Ligand design strategies to increase stability of gadolinium-based magnetic resonance imaging contrast agents

Thomas J. Clough1, Lijun Jiang1,2, Ka-Leung Wong2 & Nicholas J. Long1

Gadolinium(III) complexes have been widely utilised as magnetic resonance imaging (MRI) contrast agents for decades. In recent years however, concerns have developed about their toxicity, believed to derive from demetallation of the complexes in vivo, and the relatively large quantities of compound required for a successful scan. Recent efforts have sought to enhance the relaxivity of trivalent gadolinium complexes without sacrificing their stability. This review aims to examine the strategic design of ligands synthesised for this purpose, provide an overview of recent successes in gadolinium-based contrast agent development and assess the requirements for clinical translation.

Skilful and strategic ligand design is key for any coordination chemist. Adapting and refining a ligand allows a captive metal’s potential to be unlocked and its capabilities to be fully exploited. If a metal complex is destined for use in a biological setting, it is the ligand motif which dictates the complex’s distribution, localisation and behaviour in a dynamic system. Recent history of gadolinium-based contrast agents (GBCAs) for magnetic resonance imaging (MRI) exemplifies the critical nature of ligand design in medical imaging. Contrast agents enhance the longitudinal ($T_1$) or transverse ($T_2$) relaxation rates of water molecules in their vicinity, resulting in greater contrast between different biological tissues, allowing them to be distinguished more readily1,2. Paramagnetic species are especially adept at enhancing $T_1$ relaxation2. Gd$^{3+}$ is an f-block metal ion with seven unpaired electrons, rendering it highly paramagnetic and a prime candidate for use in contrast agents3,4.

The first contrast agent to incorporate gadolinium(III), [Gd(OH$_2$)(dtpa)]$^{2-}$ (Magnevist®), was synthesised in 1981 and approved by the FDA for clinical use in 19885. Since then, a total of 11 GBCAs have been approved by the FDA, with the 5 most commonly used shown in Fig. 16. Magnevist®, which has been administered globally almost 100 million times, dominates in the clinic7. However, issues with this widespread usage have presented themselves in recent years. Chief amongst these is the link between the rare, yet potentially fatal, condition nephrogenic systemic fibrosis (NSF) and the administration of a GBCA to patients with kidney failure, which first became apparent in 20068,9. The deposition of gadolinium metal has been observed in the skin, heart and kidneys of patients with NSF and, more recently, the brains of patients with healthy kidney function10,11. In addition, Gd$^{3+}$ ions have a similar ionic radius to Ca$^{2+}$, enabling them to interfere with calcium-mediated signalling pathways—thus rendering them extremely toxic, with an LD$_{50}$ of 0.2 mmol kg$^{-1}$ observed in mice12,13. Concern over the safety of...
some GBCAs with acyclic ligands has resulted in the restriction of their administration by the European Medicines Agency (EMA) and triggered risk warnings from the U.S. Food and Drug Administration (FDA)\textsuperscript{17,20,21}. The toxicity of GBCAs has been covered extensively elsewhere in the literature\textsuperscript{22–24}, and strategies to increase complex stability through ligand design have often been motivated by the desire to reduce potential adverse effects on patients.

Due to the low sensitivity of MRI as an imaging technique, large quantities of a contrast agent, often on the gram scale, must be injected into the patient to obtain useful images. The ability to reduce the amount of GBCAs required is highly desirable, especially when considering the toxicity problems discussed above. One way in which the amount of contrast agent required can be reduced is to enhance its relaxivity. Relaxivity is a measure of how water relaxation rate changes with concentration of a contrast agent, and high relaxivities are indicative of more effective agents\textsuperscript{6,25,26}. Hydration state, i.e., the number of coordinated inner sphere water molecules, is a key contributor to a complex’s relaxivity, and increasing the hydration state is accompanied by a corresponding increase in relaxivity\textsuperscript{4,25,26}. This can be seen from Eq. (1)\textsuperscript{27}, where \( r \) is relaxivity, \( c \) is concentration, \( \tau_{1m} \) is longitudinal proton relaxation time and \( \tau_{ms} \) is water exchange lifetime, i.e., how long an inner sphere water molecule spends at the metal centre. All existing GBCAs that are used in the clinic are based on octadentate polyaminocarboxylate ligands. As trivalent gadolinium prefers a coordination number of 9, this leaves one available coordination site free for an inner sphere water molecule, allowing its relaxation rate to be enhanced, providing contrast.

\[
r = \frac{cq}{55.6} \left( \frac{1}{\tau_{1m} + \tau_{ms}} \right).
\]

The relaxivity of a contrast agent can, therefore, be improved by increasing the hydration state of the complex. This can be achieved through a reduction in the number of coordination sites provided by the ligand as water molecules are generally displaced by more basic ligating species during coordination. Importantly, though, this will typically lower the thermodynamic stability of the complex and render the metal ion more accessible to endogenous anions. This accessibility may lead to demetallation of gadolinium(III) complexes in vivo, causing further toxicity issues. Many in the field have tried to master the subtle interplay between maximising relaxivity through accessing higher hydration states and forfeiting thermodynamic stability or kinetic inertness. Several innovative strategies have been employed, the discussion of which form the basis of this review. Whilst several thorough and comprehensive assessments of GBCAs have been published, these have predominantly focused on ligand design and other techniques to augment the relaxivity of gadolinium(III) complexes which could then, often hypothetically, be used as contrast agents\textsuperscript{6,6,25,28}. This review article assesses approaches to ligand design that focus on achieving greater complex stability. Initially, we will establish what is meant by complex stability in terms of thermodynamics and kinetics, before discussing and assessing the effectiveness of modifications which have been made to the cyclic and acyclic ligand families used in GBCAs.

**Decisive stability factors**

The high required dose of GBCAs for clinical use carries the risks of health problems associated with Gd\textsuperscript{3+} release, and thus requires the administration of very stable GBCAs. Gd\textsuperscript{3+} release by GBCAs can be characterised by thermodynamic stability and kinetic inertness\textsuperscript{8,29–33}, which may be manipulated through ligand design\textsuperscript{28}. Thermodynamic stability refers to the Gibbs free energy involved in the complexation reaction and is defined as stability constant \( \log K \) (also called \( \log K_{GdL} \), \( \log K_{therm} \) and \( \log K_{a} \)). Kinetic inertness refers to complex dissociation rate and is mainly reported as \( t_{1/2} \), where \( t_{1/2} \) is defined as the time required for half of the GBCA’s dissociation. It should be noted that values for \( \log K \) and \( t_{1/2} \) for a GBCA may differ slightly in the literature due to the differences between methodologies and experimental conditions used by different investigators.

