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Crystallographic and solution NMR structural analyses of four hexacoordinated gallium(III) complexes based on ligands derived from 6-amino-perhydro-1,4-diazepine†

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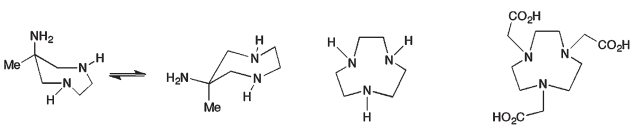
The crystal structures are reported of four gallium(III) complexes based on two pairs of 6-substituted-6-amino-perhydro-1,4-diazepine ligands, together with a study of their solution structures examined by ^{1}H and ^{71}Ga NMR spectroscopy. In each case, the ligand adopts a twisted chair conformation that creates a facial array of the three ligand nitrogen atoms. The coordination geometry about each gallium(III) ion is a slightly distorted octahedron, with the 6-phenyl series being slightly more distorted than the 6-methyl analogues. Pulsed NMR experiments allow solution NMR structures to be assessed, revealing good agreement with the solid-state structures.

Introduction

The heterocycle 6-amino-6-methyl perhydro-1,4-diazepine, **1**, possesses a seven-membered ring with three nitrogen atoms. It is constitutionally isomeric with the 9-membered ring, 1,4,7-triazacyclononane, **2**. These ligands have been studied in detail as ligand scaffolds, as N-substitution readily allows formation of heptadentate or hexadentate ligands.[1–4] The conformational plasticity of saturated, heterocyclic seven-membered rings has ample precedent[5–8] and several low-energy conformations are populated. The twisted-chair conformations are usually of lowest energy and a fast conformational equilibrium interconverts axial and equatorial sites. A more sterically bulky 6-substituent will prefer to occupy an equatorial site. Indeed, to present a facing-capping array of three ligand nitrogen donors, the 6-amino group must take up an axial position, so this is favoured when the other 6-substituent is more bulky.

The identification of ligands that bind metal ions rapidly and form kinetically stable complexes that resist premature dissociation *in vivo* is not a simple task.[9,10] Macrocyclic ligands have been shown to form more kinetically inert metal complexes than their acyclic analogues, but their higher binding stability constants are usually associated with slower rates of complexation.[11] These issues are important in modern molecular imaging in which ligands are labelled by metallic radioisotopes, with short half-lives, such as the positron emitters ^{68}Ga ($t_{1/2}$ 68 min), ^{64}Cu($t_{1/2}$ 12.8 h), ^{52}Fe($t_{1/2}$ 8.2 h) and ^{55}Co($t_{1/2}$ 17.5 h). The need to avoid premature metal ion dissociation *in vivo* has meant that macrocyclic ligand systems are preferred, and due deference needs to be given to the matching of coordination number and donor type for the given metal ion.



1 2 3 (NOTA)

The hexadentate ligands NOTA[12] **3**, and its triphosphinate analogues,[13,14] have been studied actively for labelling with ^{67}Ga(γ, 7.8 h), ^{68}Ga and ^{111}In(γ, $t_{1/2}$ 68 h).[15] The gallium(III) ion with an effective ionic radius of 0.62 Å, prefers octahedral coordination and usually favours binding to 'hard' donor atoms. The radiolabelled complexes of NOTA and its analogues are remarkably resistant to acid catalysed dissociation *in vivo*[16,17] but can be rather slow to label at ambient pH and temperature, at the sub-nanomolar concentrations used. The slowest step in metal ion association in water probably involves N-deprotonation of the ligand. Such a process is inhibited by the conformational rigidity of the triazacyclononane ligand, where the tendency to maintain the square [333] conformation is enhanced by the presence of a bifurcated hydrogen bond between ring nitrogens. The short half-life of the positron-emitting isotope, ^{68}Ga, makes the issue of radiolabelling kinetics particularly important.

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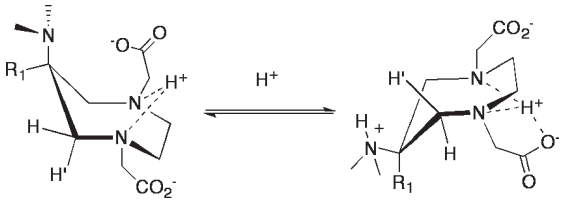
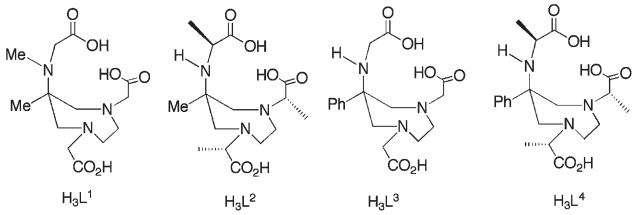


Scheme 1

Recently we have introduced a set of hexadentate aza-carboxylate ligands, L^1–L^4, based on the perhydro-diazepine (DAZA) scaffold,[18,19] and found that they bind ^{68}Ga in over 98% yield within 5 minutes at room temperature, over the pH range 4 to 7. In the derivatives examined to date, the 6-substituent is either a methyl or phenyl group. The free ligands L^3 and L^4 favour a solution conformation that is more pre-organised to metal binding, as the bulkier phenyl substituent prefers an equatorial site compared to the $NHCH_2CO_2^-$ moiety (Scheme 1). Here, we report the detailed structures of the gallium(III) complexes of each ligand and compare the NMR solution structures using 2D NOESY and Pureshift methods of analysis.

Results and discussion

Equimolar amounts of gallium nitrate hexahydrate and the ligand were mixed in aqueous methanol and the pH of the solution adjusted to 4.5. The reaction was heated for 1 h at 60 °C, and the mixture set aside and held at 18 °C. The Ga(III) complexes crystallised from this solution as thin plates over the course of 36 h, and were isolated and examined by X-ray analysis.



