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High kinetic inertness of a bis-hydrated Gd-complex with a constrained AAZTA-like ligand [‡]

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Kinetic inertness is a key property for a Gd-based contrast agent. The Gd[III] complex of a cyclohexyl-fused AAZTA derivative shows the highest kinetic inertness for non-macrocyclic bis hydrated (q = 2) Gd[III]-complexes with a dissociation half-life of 91 years at physiological conditions, very close to that of macrocyclic clinically approved contrast agents. It also shows optimal relaxometric performance (r_1 = 8.3 mM^{-1}s^{-1} at 20 MHz and 25 °C) due to the presence of two inner sphere water molecules in fast exchange with bulk water and not displaced by endogenous anions.

Currently employed contrast agents (CAs) for Magnetic Resonance Imaging (MRI) are Gd[III] complexes with one coordinated water molecule (q = 1).[1] As MRI is a relatively poorly-sensitive technique, for emerging applications such as molecular imaging or cell imaging, amplification strategies have been devised for accumulation of Gd-chelates at the target site.[2] Such applications require very efficient CAs able to produce relaxation effects also at low concentration of the agent. Thus, one approach addresses the increase of the hydration state q of the metal ion that can be obtained by reducing the number of donor atoms of the chelating ligand. Several examples of high relaxivity q = 2 Gd-complexes with heptadentate cyclic and acyclic ligands have been reported.[3-5] However, high thermodynamic stability and kinetic inertness of the complexes in combination with the ability to retain two water molecules coordinated to the Gd[III] ion in physiological

media is not a trivial combination of properties to achieve. In particular, to avoid the release of toxic Gd^{3+} ions in the body, the kinetic inertness of a Gd-complex is as important as its thermodynamic stability due to the *in vivo* metal- and ligand-exchange reactions, which might occur with endogenous metal ions and /or ligands (e.g. citrate, phosphate and carbonate/bicarbonate ions).[6] Macrocyclic ligands such as DO3A and PCTA (Scheme 1) form q=2 Gd-complexes with good kinetic inertness. However, their use as CAs has been hampered by the observation that Gd(DO3A) and Gd(PCTA) form ternary complexes with bidentate anions such as lactate or bicarbonate, typically displacing one of the coordinated water molecules.[4]

AAZTA is a heptadentate polyaminocarboxylic ligand that does not fit either into the definition of macrocyclic or acyclic ligands, because it contains a medium-sized seven-membered 1,4-diazepine ring and an iminodiacetic exocyclic group.[3] Gd(AAZTA) has been thoroughly investigated in terms of its solution properties showing excellent thermodynamic stability and relaxivity, mainly as a result of the two water molecules in the inner coordination sphere of Gd[III] in rapid exchange with the bulk water.[3, 6] However, the kinetic inertness of Gd(AAZTA) ($t_{1/2}$ at pH 7.4 = 4.3 x 10^3 h), although sufficient for pre-clinical imaging studies, is far lower than that reported for the macrocyclic, clinically approved CAs and lower than macrocyclic q=2 complexes such as Gd(DO3A) ($t_{1/2}$ at pH 7.4 = 2.1 x 10^5 h).[7, 8]

It has been reported that a route to attain an enhanced stability of metal complexes consists of introducing a "structural stiffening" in the chelator by the fusion of one or more cyclohexyl rings into the ligand backbone. For example, the replacement of a 1,2-diaminoethane moiety of EDTA or DTPA by the trans-1,2-diaminocyclohexyl group (CDTA, CyPic3A and CHX-DTPA) results in the increase of the thermodynamic stability and kinetic inertness of the metal complexes formed by these ligands.[5d, 9, 10] In this context, we have recently reported the synthesis of the cyclohexane-fused CyAAZTA ligand (CyAAZTA = *trans*-3-amino-3-

