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Thermodynamic and structural properties of Gd(III) complexes with polyamino-polycarboxylic ligands: basic compounds for the development of MRI contrast agents

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Contents

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Abstract

The main purpose of this review is to collect equilibrium data in aqueous solution and structural properties in the solid state for significant examples of Gd(III) complexes with both acyclic and macrocyclic polyamino-polycarboxylic ligands. The intent is to determine the ligand characteristics which contribute to the complexes' stability. Several aspects connected with the use of similar Gd(III) complexes as contrast agents in nuclear magnetic resonance imaging are also considered.

Keywords: Gadolinium; Contrast agents; Imaging; Lanthanides; Complexation thermodynamics

1. Introduction

Nuclear magnetic resonance imaging (MRI) has become a powerful tool for clinical diagnostics thanks both to the progress of the relevant technology and the development of a new class of pharmaceuticals administered to patients to enhance the contrast between normal and diseased tissues. Such contrast agents are mostly based on metal complexes of paramagnetic metal ions, since they enhance the relaxivity of water protons, the main factor determining the intensity of the ^{1}H-NMR image [1–5]. In this context, complexes of Fe(III), Gd(III) and Mn(II) have received the greatest interest because of their high magnetic moments and relaxation efficiency.

To date, several Gd(III) complexes are the active constituents of pharmaceuticals employed as contrast agents in clinical MRI diagnostics. The first human MRI study employing a Gd(III) complex was reported in 1984 by Carr et al., who made use of the $[Gd(DTPA)]^{2-}$ (DTPA = diethylentriaminepentacetic acid) complex to identify the presence of cerebral tumors [6]. This complex has been the only contrast agent available for many years until a few other polyamino-polycarboxylic complexes, such as [Gd(HP-DO3A)], $[Gd(DOTA)]^{-}$ and $[Gd(BOPTA)]^{2-}$ (HP-DO3A = 10-(hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, DOTA = 1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid, BOPTA = 4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oic acid (see Tables 1 and 2 for ligand drawings), were recognized to be of practical use in clinical diagnostics [7].

Free Gd(III) ion is extremely toxic at the concentrations needed for MRI studies, for this reason it must be administered in the form of stable complexes, unable to release the metal ion before excretion. Furthermore, the use of synthetic ligands offers an additional advantage consisting of the possibility to prepare specific contrast agents that accumulate in target tissues or a physiological district. For these purposes a large number of existing ligands have been studied and many others have been expressly designed and synthesized. Among these ligands, polyamino-polycarboxylic compounds have proven useful in forming Gd(III) complexes characterized by efficient relaxivity properties, high thermodynamic stability and acceptable toxicity.

In this review we focus our attention on the thermodynamic [8–116] and structural [36,83,93,117–123] properties of significant examples of Gd(III) complexes with polyamino-polycarboxylic ligands, and a few derivatives containing ethereal and alcoholic functions, in order to define the ligand characteristics which determine the complex stability. As discussed later on, the toxicity of these complexes, and consequently their applicability as contrast agents, is strictly connected with their thermodynamic stability in aqueous solution. Accordingly, only thermodynamic data obtained in aqueous solution will be considered.

Although many other ligands have been considered for Gd(III) complexation we have restricted our review to these compounds which represent the substrate for the evolution of metal-containing contrast agents.

The nomenclature of the ligands reported in this review is rather cumbersome. For this reason the first time a ligand is encountered in the text we shall use the IUPAC name and/or a progressive numerical designation corresponding to the structural formula reported in the tables of thermodynamic data. In the tables we have also included some simplified names used for the ligands. In some cases such names have also been used in the text.

An apology is offered to those authors whose work has been inadvertently omitted.

2. Complex stability and complex toxicity

The toxic effects of metal complexes administered to patients principally stem, apart from the intrinsic toxicity of the complex itself, from the free metal ion and the free ligand released before excretion. As shown in Table 1, where the acute

Table 1
Acute LD_{50} values for uncomplexed Gd(III), free ligands and Gd(III) complexes

Compound	LD_{50} (mmol kg^{-1})	Animal	Route of administration[a]	Ref.
$GdCl_3$	0.5	Rat	iv	[124]
	0.4	Mice	iv	[125,126]
$Gd(OH)_3$	0.1	Mice	iv	[125,126]
$(Meg)_3H_2DTPA$[b]	0.15	Mice	iv	[126]
Na_2H_3DTPA	0.1	Mice	iv	[125]
$(Meg)_2H_2DOTA$	0.18	Mice	iv	[126]
Meg[Gd(EDTA)]	0.3	Rat	iv	[124]
$(Meg)_2$[Gd(DTPA)]	6–10	Rat	iv	[124,127]
Na_2[Gd(DTPA)]	5.6	Rat	iv	[131]
Meg[Gd(DOTA)]	11	Mice	iv	[127]
Na[Gd(DOTA)]	>10	Mice	iv	[126]
[Gd(HP-DO3A)]	12	Mice	iv	[127]
$(Meg)_2$[Gd(BOPTA)]	5.8	Mice	iv	[128]

[a] Route of administration: iv = intravenous.
[b] Meg = *N*-methylglucamine.

LD_{50} values (lethal dose for 50% of test animals) for some Gd(III) complexes are compared with the analogous values for free metal ion and ligands, metal complexes are commonly less toxic than uncoordinated Gd(III) and ligands. This is due to the fact that the toxicity of both metal ion and ligands is determined by their ability to bind to biological substrates, interfering in vital processes; by neutralizing to a large extent their binding properties, complexation reduces their toxicity. Accordingly, a high thermodynamic stability is commonly associated with a low toxicity for these Gd(III) complexes. However, the toxicity of these metal complexes depends on the variety of competitive equilibria that arise in vivo, such as ligand protonation, transmetallation reactions involving endogenous metal ions, binding of Gd(III) by endogenous ligands, precipitation of insoluble Gd(III) compounds [113,129–131], in addition to the alteration of physiological functions brought about by the administration of compounds which may affect the viscosity and the osmolality of physiological fluids.

For example both $[Gd(EDTA)]^-$ and $[Gd(DTPA)]^{2-}$ complexes (EDTA = ethylenediaminetetraacetic acid) are characterized by very high thermodynamic stability ($\log K = 17.35$ and $\log K = 22.55$, respectively [116]), but the EDTA complex displays very high toxicity, the same as free Gd(III), as denoted by the LD_{50} values reported in Table 1, in contrast to $[Gd(DTPA)]^{2-}$, one of the less toxic compounds of this class. This behavior can be predicted by considering the main equilibria involving these complexes in serum, accounting for an almost complete dissociation of $[Gd(EDTA)]^-$ in this medium [1]. This example seems to suggest that only Gd(III) complexes with stability constants higher than $[Gd(DTPA)]^{2-}$ are worth screening, although there are complexes more stable, but more toxic, that $[Gd(DTPA)]^{2-}$. This is the case, for instance, for the $[Gd(TTHA)]^{3-}$ complex (TTHA = triethylenetetraaminehexaacetic acid), whose higher toxicity has been ascribed to its larger osmolality [86]. Hence, simple rules merely based on complex stability constants are not of general validity, although they have been of great importance in promoting the synthesis of target ligands.

Actually, the research groups presently involved in the study of MRI contrast agents based on Gd(III) complexes do not disregard complexes with stability constants even smaller than that of $[Gd(DTPA)]^{2-}$. This is due both to thermodynamic and kinetic considerations. Effectively, it is of fundamental importance that a Gd(III)-containing contrast agent remains associated during the time it resides in the body, and hence, its applicability can be determined by kinetic as well as by thermodynamic factors. Obviously the better situation is represented by a complex of very high thermodynamic stability and marked dissociation inertness. To this purpose the present search for new contrast agents is largely devoted to metal complexes with macrocyclic ligands, which are known to combine the properties of high thermodynamic and kinetic complex stability.

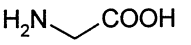
3. General information about the determination of equilibrium data

A problem which is generally encountered in compiling a collection of thermodynamic equilibrium data is that the data are difficult to compare because they come from different sources and have been obtained under different experimental

Table 2
Equilibrium constants for protonation and Gd(III) complexation reaction with acyclic polyamino-polycarboxylic ligands[a]

Aminoacetic acid

glycine

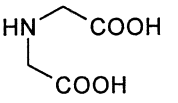


HL **L1**

Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^- + H^+ = LH^+$	9.75	pot.			35	0.1 KNO_3	13
	9.57	pot.			25	0.1 $NaClO_4$	14
$LH^+ + H^+ = LH_2^+$	2.50	pot.			35	0.1 KNO_3	13
	2.36	pot.			25	0.1 $NaClO_4$	14
$Gd^{3+} + L^- = GdL^{2+}$	3.72	pot.			35	0.1 KNO_3	13
	0.73	pot.			25	0.1 $NaClO_4$	14
	4.0	pot.			25	0.1	15
	3.4	pot.			25	0.1	15
	3.3	pot.			25	0.1	15
$Gd^{3+} + 2L^- = GdL_2^+$	6.5	pot.			25	0.1	15

Iminodiethanoic acid, Iminodiacetic acid

IDA, IMDA



H_2L **L2**

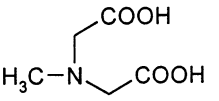
Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{2-} + H^+ = LH^-$	9.33	pot.			25	0.1 KNO_3	17
$LH^- + H^+ = LH_2$	2.58	pot.			25	0.1 KNO_3	17
$Gd^{3+} + L^{2-} = GdL^+$	6.78	pot.			25	0.2 $NaClO_4$	16

Table 2 (*Continued*)

	6.68	pot.		25	0.1 KNO_3	17
	7.02	pot.		25	0.1 KCl	18
$GdL^+ + L^{2-} = GdL_2^-$	5.53	pot.		25	0.2 $NaClO_4$	16
	5.39	pot.		25	0.1 KNO_3	17

N-Methyliminodiacetic acid

MIDA,MIMDA

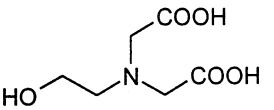


H_2L **L3**

Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$Gd^{3+} + L^{2-} = GdL^+$	6.68	pot.			25	0.1 KCl	26
	7.02	pot.			25	0.1 KCl	32
$GdL^+ + L^{2-} = GdL_2^-$	5.30	pot.			25	0.1 KCl	26
	5.55	pot.			25	0.1 KCl	32
$Gd^{3+} + 3L^{2-} = GdL_3^-$	14.82	pot.			25	0.1 KCl	26
$Gd^{3+} + L^{2-} + 2OH^- =$ $GdL(OH)_2^-$	16.56	pot.			25	0.1 KCl	26

N-(2-Hydroxyethyl)iminodiacetic acid

HIDA, HIMDA



H_2L **L4**

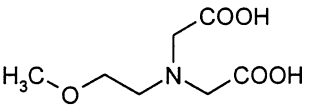
Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{2-} + H^+ = LH^-$	8.57	pot.			25	0.1 KCl	19
	8.72	pot.			25	0.1 KNO_3	20
$LH^- + H^+ = LH_2$	2.25	pot.			25	0.1 KCl	19
	1.91	pot.			25	0.1 KNO_3	20
$Gd^{3+} + L^{2-} = GdL^+$	9.01	pot.			25	0.1 KNO_3	20
	9.0	distr.			20	0.1 $NaNO_3$	21
$GdL^+ + L^{2-} = GdL_2^-$	8.04	pot.			25	0.1 KNO_3	20

Table 2 (*Continued*)

	7.95	distr.			20	0.1 $NaNO_3$	21
$Gd^{3+} + 2L^{2-} = GdL_2^-$	16.08	pol.					19

N-(2-Methoxyethyl)iminodiacetic acid

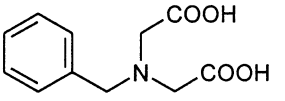
H_2L **L5**



Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{2-} + H^+ = LH^-$	8.95				25	0.1	22
$LH^- + H^+ = LH_2$	2.18				25	0.1	22
$Gd^{3+} + L^{2-} = GdL^+$	7.88				25	0.1	22
$Gd^{3+} + 2L^{2-} = GdL_2^-$	15.51				25	0.1	22

N-Benzyliminodiacetic acid

H_2L **L6**

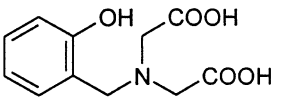


Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$Gd^{3+} + L^{2-} = GdL^+$	7.04	pot.			25	0.1 KCl	32
$GdL^+ + L^{2-} = GdL_2^-$	5.75	pot.			25	0.1 KCl	

N-(2-Hydroxybenzyl)iminodiacetic acid

HBIDA

H_3L **L7**



Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{3-} + H^+ = LH^{2-}$	11.94	sp.			25	0.1 KNO_3	25
$LH^{2-} + H^+ = LH_2^-$	8.15	pot.			25	0.1 KNO_3	25
$LH_2^- + H^+ = LH_3$	2.34	pot.			25	0.1 KNO_3	25

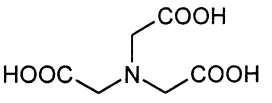
Table 2 (*Continued*)

$Gd^{3+} + L^{3-} = GdL$	13.55	pot.		25	0.1 KNO_3	25
$Gd^{3+} + 2L^{3-} = GdL_2^{3-}$	24.13	pot.		25	0.1 KNO_3	25
$Gd^{3+} + LH^{2-} = GdLH^{+}$	5.82	pot.		25	0.1 KNO_3	25
$Gd^{3+} + 2LH^{2-} = Gd(LH)_2^{-}$	12.23	pot.		25	0.1 KNO_3	25