H_3L^1 H_3L^2 H_3L^3 H_3L^4

Solid state structures of gallium complexes

The Ga(III) complexes of L^1 and L^2 crystallised as hemi- and mono-hydrates respectively, whilst those of L^3 and L^4 did not contain any solvent of crystallisation in the unit cell. Solvent water molecules in the complexes of L^1 and L^2 form hydrogen bonds with the carbonyl oxygen atom of one of the pendant arm and do not affect noticeably the coordination geometry (see below). In every complex, the Ga(III) ion is coordinated by the N_3O_3 donor set of the ligand to give charge neutral complexes. The conformation of the 7-membered ring, location of the Ga(III) ion and arrangement of the N-substituents reveal a common coordination geometry (Fig. 1). The lattices of [Ga·L^1] and [Ga·L^3] contain enantiomeric complexes within the unit cell, with opposite ring conformations and helicities of the carboxylic pendant arms. In each complex, two of the pendant arms have the same torsion angle sign, whilst the third has the opposite sense. These can be described, overall, as either Λ or Δ (Table 1).

Crystals of [Ga·L^3] contain two crystallographic independent molecules, which differ significantly in their NCCO torsion angles (Table 1). Every other angular parameter shows less than a 5° variation between the two conformers. The enantiomerically pure complexes, [Ga·L^2] and [Ga·L^4], can be considered as Λ overall and have consistently higher N–C–C–O torsion angles (Table 1). There is a smaller degree of helicity in [Ga·L^3] compared to the other three complexes, as indicated by their lower N–C–C–O torsion angles. This behaviour contrasts with the Ga complexes of the NOTA and 9-N_3-triphosphinate gallium complexes, where the analogous NCCO and NCPO torsional angles have the same sign.[14,15]

Selected molecular parameters are presented in Table 2 for [Ga·L^n], n = 1–4. As indicated by the N–Ga–O angles (≠180°) and non-parallel O_3 and N_3 faces, each complex adopts a distorted octahedral geometry around the Ga(III) centre, typical of hexadentate complexes of gallium.[20–22]

The octahedral distortion parameter (Σ) and the average trigonal distortion angle (Θ) define the degree of distortion from an ideal octahedron;[23,24] values are shown for [Ga·L^n] compared to [Ga·NOTA] in Table 3.

The parameters indicate that the geometry around the Ga(III) in the NOTA complex is a less distorted octahedron than that of [Ga·L^n]. This is likely to be associated with the lower symmetry relative to the C_3 symmetry inherent in NOTA.

In general, the Ga–N_{endo} bonds are slightly longer for [Ga·L^n] than for [Ga·NOTA][12] by ~0.04 Å, whilst the average Ga–O distance is approximately the same (±0.01 Å). In each case, the N_{exo}–Ga distance is shorter than both of the N_{endo}–Ga distances (Table 4). This is a feature consistently observed for metal complexes featuring a tridentate bound DAZA core, and has been considered to reflect the flexibility associated with the exocyclic nitrogen group.[25–27] The Ga–N bond distances are considerably elongated compared to the M–O bonds, consistent with the difference in donor–acceptor strength of the Ga–N and Ga–O bonds (Table 4). There is significant variation in the Ga–O bond lengths which is a consequence of a number of factors, including the asymmetry of the ring (Fig. 1).

The only examples in the literature of complexes featuring a carboxylic acid functionalised DAZA ligand incorporate either lanthanide(III) or copper(II) ions.[2b,27] The lanthanide complexes each crystallize as dimeric complexes, as a consequence of the constrained environment of the DAZA core, whose 'bite-size' is too small to encapsulate the lanthanide ion. As a result, the "face of the metal" is exposed. This is illustrated by the difference in distances of the lanthanide ion from the planes of the N_3 and O_4 donor sets in [Gd·AAZTA] (Table 4).[2b]

In the copper(II) AAZTA complex,[27b] the metal ion is coordinated by the three nitrogen atoms and the two carboxylate oxygens belonging to the iminodiacetate moiety of the ligand. A water molecule makes up the sixth donor to give a Jahn–