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methyldecahydro-1H-1,5-benzodiazepine-N,N',N'',N'' tetraacetic acid, Scheme 1), the solution properties of its Ga^{III} and Cu^{II} complexes and the ^{68}Ga labelling for application as PET radiopharmaceutical.[11] Herein we report on the exceedingly high kinetic inertness of the bis-aqua Gd(CyAAZTA) complex.
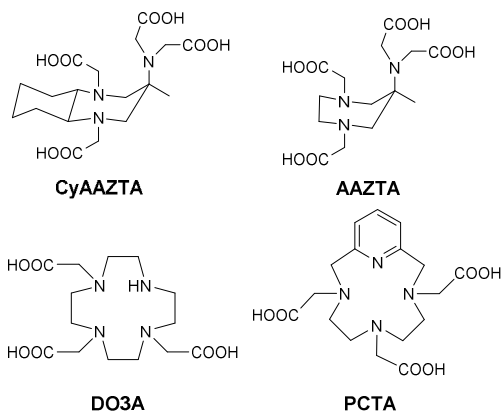

Scheme 1. Heptadentate ligands discussed in the text

The comparison of the protonation constants of CyAAZTA and AAZTA (Table S1) indicates that the total basicity values of the two ligands are very similar ($\Sigma \log K_i^H$=25.58 for CyAAZTA and 25.33 for AAZTA, measured in 0.1 M KCl and 25°C).[7] Typically, the similarity in $\Sigma \log K_i^H$ values translates into similar stability constants of the corresponding metal complexes. Unexpectedly, it has been found that the stability constants of metal complexes with CyAAZTA (Table 1 and S2) are significantly lower than those of the corresponding complexes of AAZTA. Likely, the higher thermodynamic stability of lanthanide(III) AAZTA complexes relies on its more flexible coordination cage, which can better suit the size of the metal ion.[7] The presence of the stereochemically rigid $trans$-1,2-diaminocyclohexyl moiety in the AAZTA skeleton yields a more rigid cage which does not efficiently wrap around the metal ion. Actually, CyAAZTA finds an optimal size matching around the Gd^{3+} ion with a logK$_{GdL}$ of 18.26 ± 0.02, although still two units lower than that of Gd(AAZTA). Interestingly, the trend of the $\log K_{Ln(CyAAZTA)}$ values along the lanthanide series, that increase from La^{3+} to Gd^{3+} and decrease in the second half of the series, substantially differs from that reported for Ln(AAZTA) complexes where the highest logK$_{LnL}$ was found for the smallest Lu^{3+} ion.[7] The structural rigidity of Ln(CyAAZTA) complexes is confirmed by recording the ^{1}H NMR spectra of the paramagnetic Eu- and YbCyAAZTA complexes (Figure S1 and S2) which show a number of peaks corresponding to the number of protons of the ligand. This finding highlights a rigid coordination cage that allows discrimination between axial and equatorial protons differently from that observed in case of the more flexible Eu- and Yb(AAZTA) complexes, where only nine peaks, each corresponding to a methylene or methyl group, can be detected.[3a]

The kinetic inertness of Ln^{III} complexes is generally assessed either by measuring the rate of their dissociation in very acidic conditions or by determining the rate of transmetallation reaction occurring in solution with Zn^{2+} and Cu^{2+} or Eu^{3+} ions.[12-14] In order to compare the kinetic inertness of Gd(CyAAZTA) and Gd(AAZTA), the same experimental method and conditions were used.[7] In particular, the rates of transmetallation reactions (Eq. (1)) were studied in the presence of Cu^{2+} as exchanging metal ion following the formation of CuL by spectrophotometry at 300 nm in the pH range 2.1 – 4.5 (25°C, 0.1 M KCl):

$$\text{Gd(CyAAZTA)}^- + \text{Cu}^{2+} \rightleftharpoons \text{Cu(CyAAZTA)} + \text{Gd}^{3+} \quad (1)$$
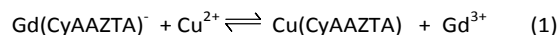
Table 1. Stability (logK$_{ML}$) and protonation (logK$_{MHiL}$, logK$_{MLH-1}$) constants of Ln(CyAAZTA) and Ln(AAZTA) complexes (25°C)