Nitrilotriethanoic acid

NTA

H_3L **L8**

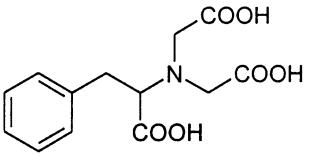


Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{3-} + H^{+} = LH^{2-}$	9.75	pot.	-19.6	36.0	25	0.1 KNO_3	27
	9.57	pot.	-24.2	30.4	25	0.5 KNO_3	28
	9.76 (2)[a]	pot.			25	0.1 $TMANO_3$	116
$LH^{2-} + H^{+} = LH_2^{-}$	2.64	pot.			25	0.5 KNO_3	28
	2.56 (3)	pot.			25	0.1 $TMANO_3$	116
$LH_2^{-} + H^{+} = LH_3$	1.57	pot.			25	0.5 KNO_3	28
	1.68 (8)	pot.			25	0.1 $TMANO_3$	116
$Gd^{3+} + L^{3-} = GdL$	11.54	pot.	4.3	70.1	25	0.1 KNO_3	27
	11.11	pot.	-3.9 cal.	59.5	25	0.5 $NaClO_4$	28
	11.63 (2)	pot.			25	0.1 $TMANO_3$	116
	11.43	pol.			20	0.1 KNO_3	29
	11.43	pot.			20	0.1 KCl	30
	11.43	pol.			20	0.1 KNO_3	31
$GdL + L^{3-} = GdL_2^{3-}$	9.26	pot.	-24.3	28.5	25	0.1 KNO_3	27
	9.18 (9)	pot.			25	0.1 $TMANO_3$	116
	9.36	pot.			20	0.1 KCl	30

Table 2 (*Continued*)

DL-2-Benzylnitrilotriacetic acid

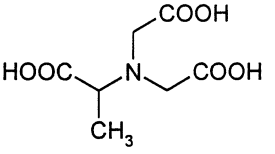
H_3L **L9**



Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$GdL + L^{3-} = GdL_2^{3-}$	8.97	pot.			25	0.1 KCl	32

DL-2-Methyl-alanine-N,N-diacetic acid

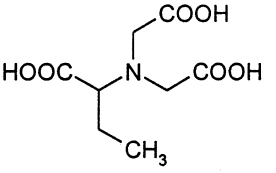
H_3L **L10**



Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$GdL + L^{3-} = GdL$	12.24	pot.			20	0.1 KNO_3	33

DL-2-Ethyl-alanine-N,N-diacetic acid

H_3L **L11**

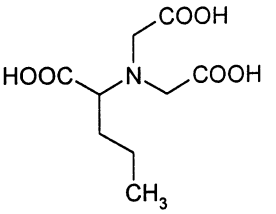


Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$GdL + L^{3-} = GdL$	11.25	pot.			20	0.1 KNO_3	33

Table 2 (*Continued*)

DL-2-Propyl-alanine-N,N-diacetic acid

H_3L **L12**

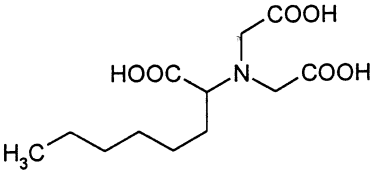


Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$GdL + L^{3-} = GdL$	10.99	pot.			20	0.1 KNO_3	33

L-2-Hexylnitrilotriacetic acid (2-aminohexanoic-N,N-diacetic acid)

KaDA

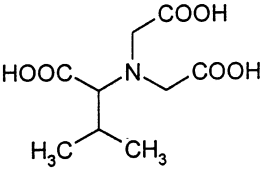
H_3L **L13**



Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{3-} + H^+ = LH^{2-}$	10.08	pot.			20	0.1 KNO_3	24
$LH^{2-} + H^+ = LH_2^-$	2.51	pot.			20	0.1 KNO_3	24
$LH_2^- + H^+ = LH_3$	1.9	pot.			20	0.1 KNO_3	24
$Gd^{3+} + L^{3-} = GdL$	11.08	pol.			20	0.1 KNO_3	24

DL-2-(2-Propyl)-valine-N,N-diacetic acid

H_3L **L14**

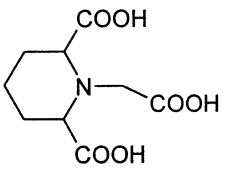


Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$GdL + L^{3-} = GdL$	9.53	pot.			20	0.1 KNO_3	33

Table 2 (*Continued*)

2,6-Dicarboxypiperidineacetic acid

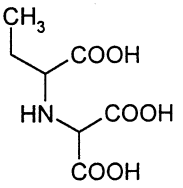
H_3L **L15**



Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{3-} + H^+ = LH^{2-}$	9.33	pot.			25	0.1 KNO_3	34
$LH^{2-} + H^+ = LH_2^-$	2.71	pot.			25	0.1 KNO_3	34
$LH_2^- + H^+ = LH_3$	1.3	pot.			25	0.1 KNO_3	34
$Gd^{3+} + L^{3-} = GdL$	10.66	pot.			25	0.1 KNO_3	34
$GdL + L^{3-} = GdL_2^{3-}$	7.96	pot.			25	0.1 KNO_3	34

DL-2-Carboxy-2'-ethliminodiacetic acid (1-carboxypropyl-aminomalonic acid)

H_3L **L16**



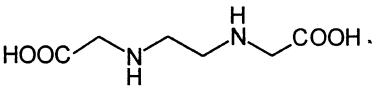
Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{3-} + H^+ = LH^{2-}$	9.05	pot.			25	0.1 KNO_3	23
$LH^{2-} + H^+ = LH_2^-$	3.75	pot.			25	0.1 KNO_3	23
$LH_2^- + H^+ = LH_3$	1.9	pot.			25	0.1 KNO_3	23
$Gd^{3+} + L^{3-} = GdL$	8.71	pot.			25	0.1 KNO_3	23

1,2-Diaminoethane-N,N'-diethanoic acid

1,2-bis(carboxymethylamino)-ethane

Ethylenediamine-N,N'-diacetic acid

EDDA



H_4L **L17**

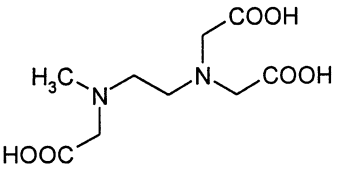
Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.

Table 2 (*Continued*)

$L^{2-} + H^+ = LH^-$	9.57	pot.			25	0.1 KNO_3	87
	9.69	pot.			25	1.0 $NaClO_4$	88
$LH^- + H^+ = LH_2$	6.48	pot.			25	0.1 KNO_3	87
$LH_2 + H^+ = LH_3^+$	2.37	pot.			25	1.0 $NaClO_4$	88
$LH_3^+ + H^+ = LH_4^{4+}$	1.66	pot.			25	1.0 $NaClO_4$	88
$Gd^{3+} + L^{2-} = GdL^+$	8.13	pot.			25	0.1 KNO_3	87
$GdL^+ + L^{2-} = GdL^-$	6.08	pot.			25	0.1 KNO_3	87
$Gd^{3+} + L^{2-} = GdL^+$			-8.9 cal.	38	25	1.0 $NaClO_4$	88
$GdL^+ + L^{2-} = GdL^-$			-16 cal.	20	25	1.0 $NaClO_4$	88

N-Methylethylenedinitrilo-N,N',N',-triacetic acid

MEDTA



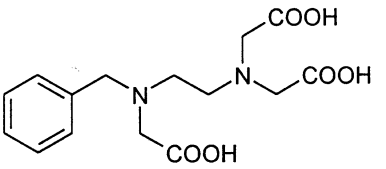
H_3L **L18**

Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{3-} + H^+ = LH^{2-}$	10.31	pot.	-31.2 cal.	28	25	0.1 KNO_3	60, 61
	10.19	pot.	-36.1 cal.	22	25	0.5 $NaClO_4$	61
$LH^{2-} + H^+ = LH_2^-$	5.42	pot.	-10.92 cal.	20	25	0.1 KNO_3	60, 61
	5.55	pot.	-13.5 cal.	18	25	0.5 $NaClO_4$	61
$LH_2^- + H^+ = LH_3$	2.45	pot.	2.6 cal.	17	25	0.1 KNO_3	60, 61
	2.40	pot.	2.76 cal.	16	25	0.5 $NaClO_4$	61
$LH_3 + H^+ = LH_4^+$	1.93	pot.	1.8 cal.	13	25	0.1 KNO_3	60, 61
	1.72	pot.	2.9 cal.	13	25	0.5 $NaClO_4$	61
$Gd^{3+} + L^{3-} = GdL$	12.98	pot.	-4.3 cal.	70	25	0.1 KNO_3	60, 61
	12.63	cal.	-11.3 cal.	61	25	0.5 $NaClO_4$	61

Table 2 (*Continued*)

N'-Benzylethylenedinitrilo-N,N,N'-triacetic acid

N-Benzyldiaminoethane-N,N',N'-triethanoic acid



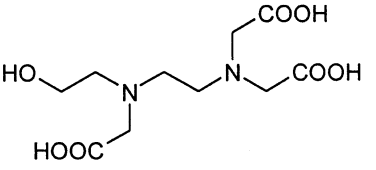
H_3L **L19**

Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{3-} + H^+ = LH^{2-}$	10.08	pot.			25	0.1 KNO_3	66
	10.150 (3)	pot.			25	0.1 $TMANO_3$	116
$LH^{2-} + H^+ = LH_2^-$	5.24	pot.			25	0.1 KNO_3	66
	5.228 (5)	pot.			25	0.1 $TMANO_3$	116
$LH_2^- + H^+ = LH_3$	2.54	pot.			25	0.1 KNO_3	66
	2.531 (8)	pot.			25	0.1 $TMANO_3$	116
$LH_3^- + H^+ = LH_4^+$	1.67	pot.			25	0.1 KNO_3	66
	1.94 (2)	pot.			25	0.1 $TMANO_3$	116
$Gd^{3+} + L^{3-} = GdL$	12.40	pot.			25	0.1 KNO_3	66
	12.581 (8)	pot.			25	0.1 $TMANO_3$	116
$GdL + H^+ = GdLH^+$	2.35 (8)	pot.			25	0.1 $TMANO_3$	116

N-(Hydroxyethyl)diaminoethane-N,N',N'-triethanoic acid

N-(Hydroxyethyl)diaminoethane-N,N',N'-triacetic acid

HEDTA



H_3L **L20**

Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{3-} + H^+ = LH^{2-}$	9.90	pot.	-28.0 cal.	28.5	25	0.5 KNO_3	28
	9.93	pot.	-30.5	26	25	0.1 KNO_3	44
	10.09	pot.			20	0.1	45

Table 2 (*Continued*)

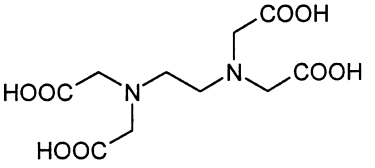
$LH^{2-} + H^+ = LH_2^-$	5.54	pot.			25	0.5 KNO_3	28
	5.37	pot.	-11.8	19	25	0.1 KNO_3	44
	5.50	pot.			20	0.1	45
$LH_2^- + H^+ = LH_3$	2.83	pot.			25	0.5 KNO_3	28
	2.39	pot.	1.4	15	25	0.1 KNO_3	44
	3.23	pot.			20	0.1	45
$Gd^{3+} + L^{3-} = GdL$	14.80	pot.	-29.5 cal.	54.9	25	0.5 $NaClO_4$	28
	15.22	pot.	-19.5	67	25	0.1 KNO_3	44
	15.44	pot.			20	0.1	45
	15.10	pot.			25	0.1 KNO_3	46
	14.4	pol.			25	0.1 KNO_3	46

1,2-Diaminoethane-N,N,N',N'-tetraethanoic acid

Ethylenedinitrilotetraacetic acid

Eethylenediaminetetraacetic acid

EDTA



H_4L **L21**

Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	10.26	pot.			20	0.1 KNO_3	35
	10.05	pot.	-7.0 cal.	50.3	25	0.5 KNO_3	28
	10.11	pot.			25	0.1 $TMANO_3$	36
	9.42	pot.			25	0.1 NaCl	36
	10.08	pot.			25	0.1 KCl	36
	10.30 (1)	pot.			25	0.1 $TMANO_3$	116
$LH^{3-} + H^+ = LH_2^{2-}$	6.16	pot.			20	0.1 KNO_3	35
	6.26	pot.	-5.4 cal.	30.3	25	0.5 KNO_3	28
	6.19	pot.			25	0.1 $TMANO_3$	36
	6.22	pot.			25	0.1 NaCl	36
	6.42	pot.			25	0.1 KCl	36
	6.09 (1)	pot.			25	0.1 $TMANO_3$	116
$LH_2^{2-} + H^+ = LH_3^-$	2.67	pot.			20	0.1 KNO_3	35
	2.68	pot.			25	0.5 KNO_3	28

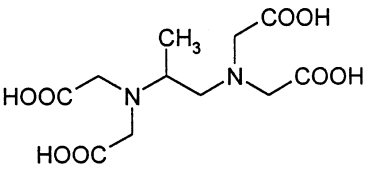
Table 2 (*Continued*)

	2.87	pot.			25	0.1 $TMANO_3$	36
	2.88	pot.			25	0.1 NaCl	36
	3.11	pot.			25	0.1 KCl	36
	2.81 (1)	pot.			25	0.1 $TMANO_3$	116
$LH_3^- + H^+ = LH_4$	1.99	pot.			20	0.1 KNO_3	35
	1.89	pot.			25	0.5 KNO_3	28
	2.26	pot.			25	0.1 $TMANO_3$	36
	2.19	pot.			25	0.1 NaCl	36
	2.33	pot.			25	0.1 KCl	36
	2.07 (1)	pot.			25	0.1 $TMANO_3$	116
$Gd^{3+} + L^{4-} = GdL^-$	16.28	pot.	-22.9 cal.	70	25	0.5 $NaClO_4$	28
	17.1	pot.			20	0.1 KCl	35
	17.37	pol.			20	0.1 KNO_3	35
	17.7	sp.			25	0.1 TMACl	36
	17.35 (1)	pot.			25	0.1 $TMANO_3$	116
	16.70	pot.			20	0.1 KCl	37
	17.12	pot.			20	0.01	38
	16.82	ion exc.			25	0.1 KCl	39
	17.60	distr.			25		40
	16.59	distr.			25		40
	17.35				25	0.1	41
	17.32						42

DL-(Methylethylene)dinitrilotetraacetic acid

1,2-Diaminopropane-N,N,N',N'-tetraethanoic acid

PDTA



H_4L **L22**

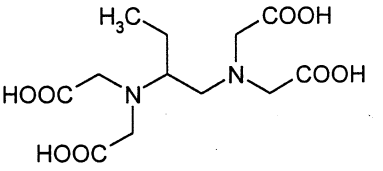
Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$Gd^{3+} + L^{4-} = GdL^-$	18.21	pol.			25	0.1 KNO_3	48