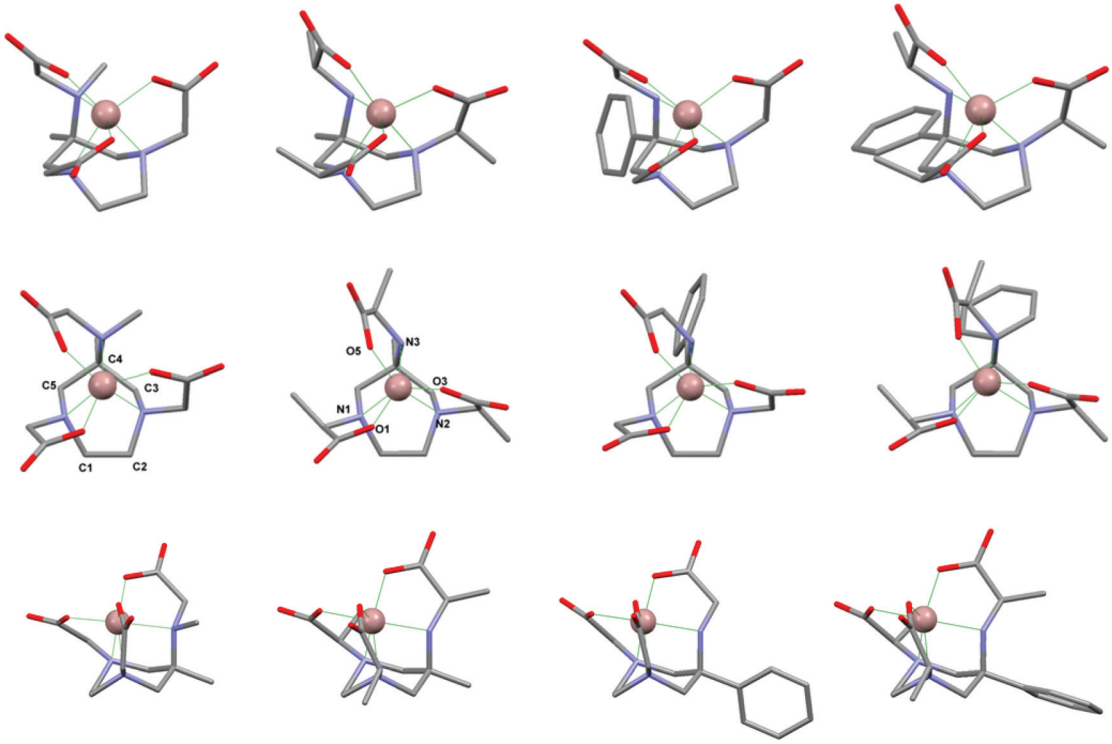


Fig. 1 Selected views of the four gallium(III) complexes. A single enantiomer is shown for [Ga·L^1] and [Ga·L^3]; only one of the crystallographic independent molecules of [Ga·L^3] is shown. *Top*: encapsulation of the metal centre by the ligand framework; *centre*: view taken perpendicular to the N_3 plane, highlighting the arrangement of the pendant arms relative to the N_3 donor set, and showing the atom numbering scheme; *bottom*: view along the C_1–C_2 diamine bridge, showing the relative position of the quaternary carbon substituent and the pseudo-chair conformation of the ring.

Table 1 Torsion angles (°, ±0.05) for the N–C–C–O pendant arms of [Ga·L^n]

	Λ-[Ga·L^1]	Λ-[Ga·L^2]	Λ-[Ga·L^3]^{a,b}	Δ-[Ga·L^3]^{a,c}	Λ-[Ga·L^4]
N1–C–C–O1	−15.3	+21.5	+10.5	+6.0	+16.9
N3–C–C–O5	+10.2	−18.9	−7.6	+8.9	−18.3
N2–C–C–O3	−24.3	−21.8	−5.8	−20.9	−27.63

[a] Superscripts 'b' and 'c' indicate the two independent molecules of [Ga·L^3].

Table 2 Selected N–Ga–O angles (°) and the angle formed between the planes of the N_3 and O_3 donor sets; see Fig. 1 for atom numbering scheme

	[Ga·L^1]	[Ga·L^2]	[Ga·L^3]^a	[Ga·L^4]
N_3/O_3 angle	3.03	3.55	4.24	2.91
N1–Ga–O3	157.25(8)	148.73(8)	152.4(2)	146.8(2)
N2–Ga–O5	165.16(7)	158.28(9)	161.5(2)	156.2(2)
N3–Ga–O1	159.68(7)	155.41(9)	157.8(2)	155.1(2)

[a] Values are the average of the two crystallographic independent molecules of [Ga·L^3].

Teller distorted octahedral geometry (Σ = 6.1). In this solid-state structure, the carboxylates of the EDDA moiety are protonated, and are not involved in metal complexation. The Ga(III) and Cu(II) ions are considerably smaller in size than Ln(III) ions, and as a result offer a better fit for the 'bite' of the

Table 3 Octahedral distortion parameter (Σ) and the average trigonal distortion angle (Θ) for [Ga·L^n] and [Ga·NOTA][12]

	[Ga·L^1]	[Ga·L^2]	[Ga·L^3]^a	[Ga·L^4]	[Ga·NOTA][23]
Σ^b	9.27	8.72	10.3	11.8	6.26
Θ^c	10.7	16.9	13.8	13.6	6.45

[a] Values from one of the two crystallographic independent molecules of [Ga·L^3] is provided. [b] Octahedral distortion parameter $\Sigma = \Sigma(|90 - \varphi_i|)/12$ [Σ = 0° for an ideal octahedron; φ_i represents the 12 smallest L–M–L angles].[23] [c] Average trigonal distortion angle $\Theta = \Sigma(|60 - i|)/24$ [Θ = 0° for an ideal octahedron; i represents the trigonal angles of the eight faces of the octahedron].[24]

Table 4 Selected bond distances (Å) for [Ga·L^n] relating to the coordination sphere of the complex, with estimated standard deviations in brackets (Fig. 1 for the atom labelling scheme)

	[Ga·L^1]	[Ga·L^2]	[Ga·L^3]^a	[Ga·L^4]
Ga–O1	1.939 (2)	1.967 (1)	1.948 (4)	1.969 (3)
Ga–O3	1.904 (2)	1.895 (2)	1.907 (4)	1.888 (3)
Ga–O5	1.933 (2)	1.934 (2)	1.917 (4)	1.925 (3)
Ga–N1	2.140 (2)	2.158 (2)	2.136 (4)	2.115 (3)
Ga–N2	2.138 (2)	2.150 (2)	2.142 (5)	2.204 (3)
Ga–N3	2.111 (2)	2.075 (2)	2.110 (4)	2.107 (3)

[a] Values given are the mean of the two crystallographic independent molecules of [Ga·L^3].

ligands, with more comparable distances between the metal centre and N_3 and O_3 planes (Table 5). It is interesting to note that there is a considerable amount of variation in each of the donor–Cu(II) bond lengths.