I	CyAAZTA				AAZTA[7]	
	0.1 M KCl					
	logK$_{ML}$	logK$_{MHL}^H$	logK$_{MH_2L}^H$	logK$_{MLH_{-1}}^H$	logK$_{ML}$	logK$_{MHL}^H$
La^{3+}	16.23 (2)	3.67 (2)	2.31 (3)	9.47 (3)	17.53	1.97
Eu^{3+}	18.22 (3)	3.79 (4)	1.90 (2)	9.93 (5)	19.93	1.91
Gd^{3+}	18.26 (2)	3.79 (1)	1.79 (3)	10.12 (2)	20.24	1.89
Lu^{3+}	17.67 (4)	3.86 (4)	1.67 (3)	10.06 (7)	21.85	–

Characteristic absorption spectra and the pseudo-first-order rate constants (k_d) of the Gd(CyAAZTA) – Cu^{2+} reacting system are reported in Figure 1. Interestingly, in the pH range 2.1 – 4.5, the rates are independent of the Cu^{2+} concentration ([Cu^{2+}]$_t$), indicating that the exchange reaction rates are determined by the dissociation of the Gd(CyAAZTA) complex followed by the fast reaction between the free CyAAZTA ligand and Cu^{2+} ions. On the other hand, the reaction rates increase with increasing the H$^+$ concentration (Figure 1C). In the 2.1-4.5 pH range, Gd(CyAAZTA) is present as GdL and monoprotonated Gd(HL) species; therefore, the spontaneous dissociation of GdL as well as the proton assisted dissociation of GdL and Gd(HL) are the reactions involved, characterized by the rate constants k_0, k_1 and k_2, respectively (Table 2). The definitions and equations used for the calculation of k_0, k_1 and k_2 rate constants are reported in the Supporting Information.

The most striking result shown in Table 2 is the remarkably high kinetic inertness of Gd(CyAAZTA) highlighted by the dissociation half-life of about 91 years at pH 7.4, lower only than the value reported for Gd(PCTA), but four times higher than Gd(DO3A) and more than two orders of magnitude higher than Gd(AAZTA). To the best of our knowledge, Gd(CyAAZTA) is characterized by the highest kinetic inertness in the class of the non-macrocyclic q = 2 Gd^{III}-complexes. In particular, the k_0 rate constant is very small and the spontaneous dissociation of Gd(CyAAZTA) has no contribution to the transmetallation reaction. The observed behaviour can be attributed to the rigid backbone of the CyAAZTA ligand. Moreover, the k_1 value, $i.e.$ the rate of proton-assisted dissociation of Gd(CyAAZTA), is 167 times smaller than that of Gd(AAZTA). In case of Gd(AAZTA), the acid catalyzed dissociation is assumed to occur by protonation of a –COO$^-$ group followed by proton transfer to a N-donor of the ligand that, in turn, leads to the dissociation of Gd^{3+}. The proton transfer more likely occurs when the complex is more flexible, e.g. in case of Gd(AAZTA) and Gd(DO3A) complexes, for which the dissociation occurred much faster

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than the more rigid Gd(PCTA) complex.[15] Thus, it can be assumed that the rigidity of the cyclohexyl ring fused into the seven-membered skeleton of AAZTA is responsible for a much slower proton transfer from the temporarily protonated –COOH group to the ring or exocyclic N donor atoms of CyAAZTA.

comparable molecular weight, as shown in Table 3. The experimental data, ^{1}H NMRD and ^{17}O NMR, were fitted simultaneously, according to the established theory of paramagnetic relaxation.[17-19] Information on the parameters used during the fitting procedure are given in the ESI. In Table 3 the most relevant best-fit parameters are compared to the corresponding ones of related q = 2 Gd^{3+} complexes.