Table 2 (*Continued*)

(Ethylethylene)dinitrilotetraacetic acid

1,2-Diaminobutane- N,N,N',N'-tetraethanoic acid

DBUTA



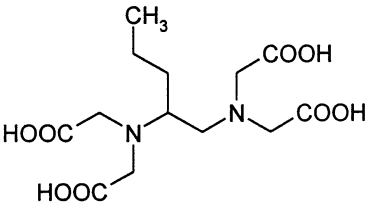
H_4L **L23**

Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$Gd^{3+} + L^{4-} = GdL^-$	18.56	pol.			20	0.1 KNO_3	54

(Propylethylene)dinitrilotetraacetic acid

1,2-diaminopentane- N,N,N',N'-tetraethanoic acid

PEDTA



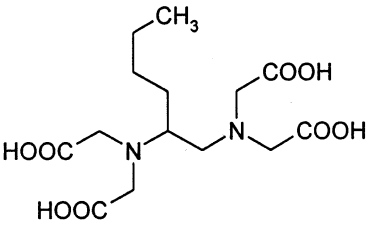
H_4L **L24**

Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$Gd^{3+} + L^{4-} = GdL^-$	18.53	pol.			20	0.1 KNO_3	56

(Buthylethylene)dinitrilotetraacetic acid

1,2-diaminohexane- N,N,N',N'-tetraethanoic acid

HEDTA



H_4L **L25**

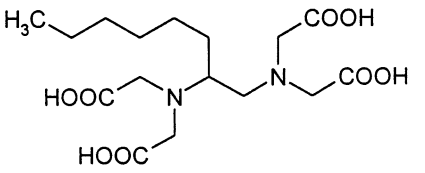
Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$Gd^{3+} + L^{4-} = GdL^-$	18.47	pol.			20	0.1 KNO_3	56

Table 2 (*Continued*)

(Hexylethylene)dinitrilotetraacetic acid

1,2-diaminooctane- N,N,N',N'-tetraethanoic acid

ODTA



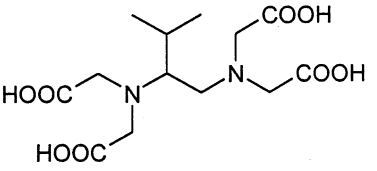
H_4L **L26**

Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	10.95	pot.			20	0.1 KNO_3	57
$LH^{3-} + H^+ = LH_2^{2-}$	6.05	pot.			20	0.1 KNO_3	57
$LH_2^{2-} + H^+ = LH_3^-$	2.98	pot.			20	0.1 KNO_3	57
$LH_3^- + H^+ = LH_4$	2.28	pot.			20	0.1 KNO_3	57
$Gd^{3+} + L^{4-} = GdL^-$	18.43	pol.			20	0.1 KNO_3	57

(2-Propylethylene)dinitrilotetraacetic acid

3-Methyl-1,2-diaminobutane- N,N,N',N'-tetraethanoic acid

IPDTA



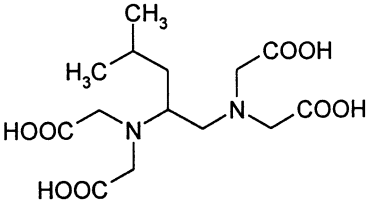
H_4L **L27**

Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$Gd^{3+} + L^{4-} = GdL^-$	18.44	pol.			20	0.1 KNO_3	55

(2-Methylpropylethylene)dinitrilotetraacetic acid

4-Methyl-1,2--Diaminopentane- N,N,N',N'-tetraethanoic acid

IHDTA



H_4L **L28**

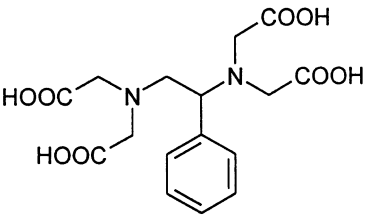
Table 2 (*Continued*)

Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$Gd^{3+} + L^{4-} = GdL^-$	18.48	pol.			20	0.1 KNO_3	54

DL-(Phenylethylene)dinitrilotetraacetic acid

1-Phenyl-ethylenediamine-N,N,N',N'-tetraethanoic acid

PHEDTA



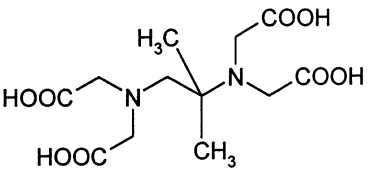
H_4L **L29**

Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	9.95	pot.			20	0.1 KNO_3	62
$LH^{3-} + H^+ = LH_2^{2-}$	5.42	pot.			20	0.1 KNO_3	62
$LH_2^{2-} + H^+ = LH_3^-$	3.23	pot.			20	0.1 KNO_3	62
$LH_3^- + H^+ = LH_4$	2.10	pot.			20	0.1 KNO_3	62
$Gd^{3+} + L^{4-} = GdL^-$	17.40	pol.			20	0.1 KNO_3	62

1,1-Dimethylethylenedinitrilotetraacetic acid

2-Methyl-1,2-diaminopropane- N,N,N',N'-tetraethanoic acid

MPDTA



H_4L **L30**

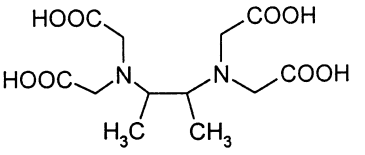
Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	11.46	pot.			20	0.1 KNO_3	53
$LH^{3-} + H^+ = LH_2^{2-}$	5.38	pot.			20	0.1 KNO_3	53
$LH_2^{2-} + H^+ = LH_3^-$	3.25	pot.			20	0.1 KNO_3	53
$LH_3^- + H^+ = LH_4$	2.45	pot.			20	0.1 KNO_3	53
$Gd^{3+} + L^{4-} = GdL^-$	17.09	pol.			20	0.1 KNO_3	53

Table 2 (*Continued*)

meso-(1-2-dimethylethylene)dinitrilotetraacetic acid

meso-2,3-diaminobutane-N,N,N',N'-tetraethanoic acid

meso-DIMEDTA



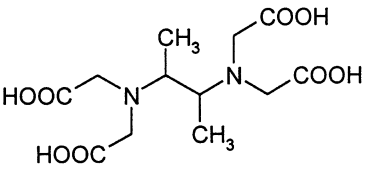
H_4L **meso-L31**

Reaction	LogK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$Gd^{3+} + L^{4-} = GdL^-$	16.51	pol.			20	0.1 KNO_3	58
	17.03	sp.			20	0.1 $NaClO_4$	59

DL-(1-2-dimethylethylene)dinitrilotetraacetic acid

DL-2,3-diaminobutane-N,N,N',N'-tetraethanoic acid

DL-DIMEDTA



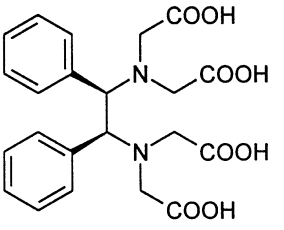
H_4L **dl-L31**

Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$Gd^{3+} + L^{4-} = GdL^-$	18.84	pol.			20	0.1	59
	18.64	sp.			20	0.1 $NaClO_4$	59

meso-N,N'-(1,2-diphenyl-1,2-1,2-ethanediyl)bis[N-carboxymethyl)]glycine

meso-1,2-diphenylethylenediamine-N,N,N',N'-tetraacetic acid

meso-DPHEDTA



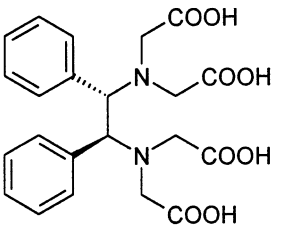
H_4L **meso-L32**

Reaction	LogK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.

Table 2 (*Continued*)

$L^{4-} + H^+ = LH^{3-}$	9.98	pot.		20	0.1 KNO_3	47
$LH^{3-} + H^+ = LH_2^{2-}$	6.18	pot.		20	0.1 KNO_3	47
$LH_2^{2-} + H^+ = LH_3^-$	2.80	pot.		20	0.1 KNO_3	47
$LH_3^- + H^+ = LH_4$	2.00	pot.		20	0.1 KNO_3	47
$Gd^{3+} + L^{4-} = GdL^-$	11.66	pol.		20	0.1 KNO_3	47

S-(R,R*)-N,N'-(1,2-diphenyl-1,2-1,2-ethanediyl)bis[N-carboxymethyl)]glycine



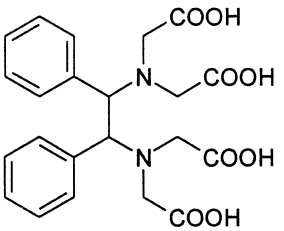
H_4L **dl-L32**

Reaction	LogK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	11.85 (4)	pot.			25	0.1 $TMANO_3$	116
$LH^{3-} + H^+ = LH_2^{2-}$	5.62 (4)	pot.			25	0.1 $TMANO_3$	116
$LH_2^{2-} + H^+ = LH_3^-$	3.84 (4)	pot.			25	0.1 $TMANO_3$	116
$LH_3^- + H^+ = LH_4$	2.47 (4)	pot.			25	0.1 $TMANO_3$	116
$LH_4 + H^+ = LH_5^+$	1.3 (1)	pot.			25	0.1 $TMANO_3$	116
$Gd^{3+} + L^{4-} = GdL^-$	20.29 (2)	pot.			25	0.1 $TMANO_3$	116

rac-N,N'-(1,2-diphenyl-1,2-1,2-ethanediyl)bis[N-carboxymethyl)]glycine

rac-1,2-diphenylethylenediamine-N,N,N',N'-tetraacetic acid

rac-DPHEDTA



H_4L **rac-L32**

Reaction	LogK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	9.97	pot.			20	0.1 KNO_3	47
$LH^{3-} + H^+ = LH_2^{2-}$	5.44	pot.			20	0.1 KNO_3	47

Table 2 (*Continued*)

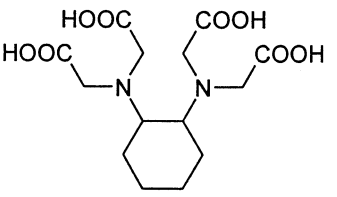
$LH_2^{2-} + H^+ = LH_3^-$	3.76	pot.		20	0.1 KNO_3	47
$LH_3^- + H^+ = LH_4$	2.44	pot.		20	0.1 KNO_3	47
$Gd^{3+} + L^{4-} = GdL^-$	17.48	pol.		20	0.1 KNO_3	47

trans-1,2-Cyclohexylenedinitrilotetraacetic acid

trans-1,2-Diaminocyclohexane-N,N,N',N'-tetraethanoic acid

trans-1,2-Diaminocyclohexane-N,N,N',N'-tetraacetic acid

CDTA, DCTA



H_4L **L33**

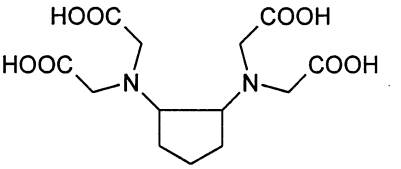
Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	11.58	pot.	-7.3	59	25	0.1 KNO_3	50
	11.30	pot.			25	0.5 KNO_3	28
	12.73	pot.			25	1.0 KCl	51
$LH^{3-} + H^+ = LH_2^{2-}$	6.12	pot.	-1.3	34	25	0.1 KNO_3	50
	6.51	pot.			25	0.5 KNO_3	28
	6.005	pot.			25	1.0 KCl	51
$LH_2^{2-} + H^+ = LH_3^-$	3.01	pot.			25	0.5 KNO_3	28
	3.25	pot.			25	1.0 KCl	51
$LH_3^- + H^+ = LH_4$	2.38	pot.			25	0.5 KNO_3	28
	2.42	pot.			25	1.0 KCl	51
$LH_4 + H^+ = LH_5^+$	1.56	pot.			25	1.0 KCl	51
$Gd^{3+} + L^{4-} = GdL^-$	18.80	pot.	24	131	25	0.1 KNO_3	50
	18.12	pot.			25	0.5 $NaClO_4$	28
	18.97	pot.			25	1.0 KCl	51
	18.77	pol.			20	0.1 KNO_3	35
	19.66				25	0.1	52

Table 2 (*Continued*)

trans-1,2-Cyclopentylenedinitrilotetraacetic acid

trans-1,2-Cyclopentane-iminodiacetic acid

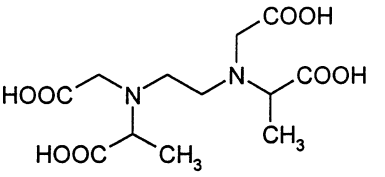
CPDTA



H_4L **L34**

Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	10.09	pot.			20	0.1	63
$LH^{3-} + H^+ = LH_2^{2-}$	7.48	pot.			20	0.1	63
$LH_2^{2-} + H^+ = LH_3^-$	2.44	pot.			20	0.1	63
$LH_3^- + H^+ = LH_4$	1.87	pot.			20	0.1	63
$Gd^{3+} + L^{4-} = GdL^-$	18.24	pot.			20	0.1	63

DL-Ethylenedinitrilo-N,N'-di(2-propanoic)-N,N'-diacetic acid



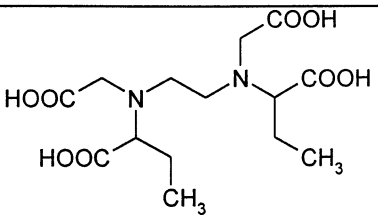
H_4L **L35**

Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	10.42				20	0.1	65
$LH^{3-} + H^+ = LH_2^{2-}$	6.65				20	0.1	65
$LH_2^{2-} + H^+ = LH_3^-$	2.00				20	0.1	65
$LH_3^- + H^+ = LH_4$	1.90				20	0.1	65
$Gd^{3+} + L^{4-} = GdL^-$	17.0				20	0.1	65

Table 2 (*Continued*)