A comparison of the distances in Table 5 reveals some variation in the positioning of the Ga(III) ion relative to the plane of the N_3 and O_3 donor sets. It is interesting to note that although the Ga(III) ion lies closer to the N_3 donor set in [Ga·NOTA], it is better encapsulated by the ligands in [Ga·L^2] and [Ga·L^3]. This is not the case for [Ga·L^1], where the Ga(III) ion is slightly closer to the O_3 plane, and further from the N_3 plane, compared to [Ga·NOTA]. It is noteworthy that there is a considerably greater degree of rotation of the phenyl group, relative to the C–N_{exo} substituent, for [Ga·L^4] (68.0°) compared to [Ga·L^2] (16.7°). This is likely to be a result of the steric effect of the methyl group in the propionic acid pendant arm, which is directed in the same direction as the phenyl substituent (Fig. 1). The shortest interatomic contact between these two groups is 2.77 Å, involving a methyl hydrogen atom and the *ipso*-carbon atom of the phenyl ring.

Conformation of the 7-membered ring

It was expected that tridentate binding of the nitrogens in the 6-amino-perhydro-1,4-diazepine (DAZA) core requires a near perfect chair conformation (Fig. 2). Indeed, the vast majority of metal complexes involving tridentate DAZA ligands show less than a 2° deviation from the perfectly eclipsed arrangement of the N–CH_2–CH_2–N fragment, which is characteristic of the chair conformation.[3,25–29] Representative examples of complexes containing the DAZA core in various chair conformations are shown below (Fig. 2). Another characteristic of the chair conformation is that the torsion angles are approximately equal in size and opposite in sign at symmetry related sites of the ring (Table 6).

The gadolinium(III) and europium(III) complexes of the AAZTA-CH_2CH_2OH[27] ligand adopt a conformation with a N–CH_2–CH_2–N torsion angle of −28.2°, which is similar to that of the gallium complexes reported here (Table 6). The conformation of the 7 membered ring has been described as a pseudo-chair, however the torsion angles (and side-on view: Fig. 2) suggest

Table 5 Distances (Å, ±0.01) between the metal ion and the mean plane of the N and O donor sets

	[Ga·L^1]	[Ga·L^2]	[Ga·L^3][a]	[Ga·L^4]	[Ga·NOTA][23]	[Gd·AAZTA][9 b]
M–O_{plane} (Å)	0.98	1.07	1.03	1.06	1.02	0.13
M–N_{plane} (Å)	1.40	1.42	1.42	1.44	1.33	2.09

[a] Values are the average of the two crystallographic independent molecules of [Ga·L^3]. [b] For [Cu·AAZTA],[27b] the Cu–O(plane) and Cu–N(plane) distances are 1.12 and 1.41 Å respectively.

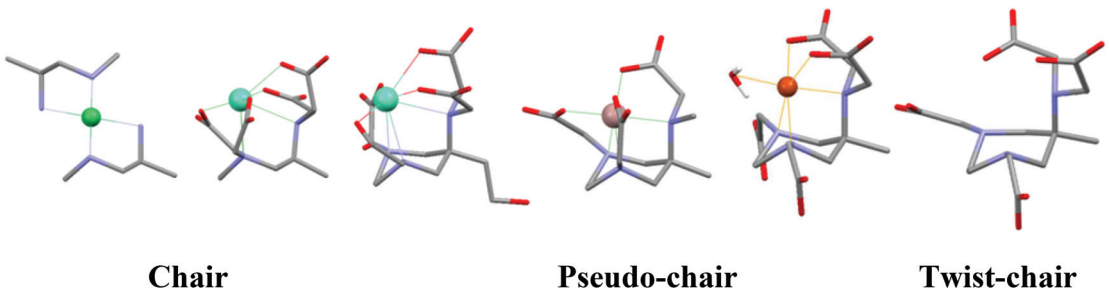


Fig. 2 Selected examples of the ring conformation in coordinated 6-amino-perhydro-1,4-diazepine ligands and (*right*) the heptadentate AAZTA ligand.[2b,25,27]

Table 6 Torsion angles (°) for the seven membered rings of [Ga·L^n] and relevant literature examples (see Fig. 1 for the atom labelling scheme)

Bond torsion/°	[Ga·L^1]	[Ga·L^2]	[Ga·L^3][a]	[Ga·L^4]	Eu(AAZTACH_2CH_2OH)[27a]	AAZTA[b 2b]	[Eu·AAZTA][c 2b]
N1–C1–C2–N2	25.6	29.1	29.0	24.8	−28.2	−45.2	−2.9
C1–C2–N2–C3	−58.8	−56.9	−58.0	−58.5	58.4	40.3	77.0
C2–N2–C3–C4	103.2	101.9	101.4	101.6	−100.77	−96.4	−91.5
N2–C3–C4–C5	−68.3	−68.1	−64.2	−68.9	64.59	70.4	57.7
C3–C4–C5–N1	52.1	51.6	46.7	54.1	−48.2	−47.0	−57.9
C4–C5–N1–C1	−86.7	−82.5	−81.6	−84.8	80. 9	67.5	92.1
C5–N1–C1–C2	99.6	98.9	101.3	96.5	−94.7	−91.1	−75.1

[a] One of the two crystallographic independent molecules of [Ga·L^3] is shown. There is no significant difference between the two ring conformations. [b] Twist-chair conformation. [c] Chair conformation; for [Cu·AAZTA],[27b] the torsion angles, as defined above are: 23.7, −57.5, 96.4, 69.1, 56.6, −83.9, 90.0.

that the ring conformation is closer to that of the twisted-chair (TC) adopted by the free ligand AAZTA[2b] (Table 6).

A number of factors contribute towards defining the lowest energy conformation adopted by the ring. The reduced torsional strain (relative to the chair conformation) within the N–CH_2–CH_2–N fragment is favourable, perhaps aided by the 'willingness' of Ga(III) to adopt a distorted octahedral geometry.[20] In addition, the presence of the coordinating pendant arms is also expected to be influential. Analysis of the torsion angles of the ring indicate that there is a further common feature in the four structures reported here. The absence of any significant conformational change resulting from the Me/Ph permutation is evident. Indeed, it is tempting to speculate that the C–Ph systems not only improve the degree of pre-organisation of the ligand for metal binding, but also enhance the rigidity of the desired conformation.

