and labelled r_1. According to the well established Solomon–Bloembergen–Morgan (SBM) theory and its improvement called generalised SBM (GSBM),[45] the relaxivity is governed by a number of parameters.[1] The overall relaxivity can be correlated with a set of physico-chemical parameters, which characterize the complex structure and dynamics in solution. Those that can be chemically tuned, are of primary importance in the ligand design (Fig. 1).[1] They are (*i*) the number of inner-sphere water molecules directly coordinated to the Gd(III) centre – q, (*ii*) the residence time of the coordinated water molecule – τ_M, (*iii*) the rotational correlation time representing the molecular tumbling time of a complex – τ_R, (*iv*) interaction of the complex with water molecules in the second and outer spheres (hydration number q_{ss} and mean residence time τ_{Mss}) and (*v*) electronic parameters.

As described elsewhere, the physico-chemical parameters are accessible from NMR investigations (on the basis of the SBM theory); this procedure is commonly used for characterization of all compounds considered as CAs. Typical values for T_1-CAs currently used in clinics are: one coordinated water molecule, more

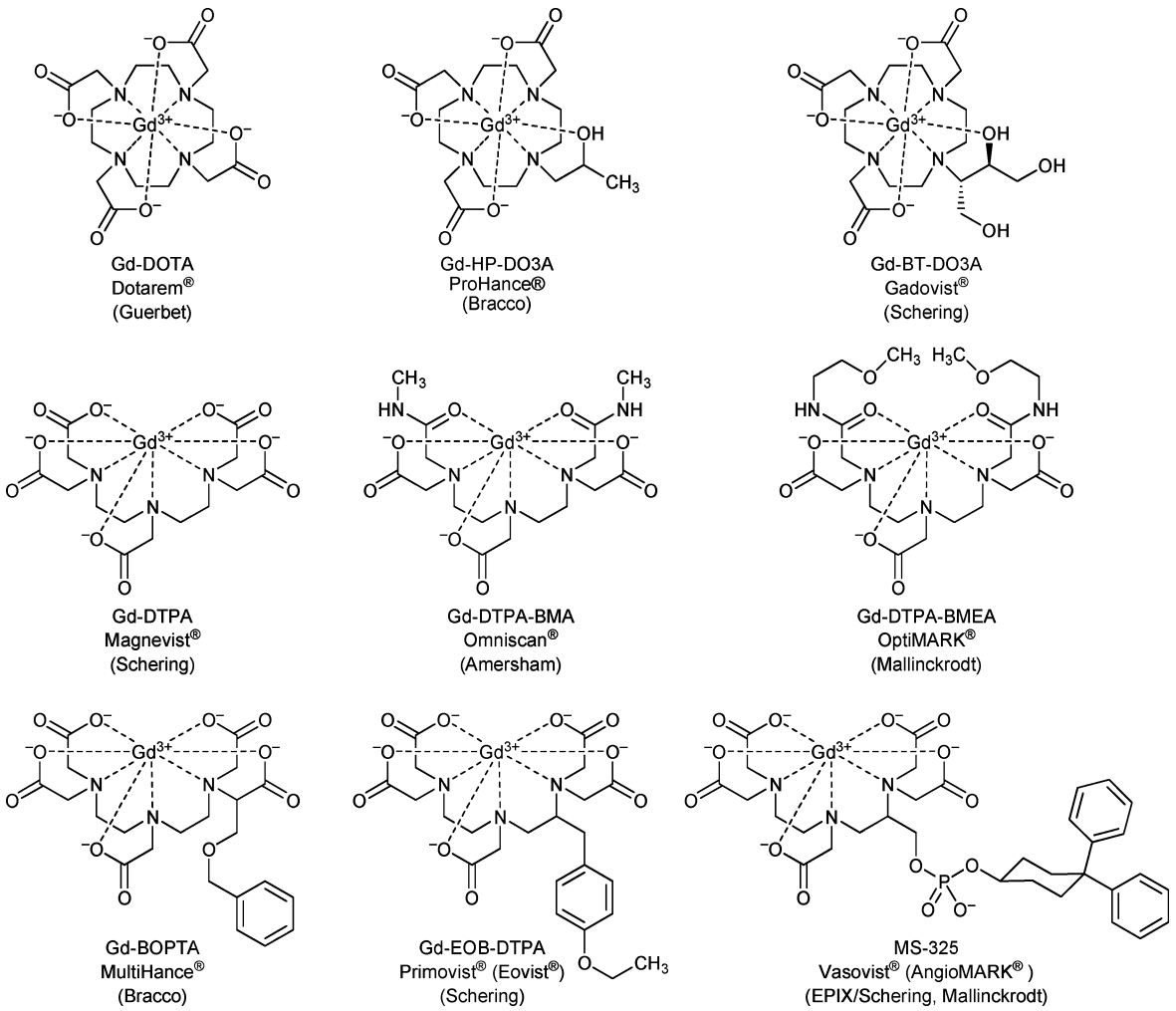

Chart 1 Clinically used contrast agents. Only the Gd-containing parts are shown instead of a full chemical formula; coordinated water molecules (q = 1 in all cases) were omitted for clarity.

Table 1 Selected characteristics of the clinically used gadolinium(III)-based contrast agents[a]

Trademark	Abbreviation of the active component	Structure	Ionicity	Osmolality (mOsm/kg H_2O, 37 °C)	r_1/mM^{-1} s^{-1}	log K_{ML}	Clearance, elimination lifetime/h	Indication	Dosage
Dotarem®	Gd-DOTA	Macrocyclic	Ionic	1350	4.2[b]	25.3[c]	Renal	CNS/whole body	0.1 mmol kg^{-1}
ProHance®	Gd-HP-DO3A	Macrocyclic	Non-ionic	630	4.4[b]	23.8[c]	Renal, 1.57[h]	CNS/whole body	0.1 mmol kg^{-1}
Gadovist®	Gd-BT-DO3A	Macrocyclic	Non-ionic	560	5.3[b]	20.8[d]	Renal	CNS/whole body	0.1 mmol kg^{-1}
Magnevist®	Gd-DTPA	Linear	Ionic	1960	4.3[b]	22.2[c]	Renal, 1.60[h]	CNS/whole body	0.1–0.3 mmol kg^{-1}
Omniscan®	Gd-DTPA-BMA	Linear	Non-ionic	800	4.6[b]	16.8	Renal, 1.30[h]	CNS/whole body	0.1–0.2 mmol kg^{-1}
OptiMARK®	Gd-DTPA-BMEA	Linear	Non-ionic	1110	5.2[b]	16.8[e]	Renal, 1.73[h]	CNS/whole body	0.1 mmol kg^{-1}
MultiHance®	Gd-BOPTA	Linear	Ionic	1970	6.7[b]	18.4[f]	96% renal, 4% hepatic, 1.2–2[h]	CNS/liver	0.05–0.1 mmol kg^{-1}
Primovist®	Gd-EOB-DTPA	Linear	Ionic	1660	7.3[b]	23.5	50% renal, 50% hepatic	Liver	1.25–25 μmol kg^{-1}
Vasovist®	MS-325	Linear	Ionic	700–950	19[b]	23.2[g]	91% renal, 9% hepatic, 18.5	Blood pool	—

[a] If not specified, data are taken from MRI web information portal[36] or from ref. 37. [b] Ref. 38, blood, 37 °C, 1.5 T. [c] Ref. 39, 0.1 M NMe_4Cl. [d] Ref. 40, 0.1 M KCl. [e] Ref. 41. [f] Ref. 42, 0.1 M KCl. [g] Ref. 43, 0.1 M NMe_4Cl. [h] Ref. 44.

Fig. 1 Model of Gd(III)-based contrast agent in solution.

than 100 ns for τ_M and 0.1 ns for τ_R. The optimal values should be about 10 ns for τ_M and at least 10 ns for τ_R at 1.5 T (the most common magnetic field used in MRI scanners nowadays).[1,11] The differences between real and optimal values result in quite a low relaxivity, about 5 s^{-1} mM^{-1}, whereas the SBM model indicates that an up to twenty times higher value can be attained theoretically by optimization of the parameters by ligand design. Logically, tuning of the ligand structure has been the subject of intensive research for last 20 years because an increase in the efficacy allows for a dramatic decrease in the application dose. In other words, the structure of a complex needs to be tuned to allow faster water exchange by one order of magnitude and slower molecular tumbling by two orders of magnitude. In addition, only highly efficient ("optimized") CAs can be used in molecular imaging performed at "high" magnetic fields (see also below). It should be noticed that the current clinical imaging fields range from 0.3 T (12.5 MHz) to 3 T (125 MHz) but commercial suppliers of MRI hardware have already invested in 4.7 T (200 MHz), 7 T (300 MHz) and even 11.7 T (500 MHz) systems.[46]

It has been proved that some of the parameters mentioned above (q, τ_M and τ_R, the second hydration sphere) could be tuned on a chemical basis by ligand design. Additional physical parameters and aspects resulting from the SBM theory, such as electronic relaxation of the Gd(III) ion ($T_{1e,2e}$), the trace of zero-field splitting (ZFS) tensor (Δ^2) and electronic modulation time (τ_v) also contribute to the overall relaxivity. The theory dealing with the electronic relaxation has been reviewed.[19,47] Despite the values of these parameters depending intrinsically on the structure of the complexes (*i.e.* on ligand structures), they have so far been hardly predicted/tuned on a rational basis and seem to be more convenient for more symmetrical complexes.[48,49] Moreover, the theory describing electronic relaxation especially of macromolecular systems (long τ_R) is not yet fully adequate, which complicates evaluation of experimental relaxometric data.[50,51]

The vascular system transports common MRI CAs in the body; however, medical examination is mostly focused on some organ or its function. Therefore, the structural motifs of DOTA and DTPA were further modified to tune the response of contrast agents (responsive CAs, RCAs) or to obtain CAs with organ selectivity. The RCAs are diagnostic agents which are sensitive to

physicochemical changes in their microenvironment, such as pH, O_2 or ion concentrations, temperature and enzymatic activity. Both RCAs and CAs with organ selectivity are intensively investigated in many laboratories and the research progress has been presented in several reviews.[28–31,52,53] However, this issue is not included in this paper except for cases where it is reasonable to compare their properties with common CAs.

Ligands and their complexes

To make more effective CAs, a big effort has been made to design new ligands. However, the design has been mostly oriented on modifications of the structural motifs of DOTA (Chart 2) and DTPA (Chart 3). Thus, a number of ligands bearing functionalities different from carboxylic acids in the pendant arms, such as amides, alcohols, phosphonic or phosphinic acids and phenols, were synthesized and their lanthanide(III) complexes studied.[54] In addition to the ligands mentioned, and their complexes that contain one water molecule coordinated to Gd(III) ion, other ligands such as DO3A (Chart 2) forming Gd(III) complexes with two water molecules in the inner coordination sphere were synthesized and investigated. The DO3A and also its derivatives are prototypes of heptacoordinated ligands based on the cyclen ring bearing only three coordinating pendants. Unfortunately, Gd(III) complexes of the ligands mostly contain the expected two water molecules only in a pure and dilute aqueous solution. In the presence of citrate, carbonate, amino acids *etc.*, the complexes tend to lose the bound water molecule(s) due to the formation of rather thermodynamically stable ternary complexes containing the simple ligands. At high concentrations, the formation of dimeric species similar to the structures found in the solid state (see below) is also expected.