The thermodynamic stability constant can be calculated by the equilibrium concentration of each component with the assumption that the ligand is fully deprotonated. There are several
methods for the determination of log $K$. These include pH-potentiometry, spectrophotometry and proton relaxometry, which are respectively conducted by recording changes of pH value, absorbance/emission intensity or proton relaxivity of a solution containing equimolar amounts of metal ion and ligand as a function of added acid or base. Complexation of lanthanide solution containing equimolar amounts of metal ion and ligand value, absorbance/emission intensity or proton relaxivity of a which are respectively conducted by recording changes of pH potentiometry, spectrophotometry and proton relaxometry, reference ligand or metal ion. The hard acid Gd$^{3+}$ is released at equilibrium under certain conditions. Since the rate at which equilibrium is reached for macrocyclic gadolinium(III) complexes in vivo is very slow and normally cannot be reached during their residence time, thermodynamic stability cannot accurately predict Gd$^{3+}$ release for macrocyclic GBCAs. Thus, Tweddel et al.41 have concluded that thermodynamic stability alone is insufficient to predict the in vivo dissociation of macrocyclic chelates. Wedeking et al.42 have shown that $^{153}$Gd accumulation in mouse liver and bone tissue is proportional to the dissociation rate of several $^{153}$Gd chelates. Also, $[\text{Gd(OH}_2\text{(dota))}]^−$ which is stable in both thermodynamic and kinetic terms, resulted in low in vivo deposition; while $[\text{Gd(OH}_2\text{(dipa))}]^2−$ with a high thermodynamic stability but low kinetic inertness, has had its administration restricted. The ligand tetra-glycine amide analogue of H$_2$dota, H$_4$(dota)/(gly)$_4$, forms a kinetically inert complex with Gd$^{3+}$, and its analogous complex with Eu$^{3+}$ has been confirmed as non-toxic in vivo, even at a much higher dosage (1.0 mmol kg$^{−1}$) than clinically used—this is despite a much lower thermodynamic stability than $[\text{Gd(OH}_2\text{(dota))}]^−$. This combined information suggests that it is kinetic inertness rather than thermodynamic stability that appears to be the useful predictor of in vivo Gd$^{3+}$ release from GBCAs. One recent striking finding is the observed gadolinium deposition in the brain for subjects with normal renal function and an intact blood–brain barrier14,43–46. Although uncertainty exists around the specific diseases and conditions associated with gadolinium deposition in the brain, it has been shown that Gd$^{3+}$ in the brain is toxic47–49. Thus, maximising kinetic inertness should be a critical concern for those seeking to develop future GBCAs.

**Cyclic ligands for gadolinium(III)**

One ligand is frequently referred to as the “gold standard” in trivalent gadolinium chelation: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (H$_4$dota). This ligand consists of the macrocycle cyclen, which is N-functionalised with four acetic acid pendant arms and is octadentate with four nitrogen and four oxygen donor atoms (Fig. 1c) and $[\text{Gd(OH}_2\text{(dota))}]^−$ remains the most thermodynamically stable GBCA in clinical use50. Whilst there is some variation in the literature due to different measurement methodologies, the high stability constant for $[\text{Gd(OH}_2\text{(dota))}]^−$ ranges from 24.0 to 27.0, and for the purposes of this review will be referred to as 25.6, the value determined by Moreau et al.51. Due to its excellent chelating abilities, H$_2$dota has thus proven to be an attractive scaffold for modification.

To understand the logic behind some of the design strategies employed in this field, it is necessary to consider the solution behaviour of lanthanide(III) complexes of H$_2$dota. There are known to be four different stereoisomers of $[\text{Ln}(dota)]^−$ in solution, which arise from the orientation of the five-membered coordination metallacycles formed by ethylene bridges in the macrocycle ($\Lambda\Lambda\Lambda\Lambda$ or $\Delta\Delta\Delta\Delta$) and the corresponding positions of the pendant arms ($\Lambda$ or $\Delta$)26,52–55. In geometric terms, the shapes adopted by these stereoisomers are described as square antiprismonic (SAP) or twisted SAP (TSAP), (Fig. 2)26,54. Each of these isomers may be characterised by the twist angle between the nitrogen and oxygen donor atom planes, $\theta$. This angle varies according to which Ln$^{3+}$ centre the ligand is complexed to, but is typically around 40° for SAP structures and between −20° and −30° for TSAP geometries26,55. The two SAP and two TSAP isomers are enantiomeric pairs, and interconversion between them is possible on the nuclear magnetic resonance (NMR) timescale, leading to the broadening often seen in proton NMR spectra of lanthanide(III) complexes of H$_2$dota52. Interconversion occurs through two mechanisms: rotation of the acetate arms or inversion of the macrocyclic ring26,52–55.