Solution state multinuclear NMR studies

The Ga(III) (d^{10}) ion is diamagnetic, and ^{1}H, ^{13}C and ^{71}Ga NMR studies were undertaken. Crystalline samples of each complex were dissolved in D_2O, and NMR studies carried out at pD 6. Consistent with the solid-state structure, mass spectrometry analysis revealed only the presence of a 1 : 1 complex, observed by electrospray mass spectrometry as the singly protonated monocationic species.

Single resonances were found in the ^{71}Ga (I = 3/2, 39.6% natural abundance, quadrupolar moment = 0.112) NMR spectra of each complex (Table 7). Chemical shifts are given relative to a strongly acidic solution of $[Ga(D_2O)_6]^{3+}$. Also shown are the linewidth ($\omega_{1/2}$) values. For the quadrupolar ^{71}Ga nucleus, the observed linewidth is a function of the local molecular symmetry and the rotational correlation time, τ_R. The latter parameter typically scales with molecular volume. In the C_3-symmetric Ga(III) complex of NOTA, relatively little line broadening was observed at 5.88 T (δ = +170 ppm, $\omega_{1/2}$ = 210 Hz) compared to that of the $[Ga(D_2O)_6]^{3+}$ reference ($\omega_{1/2}$ = 140 Hz).[17]

For [Ga·NOTA], the narrow line width of the ^{71}Ga NMR signal is consistent with a complex in which the metal ion donor set is tightly bound and highly symmetrical. Intrinsic line broadening in the NMR spectra of quadrupolar nuclei can often be attributed to the interaction of the nuclear quadrupole moment with the electric field gradient at the nucleus. The magnetic dipole and electric dipole are strongly coupled, because quadrupolar transitions perturb the electromagnetic environment. Therefore, relaxation of the nuclear electric quadrupole, associated with changes in the local electric field gradient (due to molecular motion in the fluid state), also relaxes the nuclear spin. For octahedral complexes with facial N_3 and O_3 donor sets, the gradient in the x–y plane tends to zero and the resultant field gradient at the nucleus is highly anisotropic. This results in a reduced rate of quadrupolar relaxation, and hence, minimal line broadening associated with this aspect.[17]

The ^{71}Ga NMR linewidth values and octahedral distortion parameters (Σ, Table 3) are each a measure of the relative symmetry in the different complexes. In terms of the relative order of asymmetry in the complexes, these parameters are in reasonable agreement with the values for [Ga·NOTA] and the 10-N_3-triacetate analogue. This suggests that the structures in solution and at 120 K in the solid state are similar.

The ^{1}H NMR spectrum of [Ga·L^1] (14.1 T) is particularly well resolved, making it possible to unambiguously assign all protons, except for H^4 and H^5 (Fig. 3), with the aid of 2D COSY, HSQC- and HMBC-NMR experiments. The methyl signals, $H^{1'}$ and H^{14}, resonated as singlets at 1.03 and 2.43 ppm respectively. The remaining protons are all diastereotopic, with a coupling pattern that was typical of two *AB*-doublets for $H^{2,7}$ (ring methylene protons), two *AB*-multiplets for $H^{4,5}$ (ethylene bridge CH_2's) and *AB*-doublets for $H^{8,10,12}$ (acetate CH_2's) structure.

With respect to the free ligand (at the same pH), the ^{1}H NMR signals of the two methyl signals ($H^{1'}$ and H^{14}) of the ligand in the bound complex are shifted to lower frequency, whilst remaining protons resonated to higher frequency (Fig. 3 *top left*). In the free ligand, L^1, rapid exchange between enantiomers, on the NMR time-scale, was manifested as a single *AB*-doublet (4H) for H^8 and H^{10}, *i.e.* there were 2 pairs of equivalent diastereotopic protons. A similar splitting pattern was observed for H^2–H^7.

However, in the case of the gallium complex of L^1, each 'pair' of diastereotopic protons appeared as separate *AB*-doublets, consistent with a lower time averaged symmetry. The same was observed for H^4–H^5, which resonated as more complex multiplets, due to the presence of anisogamous vicinal and geminal proton coupling constants. In the proton decoupled ^{13}C NMR spectra, the signals of the carbons which appeared as single resonances in the free ligand (C^4–C^5, C^2–C^7 and C^8–C^{10}) were resolved into separate signals in the bound ligand, as expected.

In the case of C_3-symmetric complexes, for example [Ga·NOTA], it is possible to assign the ring protons to their axial and equatorial orientations. Using 2D NOESY and Pure-shift (homonuclear broadband decoupling) NMR experiments,

Table 7 Variation of ^{71}Ga NMR spectral parameters for selected complexes (182.9 MHz, 14.1 T, 298 K, D_2O, pD 6, unless otherwise stated)

Complex	δ_{Ga} (ppm)[a]	$\omega_{1/2}$ (Hz)
$[Ga(D_2O)_6]^{3+}$	0	150
[Ga·L^1]	129	980
[Ga·L^2]	123	1170
[Ga·L^3]	125	1650
[Ga·L^4]	124	1820
[Ga·(10N_3-triacetate)][b,28]	133	2000
[Ga·NOTA][b]	170	210
$[Ga(OH)_4]^{-}$[b]	223	220