A stable Gd(III) chelate containing two coordinated water molecules is formed by ligands analogous to pyDO3A (Chart 4), which are based on a pyridine-containing twelve-membered macrocycle. Another family of ligands forming gadolinium(III) complexes with two coordinated water molecules is formally derived from DTPA. Here, the coordinating pendant arm on the central nitrogen atom of diethylenetriamine is replaced with a gadolinium(III) non-coordinating substituent (*e.g.* bipy(DTTA)$_2$ in Chart 3).[55–57]

Recently, a new prototype of the heptadentate ligand, 6-amino-6-methylperhydro-1,4-diazepine-1,4,N^6,N^6-tetraacetic acid (AAZTA, Chart 4), was introduced.[58] More promising hexadentate ligands, and their complexes, seem to be those based on the HOPO motif, developed by Raymond and co-workers.[59] These ligands are based on 3-hydroxy-2-oxo-1,2-dihydropyridine-4-carboxyamide units (2,3-HOPO motif; Chart 4). Very recently, an analogous motif has also been developed in the octadentate ligand H(2,2)-1,2-HOPO (1,2-HOPO motif; Chart 4), whose

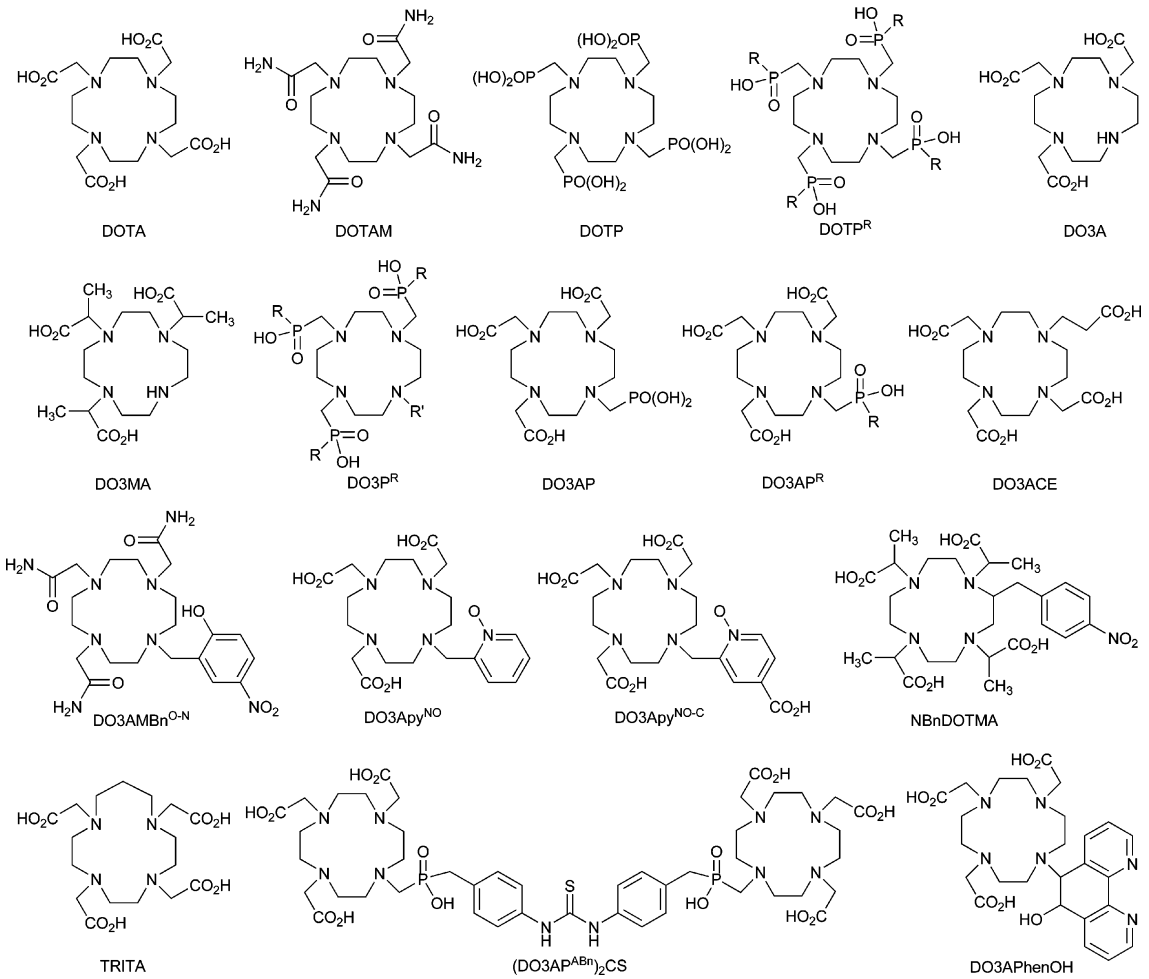

Chart 2 DOTA-like ligands discussed in the text.

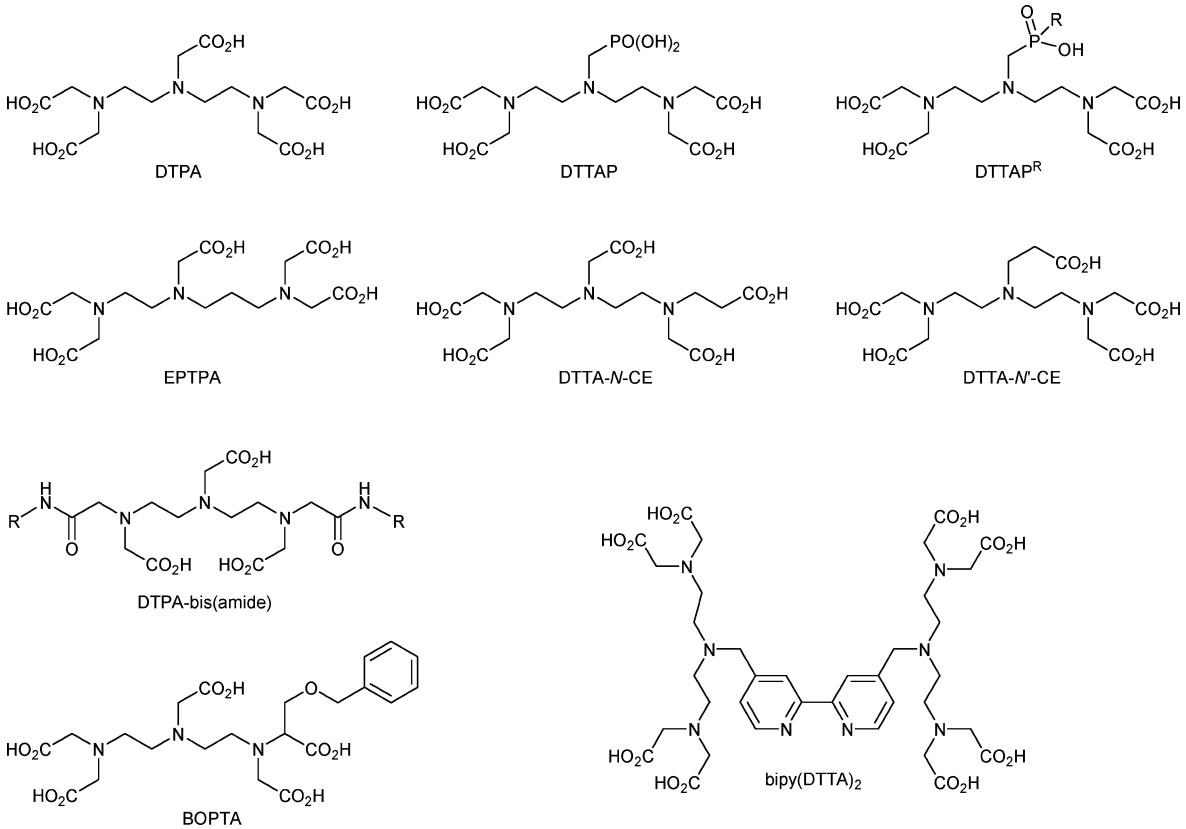

Chart 3 DTPA-like ligands discussed in the text.

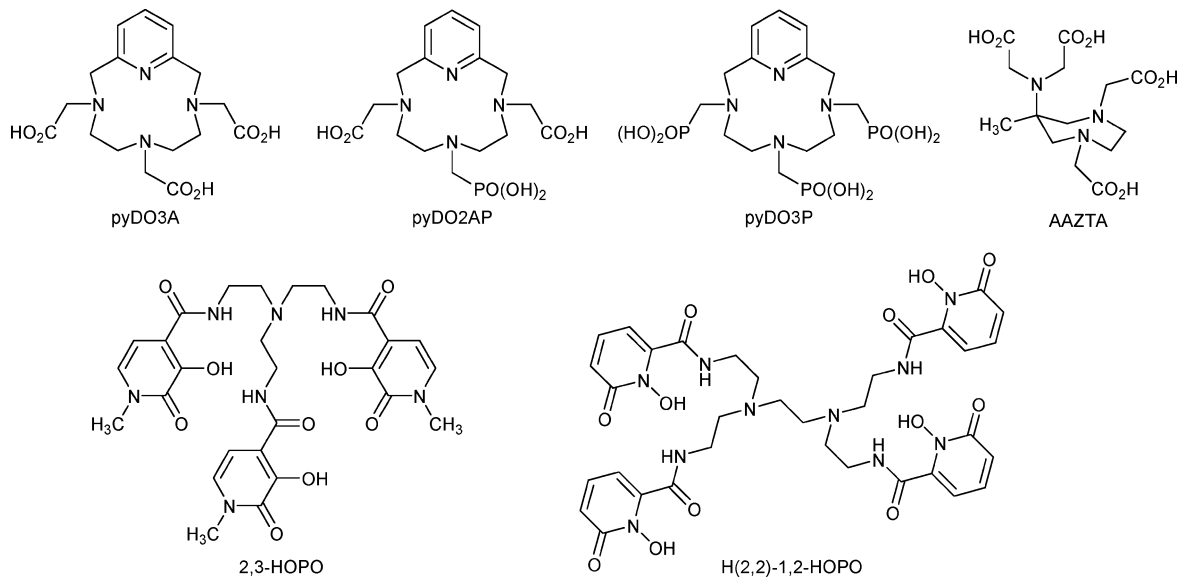

Chart 4 Other hexadentate/heptadentate ligands discussed in text.

Gd(III) complex has one coordinated water molecule and shows better relaxometric properties than the complexes of ligands based on the DOTA or DTPA skeleton.[60]

Structures with DOTA-like ligands

The prototype dota^{4-} anion is coordinated to a lanthanide(III) ion by four ring nitrogen atoms and four carboxylate groups in a well-known fashion. The nitrogen atoms as well as oxygen atoms form N_4 and O_4 bases, which are planar and parallel to each other. The O_4 plane is capped with a coordinated water molecule. The ethylene groups of the macrocycle adopt a gauche conformation forming a five-membered coordination metallacycle with either δ or λ configuration. This results in two possible square [3,3,3,3] conformations of the macrocycle, δδδδ and λλλλ. The pendant acetate arms may occupy two orientations, Δ or Λ. Therefore, in

solution, the ring interconversion $\delta \rightleftharpoons \lambda$ or acetate arm rotation $\Delta \rightleftharpoons \Lambda$ lead to formation of four stereoisomers (two diastereoisomers $\Delta\delta\delta\delta/\Lambda\lambda\lambda\lambda\lambda$ and $\Delta\lambda\lambda\lambda\lambda/\Lambda\delta\delta\delta\delta$; Fig. 2). Both diastereoisomers differ in structural parameters, *e.g.* in the angle ω formed by the mutual rotation of the O_4 and N_4 planes (Fig. 3). In the $\Delta\lambda\lambda\lambda\lambda/\Lambda\delta\delta\delta\delta$ isomers, a rotation of ~40° leads to the square-antiprismatic isomer SA (ideal angle 45°). This diastereoisomer is also traditionally termed "MAJOR" (M) due to its higher abundance in solutions of the $[Gd(dota)(H_2O)]^-$ complex; in the pair of $\Lambda\lambda\lambda\lambda\lambda/\Delta\delta\delta\delta\delta$ enantiomers, a rotation of ~24° corresponds to the twisted square-antiprismatic isomer TSA (ideal angle 22.5°) or "minor" (m) isomer.[61] Lanthanide(III) complexes of DOTA form mostly SA isomers. The TSA isomers were observed in structures of large ions such as lanthanum(III)[62] or cerium(III)[63] or for small ions *e.g.* thulium(III);[63] but without a coordinated water molecule in the case of Tm(III) (such arrangement with no bound water molecule is often denoted TSA′ or m′). The corresponding SA′ isomer (SA without coordinated water) was found only for the small scandium(III) ion.[63]

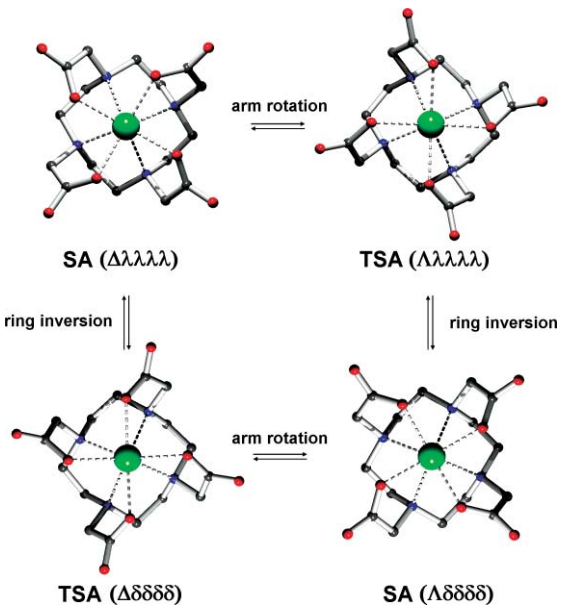

Fig. 2 Possible isomers for lanthanide(III) complexes with H_4dota-like ligands.