Table 2. The rate constants (k), the protonation constants (K_{GdHL}), and the half-lives ($t_{1/2}$=ln2/k_d) characterizing the dissociation reactions of Gd(CyAAZTA), Gd(AAZTA),[7] Gd(DO3A),[13] Gd(PCTA)[15] and Gd(DOTA)[16] (25°C).

| I	Gd(CyAAZTA) 0.1 M KCl	Gd(AAZTA) 1.0 M KCl	Gd(DO3A) 0.1 M KCl	Gd(PCTA) 1.0 M KCl	Gd(DOTA) 0.15 M NaCl
k_0 (s[-1])	(7 ± 10)×10^{-9}	–	-2 × 10^{-9}	–	6.7 × 10^{-11}
k_1 (M[-1]s[-1])	(6.0 ± 1.0) ×10^{-3}	1.05	0.023	1.1×10^{-3}	1.8×10^{-6}
k_2 (M[-2]s[-1])	53 ± 4	–	–	6.3×10^{-4}	–
K_{GdHL} (M[-1])	6166 (pH-pot.)	233	–	1.72	14
k_d (s[-1]) pH=7.4	2.4×10^{-10}	4.0×10^{-8}	9.2×10^{-10}	4.4×10^{-11}	7.2×10^{-14}
$t_{1/2}$ (h) pH=7.4	8.0×10^{5}	4.3×10^{3}	2.1×10^{5}	4.4×10^{6}	2.7×10^{9}

The relaxivity of Gd(CyAAZTA) was measured as 8.3 and 7.9 mM[-1]s[-1] at 20 and 60 MHz, respectively (25 °C, pH = 7). These values are almost double those of clinically used Gd-based CAs, clearly indicating the presence of two water molecules in the inner coordination sphere of the metal ion. The $^{20}r_1$ value also matches very well with those of related q = 2 complexes of

Table 3. Parameters obtained from the simultaneous analysis of ^{1}H NMRD profiles and ^{17}O NMR Data (11.75 T) for the Gd[III] complexes of CyAAZTA and related ligands (AAZTA,[3a] DO3A,[4] PCTA,[4] DOTA[20]).

Parameters	Gd(CyAAZTA)	Gd(AAZTA)	Gd(DO3A)	Gd(PCTA)	Gd(DOTA)
$^{20}r_1^{298}$ (mM[-1] s^{-1})	8.3	7.1	6.0	6.9	4.7
Δ^2 (10[19] s^{-2})	1.0±0.1	2.2	4.6	5.9	1.6
τ_V^{298} (ps)	59±4	31	14	15	11
k_{ex}^{298} (10[6] s^{-1})	9.1±0.5	11.1	6.4	14.3	4.1
τ_R^{298} (ps)	97±4	74	66	70	77
q	2*	2	1.9	2	1
r (Å)	3.10*	3.10	3.15	3.10	3.13
ΔH_V (kJ/mol)	1.0*	-	1.7	3.6	1.0
$\Delta H^\#_M$ (kJ/mol)	27.8±0.6	-	44	45	49.8
$A_O/\hbar$ (10[6] rad/s)	-3.8±0.2	-3.8	-3.8	-3.8	-3.7