In order to maximise complex inertness, it is imperative that interconversion is minimised26. Chirality is widely exploited in
catalysis and natural product synthesis to attain enantiomer formation, and similar principles may be applied to macrocyclic ligands. Introduction of chirality to the macrocycle itself and the pendant arms can render both interconversion mechanisms unfavourable and cause the complex to favour a particular geometry, thus reducing kinetic lability of the complex. Substitution on the macrocyclic ring itself has been exploited to render ring inversion unfavourable. Recently, Dai et al.\textsuperscript{56} published a comprehensive investigation of lanthanide(III) complexes of chiral chelators based on H\textsubscript{4}dota, and their solution kinetics. The group synthesised a series of H\textsubscript{4}dota analogues with substituents ranging in size from methyl to 4-aminobutyl, with the hypothesis that introducing chirality would lock ring conformation and aid ligand pre-organisation, resulting in greater complex inertness\textsuperscript{56}. The synthesised gadolinium(III) complexes illustrated that increased steric bulk in the substituent resulted in a greater propensity for TSAP isomer formation, potentially due to steric clashes with the acetate arms rendering SAP geometry unfavourable. The SAP and TSAP isomers of the Gd\textsuperscript{3+} complex of the tetraethyl-substituted ligand (H\textsubscript{4}Et\textsubscript{4}dota, Fig. 3a) were separated and their kinetic inertness analysed\textsuperscript{56}. Both isomers of the gadolinium(III) complex of H\textsubscript{4}Et\textsubscript{4}dota have been shown to survive for 7 days in the presence of 1000 equivalents of H\textsubscript{2}dtpa and exhibit no demetallation after 100 h at 50 °C in the presence of a 100-fold excess of ZnCl\textsubscript{2}\textsuperscript{56}. The remarkable kinetic inertness is attributed to the influence of the chiral substituents, i.e., the introduction of stereochirality enhances complex rigidity, leading to the restricted and non-interconvertible SAP and TSAP structures\textsuperscript{56}. Ranganathan et al. reported lanthanide(III) complexes of tetra-methyl substituted H\textsubscript{4}dota (H\textsubscript{4}Me\textsubscript{4}dota, Fig. 3b). Here also, the introduction of chirality to the macrocycle was found to reduce the rate of isomer interconversion\textsuperscript{57–59}. One important consideration with this approach is that of over-rigidification, i.e., the steric bulk of the substituent dictating enantioselectivity is critical. Edlin et al. synthesised H\textsubscript{4}Phdota with the intention of increasing the energy barrier to ring inversion (Fig. 3c), as bulky cyclen substituents have been observed to introduce stereoselectivity in complexation\textsuperscript{60}. However, the lanthanide(III) complexes were less thermodynamically
stable and kinetically inert than those of H₄dota⁶⁰. The observation that large benzylic substituents can “lock” the conformation of the macrocycle into the δδδδ configuration forming SAP Λ (δδδδ) and TSAP Λ (δδδδ) isomers has been confirmed by the work of Payne and Woods with the synthesis of H₄nb-dota, (Fig. 3d)⁶¹,⁶². The large steric bulk did not significantly impact the thermodynamic stability or kinetic inertness of the Gd³⁺ complex of H₄nb-dota⁶². One possible reason could be the interconversion between two pairs of isomers (side or corner of the nitrobenzyl substituent on the macrocycle) which was not observed in the work of Dai et al.⁵⁶,⁶¹. In employing this approach, it is clear that care must be taken when considering which substituents to introduce, i.e., enough steric bulk to confer enantioselectivity is critical and can favourably impact the inertness of gadolinium(III) complexes. Substitution onto the arms can hinder isomer interconversion by arm rotation. (R)-2-[4,7,10-Tris-((R)-carboxyethyl)-1,4,7,10-tetraazacyclododecan-1-yl] propionic acid, H₄dotma, which contains a methyl group at the α position of the arm, was originally reported by Brittain and Desreux in 1984, and has been extensively studied⁶³. It was found that substitution on the arm introduces preference for one stereoisomer, (TSAP Λ (λλλλ) over SAP Λ (δδδδ)) for the all (R) analogue (Fig. 4a), with interconversion between the two stereoisomers possible by ring inversion, and that the lanthanide(III) complexes formed are conformationally rigid on the NMR timescale. This suggests that kinetic inertness may be enhanced by substitution at the α position of the acetate arm⁵⁹,⁶³,⁶⁴. Despite this preference in geometry, it has been determined that the lanthanide(III) complexes of H₄dotma are less thermodynamically stable than those of H₄dota, albeit only slightly. Log K for the respective Gd³⁺ complexes have been reported as 23.6 and 24.7, respectively⁶⁴. This is attributed by the authors to the less thermodynamic stable TSAP geometry adopted by H₄dotma compared to the SAP geometry⁶⁴,⁶⁵. Another example of a chiral substituent on the pendant arm is that of 1,4,7,10-tetrakis-[(R)-1-(1-phenyl)ethylcarbamoylmethyl]-1,4,7,10-tetraazacyclododecane, dotamPh, the lanthanide(III) complexes of which adopt only SAP geometry in solution (Fig. 4b)⁶⁶,⁶⁷. A preference for a specific complex geometry can also be enhanced through the introduction of chirality into both the cyclen ring and the acetate arms. This was achieved by Ranganathan et al.⁵⁷, who synthesised the H₄dotma derivative H₄Me₄dotma (Fig. 4c), which contains methyl groups on the macrocycle and at the α position. In solution, the free ligand is highly conformationally rigid, and this results in extremely slow exchange between isomers of the lanthanide(III) complexes. Subsequent investigations by Opina et al.⁶⁸ have found that lanthanide(III) complexes of H₄Me₄dotma and analogous ligands are extremely rigid in solution, with very little interconversion between isomers taking place at ambient temperatures. [Gd(Me₄dotma)]⁻ adopts an SAP geometry almost exclusively when all stereocentres are S, and the inverse is the case when they are all R⁶⁸.

One innovative example of chirality being utilised for the enhancement of relaxivity and inertness comes from Messeri et al., who synthesised the ligand H₄R,R,R,gado₃a (Fig. 4d)⁶⁹. This ligand possesses only three pendant arms, each of which is modified at the alpha position with the addition of a butanoic acid side chain. These additional carboxylic acid groups are deprotonated at physiological pH yet remain uncoordinated to the Gd(III) centre during complexation, likely due to steric hindrance. This renders the ligand hexadentate, allowing a hydration state of 2 to be accessed and a relaxivity value of 12.3 mM⁻¹ s⁻¹ to be obtained⁶⁹. There is a high

![Fig. 4 Ligands where chirality has been introduced into the pendant arm of the N4 macrocyclic ring. Substitution onto the arms can hinder isomer interconversion by preventing arm rotation and encouraging preference for a specific complex geometry.](https://doi.org/10.1038/s41467-019-09342-3)
degree of kinetic inertness for \([\text{Gd(OH}_2\text{)}_2(R,\text{R,R-gado3a})]\)^3^−, the authors report as an order of magnitude greater than that of \([\text{Gd(OH}_2\text{)}_2(\text{dtpa})]^-\) \((t_{1/2} \text{ for } [\text{Gd(OH}_2\text{)}_2(\text{dtpa})]^- \text{ is } 4.5 \text{ h})\)^3^0. However, when compared to the approved macrocyclic agents \([\text{Gd(OH}_2\text{)}_2(\text{dota})]^-\) and \([\text{Gd(OH}_2\text{)}_2(\text{hp-do3a})]\), both of which have a \(t_{1/2}\) greater than 83 h, \([\text{Gd(OH}_2\text{)}_2(R,\text{R,R-gado3a})]\) is still more kinetically labile\(^3^8\).

A slightly more unorthodox method to introduce chirality to macrocyclic ligands for \(\text{Gd}^{3^+}\) utilises phosphinic acid or phosphonic acid monoester pendant arms, rather than acetic acid. This has been shown to increase the energy barrier to ring inversion to around 100 kJ mol\(^{-1}\) in \([\text{Ln(dotp)}]^-\) \((\text{Fig. 4e})\), a value higher than \([\text{Ln(dota)}]^-\) which could theoretically enhance kinetic inertness by reducing the rate of isomer interconversion\(^7^1\). Extensive exploration of the effect of phosphonic acid substituents, \([\text{Ln(dotp)}]^-\), on hydration state and relaxivity has been carried out, and this is discussed elsewhere\(^2^7\).

**Impact of ligand basicity and charge**

A ligand’s basicity can be thought of as its affinity for protons and shown by the sum of protonation constant of each donor atoms in the ligand. Therefore, assumptions of how many protonation constants to include in the calculation need to be made. As early as 1990, Cacheris et al.\(^3^5\) showed that the more basic \([\text{Gd(OH}_2\text{)}_2(\text{dtpa})]\)^2^− demonstrated a higher thermodynamic stability than \([\text{Gd(OH}_2\text{)}_2(\text{dota})]\), the idea of a linear relationship between thermodynamic stability and basicity for \(\text{Gd}^{3^+}\) chelates was first reported by Kumar et al.\(^7^4\). The research investigated a series of 10-(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane 1,4,7-tetraacetate, \(\text{H}_3\text{hedo3a}\), derivatives with the introduction of a methyl group to the alcoholic pendant arm, the idea being to influence the basicity of the adjacent nitrogen \((\text{Fig. 5a})\). \(\text{H}_3\text{hedo3a}\) was employed as an analogue of 1, 4, 7-tris(carboxymethyl)-1, 4, 7, 10-tetraazacyclododecane, \(\text{H}_3\text{do3a}\), replacing one carboxylic pendant arm with an alcohol group, thus decreasing its basicity. A linear correlation between log \(K\) and basicity was nicely displayed in this study, with the most basic, 10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, \(\text{H}_3\text{hpdo3a}\), showing the largest log \(K\). Log \(K\) is defined as log \(K/\alpha_1\) (\(\alpha_1\) is the sum of the stepwise protonation constants), thus log \(K\) is neither proportional nor inversely proportional to ligand basicity but depends on specific structure. It was found that the ligand with intermediate basicity had the biggest log \(K\). Doble et al.\(^7^5\) reported a similar observation for the \(\text{H}_3\text{hopo-tam}\)-based \((\text{hopo} = \text{hydropyridinonate}; \text{tam} = 2,3\text{-dihydroxyterephthalamide})\) gadolinium(III) chelates, as well as amongst aminoethyl-do3a derivatives\(^7^6\).