The comparison of all the X-ray crystal structures of the lanthanide(III) complexes of DOTA, its amides and several derivatives bearing one methylphosphonic/phosphinic acid group[64–66] found in the literature indicated the same structural properties of the coordination polyhedron. The TSA/SA ratio is influenced by the size of the lanthanide(III) ion and by the shape of the ligand cavity. The geometry and the size of the complex cavities formed by these ligands are mostly governed by rotation of the pendants. It was shown that different orientations of the pendant arms lead to different distances between the N_4 and O_4 planes (Fig. 3). The lighter lanthanide(III) ions such as lanthanum(III) and cerium(III) ions require a larger cavity and, thus, the N_4–O_4 distance is 2.5 Å or longer and the formation of the TSA isomer is preferred in their complexes. As the radius of the lanthanide(III) ion decreases in the lanthanide series, the ion moves towards the N_4 plane and, consequently, the coordinated oxygen atoms in the O_4 plane also move closer to the N_4 base and the structure switches to the SA arrangement with the N_4–O_4 distance of 2.3–2.4 Å.

Replacement of all carboxylic acid groups with phosphonic or phosphinic acid groups leads to the tetraphosphorus DOTA analogues, abbreviated DOTP and DOTP^R (Chart 2). In the solid state, lanthanide(III) complexes of such ligands show mostly TSA′ isomers through the lanthanide series. The coordinated water molecule (in the TSA isomer) was found only in structures of the La(III) and Ce(III) complexes.[67,68] The preferential TSA/TSA′ isomer formation is probably caused by bulky phosphorus acid pendants and the tetrahedral geometry of phosphorus atoms. This leads to a smaller opening angle ψ and expulsion of a water molecule from the first coordination sphere. In contrast to the TSA

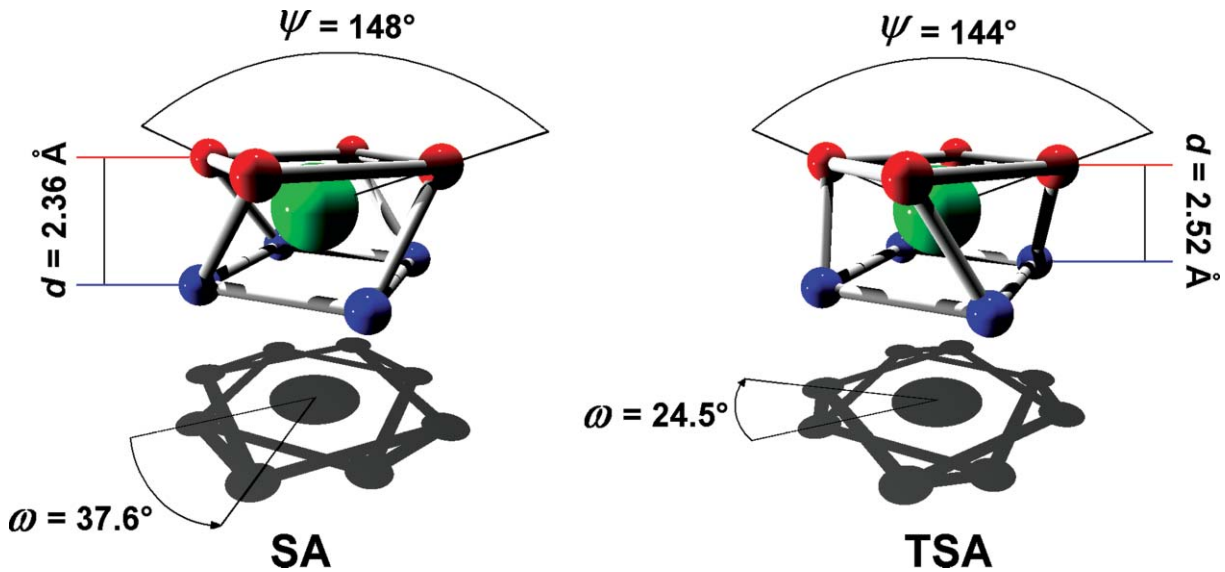

Fig. 3 The coordination polyhedrons of the SA ($[Pr(dota)(H_2O)]^-$) and TSA ($[Ce(dota)(H_2O)]^-$).[63] The coordinated water molecules (above the O_4 plane) are omitted for clarity. Oxygen atoms are red, nitrogen atoms blue and lanthanides green. The ω represents the average angle of rotation between the O_4 and N_4 planes, d is the distance between the O_4 and N_4 plane centroids and ψ is the minimal value of the O–Ln–O opening angles.

isomers of the DOTA complexes, the distances between the O_4 and N_4 planes are longer and the structures are more flexible. The presence of even one phosphorus acid pendant arm (in DO3AP or DO3AP^R, Chart 2) induces the formation of complexes with the TSA/TSA′ arrangement in the solid state.[64–66]

The opening angle ψ (the O–Ln–O angle between two transannular oxygen atoms, Fig. 3) was found (based on the crystal structures) to be a crucial parameter for coordination of the water molecule.[20] When the angle is higher than 135°, water is coordinated, but if it is lower, then the water is not bound.

In addition to the pendant forming five-membered chelates, a few ligands with pendants forming six-membered chelates were synthesized and their complexes were studied. The structure of the $[Eu(do3amBn^{O\text{–}N})(H_2O)]^{2+}$ complex ($DO3AMBn^{O\text{–}N}$ = 10-(2-hydroxy-5-nitrobenzyl)-1,4,7,10-tetraazacyclododecane-4,7,10-triacetamide; Chart 2) shows the SA isomer in the solid state.[69] In addition, the distance between the O_4 and N_4 planes is longer (2.486 Å) than that usual for the SA complexes (<2.4 Å), and the value of the opening angle 136° is just on the border for water coordination. Similar SA/SA′ species were found in the solid state for complexes of 10-[(1-oxidopyridin-2-yl)methyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetate ($DO3Apy^{NO}$; Chart 2). SA′ isomers with O_4–N_4 distances of 2.503, 2.482 and 2.451 Å were found in structures of the $[Dy(do3apy^{NO})]$,[70] $[Tm(do3apy^{NO})]$[71] and $[Yb(do3apy^{NO})]$[71] complexes, respectively. All complexes have opening angles ψ of about 125°. Water is coordinated in the $[Nd(do3apy^{NO})(H_2O)]$ complex with an opening angle of 140° and an O_4–N_4 distance of 2.418 Å.[71] Based on these data, it seems that the presence of at least one six-membered chelate ring in the complexes of the DOTA-like ligands favours the formation of the SA isomers.[72]

The La(III) complex of the ligand having all four acetate pendant arms of DOTA replaced by 2-carboxyethyl groups is the SA′ isomer with the N_4–O_4 distance 2.853 Å. So, the La(III) ion is deeply embedded in the cavity and the opening angle is only 118°. In addition, the lanthanide(III) complexes of this ligand show a very low stability in solution.[73]

Structures with DTPA-like ligands

In spite of a number of DTPA modifications, the number of X-ray structures found in CSD is rather low (~50).[74] In $Na_2[Gd(bopta)(H_2O)]$ (MultiHance®, Chart 1), the DTPA-based anion is coordinated to the Gd(III) ion with five oxygen atoms of five carboxylates and three nitrogen atoms forming a distorted tricapped trigonal prism TTP (Fig. 4).[42] The coordination polyhedron is completed with a water molecule. In $Mn[Gd(dtpa)(H_2O)]\cdot 2H_2O$, the complex anion also shows the same molecular structure[75] as well as in the analogous Ag(I)[76] and aminoguanidinium[77] salts. The coordination sphere of gadolinium(III) in contrast agent MS-325 (Vasovist®, Chart 1) reported recently shows the same features.[78] Analogous structures were found in DTPA complexes with other lanthanide(III) ions. In some other structures, *e.g.* in $(NH_4)_4[Gd_2(dtpa)_2]\cdot 6H_2O$[79] and in guanidinium salt,[77] the complex is dinuclear due to two carboxylates bridging the metal centres of the monomeric units. In such dimeric complexes, water is not coordinated. In the structures of DTPA-bis(amides), dimer formation is less pronounced, and the coordination polyhedron is similar to complexes of DTPA itself.[74]

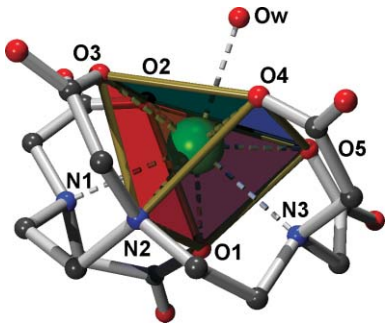

Fig. 4 Structure of Ln(III)-DTPA complexes. Oxygen atoms are red, nitrogen atoms blue, carbon atoms gray and lanthanides green ($[Gd(dtpa)(H_2O)]^{2-}$, ref. 76).

All the structures are distorted; nevertheless, some common structural features are evident from their comparison. Oxygen atoms O2, O3, O4 and O5 are in a plane (see Fig. 4). The lanthanide is placed close to the plane (~0.7 Å), the distance is close to the value found for both TSA and SA isomers of the DOTA complexes. The opening angles O3–Ln–O5 and O2–Ln–O4 are different, 140° and 150°, respectively. The Ln–O and Ln–N distances fall in the expected range 2.5–2.6 Å except for the Ln–N1 distance, which is systematically longer (2.75 Å) in all complexes. In solution, a fast exchange associated with alternation of acetates as well as a change in ethylene bridge conformation occur, which leads to an equilibrium between two enantiomers. In all complexes of the DTPA-like ligands, only coordination number 9 was found, probably due to systematically higher values of the opening angles and a larger space above the O_4 plane.

The skeleton of the parent DTPA was modified in order to tune relaxometric properties of the Gd(III) complexes. Such modification was, *e.g.* replacement of carboxylic groups by phosphinic or phosphonic group (DTTAP or DTTAP^R, Chart 3),[80] of acetate by carboxyethylene (DTTA-*N*-CE or DTTA-*N*'-CE, Chart 3)[82] or of ethylene by 1,3-propylene (EPTPA, Chart 3).[81,82] However, the crystal structures of complexes with such ligands have not been published yet.