[a] Relative to $[Ga(D_2O)_6]^{3+}$, *i.e.* $Ga(NO_3)_3$ in D_2O at pD 1. [b] At 5.88 T and 298 K in D_2O, under these conditions the aqua complex gave δ_{Ga} = 0 ppm and $\omega_{1/2}$ = 140 Hz. [Ga·AAZTA]$^-$ gives δ_{Ga} = 118 ppm and $\omega_{1/2}$ = 2220 Hz.[27b]

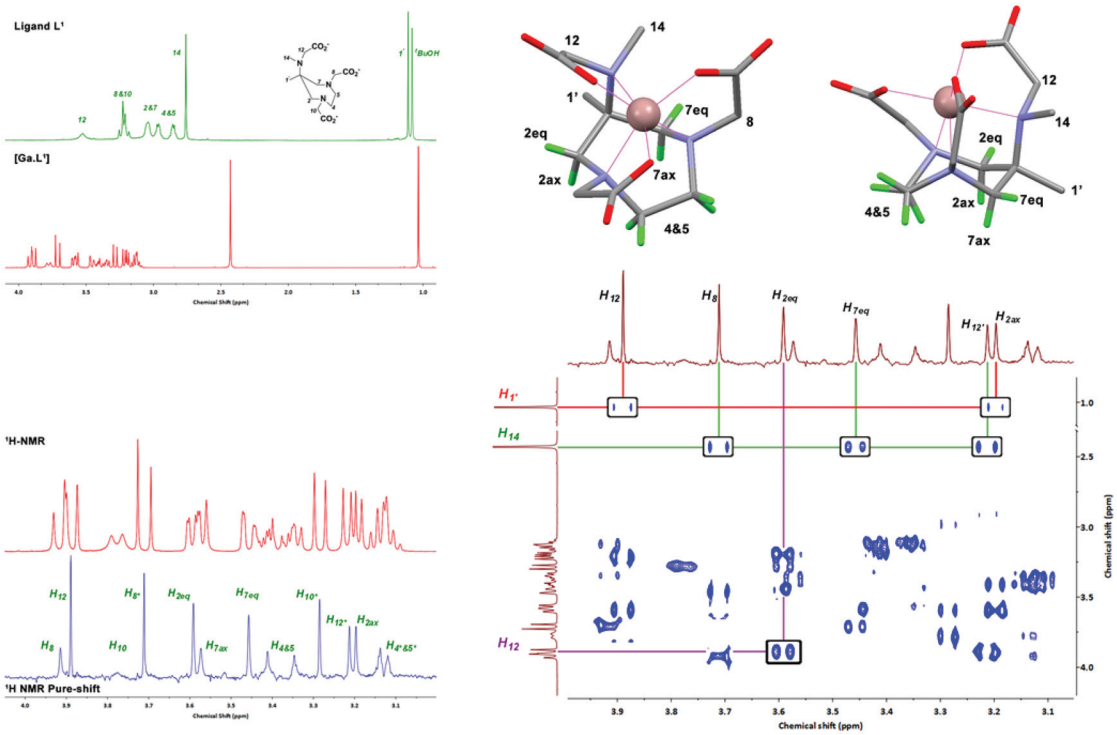


Fig. 3 NMR experiments (600 MHz, pD 6, 298 K, D_2O) used for the assignment of [Ga·L^1], with the numbering scheme used. *Top left*: comparison of the free ligand and [Ga·L^1]. *Bottom left*: expansion of the ^{1}H NMR spectrum of [Ga·L^1], and the Pureshift ^{1}H NMR spectrum with resonances assigned. *Top right*: crystal structure views of [Ga·L^1] with the protons labelled. *Bottom right*: NOESY plot with nOe correlations of interest highlighted.

together with the crystal structure of [Ga·L^1], the diastereotopic protons of H_2 and H_7 were assigned to axial and equatorial orientations, as well as their correct location, with reference to the position adopted by the N_{exo}-acetate pendant arm (Fig. 3 *top right*). The Pureshift ^{1}H NMR experiment collapses homonuclear signals into singlets (Fig. 3 *bottom left*). This significantly improves signal resolution and makes interpretation of the 2D spectra more accurate. The Pureshift ^{1}H NMR spectrum of [Ga·L^1] has been plotted as the horizontal trace of the 2D NOESY plot.

According to the 2D NOESY plot, the N_{exo}–Me group (H^{14}) shows nOe correlations with a single proton on C^7 (δ_H = 3.46 ppm), C^8 (δ_H = 3.71 ppm) and C^{12} (δ_H = 3.21 ppm). From the crystal structure, it is evident that H^{14} is closest to an equatorially orientated proton on C^7, indicating that the signal at 3.46 ppm originates from H^{7eq}. One of the protons on C^{12} (δ_H = 3.89 ppm) has an nOe correlation to a proton of C^2 (δ_H = 3.59 ppm). Similarly, this indicates that the signal at 3.59 ppm originates from H^{2eq}. Consistent with these assignments and the crystal structure, $H^{1'}$ shows an nOe correlation with the other proton on C^2 (H^{2ax}). These correlations confirm the connectivity assignments made using 2D-HSQC and -HMBC NMR experiments. It was not possible to unambiguously assign the protons of H^4 and H^5, due to the second order nature of their *AB*-multiplets. The other gallium complexes were more difficult to assign unambiguously, and the spectral assignments achieved are given in the Experimental section.

Conclusions

Solid state structures of the complexes reveal that the small Ga(III) ion is a considerably better fit for these ligands compared to the larger lanthanide ions examined previously. The conformation of the ring in each gallium complex is similar, adopting a pseudo-twisted-chair conformation. This conformation presumably has less inherent strain than the more frequently observed chair conformation, due to a more staggered arrangement of the N–CH_2–CH_2–N fragment. The C–Me substituted complexes have a less distorted octahedral geometry about the Ga(III) ion, as revealed by analysis of crystallographic and ^{71}Ga-NMR spectroscopic data. The ^{1}H NMR spectra of the complexes are characterised by well-resolved and sharp proton resonances, consistent with the adoption of a conformationally rigid solution structure in the pH range 4 to 7. The analysis of the 2D NOESY NMR of [Ga·L^1] is fully consistent with the solid-state crystal structure, showing preferential formation of a single solution species around pH 4 to 7.