---

**Fig. 5 Ligands where substitution around the N4-macrocyclic ring affects physicochemistry.**

**a.** \(\text{H}_3\text{hedo3a}\), featuring a methyl group within the alcoholic pendant arm. **b. c.** \(\text{H}_3\text{hpdo3a}\) and \(\text{H}_2\text{do3a-butrol}\) both have three pendant negatively charged acetate arms. **d.** \(\text{H}_3\text{-(dota)(gly)}_4\) \(R = \text{CH}_2\text{dtma}, R = \text{CH}_2\text{COOH}\), comprising amido-functionalised N4-macrocyclic ligands with increased basicity. **e.** \(\text{H}_2\text{cb-tedpa}\), featuring a reinforced N4-cyclam framework via an ethylene bridge. **f.** \(\text{H}_3\text{pcta}, \text{H}_3\text{L}^3\), and \(\text{H}_3\text{L}^4\), featuring a heptadentate ligand incorporating pyridine directly into the ligand framework thus rigidifying and preorganising the ligand.
Greater basicity of the chelating ligand contributes to greater overall thermodynamic stability of the complex through stronger interactions with the Lewis acidic gadolinium(III) ion. More stable complexes are also formed with ligands possessing negatively charged binding moieties, i.e., H₄hpdo3a and 10-[[2,3-dihydroxy-(1-hydroxymethyl)-propyl]-1,4,7,10-tetraazacyclodecane-1,4,7-triacetate H₄do3a butrol (Fig. 5b, c) both have 3 acetate arms and their Gd³⁺ complexes exhibit log K values of 23.8 and 18.7, respectively, compared to 25.6 for that of H₄dota. The uncharged ligand dtma (Fig. 5d) forms a Gd³⁺ complex with a log K value of 12.8. Other lanthanide(III) complexes have been formed with uncharged dota-tetraamide derivatives with K values up to 15 orders of magnitude lower than the corresponding dota⁻ species, indicating that a reduction in ligand charge is accompanied by a reduction in complex thermodynamic stability. This can be attributed to both enthalpic and entropic effects. The enthalpic contribution to the free energy change of complexation is comprised primarily of bond formation interactions and, as a result, the formation of stronger bonds gives rise to more stable lanthanide(III) complexes. Whilst the dominant contribution to the reduced stability of tetraamide derivatives is enthalpic, entropy also has a role to play, i.e., more highly charged ligands are likely to be more hydrated in aqueous solution and complex formation will therefore require a greater degree of desolvation, liberating more water molecules.

In kinetic terms, it is well-established that complex dissociation requires the displacement of a ligand donor atom. This can occur when a bond between a donor atom and a metal ion is weaker, perhaps due to a lower basicity of the ligand, or may be mediated by protonation of a donor atom. One example addressing the impact of ligand basicity is a comparison study between H₄dota and its phosphonate analogues 1,4,7,10-tetraazacyclododecane-phosphonic acid 1H₄dopa and its phosphate analogues 1H₄dopmb and 1H₄do3pmb (Fig. 4). The strong basicity of H₄dopmb increased the thermodynamic stability constant of its Gd³⁺ complex to a value higher than [Gd(OH₂)(dota)⁻]⁻ 83 and also resulted in the presence of the protonated complex at physiological pH. Though this protonated species exhibited comparative relaxivity to [Gd(OH₂)(dota)]⁻, the complex was found to have a strong affinity with bone and hydroxyapatite (by employing the radioisotopes [153Sm(dotp)]⁻ and [111In(dotp)]⁻, excluding it from use as a GBCA. The presence of non- or weakly coordinating groups susceptible to protonation can increase protometalated demetallation. A key example of this is seen with the ligands H₄hpdo3a and H₄do3a-butrol, which contain hydroxyl groups that are only weakly coordinated to the metal centre and these may be readily protonated. Through intramolecular proton transfer mechanisms, a proton can be transferred onto a cyclen nitrogen atom, resulting in dissociation 29,77. Examples discussed in this section also show the linear relationship between ligand basicity and thermodynamic stability. However, in terms of kinetic inertness, increased ligand basicity results in an enhanced rate of proton-assisted dissociation.

Introducing rigidity to complex ring systems

An interesting example of a different substitution technique for substitution onto the backbone of a macrocyclic ring comes from the work of Rodriguez-Rodriguez et al. in the form of the ligand 6,6’-’(1,4,8,11-tetraazabicyclo[6.6.2]hexadecane-4,11-diyli)bisdipicolinic acid, H₆cb-tedpa, published in 2014. This ligand is based on a reinforced cyclam framework, with an ethylene bridge linking two nitrogen atoms which are trans to one another. Two picolinic acid moieties are bound to the other nitrogen atoms in the cyclam derivative (Fig. 5e). The use of this structure as a framework may initially seem counter-intuitive, as it is known that the kinetic lability of trivalent lanthanide complexes of tetraaza macrocyclic ligands increases as the number of atoms in the ring increases, perhaps as the ligand becomes more flexible 80,90. However, the introduction of a cross-linking structure appears to prevent this reduction in kinetic stability. The authors managed to successfully crystallise the europium(III) complex of H₆cb-tedpa, which showed that the ligand completely envelops the metal ion and holds it in an extremely tight binding cavity 88. This may be due to the enhanced rigidity of the ligand system. Recent work on a similar methylated cyclam system has suggested that this greatly enhanced kinetic inertness is due to the presence of the ethylene cross-bridge 88,91. Another ligand family which has developed around this methodology is the pyclen family. Pyclen is closely related to the tetraaza macrocyclic cyclen, but incorporates pyridine into the ligand backbone at one position 88,92,93. In the mid-1990s, the ligand 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid (H₃pcta) was developed as a heptadentate chelator for lanthanide(III) ions (Fig. 5e). The heptadenticity of H₃pcta enabled a hydration state of 2 to be accessed for the gadolinium(III) complex, with a corresponding increase in the complex’s relaxivity 92. The introduction of pyridine into the ligand backbone was expected to rigidify this ligand, compensating for any potential reduction in thermodynamic stability or kinetic inertness associated with the reduction in denticity 93. Indeed, the reported range of log K values for the [Gd(OH₂)₂(pcta)]⁻ complex was from 18.3 to 21.0, indicating comparable thermodynamic stability to the Gd³⁺ complexes of the octadentate ligands H₂dtpa and H₂dutra 93-95. H₃pcta also exhibited promising complex formation kinetics: the pyridine moiety introduces an additional degree of pre-organisation into the macrocyclic ring, resulting in formation rates of Ln³⁺ species that are an order of magnitude greater than those of H₄dota. However, other macrocyclic ligands such as H₄dota and also the heptadentate H₆do3a form gadolinium(III) complexes of greater thermodynamic stability than H₃pcta 93.