Structures with DO3A-like ligands

DO3A (Chart 2) is a prototype of heptadentate ligand forming lanthanide(III) complexes with two coordinated water molecules in aqueous solution. The coordination mode of DO3A to lanthanide(III) ions is analogous to that found for the DOTA complexes. In the solid state, the complexes are mostly SA isomers with distances between the N_4 and O_3 planes of about 2.35 Å and coordination bond lengths in the usual range. The complex of the Gd(III) ion with DO3A was isolated in the solid state as trimer in which three [Gd(do3a)] units are connected through a carbonate anion and no water molecule is coordinated.[83] The complex of DO3MA (Chart 2) forms a dimeric species in the solid state, with combined SA and TSA configurations.[84] The SA unit contains two coordinated water molecules. In the TSA unit, two "free" coordination sites are occupied by bidentately coordinated acetate arms from the SA unit and, thus, no directly coordinated water molecule is present. More structures were published for lanthanide(III) complexes of DO3A amide derivatives. The expected

two water molecules were found, *e.g.* in complexes of DO3A-tris(*N*-methylamide) derivative with Eu(III)[85] and DO3A-tris(*N,N*-dimethylamide) derivative with Eu(III)[86] and Tb(III).[87] About 15 structures were reported for complexes with the DO3A-tris(*N*-phenetylamide) derivative. Two coordinated water molecules were found in the structure of its ytterbium(III) complex.[88] In addition, a series of ternary Ln(III) complexes with small bidentate ligands such as acetate,[89] hydroxyacetate,[90] amino acids[88,89] or citric acid[89] were reported. This points to a strong tendency of the complexes to bind other small ligands instead of two water molecules and, thus, to form thermodynamically stable ternary complexes.

The tris(methylphosphinic acid) analogues of DO3A, abbreviated as $DO3P^R$ (Chart 2), were synthesized with hydrophobic substituents (R = phenyl, R′ = Me;[91] or R = benzyl, R′ = H;[92]). Their lanthanide(III) complexes follow the structural properties of complexes of the DOTP and $DOTP^R$ ligands, *i.e.* show a strong preference for the TSA arrangement with analogous structural parameters (*e.g.* the same distances between the O_3 and N_4 planes). In contrast to the complexes of DO3A, these $DO3P^R$ complexes form only dimeric species in the solid state, in which two complex units are bridged by phosphinate groups, forming the eight-membered ring Ln–(O–P–O–)$_2$–Ln, usually found in complexes of simple phosphinic acids. Water is not coordinated. The complexes are uncharged and in combination with hydrophobic phenyl or benzyl groups suffer from a low solubility in aqueous media. The dimer formation was proved also in solution (by luminescence, ^{1}H NMR relaxometric and electrochemical measurements); however, it is a matter of fact that the phosphinate pendant arms are surrounded by hydrophobic substituents.

Structures of Ln(III) complexes with other hexa- and heptacoordinated ligands

Of the other ligands, only structures of complexes of HOPO-like ligands (Chart 4) were reported in the literature. The lanthanide(III) ion can be octacoordinated by six oxygen atoms from three hydroxypyridinone rings and by two water molecules. In the solid state, this structure was observed only in the Gd(III) complex (Fig. 5).[93] Because of additional functionalities in the ligand (amide groups), the formation of dimer was also observed for the Gd(III) complex and the number of coordinated water molecules drops to one per Gd(III) ion.[94] In the case of the Ce(III) complex, a polymer was formed in the solid state, again with only one water molecule per Ce(III) ion.[95] For the large La(III) ion, a polymer structure containing two types of coordination spheres

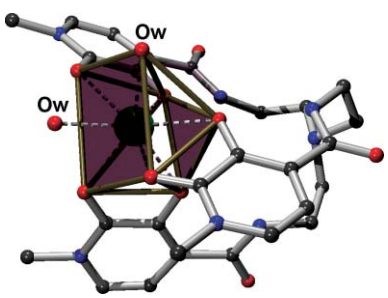

Fig. 5 Structure of complexes with HOPO-like ligands. Oxygen atoms are red, nitrogen atoms blue, carbon atoms gray and lanthanides green ([Gd(2,3-hopo)(H$_2$O)$_2$], ref. 93).

was observed: one with two coordinated water molecules and the coordination number nine and the other with only one bonded water molecule and the coordination number eight.[96] Recently, the structure of a europium(III) complex with a 1,2-HOPO-based ligand was reported; the complex forms a dimer with coordinated DMF solvate molecules.[97]

Unfortunately, no crystal structures have been reported for complexes of the heptadentate ligands such as pyDO3A, pyDO2AP, pyDO3P or DTTA derivatives (Charts 3 and 4). Very recently, the solid-state structure of Gd(III)-AAZTA was reported; the complex was found to be dimeric in the solid-state.[243]

General features of lanthanide(III) complexes with the presented ligands

This brief survey of ligands and structures of their complexes shows that lanthanide(III) ions are well wrapped in the cavity formed by the ligands. The number of coordinated water molecules depends on the number of ligand donor atoms (and the size of donor groups) and also on the geometry of the coordination polyhedron. In the crystal structures of all the DOTA complexes reported, a water molecule is coordinated if the opening angle ψ is higher than 135°.[20,64] Furthermore, if the opening angle is higher than 145°, as observed, *e.g.* in the [La(dota)]$^-$ species, the water molecule can be substituted with another (larger) group, such as carboxylate from the neighbouring complex unit, forming a coordination polymer.[62] On the other hand, for tetrakis(phosphorus acid) DOTA analogues, pendant arms are longer and lanthanide(III) ions, except La(III) and Ce(III), are located deeper in the cavity. So, opening angles are lower than 135° and no water is coordinated. A similar relationship can be observed for the other ligands, *e.g.* for DTPA complexes, where opening angles are 140–150° and, besides water coordination, dimer formation was also found in the solid state.

If the number of donor atoms decreases to 7 or 6, in principle, the number of bound water molecules can increase. However, such complexes can easily form dimers or polymers in the solid state and, in solution, often interact with small ligands (citrate, carbonate, amino acids *etc.*) common in body fluids.

Stability of the complexes in solution

Thermodynamic properties

In view of utilization of the toxic gadolinium(III) ion, the crucial condition for its *in vivo* application is its complexation in stable species. Therefore, many papers have been focused on the thermodynamic stability of Gd(III) complexes and the results were summarized in several reviews.[20–23] The stability constants of gadolinium(III) complexes ($\log K_{GdL}$) with all the considered ligands are high. Their values were often determined to be somewhat different depending on the method used, ionic strength *etc.* Nevertheless, on average they increase in the order DO3A ($\log K_{GdL}$ ~21) < DTPA (~22) < DOTA (~24). Modifications of DO3A, DTPA and DOTA parent ligands change the values depending on the functionalities in the pendant arms. The most common introduction of two amide functions into DTPA leads to a decrease of $\log K_{GdL}$ to ~15–19;[98,99] DTPA-mono(*N*-methylamides)[100] and a DTPA triamide[101] have $\log K_{GdL}$ ~19 and ~18, respectively. Similarly, the introduction of four amide groups

instead of acetates in the DOTA skeleton leads to a decrease in $\log K_{GdL}$ to ~13–15.[102–104] Introducing four methylphosphonic acid pendants increases the stability constant due to enhanced basicity of the nitrogen atoms.[20,105,106] On the other hand, the presence of four methylphosphinic acid or methylphosphonic monoester pendants generally decreases the nitrogen basicity and, consequently, the stability constants are much lower than those for the parent lanthanide(III) DOTA complexes ($\log K_{GdL}$ = 13–15).[107–110] However, replacement of only one acetate arm in DOTA with a phosphorus-containing arm shows only a small effect on overall thermodynamic stability.[111,112] A similar effect was observed for monophosphorus acid analogues of DTPA.[113,114] Analogously, substitution of one acetate arm in DOTA for an alcohol-containing group (*e.g.* ligands HP-DO3A or BT-DO3A used in ProHance® and Gadovist®, respectively, Chart 1) leads to only a small decrease in thermodynamic stability constants of the complexes of such ligands.[40,103*b*,115–117] Substitutions with a substituted aliphatic chain on the carbon atoms of the DTPA skeleton or the DOTA macrocyclic rim, as well as on the methylenes in the arms, have mostly only a minor effect on overall thermodynamic stability of the corresponding complexes.[43,118–120] Even if the values of stability constant are high, a number of competitive reactions can occur in organisms. Using a simplified plasma model, Sarka *et al.*[121] suggested a species distribution for DTPA complexes in blood. The equilibrium data indicate a partial replacement of the Gd(III) ion in the $[Gd(dtpa)(H_2O)]^{2-}$ complex with the Zn(II) ion.

Replacement of the ethylene group with 1,3-propylene inside the DTPA/DOTA skeleton leads to ligands (*e.g.* TRITA or EPTPA, Charts 2 and 3) forming a six-membered chelate ring.[81,122–124] Similarly, ligands with acetate pendant arm(s) exchanged for propionate pendant(s) were studied (DO3ACE or DTTA-*N*-CE; Charts 2 and 3).[125,126] The stabilities of their complexes are somewhat lower ($\log K_{GdL}$ = 18–21) than those for the parent ligands, DOTA and DTPA. Some amides derived from EPTPA were also prepared and investigated; their complexes have $\log K_{GdL}$ = 13–15.[127–129] The changes are analogous to those for DTPA-like ligands.

Gadolinium(III) complexes with macrocyclic DO3A-like heptadentate ligands are generally less stable than complexes of analogous DOTA derivatives. The $\log K_{LnL}$ of complexes of DO3A[115] and pyDO3A[130–132] (Charts 2 and 4) is ~21 and that of the $[Gd(pydo2ap)(H_2O)_2]^-$ complex is 23.4;[133] substitution by the phosphonic acid group has the same effect on $\log K_{LnL}$ as in the DOTA analogues. However, larger differences in stability constants were found for Eu(III) complexes of the pyDO3A derivative with glutarate arms ($\log K_{EuL}$ 18.7), analogous to TCED (Chart 5, $\log K_{EuL}$ 24.0).[134] Similar trends to those of macrocycles were found for complexes of the DTTA derivatives (Chart 3), which are less stable (~19) than the DTPA complex.[56,57] The exchange of acetate arms for propionate arms in pyDO3A led to a large decrease in stability constants.[132]

The stability constants of the $[Gd(aazta)(H_2O)_2]$ complex ($\log K_{GdL}$ = 19.3)[58] and the Gd(III) complexes with HOPO-based ligands (18–21)[59,60,97,135,136] are comparable. Thus, all the thermodynamic stabilities are sufficiently high and fall close to those of the DTPA and DOTA complexes. In addition, the data determined for HOPO-based ligands show a higher selectivity for Gd(III) than for Ca(II) or Zn(II) ions in contrast to DOTA and DTPA.[59,97,135]

Kinetic properties

Much more important than thermodynamic stability is the kinetic inertness of the complexes against substitution with other chelators and/or metal ions present in the organism.[23,137,138] As a

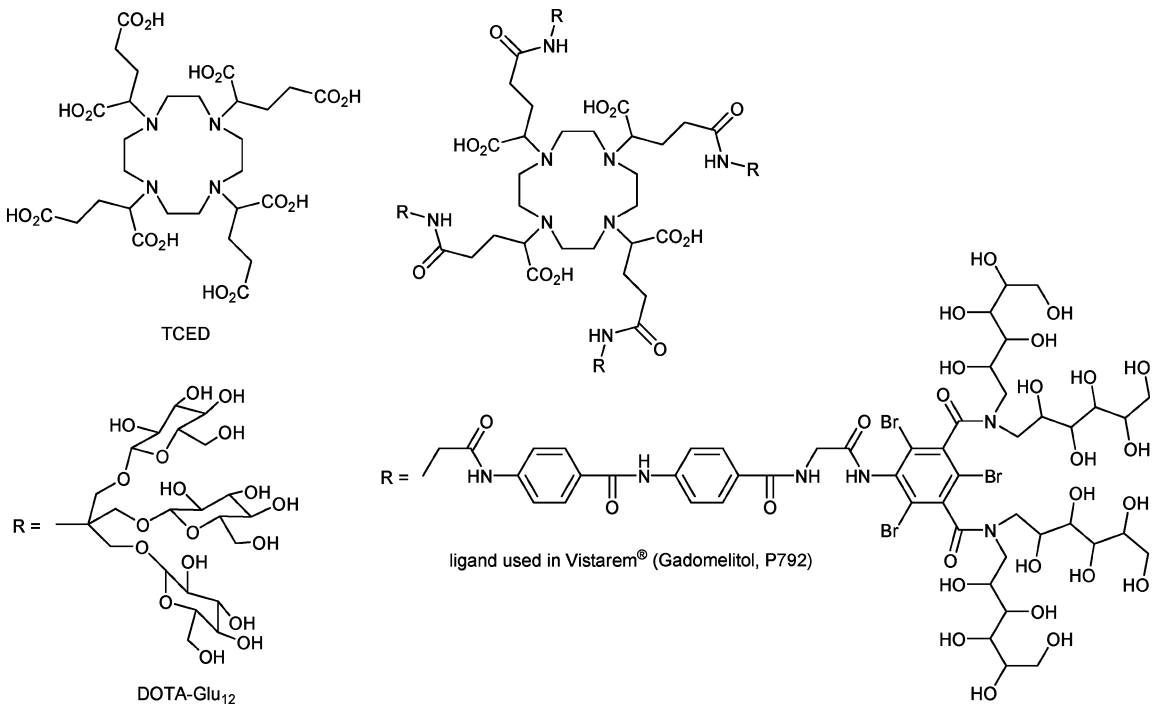

Chart 5 Other DOTA-based ligands (TCED derivatives) discussed in the text.

qualitative comparison of complexes of various ligands is similar for different lanthanide(III) ions, the data for gadolinium(III) and other Ln(III) ions will be compared here. The *in vitro* experiments were oriented in two directions, transmetallation and acid-assisted decomplexation.