DL-Ethylenedinitrilo-N,N'-di(2-butanoic)-N,N'-diacetic acid

Ethylenediamine-N,N'-diethanoic-N,N'-di-2-butyric acid

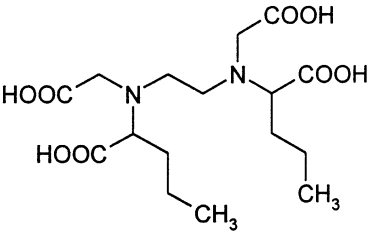


H_4L **L36**

Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	10.42	pot.			20	0.1 KNO_3	64
$LH^{3-} + H^+ = LH_2^{2-}$	6.09	pot.			20	0.1 KNO_3	64
$LH_2^{2-} + H^+ = LH_3^-$	2.69	pot.			20	0.1 KNO_3	64
$LH_3^- + H^+ = LH_4$	1.8	pot.			20	0.1 KNO_3	64
$Gd^{3+} + L^{4-} = GdL^-$	16.48	pol.			20	0.1 KNO_3	64

DL-Ethylenedinitrilo-N,N'-di(2-pentanoic)-N,N'-diacetic acid

Ethylenediamine-N,N'-diethanoic-N,N'-di-2-valeric acid



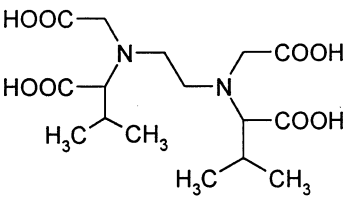
H_4L **L37**

Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	10.47	pot.			20	0.1 KNO_3	64
$LH^{3-} + H^+ = LH_2^{2-}$	6.15	pot.			20	0.1 KNO_3	64
$LH_2^{2-} + H^+ = LH_3^-$	2.79	pot.			20	0.1 KNO_3	64
$LH_3^- + H^+ = LH_4$	1.9	pot.			20	0.1 KNO_3	64
$Gd^{3+} + L^{4-} = GdL^-$	16.60	pol.			20	0.1 KNO_3	64

Table 2 (*Continued*)

DL-Ethylenedinitrilo-N,N'-bis-(2)-(3-methylbutanoic)-)-N,N'-diacetic acid

Ethylenediamine-N,N'-diethanoic-N,N'-di-2-isovaleric acid

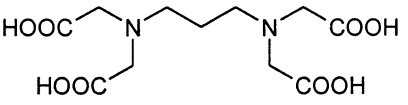


H_4L **L38**

Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	10.38	pot.			20	0.1 KNO_3	64
$LH^{3-} + H^+ = LH_2^{2-}$	5.60	pot.			20	0.1 KNO_3	64
$LH_2^{2-} + H^+ = LH_3^-$	3.02	pot.			20	0.1 KNO_3	64
$LH_3^- + H^+ = LH_4$	1.9	pot.			20	0.1 KNO_3	64
$Gd^{3+} + L^{4-} = GdL^-$	13.39	pot.			20	0.1 KNO_3	64
	13.47	pol.			20	0.1 KNO_3	64

Trimethylenedinitrilotetraacetic acid

TMTA, TMDTA



H_4L **L39**

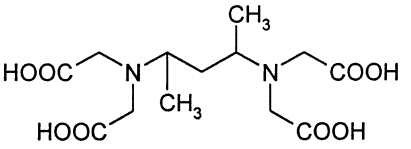
Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	10.46	pot.			20	0.1 KNO_3	68
$LH^{3-} + H^+ = LH_2^{2-}$	8.02	pot.			20	0.1 KNO_3	68
$LH_2^{2-} + H^+ = LH_3^-$	2.47	pot.			20	0.1 KNO_3	68
$LH_3^- + H^+ = LH_4$	1.88	pot.			20	0.1 KNO_3	68
$Gd^{3+} + L^{4-} = GdL^-$	13.74	pot.			20	0.1 KNO_3	68
	13.80	pol.			20	0.1 KNO_3	68
	13.73	pot.	20.7 cal.	98	20	0.1 KNO_3	68
	13.79	pot.			20	0.1 KNO_3	69
	13.60	pot.			20	0.1 KNO_3	69
	13.70	pol.			20	0.1 KNO_3	69

Table 2 (*Continued*)

DL-(1,3-Dimethyltrimethylene)dinitrilotetraacetic acid

DL-2,4-diaminopentane-N,N,N',N'-tetraacetic acid

APTA

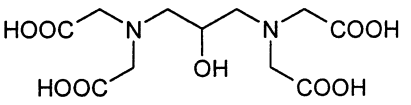


H_4L **L40**

Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	10.84	pot.			20	0.1 KNO_3	70
$LH^{3-} + H^+ = LH_2^{2-}$	8.54	pot.			20	0.1 KNO_3	70
$LH_2^{2-} + H^+ = LH_3^-$	2.42	pot.			20	0.1 KNO_3	70
$LH_3^- + H^+ = LH_4$	2.09	pot.			20	0.1 KNO_3	70
$Gd^{3+} + L^{4-} = GdL^-$	12.15	pot.			20	0.1 KNO_3	70
	12.28	pol.			20	0.1 KNO_3	70

1,3-diamino-2-hydroxypropane-N,N,N',N'-tetraacetic acid

DHPTA, HPDTA



H_4L **L41**

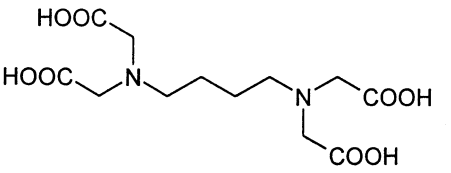
Reaction	LogK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	9.49	pot.			25	0.1 KNO_3	71
$LH^{3-} + H^+ = LH_2^{2-}$	7.04	pot.			25	0.1 KNO_3	71
$LH_2^{2-} + H^+ = LH_3^-$	2.62	pot.			25	0.1 KNO_3	71
$LH_3^- + H^+ = LH_4$	1.47	pot.			25	0.1 KNO_3	71
$Gd^{3+} + L^{4-} = GdL^-$	13.94				25	0.1 KNO_3	71

Table 2 (*Continued*)

Tetramethylenedinitrilotetraacetic acid

1,4-diaminobutane-N,N,N',N'-tetraacetic acid

TMEDTA



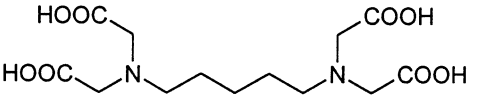
H_4L **L42**

Reaction	LogK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	10.24	pot.	-29.49 cal.	29	25	0.5 $NaClO_4$	72
$LH^{3-} + H^+ = LH_2^{2-}$	9.27	pot.	-27.97 cal.	25	25	0.5 $NaClO_4$	72
$Gd^{3+} + L^{4-} = GdL^-$	9.94	pot.	24.34 cal.	81	25	0.5 $NaClO_4$	72
	6.66	pot.			25	0.5 $NaClO_4$	72
$GdHL + H^+ = GdH_2L^+$	5.36	pot.			25	0.5 $NaClO_4$	72

1,5-diaminopentane-N,N,N',N'-tetraacetic acid

Pentamethylenedinitrilotetraacetic acid

PMDTA



H_4L **L43**

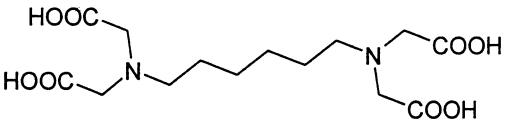
Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	10.20	pot.			25	0.1 KNO_3	43
$LH^{3-} + H^+ = LH_2^{2-}$	9.35	pot.			25	0.1 KNO_3	43
$LH_2^{2-} + H^+ = LH_3^-$	2.71	pot.			25	0.1 KNO_3	43
$LH_3^- + H^+ = LH_4$	2.24	pot.			25	0.1 KNO_3	43
$Gd^{3+} + L^{4-} = GdL^-$	10.37	pot.			25	0.1 KNO_3	43
$GdL^- + H^+ = GdHL$	6.79	pot.			25	0.1 KNO_3	43

Table 2 (*Continued*)

Hexamethylenedinitrilotetraacetic acid

1,6-diaminohexane-N,N,N',N'-tetraacetic acid

HMDTA, HhDTA



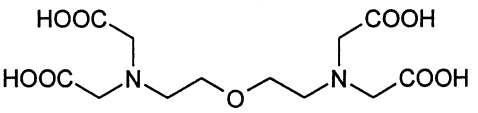
H_4L **L44**

Reaction	LogK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	10.30	pot.			25	1.0 KCl	73
$LH^{3-} + H^+ = LH_2^{2-}$	9.59	pot.			25	1.0 KCl	73
$Gd^{3+} + L^{4-} = GdL^-$	9.16	pot.			25	1.0 KCl	73
$GdL^- + H^+ = GdHL$	5.82	pot.			25	1.0 KCl	73

Oxybis(ethylenenitrilo)tetraacetic acid

1,7-diaza-4-oxaheptane-1,1,7,7-tetraacetic acid

EEDTA



H_4L **L45**

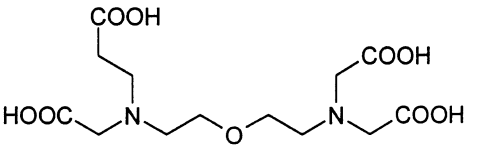
Reaction	LogK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$Gd^{3+} + L^{4-} = GdL^-$	18.13	pot.			20	0.1 KNO_3	78
	18.21	pol.			20	0.1 KNO_3	78
	18.34				20	0.1	79

Table 2 (*Continued*)

N-(2-Carboxyethyl)oxybis(ethyleneamine)-N,N',N',-triacetic acid

Bis(2-aminoethyl)ether-N,N',N'-triacetic acid N'-(3-propanoic acid

DETAP



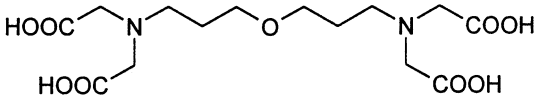
H_3L **L46**

Reaction	LogK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	9.55	pot.			25	0.1 KNO_3	80
$LH^{3-} + H^+ = LH_2^{2-}$	9.98	pot.			25	0.1 KNO_3	80
$LH_2^{2-} + H^+ = LH_3^-$	3.86	pot.			25	0.1 KNO_3	80
$LH_3^- + H^+ = LH_4$	2.63	pot.			25	0.1 KNO_3	80
$Gd^{3+} + L^{4-} = GdL^-$	15.21	pot.			25	0.1 KNO_3	80
$GdL^- + H^+ = GdHL$	9.32	pot.			25	0.1 KNO_3	80

Oxybis(trimethylenenitrilo)tetraacetic acid

Bis(3-aminopropyl)ether-N,N,N',N'-tetraacetic acid

BPETA



H_4L **L47**

Reaction	LogK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	10.03	pot.			25	0.1 KNO_3	77
$LH^{3-} + H^+ = LH_2^{2-}$	9.88	pot.			25	0.1 KNO_3	77
$LH_2^{2-} + H^+ = LH_3^-$	2.65	pot.			25	0.1 KNO_3	77
$LH_3^- + H^+ = LH_4$	2.32	pot.			25	0.1 KNO_3	77
$Gd^{3+} + L^{4-} = GdL^-$	11.74	pot.			25	0.1 KNO_3	77
$GdL^- + H^+ = GdHL$	7.30	pot.			25	0.1 KNO_3	77

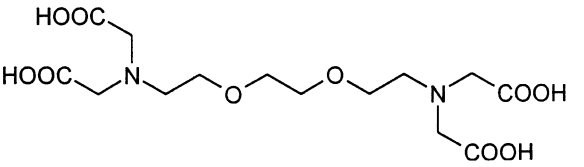
Table 2 (*Continued*)

Ethylenebis(oxyethylenenitrilo)tetraacetic acid

1,10-diaza-4,7-dioxadecane-1,1,10,10-tetraacetic acid

EGTA

H_4L **L48**



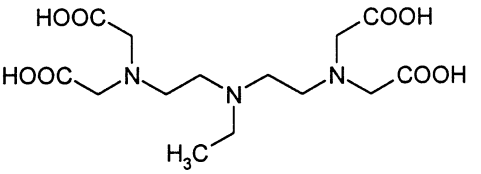
Reaction	LogK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$Gd^{3+} + L^{4-} = GdL^-$	16.94	pot.			20	0.1 KNO_3	78
	17.50	pol.			20	0.1 KNO_3	78

N-Ethyliminobis(etthylenitrilo)tetraacetic acid

N,N-bis(2-aminoethyl)ethylamine-N,N,N',N'-tetraacetic acid

DEATA

H_4L **L49**



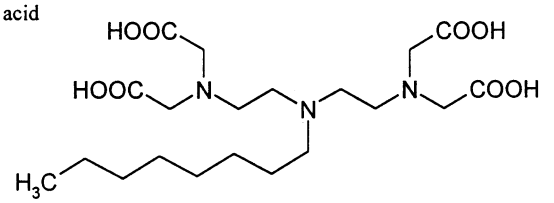
Reaction	LogK	Method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	10.44	pot.			25	0.1 KNO_3	74
$LH^{3-} + H^+ = LH_2^{2-}$	7.42	pot.			25	0.1 KNO_3	74
$LH_2^{2-} + H^+ = LH_3^-$	4.00	pot.			25	0.1 KNO_3	74
$LH_3^- + H^+ = LH_4$	2.80	pot.			25	0.1 KNO_3	74
$Gd^{3+} + L^{4-} = GdL^-$	17.79	pot.			25	0.1 KNO_3	74

Table 2 (*Continued*)

[(Octilylimino)bis(ethylenenitrilo)]tetraacetic acid

BEOTA

H_4L **L50**



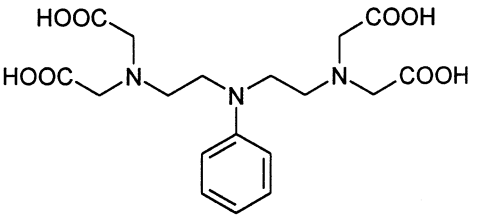
Reaction	LogK	Method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	9.6	pot.			25	0.1	75
$LH^{3-} + H^+ = LH_2^{2-}$	8.8	pot.			25	0.1	75
$LH_2^{2-} + H^+ = LH_3^-$	4.1	pot.			25	0.1	75
$LH_3^- + H^+ = LH_4$	2.9	pot.			25	0.1	75
$Gd^{3+} + L^{4-} = GdL^-$	16.23	pol.			25	0.1	75