The initial promise of H₃pcta has rendered it an attractive scaffold for further modification to enhance its stability and increase its suitability for potential in vivo applications. In 2003, Aime et al. 96 reported the synthesis of a monosubstituted methylene phosphate derivative of H₃pcta which formed a gadolinium(III) complex with a hydration state of 2. This complex exhibited a relaxivity value twice that of many clinically utilised contrast agents and an impressive log K value of 23.4, comparable to that of [Gd(OH₂)(dota)]⁻ 96. However, it was only stable above pH 3 97. More recently, Le Fur et al. have had success with the substitution of H₃pcta’s acetic acid donor groups for picolinic acid 95,96. Picolinic acid moieties are bidentate, and the synthesis of octadentate and nonadentate H₃pcta derivatives incorporating this functionality have been reported. The disubstituted analogues reported in this work exhibit particularly impressive physical properties: both the symmetric (6-(carboxymethyl)-6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,9-di(methylene)picolinic acid, referred to as H₃L₃ by the authors) and asymmetrically substituted (9-(carboxymethyl)-6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,9-di(methylene)picolinic acid), referred to as H₂L₄) variants (Fig. 5f) form Gd(III) complexes with pGd values greater than that of [Gd(OH₂)(dota)]⁻ (e.g., 20.69, 21.83 and 19.21, respectively at a ligand to metal ratio of 10:1), and their reported log K values are extremely close (23.56 for [Gd(L₃)]⁻ and 23.44 for [Gd(L₄)]⁻) 95. This greater thermodynamic stability almost certainly arises from the increased denticity of the ligands compared to H₃pcta and increased rigidity over H₄dota 95. Despite the appeal of these...
ligands, they do have some shortcomings. The most promising, H4L4, forms a gadolinium(III) complex which has been found to have a hydration state of 0, limiting any potential application as a GBCA. H3L3 forms a gadolinium(III) complex with two solution structures, one of which is also q = 0, although the other exhibits a hydration state of 1. In addition, the half-life of [Gd(L3)] in 0.1 M HCl is only 14 h. These low-hydration states could be a consequence of their nonadentate nature, or possibly the tight binding observed between the ligand and metal ion, one of the pitfalls in the search for greater thermodynamic stability.

**Acyclic ligands for gadolinium(III)**

2-[Bis[2-[bis(carboxymethyl)amino]ethyl]amino]acetic acid, also referred to as diethylentriaminepentacetic acid, (H5dtpa) was the ligand utilised in the first clinically approved GBCA — Magnevist®. Since then there has been enormous variation in the family of acyclic ligands used to chelate gadolinium(III), e.g., donor atoms have moved away from the archetypal mixed N and O systems seen in H3dota and H2dtpa to typically favour all oxygen donors. This has allowed reduced denticity to be explored to a much greater extent than with H2dota analogues.

**Exploiting basicity and oxophilicity**

The basicity of donor atoms has a critical impact on thermodynamic stability and kinetic inertness of the resultant gadolinium(III) complex. This is exemplified by the development of hopo ligands, first reported in 1995. These exploit the greater basicity of charged oxygen over nitrogen and the known oxophilicity of the lanthanide family of acyclic ligands used to chelate gadolinium(III), e.g., donors atoms have moved away from the archetypal mixed N and O systems seen in H3dota and H2dtpa to typically favour all oxygen donors. This has allowed reduced denticity to be explored to a much greater extent than with H2dota analogues.

**Example structures**

Fig. 6 Exempral chemical structures of Gd(III) complexes of the acyclic “hypo” ligands. Charged oxygen donors are a feature within the ligands: H3tren-Me-3,2-hopo (complex a) and H2tren-Me-3,2-hopotam (complex b). Enhanced stability is observed due to the significant oxophilicity of the Gd(III) ions.

MS-325 is the trisodium salt of the gadolinium(III) complex of 2-(R)-{(4,4-diphenyclohexyl)phosphonoxyoxymethyl} 2-[bis[2-[bis(carboxymethyl)amino]ethyl]amino]acetic acid, (Fig. 7e), where a large diphenyl cyclohexyl phosphoester substituent
was introduced within the ligand’s diethylenetriamine backbone\textsuperscript{26,119,120}. The steric bulk of the phosphodiester moiety was found to invoke selectivity in isomer formation, preferentially adopting a TTP with $\Lambda$ helicity, resulting in an increased kinetic inertness over the corresponding dtpa\textsuperscript{3–} complexes as the rate of isomer interconversion is reduced\textsuperscript{110,111}. The large lipophilic substituent of MS-325 allows interaction with the blood protein human serum albumin (HSA)\textsuperscript{111,121}, which enhances the lifetime of the species in vivo\textsuperscript{111,119,121}. Despite its advantages, the high affinity of MS-325 for HSA renders it mostly suitable for blood-pool imaging and limits wider application.

**Rigidification of the ligand backbone**

Demetallation can occur when the staggered conformation of the diethylenetriamine backbone of H\textsubscript{4}dtpa is inverted. One strategy that has been employed to limit this process is rigidification. The cyclohexyl motif has been extensively used to rigidify acyclic ligands. Early work focused on H\textsubscript{4}cdta (Fig. 8a), the cyclohexyl derivative of ethylenediamine tetracetic acid, H\textsubscript{4}edta. This ligand was found to have restricted flexibility and an extremely rigid coordination cage\textsuperscript{122}. Due to this rigidity, cdta\textsuperscript{4–} complexes are more resistant to demetallation, with a high activation barrier to dissociation, especially when compared to many other acyclic ligands\textsuperscript{122}. However, H\textsubscript{4}cdta also exhibits slow complex formation kinetics, with its lanthanide(III) complexes exhibiting smaller for-
The gadolinium(III) complex of H$_2$aza demonstrated high thermodynamic stability, despite its reduced denticity compared to H$_2$dtpa, its log $K$ value being 19.26. The complex did not show any demetallation at pH 2, and was also highly selective for Gd$^{3+}$ over many endogenous cations, i.e., no transmetallation of [Gd( OH$_2$)$_2$(aza)]$^{-}$ was observed in the presence of a tenfold excess of ZnCl$_2$, CaCl$_2$, or MnCl$_2$. However, the complex is more labile than macrocyclic GBCAs$^{128}$. The Gd(III) complex of H$_3$-cyaza$^{a}$ has a hydration number of 2, which comes with a corresponding increase in relaxivity$^{125,129}$. Introduction of the cyclohexyl motif proved interesting and was achieved by Vágner et al.$^{128}$, who synthesised the ligand trans-3-amino-3-methyldecahydro-1H-1,5-benzodiazepine-N$_{2}$N$_{3}$N$_{4}$N$_{5}$' tetracetic acid, H$_2$cyaza (Fig. 8f). The cyclohexyl ring results in a reduction in the thermodynamic stability of [Gd(OH)$_2$(cyaza)]$^{-}$ when compared to [Gd(OH)$_2$(aza)]$^{-}$ (log $K$ = 18.26 and 20.24, respectively), as it rigidifies the coordination cage and prevents optimal accommodation of the metal ion$^{128}$. The Gd(III) complex has a calculated half-life at pH 7.4 of 91 years, two orders of magnitude greater than [Gd(OH)$_2$(aza)]$^{-}$ itself, the highest reported for an acyclic $q = 2$ gadolinium(III) complex$^{128}$.