Kinetic stability evaluated as an extent of transmetallation of the complex in the presence of Zn(II) ion at pH 7 was suggested by Tweedle[137] and largely extended by Laurent *et al.*[139] The obtained results indicated a remarkable stability of the Gd(III) complexes with macrocyclic ligands such as DOTA and HP-DO3A (used in Dotarem® and ProHance®, respectively; Chart 1) with decomplexation lower than 10% over 3 days. The other macrocyclic chelates, such as that used in Vistarem® (Gadomelitol, P792, Chart 5), also exhibited high inertness against transmetallation.[140,141] On the other hand, for the DTPA complexes, ~20% of the $[Gd(dtpa)(H_2O)]^{2-}$ complex underwent transmetallation after 4.5 h. For complexes of the mono- and diamide derivatives of DTPA (*e.g.* those used in Omniscan® and OptiMark®, Chart 1), the transmetallation was even faster.[139] Substitutions on carbon atoms in the DTPA skeleton lead to ligands whose complexes show comparable kinetic stability to the $[Gd(dtpa)(H_2O)]^{2-}$ complex.[139,142] The complexes of the corresponding amides are not kinetically inert.[143] Replacement of the central acetate group of DTPA with a phosphorus-containing pendant arm caused much easier transmetallation in this reaction.[80,144] The Gd(III) complexes of EPTPA derivatives are, depending on substituents on the ligand skeleton, less or comparably stable to the DTPA complex in the presence of zinc(II) ions.[145] Of the heptadentate ligands, only the Gd(III) complex of pyDO3A was tested by this method, showing kinetic inertness similar to other macrocyclic complexes;[146] the complex of its 2,2′-bipyridine analog (having only one coordinated water molecule) also exhibit kinetic stability similar to the complexes of other macrocyclic ligands.[147]

In the absence of Zn(II) ion, the rate of dissociation of the gadolinium-based CAs (even for complexes of the DTPA-like ligands) is slow at physiological pH 7.4 and, thus, decomposition of these and other lanthanide(III) complexes was investigated under acid-assisted decomplexation in acid medium (*e.g.* in 0.1 M HCl or $HClO_4$).[23,138,148] The dissociation rates are about two orders of magnitude higher for the $[Ln(dtpa)(H_2O)]^{2-}$ and $[Ln(do3a)(H_2O)_2]$ complexes when compared with the $[Ln(dota)(H_2O)]^{-}$ complex.[23] For complexes of DTPA derivatives, a combination of proton- and M-assisted ($M = Zn^{2+}$ or Cu^{2+}) pathways for their decomplexation should be considered.[121] Proton-assisted dissociation rates of complexes of DTPA amide derivatives are much faster but they are somewhat compensated by a slower metal-assisted pathway.[23,101,149] The overall k_{obs} for the $[Gd(dtpa\text{-}bma)(H_2O)]$ complex is about one order of magnitude higher than that for the $[Gd(dtpa)(H_2O)]^{2-}$ complex. However, the kinetics of decomposition of Ln(III) complexes of DTPA amides depends on substituents on the amide nitrogen atoms.[98] Lanthanide(III) complexes of DOTA tetraamides (important as possible PARACEST CAs, see below) are generally more kinetically inert than those of DOTA due to the lower basicity of macrocyclic nitrogen atoms and overall positive charge of the complexes.[102,104] Complexes of other derivatives of DTPA or DOTA substituted on carbon atoms are usually more kinetically inert. The exchange of acetate pendant arms for other coordinating group(s) mostly alters the kinetic behaviour. Replacement of one acetate pendant of DOTA with an alcohol group leads to a lower kinetic inertness than that for complexes of the parent ligand.[40,117,150] Replacement of the central acetate in DTPA with methylphosphonic/inic acid group (DTTAP and DTTAP^R, Chart 3) gives ligands whose complexes are much more labile than the DTPA complex.[113] A similar increase in lability was observed for a DTPA derivative having one acetate arm replaced with propionate arm (DTPA-*N*-CE, Chart 3).[126]

For complexes of monophosphorus acid analogues of DOTA, the lowering of kinetic inertness is less pronounced and, in addition, the rate of decomplexation depends on the substituent on phosphorus and can be even slower than that for the corresponding DOTA complexes.[111,112,151] The DO3ACE complexes are also less kinetically inert.[126] Complexes of DOTP (Chart 2) are similarly kinetically inert to the complexes of DOTA;[109,152,153] the inertness of the complexes of phosphinic acid and phosphonic monoester analogues of DOTA (DOTP^R, Chart 2) again depends on substituents on the phosphorus atom.[107–110,148] The expansion of the macrocycle by one carbon atom in TRITA (Chart 2) caused a significant increase in lability of its gadolinium(III) complex but its inertness is still higher than that for the $[Gd(dtpa)(H_2O)]^{2-}$ complex.[154] Derivatives of DO3A are generally less kinetically inert than complexes of DOTA;[23] a similar correlation is valid for pyDO3A.[131] The $[Gd(pydo2ap)(H_2O)_2]^{-}$ complex was found to be stable only above pH 3 (on the basis of the relaxivity *vs.* pH dependence).[133]

Similar kinetic data for Ln(III) complexes with ligands based on DTTA, HOPO and AAZTA have not been published. Investigations of behaviour of the complexes in acid solutions indicate that the complexes are only stable above pH ~3. The [Gd(2,3-hopo)$(H_2O)_2$]-like complexes at pH 3 show protonation and subsequent dissociation;[59] for the $[Gd(aazta)(H_2O)_2]^{-}$ complex, a ~25% release of free Gd(III) ions was observed after 20 min at pH 2.[58] These results indicate that the stability of such complexes with heptadentate ligands against decomplexation is similar or smaller than that found for the complexes with DTPA-like ligands. In addition, the HOPO-based ligands have shown better selectivity for Gd(III). In contrast to the DO3A complexes, relaxivity of the HOPO, AAZTA or pyDO2AP complexes is not so much influenced by the presence of other small ligands due to different shapes of the coordination polyhedron; thus, interaction of these small ligands seems to be less probable.[59,135]

In vivo consequences of solution stability

The *in vivo* experiments showed a significantly lower extent of Gd(III) displacement probably because of a fast excretion of the complexes from the organism. In an earlier paper, Tweedle *et al.* observed Gd(III) release from the complexes.[155] The experiments confirmed a strong correlation between acid-assisted dissociation rates of the complexes and their *in vivo* dissociation. The kinetically inert macrocyclic complexes, $[Gd(hp\text{-}do3a)(H_2O)]$ and $[Gd(dota)(H_2O)]^{-}$, had the lowest residual gadolinium content in the animals. Only in the case of the $[Gd(dtpa\text{-}bma)(H_2O)]$ complex, the residual amount of ^{153}Gd(III) released from the complex was somewhat larger than 1% of the injected dose. In a search for CAs endowed with a long-term stability, Aime *et al.* observed differences in the free Gd(III) concentration after internalization of CAs in living cells.[156] The concentration was found to be about one order of magnitude higher for the $[Gd(dtpa\text{-}bma)(H_2O)]$ complex than for the $[Gd(hp\text{-}do3a)(H_2O)]$

complex. The observation was explained by easier internalization of free gadolinium(III) ion originating from decomposition of the [Gd(dtpa-bma)(H_2O)] complex. This confirmed the lower stability of complexes with DTPA and its derivatives when compared with complexes of the DOTA-based ligands under *in vivo* conditions.

Although all experiments in animals and also the long time of utilization of CAs in clinical practice indicate sufficient stability, a report describing development of a condition called Nephrogenic Fibrosing Dermopathy (NFD) associated with the use of Gd(III)-based MRI CAs was published.[37,157,158] This progressive form of fibrosis develops in many organs and can result in severe contractures of joints secondary to fibrosis in the overlying skin. Of about 200 cases reported, most of them were associated with the administration of Omniscan. Other cases were associated with Magnevist® or OptiMARK exposure. A typical onset is ~25 days after administration, and this delay may explain why this problem had not been described earlier. Recently, the effect of MRI CAs on cardiovascular and renal systems has been stated.[37,44] The changes observed triggered additional clinical investigations of transmetallation of the Gd(III) complexes with other ions present in the organism[159] (see also subsequent discussion[160]). An explanation of the effect can rise from the kinetic instability of the complexes with DTPA-like ligands mentioned above.

From a chemical point of view, it is worth noting that the determination of the *in vitro* stability of the complexes has been mostly performed at physiological pH about 7. The blood pH (7.4) is regulated by the kidneys through excretion of H^+ ions to urine and by re-absorption of hydrogencarbonate anion and other cations.[161] The H^+ ions enter the filtrate in two ways: by filtration through the glomeruli and by secretion into tubules. Most of the H^+ ion secretion occurs across the wall of the proximal tubules in exchange for re-absorbing Na^+ and K^+ ions; a similar exchange occurs in the late distal tubules and cortical collecting duct. Since the kidneys normally re-absorb almost all the filtered cations and hydrogencarbonate and excrete H^+, normal urine is slightly acidic with the pH range between 5 and 7. When a person has blood pH less than 7.35 (acidosis), the urine pH almost always falls below 5.5. The acidosis has been proposed as a causual co-factor in the NSF pathogenesis.[162] The nephron, however, cannot produce a urine pH that is significantly less than 4.5 because of the buffer function of phosphates and ammonia. On the other hand, the local pH near the proton channels can be even lower. From a distribution diagram of the Gd(III)-DTPA system, it is evident that the formation of kinetically unstable protonated [Gd(Hdtpa)(H_2O)]$^-$ species starts at pH ~4.5. Comparison with the data mentioned above offers an explanation that the release of free Gd(III) ion from such complexes and possibility of its re-absorption in a similar way to other ions led to the observed toxicity of some MRI CAs based on the open-chain ligands.