N-Phenyliminobis(etthylenitrilo)tetraacetic acid

N,N-bis(2-aminoethyl)aniline-N,N,N',N'-tetraacetic acid

BEATA

H_4L **L51**



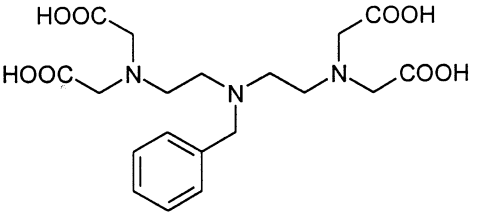
Reaction	LogK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	10.15	pot.			25	0.1 KNO_3	74
$LH^{3-} + H^+ = LH_2^{2-}$	9.18	pot.			25	0.1 KNO_3	74
$LH_2^{2-} + H^+ = LH_3^-$	3.46	pot.			25	0.1 KNO_3	74
$LH_3^- + H^+ = LH_4$	1.91	pot.			25	0.1 KNO_3	74
$Gd^{3+} + L^{4-} = GdL^-$	15.42	pot.			25	0.1 KNO_3	74

Table 2 (*Continued*)

[(Benzylimino)bis(ethylenenitrilo)]tetraacetic acid

BEBTA

H_4L **L52**



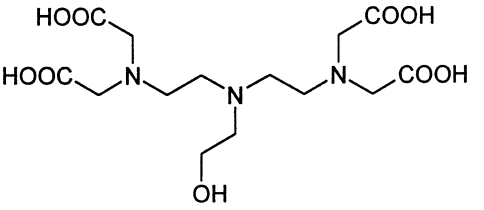
Reaction	LogK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	9.05	pot.			25	0.1	75
$LH^{3-} + H^+ = LH_2^{2-}$	7.99	pot.			25	0.1	75
$LH_2^{2-} + H^+ = LH_3^-$	3.98	pot.			25	0.1	75
$LH_3^- + H^+ = LH_4$	2.52	pot.			25	0.1	75
$Gd^{3+} + L^{4-} = GdL^-$	17.50	pol.			25	0.1	75

N'-(β-hydroxyethyl)diethylenetriamine-N,N,N'',N''-tetraacetic acid

[(N-(2-Hydroxyethyl)-2,2'-iminodiethylene)-dinitrilo]tetraethanoic acid

HDTTA, HEDTA

H_4L **L53**

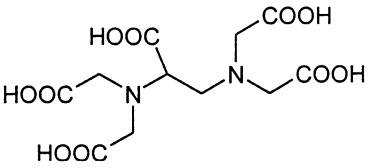


Reaction	LogK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	9.3	pot.			25	0.1 $CaCl_2$	76
$LH^{3-} + H^+ = LH_2^{2-}$	8.00	pot.			25	0.1 $CaCl_2$	76
$LH_2^{2-} + H^+ = LH_3^-$	3.54	pot.			25	0.1 $CaCl_2$	76
$LH_3^- + H^+ = LH_4$	2.58	pot.			25	0.1 $CaCl_2$	76
$Gd^{3+} + L^{4-} = GdL^-$	15.44	pot.			25	0.1	76
	13.45	pol.			25	0.1	76

Table 2 (*Continued*)

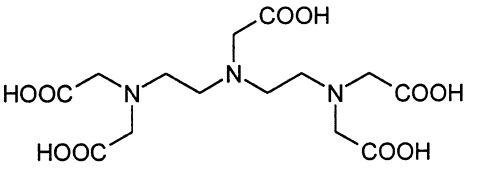
DL-2,3-Diaminopropanoic-N,N,N',N'-tetraacetic acid
CEDTA, DAPTA

H_5L **L54**



Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{5-} + H^+ = LH^{4-}$	9.52	pot.			25	0.1 KNO_3	67
$LH^{4-} + H^+ = LH_2^{3-}$	6.32	pot.			25	0.1 KNO_3	67
$LH_2^{3-} + H^+ = LH_3^{2-}$	3.40	pot.			25	0.1 KNO_3	67
$LH_3^{2-} + H^+ = LH_4^-$	2.75	pot.			25	0.1 KNO_3	67
$LH_4^- + H^+ = LH_5$	2.20	pot.			25	0.1 KNO_3	67
$Gd^{3+} + L^{5-} = GdL^{2-}$	15.93	pot.			25	0.1 KNO_3	67

Diethylenetrinitrilopentaacetic acid
Diethylenetriamine-pentaethanoic acid
DTPA



H_5L **L55**

Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{5-} + H^+ = LH^{4-}$	9.86	pot.			25	0.5 KNO_3	28
	10.41	pot.			25	0.1 TMACl	36
	9.45	pot.			25	0.1 NaCl	36
	10.10	pot.			25	0.1 KCl	36
	10.58	pot.			20	0.1 KNO_3	81
	10.73 (1)	pot.			25	0.1 $TMANO_3$	116
$LH^{4-} + H^+ = LH_2^{3-}$	8.32	pot.	-27.1 cal.	20	25	0.5 KNO_3	28
	8.37	pot.			25	0.1 TMACl	36
	8.21	pot.			25	0.1 NaCl	36
	8.34	pot.			25	0.1 KCl	36

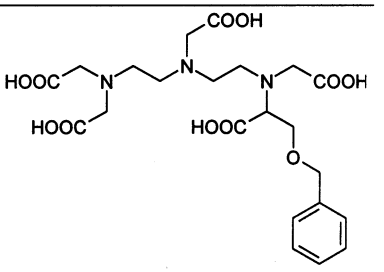
Table 2 (*Continued*)

	8.60	pot.			20	0.1 KNO_3	81
	8.62 (1)	pot.			25	0.1 $TMANO_3$	116
$LH_2^{3-} + H^+ = LH_3^{2-}$	4.12	pot.			25	0.5 KNO_3	28
	4.09	pot.			25	0.1 TMACl	36
	4.09	pot.			25	0.1 NaCl	36
	4.21	pot.			25	0.1 KCl	36
	4.33	pot.			20	0.1 KNO_3	81
	4.32 (1)	pot.			25	0.1 $TMANO_3$	116
$LH_3^{2-} + H^+ = LH_4^-$	2.85	pot.			25	0.5 KNO_3	28
	2.51	pot.			25	0.1 TMACl	36
	2.49	pot.			25	0.1 NaCl	36
	2.48	pot.			25	0.1 KCl	36
	2.55	pot.			20	0.1 KNO_3	81
	2.79 (3)	pot.			25	0.1 $TMANO_3$	116
$LH_4^- + H^+ = LH_5$	1.95	pot.			25	0.5 KNO_3	28
	2.04	pot.			25	0.1 TMACl	36
	1.87	pot.			25	0.1 NaCl	36
	1.58	pot.			25	0.1 KCl	36
	1.80	pot.			20	0.1 KNO_3	81
	2.14 (4)	pot.			25	0.1 $TMANO_3$	116
$Gd^{3+} + L^{5-} = GdL^{2-}$	20.73	pot.	-47.5 cal.	71	25	0.5 $NaClO_4$	28
	22.2	sp.			25	0.1 TMACl	36
	22.46	pot.	-31	97	25	0.1 KNO_3	81
	22.55 (9)	pot.			25	0.1 $TMANO_3$	116
	23.01	pot.			25	0.1 KCl	18
	22.46	sp.			20		82
$GdL^{2-} + H^+ = GdHL^-$	2.39	pot.			25	0.1 KNO_3	81

Table 2 (*Continued*)

4-Carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oic acid

BOPTA



H_5L **L56**

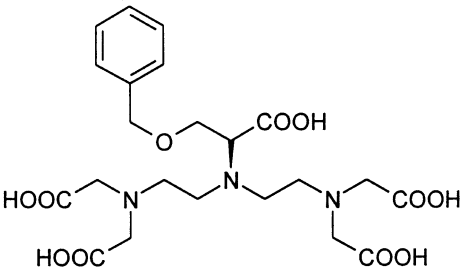
Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{5-} + H^+ = LH^{4-}$	10.71	pot.			20	0.15 KCl	83
	10.86 (3)	pot.			25	0.1 $TMANO_3$	116
	10.76 (2)	pot.	-14.91 cal.	46.9	25	0.15 NaCl	116
$LH^{4-} + H^+ = LH_2^{3-}$	8.27	pot.			20	0.15 KCl	83
	8.29 (1)	pot.			25	0.1$TMANO_3$	116
	8.17 (2)	pot.	-14.74 cal.	32.7	25	0.15 NaCl	116
$LH_2^{3-} + H^+ = LH_3^{2-}$	4.35	pot.			20	0.15 KCl	83
	4.34 (1)	pot.			25	0.1$TMANO_3$	116
	4.31 (2)	pot.	-2.81 cal.	21.8	25	0.15 NaCl	116
$LH_3^{2-} + H^+ = LH_4^-$	2.83	pot.			20	0.15 KCl	83
	2.78 (1)	pot.			25	0.1$TMANO_3$	116
	2.69 (2)	pot.	-0.92 cal.	15.1	25	0.15 NaCl	116
$LH_4^- + H^+ = LH_5$	2.07	pot.			20	0.15 KCl	83
	2.23 (1)	pot.			25	0.1$TMANO_3$	116
	2.18 (2)	pot.	0.25 cal.	13.0	25	0.15 NaCl	116
$Gd^{3+} + L^{5-} = GdL^{2-}$	22.59	pot.			20	0.15 KCl	83
	22.58 (3)	pot.	-21 cal.	108	25	0.1$TMANO_3$	116
	22.61 (4)	pot.			25	0.15 NaCl	116
$GdL^{2-} + H^+ = GdHL^-$	1.75 (3)	pot.	5.9 cal.	16	25	0.1$TMANO_3$	116

Table 2 (*Continued*)

N,N-bis-[2-[bis-(carboxymethyl)]-aminoethyl]-O-phenylmethyl-L-serine

ISOBOPTA

H_5L **L57**

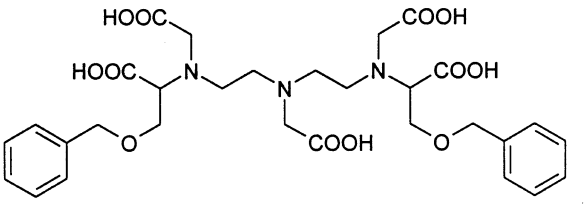


Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{5-} + H^+ = LH^{4-}$	10.74 (4)	pot.			25	0.1 $TMANO_3$	116
$LH^{4-} + H^+ = LH_2^{3-}$	9.16 (2)	pot.			25	0.1 $TMANO_3$	116
$LH_2^{3-} + H^+ = LH_3^{2-}$	4.15 (4)	pot.			25	0.1 $TMANO_3$	116
$LH_3^{2-} + H^+ = LH_4^-$	2.51 (4)	pot.			25	0.1 $TMANO_3$	116
$LH_4^- + H^+ = LH_5$	2.35 (4)	pot.			25	0.1 $TMANO_3$	116
$Gd^{3+} + L^{5-} = GdL^{2-}$	22.23 (6)	pot.			25	0.1 $TMANO_3$	116
$GdL^{2-} + H^+ = GdHL^-$	2.0 (2)	pot.			25	0.1 $TMANO_3$	116

(R*,S*)-4-carboxy-5,8,11-tris(carboxymethyl)1-phenylmetoxy)methyl]-2-oxo-5,8,11- triazatridecan-13-oic acid

DIBOPTA

H_5L **L58**



Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{5-} + H^+ = LH^{4-}$	11.08 (6)	pot.			25	0.1 $TMANO_3$	116
$LH^{4-} + H^+ = LH_2^{3-}$	7.98 (2)	pot.			25	0.1 $TMANO_3$	116
$LH_2^{3-} + H^+ = LH_3^{2-}$	4.44 (6)	pot.			25	0.1 $TMANO_3$	116
$LH_3^{2-} + H^+ = LH_4^-$	2.83 (6)	pot.			25	0.1 $TMANO_3$	116
$LH_4^- + H^+ = LH_5$	2.30 (8)	pot.			25	0.1 $TMANO_3$	116

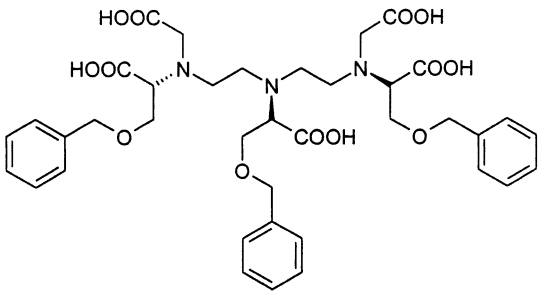
Table 2 (*Continued*)

$Gd^{3+} + L^{5-} = GdL^{2-}$	21.72 (2)	pot.			25	0.1 $TMANO_3$	116
$GdL^{2-} + H^{+} = GdHL^{-}$	2.33 (3)	pot.			25	0.1 $TMANO_3$	116

[4S-[4R*,8(R*),12R*]]-4-Carboxy-5,11-bis(carboxymethyl)-8-[1-carboxy-2- (phenylmethoxy)ethyl]-1-phenyl-12-[(phenylmetoxy)methyl]-2-oxa-5,8,11-triazatridecan-13-oic acid

TRIBOPTA

H_5L **L59**

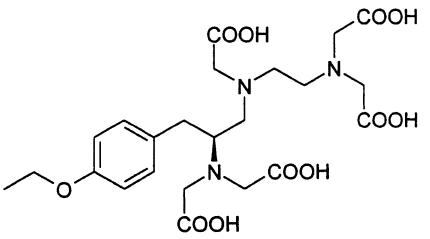


Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{5-} + H^{+} = LH^{4-}$	10.72 (2)	pot.			25	0.1 $TMANO_3$	116
$LH^{4-} + H^{+} = LH_2^{3-}$	8.84 (4)	pot.			25	0.1 $TMANO_3$	116
$LH_2^{3-} + H^{+} = LH_3^{2-}$	4.36 (6)	pot.			25	0.1 $TMANO_3$	116
$LH_3^{2-} + H^{+} = LH_4^{-}$	2.69 (8)	pot.			25	0.1 $TMANO_3$	116
$LH_4^{-} + H^{+} = LH_5$	2.09 (9)	pot.			25	0.1 $TMANO_3$	116
$Gd^{3+} + L^{5-} = GdL^{2-}$	22.18 (5)	pot.			25	0.1 $TMANO_3$	116
$GdL^{2-} + H^{+} = GdHL^{-}$	2.45 (6)	pot.			25	0.1 $TMANO_3$	116