This behaviour may be contrasted with that found for [Ga·AAZTA]$^-$ in solution, where three radiolabelled species of differing chemical stability with respect to dissociation were observed,[18] whose relative proportion varied with pH. The ligands defined herein form one main radiolabelled species with ^{68}Ga, for example, that resists dissociation in solution and hence are better candidates, compared to gallium complexes of AAZTA, for future imaging studies with the various gallium isotopes.

Experimental

General

NMR spectra (^{1}H, ^{13}C and ^{71}Ga) were recorded on a Varian VXR-400 spectrometer (^{1}H at 399.97 MHz, ^{13}C at 100.578 MHz), Varian VNMRS-700 spectrometer (^{1}H at 699.73 MHz, ^{13}C 175.95 MHz) or a 600 MHz Varian (Agilent) Premium Compact (^{1}H at 599.78 MHz, ^{13}C at 150.82 MHz, ^{71}Ga at 182.91 MHz). Unless otherwise stated, spectra were collected at 295 K in commercially available deuterated solvents, and referenced internally to the residual solvent proton resonances. All chemical shifts are given in ppm, with coupling constants and peak-width-at-half-heights in Hz.

Electrospray (ES) and high resolution (HS) mass spectrometry were performed on a Thermo-Finnigan LTQ FT system, operating in positive or negative mode as stated, using methanol as a carrier solvent. Ultra performance liquid chromatography (UPLC) electrospray mass spectrometry was performed on a LCT Premier XE mass spectrometer, operating in positive or negative mode as stated, equipped with an Acquity UPLC system. The Acquity photodiode array detector provides absorbance data from 210 nm to 400 nm. Carrier solvent is a methanol : water gradient (5% methanol → 95% methanol) elution, and a BEH C_{18} column (1.7 μm particle size, 2.1 × 50 mm dimensions).

Single crystal X-ray data at 120 K for GaL^{1-3} have been reported previously[18] (CCDC 906036–906038). The data for GaL^4 were collected on a Bruker Proteum-R diffractometer (Microstar rotating anode generator, Platinum-135 CCD detector, mirror-focused CuKα-radiation, λ = 1.54178 Å, ω-scans, 0.3° per frame) at 100 ± 2 K. The temperature was controlled using an Oxford Cryosystems Cobra open-flow nitrogen cryostat. The structure was solved by the direct method and refinement by full-matrix least squares on F^2 for all data using SHELXTL[30] and OLEX2[31] software. All non-hydrogen atoms were refined with anisotropic displacement parameters, all hydrogen atoms were placed into calculated positions and refined in 'riding'-mode. Due to poor quality and small size (0.26 × 0.02 × 0.01 mm^3) of the crystal no reflections were observed above STL = 0.55 and these data were omitted from the final refinement.

Details of the syntheses of the ligands have been reported previously.[18,19] Further details of ^{68}Ga radiolabelling experiments with these and related ligands will be reported elsewhere, in due course.

General procedure for the synthesis of gallium(III) complexes

The ligand (typically 0.1 mmol) was dissolved in a methanol : water (1 : 2) mixture (2 mL) and equilibrated at 60 °C. Gallium nitrate hexahydrate (1 equivalent) was added, and the pH adjusted to 4.5 using aqueous sodium hydroxide solution (0.1 M). The reaction mixture was stirred for 1 h, and allowed to cool slowly to room temperature. Single crystals of the complexes suitable for analysis by diffraction formed from solution upon standing over ~36 h at 18 °C, and were isolated at this stage in the presence of mother liquor. Crystalline material was isolated by filtration, and allowed to dry under reduced pressure. Isolated yields were typically in the range 60–90%. For ^{1}H NMR assignments, 'Pureshift'[32] ^{1}H NMR experiments were used to provide better signal resolution. The superscript '*' is used to denote proton resonances attached to the same carbon atom, when the conformation (*i.e.* axial or equatorial) could not be assigned.

[Ga·L^1]. ^{1}H NMR (D_2O, pD 6.2, 600 MHz): δ_H 1.03 (3H, s, H$^{1'}$); 2.43 (3H, s, H^{14}); 3.12 (1H, m, H$^{4*/5*}$); 3.14 (1H, m, H$^{5*/4*}$); 3.20 (1H, d, J 16, H^{2ax}); 3.21 (1H, d, J 12, H^{12*}); 3.28 (1H, d, J 16, H^{10*}); 3.35 (1H, m, H$^{4/5}$); 3.41 (1H, m, H$^{5/4}$); 3.46 (1H, d, J 16, H^{7eq}); 3.57 (1H, d, J 16, H^{7ax}); 3.59 (1H, d, J 16, H^{2eq}); 3.71 (1H, d, J 19, H^{8*}); 3.77 (1H, d, J 16, H^{10}); 3.89 (1H, d, J 12, H^{12}); 3.91 (1H, d, J 19, H^8). ^{13}C NMR (D_2O, pD 6.2, 151 MHz): δ_C 12.10 (C$^{1'}$); 37.96 (C^{14}); 53.01 (C^{14}); 58.22 (C$^{4/5}$); 59.80 (C^1); 60.41 (C^8); 61.31 (C^{10}); 63.57 (C^7); 64.00 (C^2); 174.10, 174.67, 174.82 (C^{9,11,13}). HRMS ES$^+$ (m/z): found 384.0677 [M + H]$^+$; $C_{13}H_{21}N_3O_6Ga$ requires 384.0686. Crystallographic data: $C_{12}H_{20}GaN_3O_6{\cdot}1/2H_2O$, M_r = 393.05, orthorhombic ($Fdd2$); a = 28.8536(7), b = 27.2438(7), c = 7.57981(19) Å, V = 5958.3(2) Å^3, Z = 16; μ = 1.888 mm^{-1}, $D_{calc.}$ = 1.753 mg mm^{-3}, T 120(2) K; 4319 independent reflections (R_{int} = 0.0417), R_1 = 0.0307 (4081 $I > 2\sigma(I)$), ωR_2 = 0.0674. CCDC # 906036.