Correlation of the structure of the complexes with the set of physico-chemical parameters governing relaxivity

Number of coordinated water molecules, *q*

This structural parameter (also called "hydration number") significantly influences the inner-sphere relaxivity. The hydration number of a complex can be assessed from X-ray structure analysis; nevertheless, it also has to be determined in solution as the solid-state structures do not always correspond to the species present in solution. There are several methods for determination such as NMR (Dysprosium Induced Shift, DIS),[18,163] luminescence[164] or EPR[165] spectroscopy. In all clinically utilized CAs, $q = 1$. Similarly, gadolinium(III) complexes of most octadentate DTPA and DOTA derivatives contain one coordinated water molecule. The exceptions are complexes of the tetraphosphorus acid derivatives of DOTA where no water molecule is directly bound to the central ion[20,26,64,166] and those of the DOTA tetraamide with an alkyl chain placed just over the water-binding site.[167] These steric constraints close to the water binding site lead to the total removal of the water molecule from its coordination site. For the complexes of DOTA-like ligands with $q = 1$, flexibility of the coordination cage (see above) seems to be more important to lead to a desired fast water exchange rate (see below); the translation of lanthanide(III) ion deeper into the coordination cage induces the steric constraints in the O_4 plane (the lowering of opening angle ψ). It is mostly caused by the presence of a bulky phosphorus atom[64–66,168,169] and/or a formation of larger chelate ring (*e.g.* six-membered) in the complex.[70,71,170]

It is desirable to find stable and useful complexes with two coordinated water molecules as this directly leads to an increase in relaxivity. Hence, utilization of the complexes with hexa- or hepta-coordinated ligands would be the simplest way of increasing the relaxivity of CAs. The first studied complex with two water molecules in the first sphere was the [Gd(do3a)(H_2O)$_2$] complex.[171] However, the relaxivity of the [Gd(do3a)(H_2O)$_2$] complex is easily quenched due to substitution of water molecule(s) with small ligands, such as carbonate or amino- or hydroxycarboxylic acids,[172–175] or even donor atoms from the surface of large proteins like HSA.[176] Formation of ternary complexes in solution is suppressed in complexes bearing a negative overall charge.[177] Complexes of pyDO3A (Chart 4) analogues, *e.g.* pyDO2AP (Chart 4), also have two water molecules in the first coordination sphere;[130,133,178–180] however, the complex of the tris(methylphosphonate) analog, pyDO3P (Chart 4) has only one bound water molecule due to three bulky phosphonate groups.[181] Complexes of other ligands, such as analogs of DTTA,[55–57] AAZTA[58,182] or HOPO[59,135] (Charts 3 and 4), also contain two coordinated water molecules. Relaxivity of their complexes is not so much influenced by the presence of small ligands in solution. Unambiguously, the relaxivity of all the complexes is about twice as high as that of CAs with only one coordinated water molecule (*i.e.* 7–10 mM^{-1} s^{-1}). Complexes of this family show reasonable thermodynamic stability but, unfortunately, there are not enough data to prove their kinetic inertness. They are expected to suffer from lower kinetic stability in comparison with complexes of most of octadentate ligands (see above). Anyway, the coordination sites of water molecules are confirmed in the "*cis*" position in all X-ray structurally characterized DO3A complexes and, on the basis of structures of other hepta- or hexacoordinated ligands, the "*cis*" arrangement is also expected in their complexes. Therefore, relaxivity of such complexes can be, in principle, quenched with small ligands. From this point of view, ligands that could form complexes with two free sites in the "*trans*" position could be a better choice; however, such ligands have not yet been synthesized.

On the other hand, the gadolinium(III) complexes of DOTP derivatives do not contain any metal-bound water but their

relaxivity is close to the clinically used CAs.[26,183] This indicates a significant influence of non-coordinated water molecules diffusing close to the complex species. Hence, water molecules in the second and outer spheres are also important (see below).

Residence time of the coordinated water molecule, τ_M

Searching for complexes with tuned τ_M plays a key role in the design of MRI CAs. The optimal values of τ_M come out from τ_R of a given complex and the magnetic field of interest (*e.g.* in MRI scanners). Generally, the residence time should be reasonably short (10–30 ns) to increase the relaxivity of macromolecular CAs at the magnetic fields presently used (*i.e.* mostly 60 MHz or 1.5 T).[1,7,10,11] For high-field applications, however, complexes with even shorter τ_M (1–10 ns) will be necessary,[184,185] possibly close to the exchange of the coordinated water molecule of the $[Gd(H_2O)_8]^{3+}$ complex itself (1.2 ns).[186]

The value of τ_M depends mainly on complex charge, solvent accessibility, steric constraints around the water-binding site, mechanism of water exchange and, for all complexes of DOTA-like ligands, on the abundance of TSA/SA isomers. As an example, some values for complexes of macrocyclic ligands are listed in Table 2. From a comparison of the Gd(III) complexes of DOTA and its amides, it is evident that negatively charged species show much shorter τ_M (~50–300 ns) than the corresponding electroneutral (*e.g.* complexes of DOTA monoamides) or even positively charged (*e.g.* complexes of DOTA tetraamides) species with τ_M up to milliseconds.[1,7,10] Similar relationships are also valid for the complexes of DTPA-like ligands and their amides. The τ_M of DOTA tetraamide complexes highly depends on the nature of the substituents on the amide groups.[187,188] It was also suggested that the τ_M can be influenced by additional groups in the side chain(s) of the pendant arms. It seems that hydrophobic/hydrophilic groups can change the access of bulky water molecules to the coordinated water molecule (so called water accessibility surface) and, thus, alter the water exchange rate.[189]

Substitution of carbon atoms of DOTA or DTPA generally leads to a shorter residence time of the bound water molecule. In the case of DOTA, however, the same substitution gives complexes with a higher abundance of the TSA isomer and both effects are difficult to distinguish. Steric constraints around the water binding site in the DTPA/DOTA complexes causes a faster water exchange. This can be induced by the formation of six-membered chelate ring(s), for example by a three carbon chain in the amine part[82,122,123,127–129,196,197] or in the pendant arm.[82,128] Introduction of the pyridine *N*-oxide pendant arm induces fast water exchange even in the SA isomer.[70,71] This shortening can also be observed in complexes with amide-containing EPTPA derivatives. Unfortunately, most of these complexes are kinetically unstable (see above). Another possibility of acceleration of the water exchange is the substitution of the acetate with a bulkier phosphorus-containing pendant arm. This was documented using DOTA-like,[65,168,198–200] DTPA-like[80,144,201] and other kinds of ligands[185,202] or on coordination of an HPO_4^{2-} anion to gadolinium(III) complexes of DO3A-tris(amides).[203]

In the case of the DOTA-like ligands it was found that their lanthanide(III) complexes with one coordinated water molecule show different residence times of their SA and TSA isomers (Table 2).[184,191–193,204–206] The water molecule is exchanged 10–100 times faster in the TSA than in the SA isomer, and τ_M may approach the optimal range for magnetic fields presently used clinically (10–30 ns). The τ_M can even be convenient for CAs suitable for high-field applications (<10 ns). Thus, gadolinium(III) complexes with a higher abundance of the desired TSA isomer should exhibit a higher relaxivity, especially in high-molecular-weight molecules with a very long τ_R (see below). The high water exchange rate in the TSA species, in contrast to the SA isomer; can be explained by a steric strain at the O_4 plane. An alternative explanation follows from the solid-state structural parameters found for the TSA, TSA′ and SA isomers of the $[Y(Hdo3aP^{ABn})]^-$ complex (Chart 2, R = ABn = 4-aminobenzyl) and their comparison with the parameters found for the lanthanide(III) complexes of DOTA-like ligands.[66] Both TSA and TSA′ isomers are flexible and, thus, any interconversion between the TSA and TSA′ isomers (*i.e.* transition between coordination numbers 9 and 8 for the dissociation-activated exchange mechanism) can proceed

Table 2 Residence times of water coordinated molecule τ_M and the corresponding rate constant k_{ex} (at 25 °C) characterizing water exchange found for selected gadolinium(III) complexes of macrocyclic ligands (Charts 2, 4 and 5)

Complex	τ_M/ns	$k_{ex}/10^6$ s^{-1}	q	% TSA	Ref.
$[Gd(dota)(H_2O)]^-$	244	4.2	1	15	186
	217	4.6			190
SA-$[Gd(dotam)(H_2O)]^{3+}$	1.33 ms	0.0083	1	—	191
TSA-$[Gd(dotam)(H_2O)]^{3+}$	3.06 μs	0.33	1	—	191
$[Gd(R,R,R,R\text{-tced})(H_2O)]^{5-}$	68	15	1	70	192
SA-$[Gd(S\text{-}R,R,R,R\text{-NBndotma})(H_2O)]^-$	120	8	1	SA only	193
TSA-$[Gd(S\text{-}S,S,S,S\text{-NBndotma})(H_2O)]^-$	15	67	1	TSA only	193
$[Gd(do3aP)(H_2O)]^{2-}$	14	71	1	60	65
$[Gd(do3aP^{OEt})(H_2O)]^-$	50	20	1	35	168
$[Gd(do3aP^{OEt2})(H_2O)]$	227	4.5	1	27	168
$[Gd(do3aP^{ABn})(H_2O)]^-$	16	62	1	50	198
$[Gd(do3apy^{NO})(H_2O)]$	39	26	1	SA only	70
$[Gd(do3ace)(H_2O)]^-$	16	61	1	—	128
$[Gd(trita)(H_2O)]^-$	3.7	270	1	—	196
$[Gd(do3a)(H_2O)_2]$	160	6.2	2	—	181
	91	11	1.8	—	194
$[Gd(pydo3a)(H_2O)_2]$	70	14	2	—	181
$[Gd(pydo3p)(H_2O)]^{3-}$	6–8	170	1	—	181,195

very easily. So, the lanthanide(III) ion can move easily up and down inside the TSA/TSA′ cage. On the other hand, the SA structure is very rigid and that of the SA′ isomer should be even more tight and, thus, the water exchange (if any) should be extremely slow. On the basis of such considerations, we suggest that the high exchange rate of the coordinated water molecule in the TSA species is caused by the flexibility of the arrangement. The Gd(III) complex showing a fast water exchange rate, *i.e.* short τ_M, should have a flexible coordination sphere and bear a negative charge. It is also supported by data for the Gd(III) complex of 2,2′-bipy analog of pyDO3A ($\tau_M = 5.2$ μs)[147] compared with the [Gd(pydo3a)$(H_2O)_2$] complex ($\tau_M = 70$ ns, Table 2)[181] where rigidity induced by the bipy fragment leads to a much longer residence time. A rather short residence time, $\tau_M = 53$ ns (25 °C), was observed for the Gd(III) complex of tetrakis(2-hydroxypropyl) cyclen derivative despite its tripositive charge;[207] the complex is present in solution as the TSA isomer and the hydroxypropyl arms are more flexible than acetates in DOTA.

Unfortunately, flexible complexes usually exhibit low stability and, from a practical point of view, solutions of negatively charged complexes have a higher osmolality.

Different water residence times were also observed on complexes of diastereoisomers of ligands derived from EPTA[208] or DTPA[209] but the differences in τ_M were smaller than those for complexes of isomers of DOTA-like ligands.