As discussed earlier, it is the inertness of a Gd$^{3+}$ complex which can determine its potential in vivo toxicity. Although [Gd( OH$_2$)$_2$(cyaza)]$^{-}$ exhibits a long half-life for a complex of an acyclic, heptadentate ligand with a hydration state of 2, this pales in comparison with that of [Gd(OH)$_2$(dota)]$^{-}$, which has a half-life more than 3000 times greater under similar conditions, and other macrocyclic species, which would likely hinder the former's application as a GBCA.

Another example of a ligand family with a ring system incorporated into its framework is the tacn-hopo series (Fig. 8g, h). These ligands, first reported in 2007 by Werner et al.$^{99}$, are based on the macrocycle 1,4,7-triazacyclononane (tacn) and the hopo ligands discussed above$^{26}$. The combination of rigidity imparted by the macrocyclic ring and the use of hard oxygen donors results in tacn-hopo ligands forming very thermodynamically stable complexes with gadolinium(III), with a pGd value of 18.7 (ligand to metal concentration ratio of 10:1) reported for the Gd$^{3+}$ complex of H$_3$-tacn-3,2-hopo$^{99}$. Whilst this is lower than many macrocyclic GBCAs in clinical use, it is particularly impressive as the heptadentate ligand results in a complex hydration state of 326$^{99}$. This results in the high relaxivity values for the Gd$^{3+}$ complexes of H$_3$-tacn-3,2-hopo and H$_3$-tacn-1,2-hopo of 13.1 and 12.5 mM$^{-1}$s$^{-1}$ respectively, among the highest known for low weight nonmononuclear gadolinium(III) complexes$^{99}$.

Perspective

The range of techniques and ideas which have emerged from the pursuit of more stable GBCAs is a testament to the ingenuity and creativity of coordination chemists. Acyclic ligands, which were at the forefront of the field at its inception in the 1980s and historically have dominated clinical usage, have been the subject of many of these developments, ranging from the alteration of ligand basicity and the nature of the donor atoms to the manipulation of isomer ratios via chiral backbone substituents. Amongst these techniques, perhaps the most successful has been rigidification of the ligand backbone through the introduction of a cyclohexyl motif, as seen with the derivatives H$_4$chxota and H$_4$cyaza, the Gd(III) complexes of which are far more kinetically inert than Magnevist$^{®}$. However, one critical factor prevents these ligands from spawning the next generation of GBCAs: they are just not inert enough. The thermodynamic stabilities of many acyclic ligands are indeed comparable to their macrocyclic counterparts but although stable complex formation is vital, this alone cannot predict the extent of Gd$^{3+}$ release in vivo. Kinetic inertness is of paramount importance in the development of GBCAs, hence the recent action by both the FDA and EMA restricting the application of contrast agents based on acyclic species. For this reason, despite logical and thoughtful design processes applied to acyclic ligands by countless researchers over...
the decades, macroyclic chelators are almost certain to be the basis of future clinical developments in this field. Amongst the myriad of macrocyclic ligands discussed in this review, some show more promise than others, and all require development in the future. Alteration of ligand basicity has proven popular, but this is limited in practical use, i.e., increased basicity results in more rapid proton-mediated dissociation and can lead to complicated interactions in biological systems. Addition of chirality to the cyclo backbone and pendant arms of H4dota to enhance complex geometry preferences is a widely used technique, but one that must be approached with caution i.e. the new substituent must be large enough to invoke the necessary isomer selectivity, but not so bulky that the ligand is over-rigidified and cannot bind to the metal ion centre tightly enough. Thus, an optimum degree of substitution and size exists and will doubtless be found by skilled chemists in future. Ligand rigidity without the introduction of chirality has also exhibited potential, especially considering the remarkable inertness of some Gd(III) complexes formed with nonadentate pyclen derivatives and cross-bridged cyclam species, which also utilise the enhanced denticity of picolinic acids over traditional acetate arms. These scaffolds, which have only come to light in the past five years or so, may well be significant as work in the field of GBCAs progresses, and hopefully moves safer and more efficient GBCAs towards the clinic. The role of the coordination chemist will be instrumental to this translation—of course, working alongside biologists, imaging scientists and clinicians.

Received: 19 July 2018 Accepted: 20 December 2018 Published online: 29 March 2019