* Values fixed in the fitting.
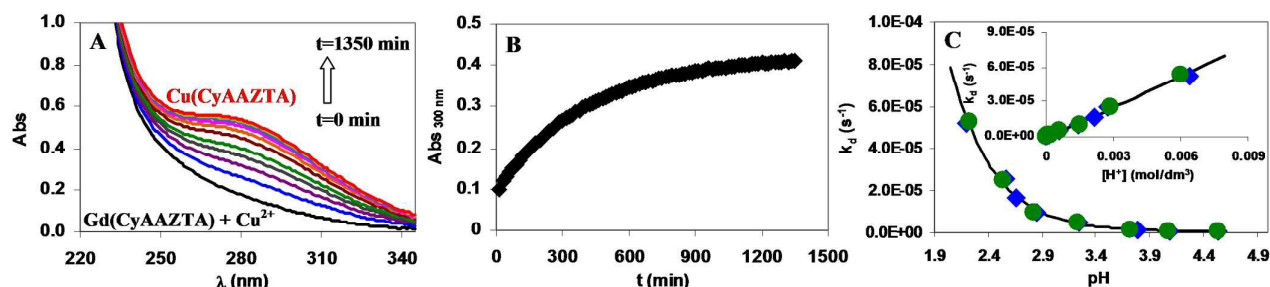
Figure 1. Absorption spectra (A), absorbance values at 300 nm (B) and the k_d pseudo-first-order rate constants (C) of Gd(CyAAZTA) – Cu^{2+} reacting system (A and B: [Gd(CyAAZTA)] = 0.2 mM, [Cu^{2+}] = 0.5 mM, [dichloroacetic acid] = 0.01 M, pH = 2.1, l = 0.874 cm; C: [Gd(CyAAZTA)] = 0.2 mM, [Cu^{2+}]$_t$ = 4 (♦) and 8 mM (●); 0.1 M KCl, 0.1 M KCl, 25°C)
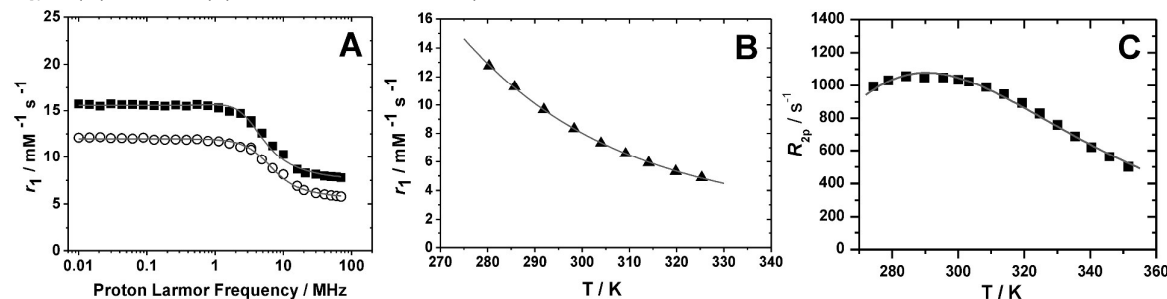
Figure 2. (A) 1/T_1 ^{1}H NMRD relaxation data for Gd(CyAAZTA) at pH = 7.4, 25 °C (■); 310 K (○). The solid lines represent the best results of the fitting to the experimental points (see Table 3); (B) Temperature dependence of the longitudinal water proton relaxivity at 20 MHz and pH = 7; (C) Temperature dependence of the transverse water ^{17}O NMR relaxation rates at 11.75 T and pH = 7 for a 20.2 mM solution of Gd(CyAAZTA).

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The slightly slower k_{ex} with respect to Gd(AAZTA) is in contrast to the data reported for other cyclohexyl-fused $q = 2$ Gd^{III}-complexes, Gd(CyPCTA)[21] and Gd(CyPic3A),[3d] where the water residence lifetime at 37 °C is quite short (34 and 14 ns, respectively). In case of Gd(CyPCTA), a steric crowding around the Gd^{3+} ion was supposed to lead to an increase of the k_{ex}.[21] In the case of Gd(CyAAZTA), one can surmise that the cyclohexyl ring does not interfere with the positions occupied by the inner sphere water molecules and their exchange process.