Generally, the water residence time is rather short for complexes with two first-sphere water molecules (Table 2); *e.g.* [Gd(aazta)$(H_2O)_2$]$^-$ has $\tau_M = 90$ ns.[58] In some cases, the acceleration of the exchange can be caused by a change of mechanism from the dissociative to the associative one.[181] This phenomenon is pronounced in complexes of HOPO-like ligands (hexacoordinated ligands) exhibiting a short τ_M (nanoseconds); the mechanism was proved to be associative.[210] On the other hand, a complex analogous to MS-325 but having two coordinated water molecules has a longer τ_M (2.3 μs)[211] than MS-325 itself (170 ns).[212]

Second-sphere parameters, q_{ss} and τ_{Mss}

It was shown that lanthanide(III) complexes of the DOTA analogues with four methylphosphonic/phosphinic acid arms (DOTP and DOTP^R, Chart 2) were found in solution exclusively as TSA (La(III), Ce(III))[67,68] or TSA′ (other Ln(III))[67,166,213] isomers as a consequence of steric requirements of phosphorus atoms. In the [Gd(dotp)]$^{5-}$ complex, no water is directly coordinated; nevertheless, relaxivity of this complex is relatively high, close to the values of commercially used CAs.[183] This points to a contribution of non-coordinated water molecules in the second sphere and to a significant influence of the phosphonic/phosphinic acid group on the organization of diffusing water molecules.[26] This "phosphorus acid effect" was applied in the design of several DOTA-like ligands bearing three carboxylic and one phosphonic/phosphinic acid pendants (Chart 2) The values of relaxivity of their Gd(III) complexes were higher in comparison with that of the [Gd(dota)(H_2O)]$^-$ complex.[65,168,198–200] Investigation of solution properties of the lanthanide(III) complexes of analogous phosphorus-containing DTPA derivatives (DTTAP or DTTAP^R; Chart 3) confirmed this effect.[80,114,144,201] It was also shown that, for the Gd(III) complexes, it is possible to distinguish the second-sphere contribution which increases relaxivity up to 20% in comparison with that of the complexes of carboxylate ligands.[168,201] This effect was also observed in the gadolinium(III) complexes of pyridine-containing macrocycles with phosphonic acid pendant arms.[133,180] The arrangement of the second-sphere water molecules due to the presence of phosphonic acid moieties is also responsible for a strong prototropic exchange in complexes of the phosphonated DOTA tetraamide.[214] An arranged second sphere was also suggested to alter relaxometric properties in DOTA tetraamides having pyridines in the amide side chains.[215] Recently, theoretical calculations suggested that the second-sphere water molecules can be hold in a vicinity of complexes by strong hydrogen bonds[216] and that the water exchange rate on TSA/SA isomers of [Gd(dota)(H_2O)]$^-$ is ruled by a rearrangement of its solvation shell.[217]

Utilization of a number of –OH groups for increasing the second-sphere contribution was recently introduced by Parker *et al.* on a series of DOTA-based ligands bearing side chains on pendant arms of TCED (Chart 5).[218] In particular, the Gd(III) complex of the derivative substituted with trisaccharide wedges (Chart 5) was found very efficient. The second-sphere and outer-sphere contributions were even higher than that of the inner-sphere water molecule. Experimental value of relaxivity was 23.5 mM^{-1} s^{-1} (20 MHz, 25 °C). In addition to the second-sphere contribution, the high relaxivity was reached by increasing τ_R (see below) due to a high formula weight and by placing of Gd(III) at the barycentre of the large single molecule.

The residence time of the second-sphere water τ_{Mss} is much shorter than τ_M and its estimation on the basis of the SBM theory and theoretical calculations falls in the picoseconds range.[219]

Rotation correlation time, τ_R

In the systems with optimized τ_M, the overall relaxivity is controlled by the rotational correlation time. Fig. 6 depicts simulations of relaxivity profiles at several values of rotational correlation time τ_R and water residence time τ_M and at fixed values of electronic parameters. It is clear that every magnetic field requires different optimal parameters of τ_R and τ_M and the maximum relaxivity can be achieved at fields corresponding to the proton Larmor frequency 10–70 MHz (magnetic field 0.24–1.65 T) with τ_R as high as possible and τ_M in the range 10–50 ns. A different situation takes

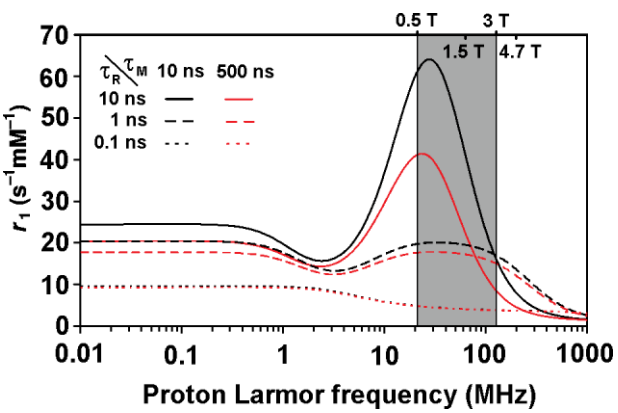

Fig. 6 Simulations of relaxivity as a function of proton Larmor frequency (^{1}H NMRD profile) with $^{298}\tau_M = 10$ ns (black) and 500 ns (red) and $^{298}\tau_R =$ 100 ps, 1 ns and 10 ns. $T = 37$ °C, $^{298}\tau_v = 40$ ps, $\Delta^2 = 10^{19}$ s^{-2}, $R_{GdH} = 3.1$ Å. The gray area shows the range of imaging fields currently used in clinics.

place at higher frequences 100–400 MHz (fields 2.35–9.4 T) where a shorter τ_M is more suitable and τ_R should have an intermediate value. In the design of gadolinium(III)-based CAs, this should be taken into account. In order to slow down the reorientational motion of gadolinium(III) complexes, several techniques have been used. Conceptually, they represent different strategies to increase the effective molecular weight (more precisely, molecular volume) accompanied by an enhancement of τ_R. In this paper, we concentrate on some strategies where the important principles of ligand design can be illustrated. It should be emphasized that the water residence time τ_M should be optimized for a particular magnetic field to take full advantage of the increased τ_R.

An elegant way to increase τ_R is the placement of Gd(III) ions into the barycenter of the molecule as the whole molecule tumbling is then efficiently transferred into rotation of the Gd–water bond vector. A good example is the $[Gd(dota\text{-}Glu_{12})(H_2O)]^-$ (Chart 5) complex mentioned above.[218] The relaxivity enhancement from ~4 mM^{-1} s^{-1} for the $[Gd(dota)(H_2O)]^-$ complex to ~23.5 mM^{-1} s^{-1} (25 °C, 20 MHz) for the above complex is caused by increasing τ_R as well as the formula weight from ~500 to ~3200. The contribution of the second-sphere hydration is important and should be also taken into account (see above).[218] Other examples of the CAs are Vistarem® (Chart 5), CA in an advanced stage of clinical trials, and analogous compounds with intermediate molecular weights and high relaxivities per gadolinium(III) centre.[140,141,192]

Non-covalent interactions are another way to slow down molecular tumbling. The most common target for the interaction is human serum albumin (HSA); in this case, CAs mostly have a hydrophobic chain (long aliphatic or aromatic substituent) at the periphery of the complex. A number of such complexes have been investigated.[1,7,10,13,15–17] The best-known example of the effect is clinically used MS-325 (Vasovist®, Chart 1). After anchoring MS-325 to HSA through its hydrophobic part (diphenylcyclohexyl), the relaxivity increases from 5 (free complex) to 40 mM^{-1} s^{-1} (bound complex) at 20 MHz and 37 °C.[209b,212] However, care should be taken when using peptides from animal sources as a different relaxivity of the agent bound to HSA or to rabbit serum albumin was observed.[220] Another commercial example is MultiHance® (Chart 1) and complexes of analogous ligands derived from DOTA.[221]

Other supramolecular species are observed after the interaction of complexes of such ligands and cyclodextrins (CD), mostly β-CD.[178,222–224] Here, the hydrophobic side chain enters the interior of CDs and the supramolecular adducts exhibit largely reduced molecular tumbling. Complexes of ligands with a long aliphatic chain also easily form micelles; principles of behaviour of micelles are very similar to those of the covalent conjugates discussed below. So far, only a small number of the complexes with really short τ_M have been investigated.[225] Another important aspect, an interplay of a local motion of the complex and a global motion of the whole molecule, also leads to a lower relaxivity than expected. This is also discussed below.

Another thoroughly investigated possibility is the linkage of a number of the Gd(III) complexes to a macromolecular carrier by covalent bonds. To realize such linkage, a suitable ligand (*bifunctional ligands*) must bear another reactive group such as –N=C=S, $–NH_2$, $–CO_2H$, –SH, $–C(O)CH_2Br$, vinyl *etc.* However, the most common way of attaching the complexes to a macromolecule is the formation of one (DOTA derivatives) or one/two (DTPA derivatives) amide bond(s) in the acetate pendant(s) of the parent ligands. The macromolecular carriers can be linear or of a spherical shape.

As an example of the linear carrier, a modified dextran polymer was used, to which the Gd(III) complex with DO3A-monoamide was attached.[226] In spite of the formula weight 52 kDa, the relaxivity increased only to 10.6 mM^{-1} s^{-1} (37 °C, 20 MHz). Another linear polymer example is inulin bearing the Gd(III) complex with DO3A-squaric acid monoamide (a complex with long τ_M)[227] or $DTTAP^{ABn}$ (a complex with short τ_M; Chart 3).[144] For the complex of the squaric acid derivative, the relaxivity is 20.3 mM^{-1} s^{-1} (37 °C, 20 MHz).[227] For the complex of a phosphinic acid derivative, despite its conveniently short τ_M, the observed relaxivity was only 18.7 mM^{-1} s^{-1} (37 °C, 20 MHz).[144] Other examples of such conjugates can be found in the reviews and their relaxivities are mostly similar.[1,7,10,13,15–17] In all these cases, the relaxivity values were lower than expected due to flexibility of the linear carrier and/or internal motion of the Gd(III) complex itself (see below).

To get more insight into the behaviour of the macromolecular conjugates, studies employing dendrimers as spherical carriers have been performed.[32] A good example is Gadomer 17 considered as a blood-pool CA.[228] In this macromolecule, 24 [Gd(dota-monoamide)(H_2O)] units are attached to a lysine-based dendrimer resulting in the conjugate formula weight ~17 kDa. The τ_M's of the amide derivatives are usually non-optimal (≥ 1 μs). Thus, the relaxivity for this compound was only 16.5 mM^{-1} s^{-1} (25 °C, 20 MHz).[229] Similar (lower than expected) relaxivities for other dendrimer conjugates[32] were originally explained by using complexes with non-optimal water exchange rates.[1,7,10] Later, conjugates of complexes with the optimal water exchange rate were investigated. So, Gd(III) complex of EPTPA (Chart 3) derivative was attached to G5–G9 PAMAM dendrimers leading to a pH-dependent relaxivity (*e.g.* 13.7–23.9 mM^{-1} s^{-1} for G-5, 37 °C, 20 MHz).[230] Another promising possibility seemed to be attachment of the $DTTAP^{ABn}$ (Chart 2) complex to the PAMAM dendrimers through the (4-aminobenzyl)phosphinic acid arm.[201] The observed relaxivity enhancement was again lower than expected: for G5-$[Gd(dttaP^{ABn})]_{63}$ it was 26.8 mM^{-1} s^{-1} (37 °C, 20 MHz). Even in these cases, the relaxivities were lower than expected and the local molecular motion of the complex was identified as the main cause of the decrease. It should be noted that, despite the lower number of gadolinium atoms, the $DTTAP^{ABn}$ dendrimer had a higher overall relaxivity due to the second-sphere contribution (see above).[201]

To better understand the phenomenon of local molecular tumbling, other dendrimer conjugates have been investigated. For the $DO3AP^{ABn}$ complex (Chart 2, Table 2), conjugates with PAMAM dendrimers of the 1st–4th generations (G1–G4 PAMAMs) were studied. Their relaxivities increased from 14.8 for G1-$[Gd(do3aP^{ABn})(H_2O)]_8$ to 19.7 for G2-$[Gd(do3aP^{ABn})(H_2O)]_{16}$ and 25.8 mM^{-1} s^{-1} for G4-$[Gd(do3aP^{ABn})(H_2O)]_{59}$ at 25 °C and 20 MHz.[200] Simulation of relaxivity *vs.* τ_R dependence based on properties of the "monomeric"[198] and "ditopic"[199] complexes even predicted the relaxivity *ca.* 65 mM^{-1} s^{-1} for the G4-$[Gd(do3aP^{ABn})(H_2O)]_{59}$ conjugate. The huge differences between the predicted and experimental values are clearly caused by internal motion of the complex moiety and are not influenced by τ_M or other parameters (Fig. 7). When a solution of polyarginine, *e.g.* $(Arg)_{56}$, was added to a solution of the G2-$[Gd(do3aP^{ABn})(H_2O)]_{16}$