References

1. Peters, J. A., Huskens, J. & Raber, D. J. Lanthanide induced shifts and relaxation rate enhancements. Prog. Nucl. Magn. Reson. Spectrosc. 28, 283–350 (1996).
2. Caravan, P., Ellison, J. J., McMurry, T. J. & Lauffer, R. B. Gadolinium(III) chelates as MRI contrast agents: structure, dynamics, and applications. Chem. Rev. 99, 2239–2352 (1999).
3. Aime, S., Bott, M. & Ciofani, E. Gd(III)-based contrast agents for MRI. Adv. Imag. Imag. Chem. 57, 173–237 (2005).
4. Caravan, P. Strategies for increasing the sensitivity of gadolinium based MRI contrast agents. Chem. Soc. Rev. 35, 512–523 (2006).
5. Bottrill, M., Kwock, L. & Long, N. J. Lanthanides in magnetic resonance imaging. Chem. Soc. Rev. 35, 557–571 (2006).
6. Werner, E. J., Datta, A., Jocher, C. J. & Raymond, K. N. High-relaxivity MRI contrast agents: where coordination chemistry meets medical imaging. Angew. Chem. Int. Ed. 47, 8568–8580 (2008).
7. Law, G. L. & Wong, W.-T. An introduction to molecular imaging. In The Chemistry of Molecular Imaging (eds. Long, N. J. & Wong, W.-T.) 1–24 (John Wiley & Sons, Hoboken, New Jersey, USA, 2015).
8. Sherry, A. D., Caravan, P. & Lenkinski, R. E. Primer on gadolinium chemistry. J. Magn. Reson. Imaging 30, 1240–1248 (2009). This primer outlines the fundamental chemistry which links the behaviour of gadolinium(III) in solution to the inertness and stability of its complexes and their dissociation in vivo.
9. Niemandt, H. P. Gadolinium-DTPA: a new contrast agent. Bristol Med. 103, 34–38 (1988).
10. Khawaja, A. Z. et al. Revisiting the risks of MRI with gadolinium based contrast agents—review of literature and guidelines. Insights Imaging 6, 533–558 (2015).
11. European Medicines Agency. Assessment report for Gadolinium-Containing Contrast Agents. EMA/470460/2010 44 (2010).
12. Grobner, T. Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? Nephrol. Dial. Transpl. 21, 1104–1108 (2006). This paper was the first to report on a suspected link between the use of GBCAs and NSF.
13. Aime, S. & Caravan, P. Biodistribution of gadolinium-based contrast agents, including gadolinium deposition. J. Magn. Reson. Imaging 30, 1259–1267 (2009).
14. McDonald, R. J. et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. Radiology 275, 772–772 (2015). The first report showing gadolinium accumulation in the brains of patients.
15. Kanda, T., Oba, H., Toyoda, K., Kitajima, K. & Furui, S. Brain gadolinium deposition after administration of gadolinium-based contrast agents. Jpn. J. Radiol. 34, 3–9 (2016).
16. Gulani, V., Calamante, F., Shellock, F. G., Kanal, E. & Reeder, S. B. Gadolinium deposition in the brain: summary of evidence and recommendations. Lancet Neurol. 16, 564–570 (2017).
17. Dekkers, I. A., Roos, R. & Van Der Molen, A. J. Gadolinium retention after administration of contrast agents based on linear chelators and the recommendations of the European Medicines Agency. Eur. Radiol. 28, 1579–1584 (2018).
18. Darnall, D. W. & Birnbaum, E. R. Lanthanide ions activate neuro-inflammatory responses in the brain: relationship to the clinical manifestations of NSF. Radiology 265, 248–253 (2012).
19. G. E. HealthCare. Omniscan™ (gadodiamide) Injection NDA 20-123 briefing document for MIDAC. Briefing Document for MIDAC 1–91 (2017).
20. Semelka, R. C. et al. Gadolinium deposition disease: Initial description of a disease that has been around for a while. Magn. Reson. Imaging 34, 1383–1390 (2016).
21. Toth, E., Helm, L. & Merbah, A. E. Relaxivity of MRI contrast agents. In Contrast Agents 1—Topics in Current Chemistry (ed. Krause, W.) 61–101 (Springer, Berlin, Germany, 2002).
22. Faulkner, S. & Blackburn, O. A. The chemistry of lanthanide MRI contrast agents. In The Chemistry of Molecular Imaging (eds. Long, N. & Wong, W.-T.) 179–197 (John Wiley & Sons, Hoboken, New Jersey, USA, 2015). This chapter offers an extensive overview of the behaviour of gadolinium(III) complexes in solution and discusses the rationale behind the design of many existing GBCAs and strategies for relaxation enhancement of gadolinium(III) complexes.
23. Geraldes, C. F. G. C. Paramagnetic NMR effects of lanthanide ions as structural reporters of supramolecular complexes. NMR in Supramolecular Chemistry (2015).
24. Nephrogenic systemic fibrosis: a review of literature and guidelines. J. Radiol. 99, 1259–1269 (2018).
25. Brücher, E. Kinetic stabilities of gadolinium(III) chelates used as MRI contrast agents. Top. Curr. Chem. 221, 103–122 (1999).
26. Delgado, R., Félix, V., Lima, L. M. P. & Price, D. W. Metal complexes of cyclen and cyclam derivatives useful for medical applications: a discussion based on thermodynamic stability constants and structural data. Dalton Trans. 2734–2745 (2007).
27. Idee, J. M. et al. Role of thermodynamic and kinetic parameters in gadolinium chelate stability. J. Magn. Reson. Imaging 30, 1249–1258 (2009).
28. Burai, L., Fabián, I., Király, R., Szilágyi, É. & Brücher, E. Equilibrium and kinetic studies on the formation of the lanthanide(III) complexes, [C(dota)3]− and [Yb(dota)]3− (H4dota)−1,4,7,10-tetraazacyclododecane−1,4,7,10-tetraacetic acid). J. Chem. Soc. Dalton Trans. 243–248 (1998).
29. Cachier, W. P., Quay, S. C. & Rocklage, S. M. The relationship between thermodynamics and the toxicity of gadolinium complexes. Magn. Reson. Imaging 8, 467–481 (1990).
30. Saska, L., Burai, L. & Brücher, E. The rates of the exchange reactions between [Gd(DTPA)]3− and the endogenous ions Cu2+ and Zn2+: a kinetic model for the prediction of the in vivo stability of [Gd(DTPA)]3− as a contrast agent in magnetic resonance imaging. Chemistry 6, 719–724 (2000).
31. Saska, L., Burai, L., Király, R., Zékáry, L. & Brücher, E. Studies on the kinetic stabilities of the Gd3+ complexes formed with the N-mono(methylamide), N+−mono(methylamide) and N,N′-bis(methylamide) derivatives of diethylamidetetramine-N,N,N′,N′-pentacetic acid. J. Inorg. Biochem. 91, 320–326 (2002).
32. Laurent, S., Van der Elst, L., Copeau, F. & Muller, R. N. Stability of MRI paramagnetic contrast media: a proton relaxometric protocol for...
39. Laurent, S., Elst, L. Vander & Muller, R. N. Comparative study of the physicochemical properties of six clinical low molecular weight gadolinium contrast agents. *Contrast Media Mol. Imaging* 1, 128–137 (2006).

40. Frenzel, T., Lengsfeld, P., Schirmer, H., Hutter, J. & Weinmann, H. J. Stability of gadolinium-based magnetic resonance imaging contrast agents in human serum at 37 °C. *Invest. Radiol.* 43, 817–828 (2008).

41. Tweedle, M. F., Hagan, J. J., Kumar, K., Mantha, S. & Chang, C. A. Reaction of gadolinium chelates with endogenously available ions. *Magn. Reson. Imaging* 9, 409–415 (1991).

42. Wedeking, P., Kumar, K. & Tweedle, M. F. Dissociation of gadolinium chelates in mice: a reevaluation to chemical characteristics. *Magn. Reson. Imaging* 10, 641–648 (1992).

43. Stojanov, D. A., Araki-Trenkic, A., Vojinovic, S., Benedeto-Stojanov, D. & Ljubisavljevic, S. Increasing signal intensity with the detachment and globus pallidus on unenhanced T1-weighted MR images: evaluation of two linear gadolinium-based contrast agents. *Radiology* 267, 228–232 (2015).

44. Ramalho, J. et al. High signal intensity in globus pallidus and dentate nucleus on unenhanced T1-weighted MR images: evaluation of two linear gadolinium-based contrast agents. *Radiology* 276, 836–844 (2015).