Gd(CyAAZTA) behaves similarly to Gd(AAZTA) in terms of reluctance to form ternary complexes with bidentate oxoanions of biological relevance. In fact, the titrations with increasing amount of lactate, citrate and phosphate did not show any displacement of water molecules up to more than 100-fold molar excess of oxoanion (10-fold excess for phosphate, Fig. S4 and S5) at neutral pH. In addition, the invariance of r_1 in a large pH range (pH 3-11) highlighted that carbonate anions dissolved in the aerated aqueous solution did not coordinate Gd^{3+} replacing the bound water molecules (Fig. S6). A further demonstration of the stability of Gd(CyAAZTA) was obtained by measuring the r_1 value in Seronorm™ over time, to simulate physiological conditions. The r_1 value of a 1.0 mM solution of the complex in Seronorm™ was measured at 20 MHz and 298K over a period of 96 h and no changes were detected (Fig. S7). This result presents a clear evidence of the stability of the complex in a simulated physiological environment. Moreover, it is worth noting that the r_1 value is 10.5 $mM^{-1}s^{-1}$ in serum (20 MHz, 298K), more than 25% higher than that in pure water. This suggests a weak interaction of the cyclohexyl ring of CyAAZTA with Human Serum Albumin, the most abundant protein in blood plasma. To confirm this observation, the R_1 value of Gd(CyAAZTA) was measured as a function of increasing concentration of HSA (Fig. S8), with the aim to assess the binding parameters. Thus, from the resulting fitted curve, a K_A of 420 M^{-1} has been obtained.

Finally, a T_1-weighted MRI phantom image of Gd(CyAAZTA) solutions with increasing concentration was obtained at 7 Tesla (298 K) and compared with pure water (Figure 3). The data clearly demonstrate an increasing signal enhancement with respect to the control sample, thus confirming relaxometric results.

In conclusion, a constrained Gd(AAZTA)-like derivative in which the ethylene bridge of the 1,4-diazepine ring is replaced by a cyclohexylene bridge, was shown to have extremely good kinetic stability that makes it directly comparable with macrocyclic systems (Figure 4). The $t_{1/2}$ value of Gd(CyAAZTA) is the highest for non-macrocyclic $q = 2$ Gd^{III}-complexes.

Moreover, the relaxometric properties do not substantially change with respect to those of the already optimal Gd(AAZTA) complex (fast water exchange rate, high relaxivity, no displacement of coordinated water molecules by endogenous anions), making this complex a promising candidate for the preparation of efficient MRI contrast agents.
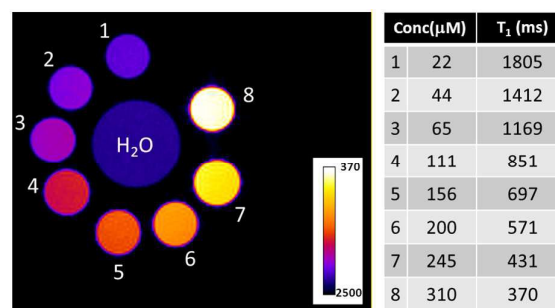

	Conc(μM)	T_1 (ms)
1	22	1805
2	44	1412
3	65	1169
4	111	851
5	156	697
6	200	571
7	245	431
8	310	370

Figure 3. T_1 weighted multislice spin-echo phantom MR-image (TR=200) for solutions of Gd(CyAAZTA) at 298 K and 7 T (300 MHz).
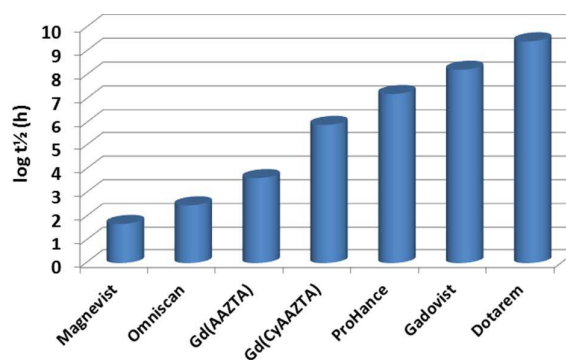

Figure 4. Dissociation half-life measured at pH=7.4 and 25 °C of Gd(CyAAZTA) compared to Gd(AAZTA)[7] and other clinically approved contrast agents.[16,22]

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