S-4-(-ethoxybenzyl)-3,6,9-tris(carboxymethyl)-3,6,9-triazaundecanedioic acid

EOB-DTPA

H_5L **L60**



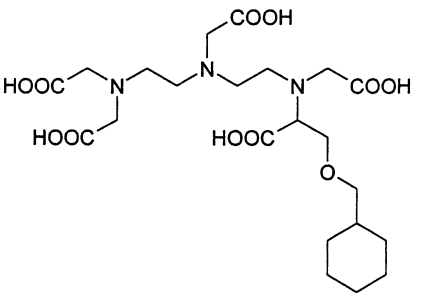
Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{5-} + H^{+} = LH^{4-}$	11.52 (6)	pot.			25	0.1 TMACl	116

Table 2 (*Continued*)

$LH^{4-} + H^+ = LH_2^{3-}$	8.83 (2)	pot.			25	0.1 TMACl	116
$LH_2^{3-} + H^+ = LH_3^{2-}$	4.45 (2)	pot.			25	0.1 TMACl	116
$LH_3^{2-} + H^+ = LH_4^-$	2.95 (3)	pot.			25	0.1 TMACl	116
$LH_4^- + H^+ = LH_5$	2.45 (4)	pot.			25	0.1 TMACl	116
$Gd^{3+} + L^{5-} = GdL^{2-}$	23.5	pot.				0.1 KCl	84
	22.76 (6)	pot.			25	0.1 TMACl	116

4-Carboxy-5,8,11-tris(carboxymethyl)-1-cicloesil-2-oxo-5,8,11-triazatridecan-13-oic acid

H_5L **L61**

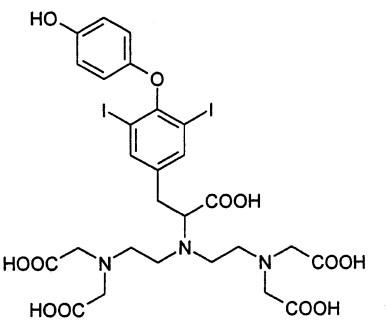


Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{5-} + H^+ = LH^{4-}$	10.70 (2)	pot.			25	0.1 $TMANO_3$	116
$LH^{4-} + H^+ = LH_2^{3-}$	8.38 (4)	pot.			25	0.1 $TMANO_3$	116
$LH_2^{3-} + H^+ = LH_3^{2-}$	4.49 (6)	pot.			25	0.1 $TMANO_3$	116
$LH_3^{2-} + H^+ = LH_4^-$	2.88 (8)	pot.			25	0.1 $TMANO_3$	116
$LH_4^- + H^+ = LH_5$	2.43 (6)	pot.			25	0.1 $TMANO_3$	116
$Gd^{3+} + L^{5-} = GdL^{2-}$	21.73 (6)	pot.			25	0.1 $TMANO_3$	116

N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-O-(4-hydroxyphenyl)-3,5-diiodo-L-tyrosine

I_2tyrDTPA

H_6L **L62**



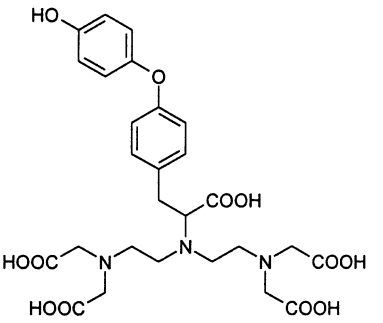
Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.

Table 2 (*Continued*)

$L^{6-} + H^+ = LH^{5-}$	10.23 (2)	pot.		25	0.1 $TMANO_3$	116
$LH^{5-} + H^+ = LH_2^{4-}$	9.91 (1)	pot.		25	0.1 $TMANO_3$	116
$LH_2^{4-} + H^+ = LH_3^{3-}$	8.91 (2)	pot.		25	0.1 $TMANO_3$	116
$LH_3^{3-} + H^+ = LH_4^{2-}$	4.21 (4)	pot.		25	0.1 $TMANO_3$	116
$LH_4^{2-} + H^+ = LH_5^-$	2.86 (4)	pot.		25	0.1 $TMANO_3$	116
$LH_5^- + H^+ = LH_6$	2.43 (5)	pot.		25	0.1 $TMANO_3$	116
$Gd^{3+} + L^{6-} = GdL^{3-}$	21.87 (5)	pot.		25	0.1 $TMANO_3$	116
$GdL^{3-} + H^+ = GdHL^{2-}$	9.55 (3)	pot.		25	0.1 $TMANO_3$	116

N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-O-(4-hydroxyphenyl)-L-tyrosine

H_6L **L63**



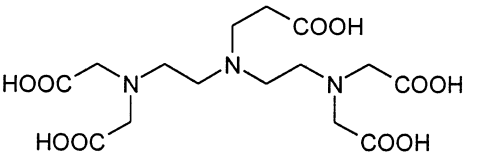
Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{6-} + H^+ = LH^{5-}$	10.49 (1)	pot.			25	0.1 $TMANO_3$	116
$LH^{5-} + H^+ = LH_2^{4-}$	9.78 (1)	pot.			25	0.1 $TMANO_3$	116
$LH_2^{4-} + H^+ = LH_3^{3-}$	8.96 (3)	pot.			25	0.1 $TMANO_3$	116
$LH_3^{3-} + H^+ = LH_4^{2-}$	4.21 (4)	pot.			25	0.1 $TMANO_3$	116
$LH_4^{2-} + H^+ = LH_5^-$	2.71 (5)	pot.			25	0.1 $TMANO_3$	116
$LH_5^- + H^+ = LH_6$	2.09 (5)	pot.			25	0.1 $TMANO_3$	116
$Gd^{3+} + L^{6-} = GdL^{3-}$	22.30 (6)	pot.			25	0.1 $TMANO_3$	116
$GdL^{3-} + H^+ = GdHL^{2-}$	9.58 (4)	pot.			25	0.1 $TMANO_3$	116

Table 2 (*Continued*)

N'-(β-hydroxyethyl)diethylenetriamine-N,N,N'',N''-tetraacetic acid

CEDTA

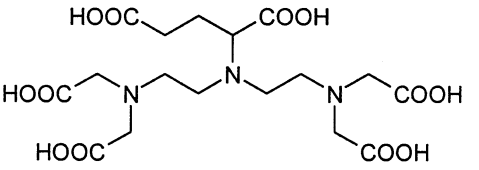
H_5L **L64**



Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{5-} + H^+ = LH^{4-}$	9.31	pot.			25	0.1	85
$LH^{4-} + H^+ = LH_2^{3-}$	8.14	pot.			25	0.1	85
$LH_2^{3-} + H^+ = LH_3^{2-}$	4.7	pot.			25	0.1	85
$LH_3^{2-} + H^+ = LH_4^-$	2.97	pot.			25	0.1	85
$LH_4^- + H^+ = LH_5$	2.58	pot.			25	0.1	85
$Gd^{3+} + L^{5-} = GdL^{2-}$	16.71	pot.			25	0.1	85
	18.4	pol.			25	0.1	85

2-(di{2-[di(carboxymethyl)amino]ethyl}amino)-pentanedioic acid

H_6L **L65**



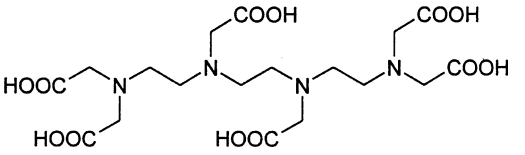
Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$L^{6-} + H^+ = LH^{5-}$	10.41 (1)	pot.			25	0.1 TMACl	116
$LH^{5-} + H^+ = LH_2^{4-}$	9.16 (1)	pot.			25	0.1 TMACl	116
$LH_2^{4-} + H^+ = LH_3^{3-}$	5.34 (1)	pot.			25	0.1 TMACl	116
$LH_3^{3-} + H^+ = LH_4^{2-}$	4.10 (1)	pot.			25	0.1 TMACl	116
$LH_4^{2-} + H^+ = LH_5^-$	2.75 (2)	pot.			25	0.1 TMACl	116
$LH_5^- + H^+ = LH_6$	2.08 (5)	pot.			25	0.1 TMACl	116
$Gd^{3+} + L^{6-} = GdL^{3-}$	21.66 (3)	pot.			25	0.1 TMACl	116
$GdL^{3-} + H^+ = GdHL^{2-}$	5.25 (2)	pot.			25	0.1 TMACl	116

Table 2 (*Continued*)

Triethylenetetranitrilohexaacetic acid

1,4,7,10-tetraazadecane-1,1,4,7,10,10-hexaacetic acid

TTHA



H_6L **L66**

Reaction	logK	method	ΔH° (kJ/mol)	TΔS° (kJ/mol)	T (°C)	medium (mol dm^{-3})	ref.
$Gd^{3+} + L^{6-} = GdL^{3-}$	28.4	pot.			25		86
	23.83	pol.					87

[a] Values in parenthesis are standard deviations in the last significant figures.

[b] Method abbreviation are pot. (potentiomeric), sp. (spectrophotometric), ca. (calorimetric), kin. (kinetic), ion exc. (ion exchange), distr. (electrophoretic). Log K values with standard devition in parentheses refer to equilibrium constants not previously reported [116,132]

conditions. In the case of Gd(III) complexes further complications in evaluating the data derive from the different approaches adopted for determining very high equilibrium constants in metal–ligand systems requiring, in many cases, long equilibration times. Furthermore, the ligands considered may coordinate the alkaline metal cations of the electrolytes employed by several authors to keep the ionic strength constant during the measurements. For instance in the case of $[Gd(DOTA)]^-$, the complex most studied of this class, stability constants ranging from log $K = 22.1$ to 28.0 have been reported [36,96–100,113] for different experiments performed at 25°C, by means of various techniques (potentiometric, spectrophotometric, kinetic), in quite different ionic media (0.1 mol dm^{-3} NMe_4Cl or NMe_4NO_3 or NaCl or KCl, and 1 mol dm^{-3} NaCl) and extensive complexation of Na^+ and K^+ occurs. Regarding the kinetic aspect, it has been observed that equilibration times of about 3 weeks are necessary in the formation of $[Gd(DOTA)]^-$ in aqueous solution at 25°C [98,100,113], while from some days to several weeks, depending on pH, are necessary for a complete acid-catalyzed dissociation of the complex at the same temperature [100]. This figure is further complicated by the presence of intermediate complex species, formed after relatively short equilibration times, which develop very slowly towards the final equilibrium [49,100,113]. Similar intermediate equilibration stages may be deceptive and erroneously interpreted as the final stage.

The problems arising from the high values of the stability constants to be determined are commonly resolved by the use of auxiliary competing ligands, while the kinetic inertness can be overcome by performing out-of-cell experiments in

which individual solutions corresponding to single points of a conventional titration are stored in a thermostat and periodically checked to ensure achievement of the equilibrium.

In order to make our presentation of equilibrium data as homogeneous as possible we will refer, when possible, to data obtained under equal, or very similar, experimental conditions in the absence of interacting electrolytes (Na^+, K^+). This does not mean that we are not confident with the other results. To help readers in the evaluation of the equilibrium data reported, we have included, when possible, the ligand protonation constants employed by the respective authors in the determination of the complex stability constants.

Tables 2 and 3 also contain equilibrium data determined in our laboratories, that have not been previously published. For a critical evaluation of the experimental procedures we employed in the determination of these new data we address the readers to Ref. [132].

In several parts of this review we will compare the stability of Gd(III) complexes with different ligands. In such cases the comparison will refer to the stability constants of the complexes formed by the fully deprotonated forms of the ligands, unless otherwise noted. Should our readers be interested in analyzing the binding properties of these ligands under particular pH conditions and concentration of metal ion and ligands, a common computer program for the determination of species distribution diagrams can be used to obtain the desired information. For this purpose we suggest the use of the computer program HySS which is readily available on the Web (http://www.chim1.unifi.it/group/vacsab/hyss.htm).

All difficulties found in the determination of the stability constants of Gd(III) complexes with polyamino-polycarboxylic ligands, are also encountered in the determination of the enthalpy changes associated with such complexation reactions, in addition to other problems connected with the relevant instrumentation and methodologies. There are two ways in which the enthalpy change accompanying a chemical process can be determined. One is to measure directly, by means of a calorimeter, the amount of heat involved in the reaction. In this case, there are instrumental limitations, at present, to the accurate determination of thermal effects that develop over very long times (days or weeks), such as those required by the complexation reactions of Gd(III) with macrocyclic polyamino-polycarboxylic ligands. As a matter of fact no calorimetrically determined enthalpy changes have been so far reported for similar complexation reactions.

The other problem consists of determining the equilibrium constants at various temperatures, and applying the Van't Hoff isochore to derive the value of $\Delta H°$.

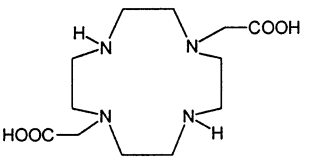
Once $\Delta H°$ is known, the entropy term $\Delta S°$ can be obtained from the relationship $\Delta G° = \Delta H° - T\Delta S°$, the standard free energy change being related to the equilibrium constant by the expression $\Delta G° = -RT \ln K$.