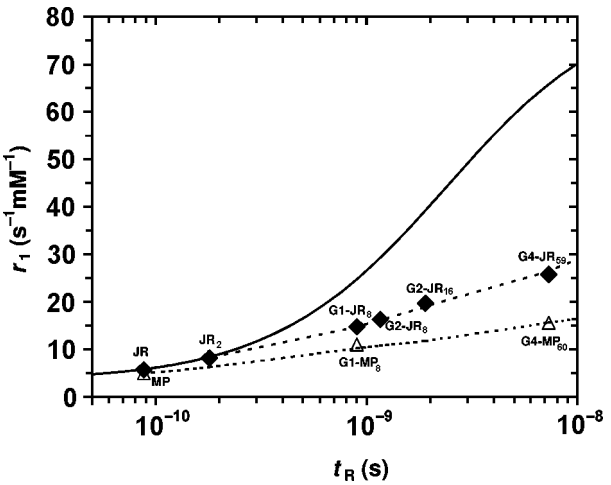

Fig. 7 Experimental relaxivities (20 MHz, 25 °C) as a function of theoretical τ_R for our G*n*-PAMAM-[Gd(do3aP^{ABn})$(H_2O)]_x$ (full diamonds, G*n*-JR_x)[200] and -[Gd(do3a$py^{NO\text{-}C}$)$(H_2O)]_y$ (open triangles, G*n*-MP_y)[71] conjugates. Corresponding relaxivities of parent [Gd(DO3AP^{ABn})$(H_2O)]^-$ (JR)[198] and [Gd(do3a$py^{NO\text{-}C}$)$(H_2O)]$ (MP)[71] complexes are given for comparison, together with the relaxivity of ditopic complex $[\{Gd(do3aP^{ABn})(H_2O)\}_2CS\}]^{2-}$ (JR_2).[199] For structures of ligands, see Chart 2. The dashed lines are guides for the eyes. The solid line simulates the relaxivity for $\tau_M = 50$ ns, $\tau_v = 30$ ps, $\Delta^2 = 10^{19}$ s^{-2}, $q = 1$, $R_{GdH} = 3.1$ Å, $a = 3.5$ Å and $D = 2.24 \times 10^{-5}$ cm^2.

conjugate, the relaxivity increased to 30.8 mM^{-1} s^{-1} due to Coulombic interaction of the positively charged poly(Arg) with the negatively charged dendrimer conjugates ("molecular glue effect"). This led to an increased rigidity and molecular weight of such supramolecular species compared with a simple covalent conjugate.[200,231]

Local molecular tumbling can be caused by movement of the polymer end chain (3-aminopropyl in PAMAMs) or by flexibility of the linker in the complex moiety (benzylthiourea chain in the above cases). To reduce the flexibility of the linker, a bifunctional ligand DO3A$py^{NO\text{-}C}$ with the $-CO_2H$ group directly bound to the pyridine ring was synthesized and studied.[71] Its Gd(III) complex, [Gd(do3a$py^{NO\text{-}C}$)(H_2O)], showing the optimal water residence time of water (τ_M = 34 ns, 25 °C), was conjugated to G1- and G4-PAMAM dendrimers. Despite the expected higher rigidity of the spacer (compared with the above conjugates), the relaxivity was rather low and only slightly dependent on the dendrimer generation (*i.e.* 11.0 mM^{-1} s^{-1} and 15.6 mM^{-1} s^{-1} for G1- and G4-conjugates, respectively; Fig. 7). A very similar decrease in overall relaxivity (in comparison with a charged analog) was observed after attachment of a DOTA monoamide complex to G4-PAMAM.[232] The results for both conjugates can probably be explained by the non-charged nature of the conjugates leading to a rather high flexibility of the PAMAM backbone (mainly the outermost propyl chain). For the polymeric CAs employing complexes with the optimal water residence time, the rigidity of both the ligand linker and polymer should be tuned to reach a much higher relaxivity. Some steps in the direction of different polymer backbones have recently been taken with *e.g.* polyaminoamine dendrimers[232] or biotin–avidin interaction.[233]

Another strategy leading to rigid molecules was introduced by Desreux *et al.*[234–236] Aggregation of a complex-forming group at the periphery of the Gd(III) complex to another metal ion (Fe(II), Fe(III) or Al(III)) leads to higher adducts of intermediate molecular weights suitable, *e.g.*, as CAs for higher magnetic fields (see above). As an example, the gadolinium(III) complex of a phenanthroline derivative of DO3A (DO3APhenOH, Chart 2) reacts with ferrous ion to form an octahedral "supramolecular" adduct of three macrocyclic Gd(III) units.[236] Relaxivity of the supramolecular tritopic adduct (~11 mM^{-1} s^{-1}; 25 °C, 20 MHz) is higher than that of the "monomeric" complex (~5.5 mM^{-1} s^{-1}; 25 °C, 20 MHz) due to higher molecular weight and its rigidity. The water residence time is not optimal (τ_R = ~1 μs). Unfortunately, there are no data characterizing the local tumbling of the gadolinium-containing moiety. The complex of the DTPA monoamide derivative with the phenantroline moiety bound through the amide bond to the central arm and its Fe(II) tris(adduct) were also investigated with similar results (9.5 mM^{-1} s^{-1}; 37 °C, 20 MHz).[237]

In the group of complexes with two inner-sphere water molecules, a similar approach was used by the Merbach group.[55,56] They used Gd(III) complexes of bipyridine/terpyridine-containing ligands (*e.g.* bipy(DTTA) in Chart 3) for further coordination to Fe(II) or other transition metal ions forming octahedral complexes, which contained up to six Gd(III) units. The highest relaxivity enhancement (r_1 = 33.6 mM^{-1} s^{-1}) for this type of complex was reported by Livramento *et al.* for the Fe(II) tris(aduct) of the $[Gd_2\{bipy(dtta)_2\}(H_2O)_4]^{2-}$ complex.[56] This strategy led to CAs with a number of Gd(III) ions present in a small area of space, which can be convenient in CAs suitable for higher magnetic fields.

The Aime group in Torino recently introduced a lipophilic Gd(III) chelate based on AAZTA (Chart 4) bearing a long aliphatic chain.[182] Relaxivity of the complex was 10.2 mM^{-1} s^{-1} due to two coordinated water molecules and short τ_M. The complex easily forms micelles with a diameter of 5.5 nm and relaxivity increased to *ca.* 30 mM^{-1} s^{-1} at 20 MHz and 25 °C. After interaction with HSA, the relaxivity of the supramolecular system increased to 84 mM^{-1} s^{-1}, which is the highest value reported for a Gd(III) complex. A study of the micelles with 98% diamagnetic Y(III) complexes showed magnetic interaction of the Gd(III) ions on the surface of $[Gd(aazta\text{-}C_{17})(H_2O)_2]_n$ micelles, which causes a decrease in the electronic relaxation time. The magnetic interactions explain the lower than expected relaxivity.

Rigidifying the gadolinium(III) complexes with iron(III) ions (bound through the 2,3-dihydroxyterephthalamide moiety) was also used with ligands based on HOPO and led to an increased relaxivity similar to the above results.[238]

Conclusion and outlook

MRI has assumed a critical role in medical diagnosis, and applications of CAs in examinations are expanding. In addition, MRI is used in the investigation of many processes in molecular biology and preclinical research. For this purpose, specific CAs have been developed, changing relaxivity after cleavage of some bonds, sensitive to the presence of specific ions or metabolites *etc.* This is a large field, open for modification of the known CAs, and for testing new ones. As mentioned in the introduction, the presently utilized CAs suffer from low efficacy and they are not fully suitable for the new instrumentation working at magnetic fields of 3 T or higher.

Considering the physico-chemical parameters governing properties of CAs as discussed above, we can summarize:

(*i*) The crucial issue for clinical applications is *in vivo* stability. The DOTA-like ligands form more stable complexes, especially kinetically, than the open-chain ligands. The Gd(III) complexes of HOPO, AAZTA or pyDO3A derivatives with two water molecules in the first coordination sphere show better MRI properties than the $[Gd(do3a)(H_2O)_2]$ complex. Unfortunately, only approximate data on their stability in the acid region have been published. As the microenvironment in the kidneys is acidic, all complexes considered as CAs should exhibit long-term stability at pH ~4.5 and should be tested with respect to this fact. From this point of view, the macrocylic DOTA-like ligands are much more suitable than the open-chain ones as their complexes are kinetically inert. In addition, the alteration of pendant arms in the DOTA derivatives has a lower effect on kinetic properties of the complexes than analogous changes to the DTPA skeleton.

(*ii*) It is desirable that the number of coordinated water molecules q is higher than 1. The complexes with $q = 2$ show two-fold enhancement of relaxivity but, unfortunately, they have a lower stability than those of DOTA. Some additional functionalities in the side chains capable of protonation in acid media may increase stability of the complexes due to repulsion between positive charges in the protonated side chains and protons in solution. Another possibility is increasing the number of the second- (q_{ss}) and outer-sphere water molecules by the presence of hydrophilic groups as it has been shown for, *e.g.*, phosphonic acid group in pendant or oligosaccharide moiety in the side chain of DOTA. Such contributions to the overall relaxivity could be the same as the effect of the second directly coordinated water molecule.

(*iii*) The water residence lifetime of the coordinated water does not significantly influence relaxivity of the low-molecular-weight CAs; however, it has to be optimized for CAs with a slow tumbling. Complexes with optimal τ_M should bear a negative charge and their ligands should contain arms inducing steric hindrance close to the water-binding site (TSA isomers for DOTA-like ligands, bulky substituents, six-membered coordination rings). In addition, flexibility of the coordination sphere is desirable. There are several groups, such as phosphonates or phosphinates, that efficiently decrease τ_M.

(*iv*) Rotational correlation time representing the molecular tumbling time of a complex seems to be a crucial parameter for the design of new CAs. So far, not all attempts have led to the expected enhancement of relaxivity because of the internal motion. Thus, more rigid agglomerates are required, with relatively rigid macromolecular/micellar carriers (preferably spherical rather than linear), to which complex molecules would be bound *via* rigid spacers.

(*v*) The gadolinium-based CAs suitable for higher imaging fields are highly desirable. They should have an intermediate molecular weight and very fast water exchange. If they are conjugated, rigid spacers are important as well.

(*vi*) A better understanding of electronic relaxation of the gadolinium(III) complexes is desirable due to its importance mainly in macromolecular/micellar systems. Too fast electronic relaxation can efficiently decrease the overall relaxivity. At this moment, it seems that a more symmetric donor atom environment can afford complexes with longer electronic relaxation.

Currently, some applications can be seen where ligand design should be properly addressed.

(*i*) Utilization of biological vectors (*e.g.* monoclonal antibodies or oligopeptides) in targeting of CAs would be very fruitful in medicinal and/or molecular biology practice. Unfortunately, these materials are very expensive and, generally, cannot be used in doses similar to those of approved CAs. In addition, the concentration of targeted receptors in the body is not high enough. For such conjugates, macromolecular/micellar CAs can be used. Alternatively, small molecule CAs showing a much higher relaxivity should be found, *e.g.* those based on molecules having a number of Gd(III) ions present inside a small space. Unfortunately, complexes of the most easily available DOTA-monoamide or DTPA-mono or -diamide derivatives may not have the appropriate stability and/or NMR characteristics.

(*ii*) Cellular imaging will be very important in the future. At this moment, there is no generally accepted way of labelling of cells. Again, complexes based on macrocyclic ligands seem to be more suitable due to their kinetic inertness.

(*iii*) Multimodal probes enabling utilization of several kinds of imaging (combination of MRI with optical/fluorescence, CT, SPECT, PET *etc.* imaging) will probably draw more attention in the near future.

(*iv*) Entirely different approaches to CA design can be discovered. In the last years, complexes exhibiting paramagnetic chemical exchange saturation transfer (PARACEST) have gained much attention.[14,239–242] The method uses other lanthanide(III) ions and some aspects mentioned in this review are valid for the new CAs as well.

(*v*) Gadolinium(III)-based CAs can be attached to nanoscale objects such as viral particles or solid nanoparticles (metal oxides, quantum dots). The potential of such conjugates is to be discovered.

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