[Ga·L^2]. ^{1}H NMR (D_2O, pD 6.1, 600 MHz): δ_H 1.13 (3H, d, J 7, H$^{10/13/16}$); 1.21 (3H, s, H$^{1'}$); 1.36 (3H, d, J 7, H$^{10/13/16}$); 1.46 (3H, d, J 7, H$^{10/13/16}$); 2.83 (1H, d, J 15, H^{7ax}); 2.85 (1H, m, H$^{4*/5*}$); 3.07 (1H, m, H$^{4/5}$); 3.21 (1H, m, H$^{5*/4*}$); 3.42 (2H, m, H$^{5/4\ \&\ 7eq}$); 3.63 (1H, d, J 15, H^{2eq}); 3.78–3.84 (3H, m, H^{8,11,14}). ^{13}C NMR (D_2O, pD 6.1, 151 MHz): δ_C 10.49, 14.23, 17.36 (C^{10,13,16}); 17.95 (C$^{1'}$); 41.15 (C$^{4/5}$); 46.68 (C$^{4/5}$); 49.66 (C^{14}); 56.94 (C^7); 60.64 (C^1); 64.77 (C^2); 64.44, 66.38 (C^{8,11}); 176.96, 178.42, 179.07 (C^{9,12,15}). HRMS ES$^+$ (m/z): found 412.1008 [M + H]$^+$; $C_{15}H_{25}N_3O_6Ga$ requires 412.0999.

Crystallographic data: $C_{15}H_{24}GaN_3O_6{\cdot}H_2O$, M_r = 430.11, monoclinic ($P2_1$); a = 7.58267(20), b = 12.6657(3), c = 9.2185(2) Å, β = 100.735(3)°, V = 869.85(4) Å^3, Z = 2; μ = 1.627 mm^{-1}, $D_{calc.}$ = 1.642 mg mm^{-3}, T 120(2) K; 4501 independent reflections (R_{int} = 0.0433), R_1 = 0.0322 (4125 $I > 2\sigma(I)$), ωR_2 = 0.0670. CCDC # 906037.

[Ga·L^3]. HRMS ES$^+$ (m/z): found 431.0599 [M + H]$^+$; $C_{17}H_{21}N_3O_6Ga$ requires 431.0608. Crystallographic data: $C_{17}H_{20}GaN_3O_6$, M_r = 432.08, triclinic ($P\bar{1}$); a = 10.6961(8), b = 13.0778(12), c = 12.8414(12) Å, α = 116.076(9)°, β = 105.208(7)°, γ = 92.002(2)°, V = 1652.8(2) Å^3, Z = 4; μ = 1.709 mm^{-1}, $D_{calc.}$ = 1.736 mg mm^{-3}, T 120(2) K; 7571 independent reflections (R_{int} = 0.0881), R_1 = 0.0699 (4908 $I > 2\sigma(I)$), ωR_2 = 0.1864. CCDC # 906038.

[Ga·L^4]. ^{1}H NMR (D_2O, pD 6.0, 600 MHz): δ_H 0.86 & 1.25 & 1.42 (9H, d, J 7, H^{10,13,16}); 2.94 (1H, m, H$^{4*/5*}$); 3.13 (1H, m, H$^{4*/5*}$); 3.33 (1H, m, H$^{5*/4*}$); 3.53 (1H, q, H^{14}); 3.56 (1H, m, H$^{5/4}$); 3.65 (1H, d, J 14 H$^{2*/7*}$); 3.75 (2H, d + d, H$^{7*/2*\ \&\ 7/2}$); 3.97 (2H, m, H$^{2/7\ \&\ 8*/11*}$); 4.17 (1H, d, J 16 H$^{8/11}$); 7.42 (5H, m, H$^{2',3',4'}$). ^{13}C NMR (D_2O, pD 6.0, 151 MHz): δ_C 10.69, 14.38, 16.29 (C^{10,13,16}); 46.67 (C$^{4/5}$); 50.67 (C^{14}); 55.58 (C$^{2/7}$); 58.92 (C^1); 61.04 (C$^{4/5}$); 64.34 (C$^{2/7}$); 65.79, 67.06 (C^{8,11}); 77.73 (C$^{1'}$); 126.47, 129.32, 129.96 (C$^{2',3',4'}$); 177.04 & 177.47 & 178.32

($C^{9,12,15}$). HRMS ES^+ (*m*/*z*): found 474.1149 $[M + H]^+$; $C_{20}H_{27}N_3O_6Ga$ requires 474.1156.

Crystallographic data: $C_{20}H_{26}GaN_3O_6$, M_r = 474.16, orthorhombic ($P2_12_12_1$); a = 7.3312(7), b = 13.9288(12), c = 19.6479(19) Å, V = 2006.3(3) Å^3, Z = 4; μ = 2.262 mm^{-1}, $D_{calc.}$ = 1.570 mg mm^{-3}, T 100(2) K; 2584 independent reflections (R_{int} = 0.0471), R_1 = 0.0477 (2304 $I > 2\sigma(I)$), ωR_2 = 0.1237. CCDC # 921780.

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