Of these two methods, the second may lead to high uncertainties if not used with great care. Since there is a logarithmic correlation between stability constants and $\Delta H°$, the propagation of the experimental errors in the determination of

Table 3
Equilibrium constants for protonation and Gd(III) complexation reaction with macrocyclic polyamino-polycarboxylic ligands[a]

1,4,7,10-tetraazacyclododecane-1,7-diacetic acid
DO2A

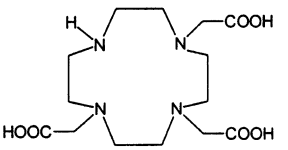
H_2L **C1**



Reaction	logK	method	T (°C)	medium (mol dm^{-3})	ref.
$L^{2-} + H^+ = LH^-$	11.38	pot.	25.0	0.1 NMe_4Cl	102
	10.91	pot.	25.0	0.1 KCl	102
	10.94	pot.	25.0	0.1 NMe_4Cl	114
$LH^- + H^+ = LH_2$	9.62	pot.	25.0	0.1 NMe_4Cl	102
	9.45	pot.	25.0	0.1 KCl	102
	9.55	pot.	25.0	0.1 NMe_4Cl	114
$LH_2 + H^+ = LH_3^+$	3.95	pot.	25.0	0.1 NMe_4Cl	102
	4.09	pot.	25.0	0.1 KCl	102
	3.85	pot.	25.0	0.1 NMe_4Cl	114
$LH_3^+ + H^+ = LH_4^{2+}$	2.62	pot.	25.0	0.1 NMe_4Cl	102
	3.18	pot.	25.0	0.1 KCl	102
	2.55	pot.	25.0	0.1 NMe_4Cl	114
$Gd^{3+} + L^{2-} = GdL^+$	19.4	pot.	25.0	0.1	102
	19.1	pot.	25.0	0.1	102
	13.06	c.e.	25.0	0.1 NMe_4Cl	114

1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid
DO3A

H_3L **C2**



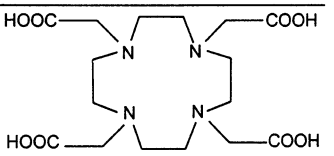
Reaction	logK	method	T (°C)	medium (mol dm^{-3})	ref.

Table 3 (*Continued*)

$L^{3-} + H^+ = LH^{2-}$	11.59	pot.	25.0	0.1 NMe_4Cl	36
	12.46	pot.	25.0	0.1 NMe_4Cl	113
$LH^{2-} + H^+ = LH_2^-$	9.24	pot.	25.0	0.1 NMe_4Cl	36
	9.49	pot.	25.0	0.1 NMe_4Cl	113
$LH_2^- + H^+ = LH_3$	4.43	pot.	25.0	0.1 NMe_4Cl	36
	4.26	pot.	25.0	0.1 NMe_4Cl	113
$LH_3 + H^+ = LH_4^+$	3.48	pot.	25.0	0.1 NMe_4Cl	36
	3.51	pot.	25.0	0.1 NMe_4Cl	113
$LH_4^+ + H^+ = LH_5^{2+}$	1.97	pot.	25.0	0.1 NMe_4Cl	113
$Gd^{3+} + L^{3-} = GdL$	21.0	sp.	25.0	0.1 NMe_4Cl	36
	22.02	pot.	25.0	0.1 NMe_4Cl	49, 113
$GdL + H^+ = GdHL^+$	2.1	sp.	25.0	0.1 NaCl	115

1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid
DOTA

H_4L **C3**



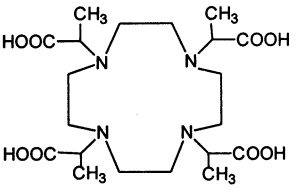
Reaction	logK	Method	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	11.14	pot.	25.0	0.1 KCl	94
	12.09	pot.	25.0	0.1 NMe_4NO_3	95
	11.73	pot.	25.0	0.1 NMe_4Cl	36
	11.74	pot.	25.0	0.1 NMe_4Cl	113
$LH^{3-} + H^+ = LH_2^{2-}$	9.69	pot.	25.0	0.1 KCl	94
	9.680	pot.	25.0	0.1 NMe_4NO_3	95
	9.40	pot.	25.0	0.1 NMe_4Cl	36
	9.76	pot.	25.0	0.1 NMe_4Cl	113
$LH_2^{2-} + H^+ = LH_3^-$	4.84	pot.	25.0	0.1 KCl	94
	4.548	pot.	25.0	0.1 NMe_4NO_3	95
	4.50	pot.	25.0	0.1 NMe_4Cl	36
	4.68	pot.	25.0	0.1 NMe_4Cl	113
$LH_3^- + H^+ = LH_4$	3.95	pot.	25.0	0.1 KCl	94
	4.130	pot.	25.0	0.1 NMe_4NO_3	95
	4.19	pot.	25.0	0.1 NMe_4Cl	36

Table 3 (*Continued*)

	4.11	pot.	25.0	0.1 NMe_4Cl	113
$LH_4^- + H^+ = LH_5^+$	2.37	pot.	25.0	0.1 NMe_4Cl	113
$Gd^{3+} + L^{4-} = GdL^-$	28.0	pot.	25.0	1 NaCl	96
	24.6	sp.	25.0 ?	0.1 NaCl?	97
	24.0	pot.	25.0	0.1 KCl	97
	27.0	pot.	25.0	0.1 NMe_4NO_3	99
	22.1	kin.	25.0	1.0 NaCl	100
	23.6	sp.	37.0	1.0 NaCl	101
	25.3	sp.	25.0	0.1 NMe_4Cl	36
	24.67	pot.	25.0	0.1 NMe_4Cl	113
$GdL^- + H^+ = GdHL$	2.3	pot.	25.0	0.1 KCl	97
	2.8	sp.	25.0	0.1 NaCl	115
	2.3	pot.	25.0	0.1 KCl	98
	1.35	pot	25.0	0.1 NaCl	96

α,α'α''α'''-tetramethyl-1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid
DOTMA

H_4L **C4**

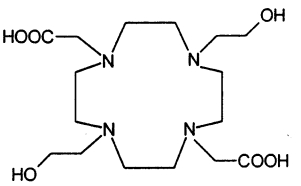


Reaction	logK	method	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	12.04(4)[a]	pot.	25.0	0.1 NMe_4NO_3	116
$LH^{3-} + H^+ = LH_2^{2-}$	8.38(1)	pot.	25.0	0.1 NMe_4NO_3	116
$LH_2^{2-} + H^+ = LH_3^-$	5.11(1)	pot.	25.0	0.1 NMe_4NO_3	116
$LH_3^- + H^+ = LH_4$	5.37(1)	pot.	25.0	0.1 NMe_4NO_3	116
$LH_4 + H^+ = LH_5^+$	2.53(3)	pot.	25.0	0.1 NMe_4NO_3	116
$Gd^{3+} + L^{4-} = GdL^-$	23.6(1)	pot.	25.0	0.1 NMe_4NO_3	116

Table 3 (*Continued*)

4,10-bis(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane-1,7-diacetic acid
DO2A-2HE

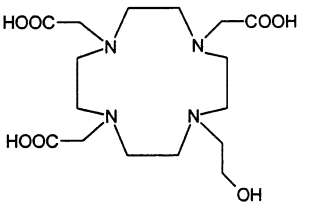
H_2L **C5**



Reaction	logK	method	T (°C)	medium (mol dm^{-3})	ref.
$L^{2-} + H^+ = LH^-$	10.71	pot.	25.0	0.1 KCl	102
$LH^- + H^+ = LH_2$	8.98	pot.	25.0	0.1 KCl	102
$LH_2 + H^+ = LH_3^+$	4.06	pot.	25.0	0.1 KCl	102
$LH_3^+ + H^+ = LH_4^{2+}$	2.73	pot.	25.0	0.1 KCl	102
$Gd^{3+} + L^{2-} = GdL^+$	21.1	pot.	25.0	0.1	102

10-(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane-1,4,7 -triacetic acid
HE-DO3A

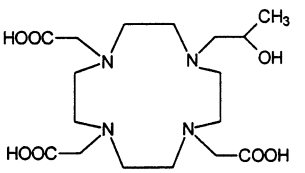
H_3L **C6**



Reaction	logK	method	T (°C)	medium (mol dm^{-3})	ref.
$L^{3-} + H^+ = LH^{2-}$	11.01	pot.	25.0	0.1 NMe_4Cl	103
$LH^{2-} + H^+ = LH_2^-$	9.28	pot.	25.0	0.1 NMe_4Cl	103
$LH_2^- + H^+ = LH_3$	4.50	pot.	25.0	0.1 NMe_4Cl	103
$LH_3 + H^+ = LH_4^+$	3.49	pot.	25.0	0.1 NMe_4Cl	103
$Gd^{3+} + L^{3-} = GdL$	22.3	sp.	25.0	0.1 NMe_4Cl	103

10-(hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid
HP-DO3A

H_3L **C7**



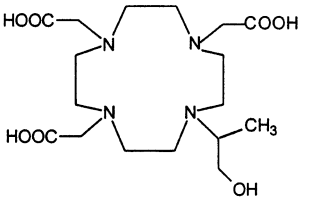
Reaction	logK	method	T (°C)	Medium (mol dm^{-3})	ref.

Table 3 (*Continued*)

$L^{3-} + H^+ = LH^{2-}$	11.96	pot.	25.0	0.1 NMe_4Cl	36
	11.17	pot.	25.0	0.1 NMe_4Cl	113
$LH^{2-} + H^+ = LH_2^-$	9.43	pot.	25.0	0.1 NMe_4Cl	36
	9.33	pot.	25.0	0.1 NMe_4Cl	113
$LH_2^- + H^+ = LH_3$	4.30	pot.	25.0	0.1 NMe_4Cl	36
	4.99	pot.	25.0	0.1 NMe_4Cl	113
$LH_3 + H^+ = LH_4^+$	3.26	pot.	25.0	0.1 NMe_4Cl	36
	3.80	pot.	25.0	0.1 NMe_4Cl	113
$LH_4^+ + H^+ = LH_5^{2+}$	2.84	pot.	25.0	0.1 NMe_4Cl	113
$Gd^{3+} + L^{3-} = GdL$	23.8	sp.	25.0	0.1 NMe_4Cl	36
	24.5	pot.	25.0	0.1 NMe_4Cl	113
$GdL + H^+ = GdHL^+$	2.4	sp.	25.0	0.1 NaCl	115
	1.1	pot.	25.0	0.1 NaCl	112

10-(2-hydroxyisopropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid
HIP-DO3A

H_3L **C8**



Reaction	logK	method	T (°C)	medium (mol dm^{-3})	ref.
$L^{3-} + H^+ = LH^{2-}$	12.4	pot.	25.0	0.1 NMe_4Cl	103
$LH^{2-} + H^+ = LH_2^-$	9.48	pot.	25.0	0.1 NMe_4Cl	103
$LH_2^- + H^+ = LH_3$	4.3	pot.	25.0	0.1 NMe_4Cl	103
$LH_3 + H^+ = LH_4^+$	3.41	pot.	25.0	0.1 NMe_4Cl	103
$Gd^{3+} + L^{3-} = GdL$	23.9	sp.	25.0	0.1 NMe_4Cl	103

4,10-bis(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,7-diacetic acid
DO2A-2HP

H_2L **C9**

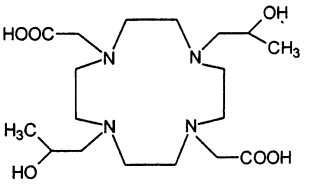
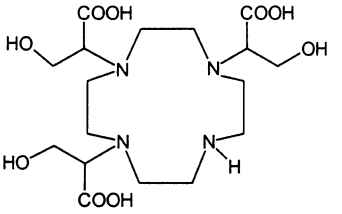


Table 3 (*Continued*)

Reaction	logK	method	T (°C)	medium (mol dm^{-3})	ref.
$L^{2-} + H^+ = LH^-$	12.23	pot.	25.0	0.1 KCl	102
$LH^- + H^+ = LH_2$	8.92	pot.	25.0	0.1 KCl	102
$LH_2 + H^+ = LH_3^+$	4.04	pot.	25.0	0.1 KCl	102
$LH_3^+ + H^+ = LH_4^{2+}$	3.00	pot.	25.0	0.1 KCl	102
$Gd^{3+} + L^{2-} = GdL^+$	22.5	pot.	25.0	0.1	102

α,α',α''-tris(hydroxymethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid
DO3A-3HM

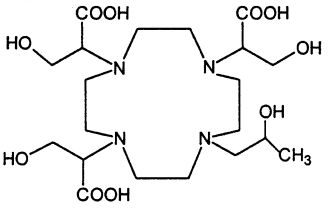
H_3L **C10**



Reaction	logK	method	T (°C)	medium (mol dm^{-3})	ref.
$L^{3-} + H^+ = LH^{2-}$	10.93	pot.	25.0	0.1 NMe_4Cl	113
$LH^{2-} + H^+ = LH_2^-$	7.07	pot.	25.0	0.1 NMe_4Cl	113
$LH_2^- + H^+ = LH_3$	4.04	pot.	25.0	0.1 NMe_4Cl	113
$LH_3 + H^+ = LH_4^+$	3.49	pot.	25.0	0.1 NMe_4Cl	113
$Gd^{3+} + L^{3-} + = GdL$	18.82	pot.	25.0	0.1 NMe_4Cl	113
$GdL + OH^- + = GdLOH^-$	2.63	pot.	25.0	0.1 NMe_4Cl	113

α,α',α''-tris(hydroxymethyl)-10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid
HPDO3A-3HM

H_3L **C11**



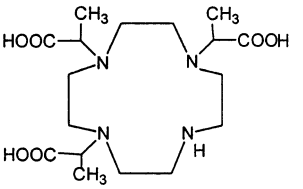
Reaction	LogK	method	T (°C)	medium (mol dm^{-3})	ref.
$L^{3-} + H^+ = LH^{2-}$	10.68	pot.	25.0	0.1 NMe_4Cl	113
$LH^{2-} + H^+ = LH_2^-$	7.81	pot.	25.0	0.1 NMe_4Cl	113
$LH_2^- + H^+ = LH_3$	4.14	pot.	25.0	0.1 NMe_4Cl	113
$LH_3 + H^+ = LH_4^+$	3.37	pot.	25.0	0.1 NMe_4Cl	113

Table 3 (*Continued*)

$Gd^{3+} + L^{3-} + = GdL$	19.4	pot.	25.0	0.1 NMe_4Cl	113

(1R,4R,7R)-α,α'-α''-trimethyl-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid
DO3MA

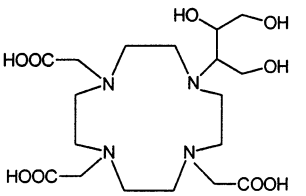
H_3L **C12**



Reaction	logK	method	T (°C)	Medium (mol dm^{-3})	ref.
$L^{3-} + H^+ = LH^{2-}$	13.46	sp.	25.0	0.1 NMe_4Cl	104
	13.38	pot.	25.0	0.1 NMe_4Cl	104
$LH^{2-} + H^+ = LH_2^-$	9.15	pot.	25.0	0.1 NMe_4Cl	104
$LH_2^- + H^+ = LH_3$	5.30	pot.	25.0	0.1 NMe_4Cl	104
$LH_3 + H^+ = LH_4^+$	4.07	pot.	25.0	0.1 NMe_4Cl	104
$Gd^{3+} + L^{3-} = GdL$	25.3	sp.	25.0	0.1 NMe_4Cl	104