45. Robert, P. et al. T1-weighted hypersignal in the deep cerebellar nuclei after gadolinium deposition in the brain: we need to differentiate the transmetallation of a gadolinium complex. *Contrast Media Mol. Imaging* 5, 1095–1105 (1999).

46. Payne, K. M. & Woods, M. Isomerism in benzyl-DOTA derived bifunctional chelates: implications for molecular imaging. *Bioconjug. Chem.* 26, 338–344 (2015).

47. Desreux, J. F. Nuclear magnetic resonance spectroscopy of lanthanide cations Eu3+ and Tb3+ with 1,4,7,10-tetraazacyclododecane (dota). *Chem. Eur. J.* 10, 5218–5232 (2015).

48. Frullano, L., Rohovec, J., Peters, J. A. & Geraldes, C. F. G. C. Structures of MRI contrast media studied by 1H-NMR spectroscopy. *Invest. Radiol.* 50, 1462 (1998).

49. Toth, E., Kiraly, R., Platzek, J., Raduchel, B. & Brucher, E. Equilibrium and conformational isomers of lanthanide complexes with an optically active chiral chelator. *Dalton Trans.* 25, 724–726 (2000).

50. Tiezzi, G., Webster, R. E., Kucera, B. E., Young, V. G. & Woods, M. Analysis of the conformational behavior and stability of the SAP and TSAP isomers of lanthanide(III) NB-DOTA - type chelates. *Inorg. Chem.* 70, 7966–7979 (2011).

51. Moreau, J. et al. Complexing mechanism of the lanthanide cations Eu3+ and Tb3+ with 4,7,10,13-tetraazadodecane (dota, and an investigation into the solution kinetics of their lanthanide complexes. *Eur. J. Inorg. Chem.* 1462 (1998).

52. Roman-Goldstein, S. M. et al. Effects of gadopentetate dimeglumine on unenhanced T1-weighted MR images: relationship to chemical characteristics. *Eur. Radiol.* 10, 4723 (2000).

53. Geraldes, C. F. G. C., Sherry, A. D. & Kiefer, G. E. The solution structure of Ln (III) complexes of aminoethyl-DO3A as pH-responsive T1-magnetic chelates in mice: relationship to chemical characteristics. *Eur. J. Inorg. Chem.* 2933 (2001).

54. Aime, S. et al. Conformational and coordination equilibria on DOTA complexes and the implications on protein structural studies. *Dalton Trans.* 45, 4673–4687 (2016).

55. Bányai, I., Brücher, E., Király, R. & Terreno, E. Kinetics of the transmetallation of a gadolinium complex. *J. Magn. Reson.* 113, 290–304 (1992).

56. Bányai, I., Király, R., Platzek, J., Raduchel, B. & Brucher, E. Equilibrium and conformational isomers of lanthanide(III) NB-DOTA complexes of lanthanide(III) complexes. *Eur. J. Inorg. Chem.* 11, 724–726 (2000).

57. Aime, S. et al. Conformational and coordination equilibria on DOTA complexes of lanthanide metal ions in aqueous solution studied by 1H-NMR spectroscopy. *Inorg. Chem.* 33, 832–838 (1994).

58. Damien, S. & Tormene, C. F. G. C. Structures of MRI contrast media studied by 1H-NMR spectroscopy. *Invest. Radiol.* 30, 191–199 (1996).

59. Geraldes, C. F. G. C., Sherry, A. D. & Kiefer, G. E. The solution structure of Ln (DTPA)2 complexes. *Top. Curr. Chem.* 1364 (1998).

60. Bányai, I., Király, R., Platzek, J., Raduchel, B. & Brucher, E. Equilibrium and conformational isomers of lanthanide(III) NB-DOTA complexes. *Dalton Trans.* 25, 2532–2551 (2006). This paper provides a detailed overview of the solution behaviour of H4DOTA ligands and their lanthanide(III) complexes.

61. Ranganathan, R. S. et al. Polymethylated DOTA ligands. 1. synthesis of gadolinium-based magnetic resonance imaging contrast agents in human serum at 37 °C. *Inorg. Chem.* 43, 2845–2851 (2004).

62. Bányai, I., Király, R., Platzek, J., Raduchel, B. & Brucher, E. Equilibrium and conformational isomers of lanthanide(III) complexes of amide derivatives of DOTA exhibit an unusual variation in stability across the lanthanide series. *Inorg. Chem. Acta* 357, 859–863 (2004).

63. Aime, S. et al. Thermodynamic and structural properties of gadolinium(III) complexes with functionalized macrocyclic ligands based upon 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraazacyclododecane. *Eur. J. Inorg. Chem.* 4666 (1984).

64. Pasha, A., Tirsén, G., Bényő, E. T., Brücher, E. & Sherry, A. D. Synthesis and characterization of DOTA-(amide), derivatives: equilibrium and kinetic behavior of their lanthanide(III) complexes. *Eur. J. Inorg. Chem.* 2007, 4340–4349 (2007).

65. M. B. Di Bari, L. & Salvadori, P. Static and dynamic stereochemistry of chiral Ln(III) complexes. *NATURE COMMUNICATIONS | https://doi.org/10.1038/s41467-019-09342-3 | www.nature.com/naturecommunications*
99. Werner, E. J. et al. Highly soluble tris-hydroxypyridonate Gd(III) complexes. Nature Commun. 10, 1420 (2019).

68. Alves, F. C. et al. Silencing of phosphonate-gadolinium magnetic resonance imaging contrast by hydroxypatite binding. Invest. Radiol. 38, 750–760 (2003).

107. McMurry, T. J. et al. Physical parameters and biological stability of yttrium complexes. Inorg. Chem. 54, 1977–1981 (2015).

113. Tyeklár, Z. et al. Structural, kinetic, and thermodynamic characterization of the diastereomers of MS-325, a gadolinium(III)-based magnetic resonance angiography contrast agent. Inorg. Chem. 46, 6632–6639 (2007).

115. Port, M. et al. Efficiency, thermodynamic and kinetic stability of marketed gadolinium chelates and their possible clinical consequences: a critical review. Biometals 21, 469–490 (2008).

121. Caravan, P. et al. Albumin binding, relaxivity, and water exchange kinetics of the diastereoisomers of MS-325, a gadolinium(III)-based magnetic resonance angiography contrast agent. Inorg. Chem. 46, 6621–6631 (2007).

122. Fusaro, L., Mocci, F., Muller, R. N. & Luhmer, M. Insight into the dynamics of lanthanide-DTPA complexes as revealed by oxygen-17 NMR. Inorg. Chem. 51, 4455–4461 (2012).
Author contributions
All the authors contributed to the writing of this review article.

Additional information
Competing interests: The authors declare no competing interests.

Reprints and permission information is available online at http://npg.nature.com/reprintsandpermissions/

Journal peer review information: Nature Communications thanks the anonymous reviewers for their contribution to the peer review of this work.

Publisher’s note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.