0-[2,3-dihydroxy-81-hydroxymethil)-propyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid
DO3A-B

H_3L **C13**



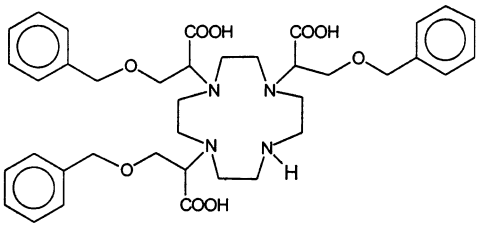
Reaction	logK	method	T (°C)	medium (mol dm^{-3})	Ref.
$L^{3-} + H^+ = LH^{2-}$	9.46	pot.	25.0	0.1 NaCl	112
	11.46	pot.	25.0	0.1 KCl	112
	11.75	pot.	25.0	0.1 Me_4NCl	112
$LH^{2-} + H^+ = LH_2^-$	9.36	pot.	25.0	0.1 NaCl	112
	9.26	pot.	25.0	0.1 KCl	112
	9.23	pot.	25.0	0.1 Me_4NCl	112
$LH_2^- + H^+ = LH_3$	4.17	pot.	25.0	0.1 NaCl	112
	4.14	pot.	25.0	0.1 KCl	112
	4.13	pot.	25.0	0.1 Me_4NCl	112

Table 3 (*Continued*)

$LH_3 + H^+ = LH_4^+$	3.02	pot.	25.0	0.1 NaCl	112
	2.96	pot.	25.0	0.1 KCl	112
	2.97	pot.	25.0	0.1 KCl	112
$Gd^{3+} + L^{3-} + = GdL$	18.7	pot.	25.0	0.1 NaCl	112
	21.8	pot.	25.0	0.1 KCl	112
	20.8	pot.	25.0	0.1 NMe_4Cl	112
$GdL + H^+ = GdHL^+$	1.1	pot.	25.0	0.1 NaCl	112

Tris[(phenylmetoxy)methyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid

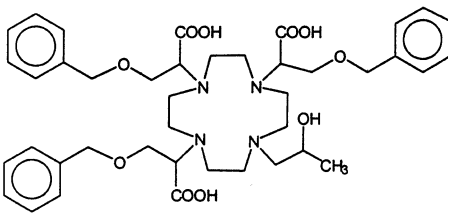
H_3L **C14**



Reaction	logK	method	T (°C)	medium (mol dm^{-3})	ref.
$L^{3-} + H^+ = LH^{2-}$	10.21(3)	pot.	25.0	0.15 NaCl	116
$LH^{2-} + H^+ = LH_2^-$	7.16(4)	pot.	25.0	0.15 NaCl	116
$LH_2^- + H^+ = LH_3$	4.53(7)	pot.	25.0	0.15 NaCl	116
$LH_3 + H^+ = LH_4^+$	4.03(6)	pot.	25.0	0.15 NaCl	116
$Gd^{3+} + L^{3-} + H^+ = GdHL^+$	18.21(3)	pot.	25.0	0.15 NaCl	116

10-(2-hydroxypropyl)-α,α',α''-tris[(phenylmetoxy)methyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid

H_3L **C15**



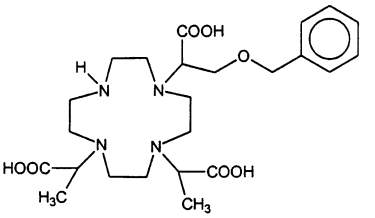
Reaction	LogK	method	T (°C)	medium (mol dm^{-3})	Ref.
$L^{3-} + H^+ = LH^{2-}$	11.35(3)	pot.	25.0	0.1 NMe_4Cl	116
$LH^{2-} + H^+ = LH_2^-$	8.04(3)	pot.	25.0	0.1 NMe_4Cl	116
$LH_2^- + H^+ = LH_3$	4.41(3)	pot.	25.0	0.1 NMe_4Cl	116

Table 3 (*Continued*)

$LH_3 + H^+ = LH_4^+$	3.53(4)	pot.	25.0	0.1 NMe_4Cl	116
$LH_4^+ + H^+ = LH_5^{2+}$	1.84(4)	pot.	25.0	0.1 NMe_4Cl	116
$Gd^{3+} + L^{3-} + = GdL$	18.37(5)	pot.	25.0	0.1 NMe_4Cl	116

α^1,α^7,dimethyl-α^4-(phenylmetoxy)methyl-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid

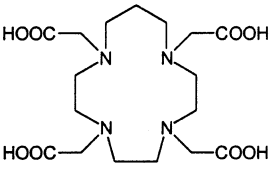
H_3L **C16**



Reaction	LogK	method	T (°C)	medium (mol dm^{-3})	Ref.
$L^{3-} + H^+ = LH^{2-}$	11.57(1)	pot.	25.0	0.1 NMe_4Cl	116
$LH^{2-} + H^+ = LH_2^-$	8.44(2)	pot.	25.0	0.1 NMe_4Cl	116
$LH_2^- + H^+ = LH_3$	4.64(2)	pot.	25.0	0.1 NMe_4Cl	116
$LH_3 + H^+ = LH_4^+$	3.92(3)	pot.	25.0	0.1 NMe_4Cl	116
$LH_4^+ + H^+ = LH_5^{2+}$	1.69(4)	pot.	25.0	0.1 NMe_4Cl	116
$Gd^{3+} + L^{3-} + = GdL$	18.57(9)	pot.	25.0	0.1 NMe_4Cl	116
$GdL + OH^- + = GdLOH^-$	3.4(1)	pot.	25.0	0.1 NMe_4Cl	116

1,4,7,10-tetraazacyclotetradecane-1,4,7,10 - tetraacetic acid
TRITA

H_4L **C17**

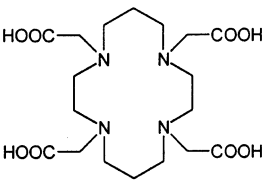


Reaction	logK	method	T (°C)	medium (mol dm^{-3})	Ref.
$L^{4-} + H^+ = LH^{3-}$	11.79	pot.	25.0	0.1 KCl	94
$LH^{3-} + H^+ = LH_2^{2-}$	9.20	pot.	25.0	0.1 KCl	94
$LH_2^{2-} + H^+ = LH_3^-$	4.00	pot.	25.0	0.1 KCl	94
$LH_3^- + H^+ = LH_4$	2.57	pot.	25.0	0.1 KCl	94
$Gd^{3+} + L^{4-} = GdL^-$	19.17	pot.	25.0	0.1 KCl	98
$GdL^- + H^{+-} = GdHL$	3.2	pot.	25.0	0.1 KCl	98

Table 3 (*Continued*)

1,4,8,11-tetraazacyclotetradecane-N,N',N'',N'''-tetraacetic acid
TETA

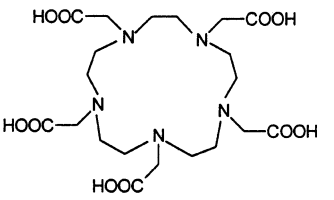
H_4L **C18**



Reaction	logK	method	T (°C)	medium (mol dm^{-3})	ref.
$L^{4-} + H^+ = LH^{3-}$	10.11	pot.	80.0	1 NaCl	105
	10.28	pot.	25.0	0.1 KCl	94
$LH^{3-} + H^+ = LH_2^{2-}$	9.50	pot.	80.0	1 NaCl	105
	10.10	pot.	25.0	0.1 KCl	94
$LH_2^{2-} + H^+ = LH_3^-$	4.02	pot.	80.0	1 NaCl	105
	4.15	pot.	25.0	0.1 KCl	94
$LH_3^- + H^+ = LH_4$	3.29	pot.	80.0	1 NaCl	105
	3.21	pot.	25.0	0.1 KCl	94
$LH_4 + H^+ = LH_5^+$	1.90	pot.	80.0	1 NaCl	105
$Gd^{3+} + L^{4-} = GdL^-$	15.75	pot.	80.0	1 NaCl	106
	13.77	pot.	25.0	0.1 KCl	98
$GdL^- + H^+ = GdHL$	3.75	pot.	80.0	1 NaCl	106
	4.52	pot.	25.0	0.1 KCl	98

1,4,7,10,13-pentaazacyclopentadecane-N,N',N'',N''',N''''-pentaacetic acid
PEPA

H_5L **C19**



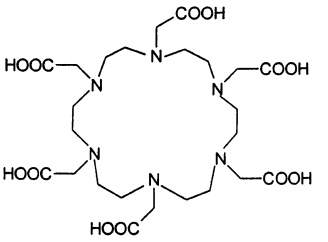
Reaction	logK	method	T (°C)	medium (mol dm^{-3})	ref.
$L^{5-} + H^+ = LH^{4-}$	10.15	pot.	25.0	0.2 $NaNO_3$	107
$LH^{4-} + H^+ = LH_2^{3-}$	9.41	pot.	25.0	0.2 $NaNO_3$	107
$LH_2^{3-} + H^+ = LH_3^{2-}$	6.14	pot.	25.0	0.2 $NaNO_3$	107
$LH_3^{2-} + H^+ = LH_4^-$	4.11	pot.	25.0	0.2 $NaNO_3$	107
$LH_4^- + H^+ = LH_5$	3.19	pot.	25.0	0.2 $NaNO_3$	107

Table 3 (*Continued*)

$Gd^{3+} + L^{5-} = GdL^{2-}$	15.88	pot.	25.0	0.2 $NaNO_3$	107

1,4,7,10,13,16-hexaazacyclooctadecane-N,N',N'',N''',N'''',N'''''-hexaacetic acid
HEHA

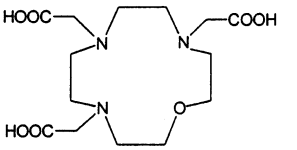
H_6L **C20**



Reaction	logK	method	T (°C)	medium (mol dm^{-3})	ref.
$L^{6-} + H^+ = LH^{5-}$	10.10	pot.	25.0	0.2 $NaNO_3$	107
$LH^{5-} + H^+ = LH_2^{4-}$	10.01	pot.	25.0	0.2 $NaNO_3$	107
$LH_2^{4-} + H^+ = LH_3^{3-}$	8.92	pot.	25.0	0.2 $NaNO_3$	107
$LH_3^{3-} + H^+ = LH_4^{2-}$	8.20	pot.	25.0	0.2 $NaNO_3$	107
$LH_4^{2-} + H^+ = LH_5^-$	4.64	pot.	25.0	0.2 $NaNO_3$	107
$LH_5^- + H^+ = LH_6$	3.53	pot.	25.0	0.2 $NaNO_3$	107
$Gd^{3+} + L^{6-} = GdL^{3-}$	22.95	pot.	25.0	0.2 $NaNO_3$	107
$Gd^{3+} + H_2L^{4-} = GdH_2L^-$	17.26	pot.	25.0	0.2 $NaNO_3$	107

1-oxa-4,7,10-triazacyclododecane-N,N',N''-triacetic acid
N-ac3[12]ane N_3O

H_3L **C21**

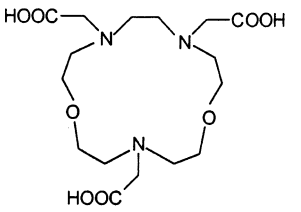


Reaction	logK	method	T (°C)	medium (mol dm^{-3})	ref.
$L^{3-} + H^+ = LH^{2-}$	11.24	pot.	25.0	0.1 KCl	108
$LH^{2-} + H^+ = LH_2^-$	7.76	pot.	25.0	0.1 KCl	108
$LH_2^- + H^+ = LH_3$	4.00	pot.	25.0	0.1 KCl	108
$LH_3 + H^+ = LH_4^+$	2.59	pot.	25.0	0.1 KCl	108
$Gd^{3+} + L^{3-} = GdL$	21.6	pot.	25.0	0.1 KCl	108
$GdL + H^+ = GdHL^+$	1.45	pot.	25.0	0.1 KCl	108
$GdL + OH^- = GdLOH^-$	3.43	pot.	25.0	0.1 KCl	108

Table 3 (*Continued*)

1,7-dioxa-4,10,13-triazacyclopentadecane-N,N',N''-triacetic acid
N-ac$_3$[15]ane N_3O_2

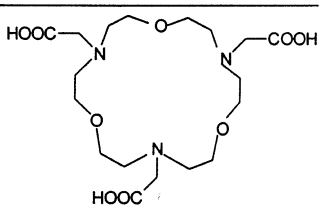
H_3L **C22**



Reaction	logK	method	T (°C)	medium (mol dm^{-3})	ref.
$L^{3-} + H^+ = LH^{2-}$	9.55	pot.	25.0	0.1 KCl	108
$LH^{2-} + H^+ = LH_2^-$	8.92	pot.	25.0	0.1 KCl	108
$LH_2^- + H^+ = LH_3$	4.51	pot.	25.0	0.1 KCl	108
$LH_3 + H^+ = LH_4^+$	1.59	pot.	25.0	0.1 KCl	108
$Gd^{3+} + L^{3-} = GdL$	17.23	pot.	25.0	0.1 KCl	108
$GdL + H^+ = GdHL^+$	2.32	pot.	25.0	0.1 KCl	108
$GdL + OH^- = GdLOH^-$	10.79	pot.	25.0	0.1 KCl	108

1,4,7-trioxa-4,10,16-triazacycloctadecane-N,N',N''-triacetic acid
N-ac$_3$[18]ane N_3O_3

H_3L **C23**

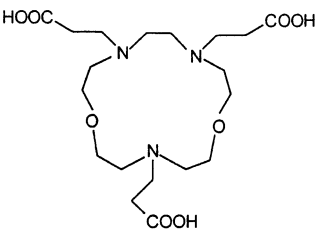


Reaction	LogK	method	T (°C)	medium (mol dm^{-3})	Ref.
$L^{3-} + H^+ = LH^{2-}$	9.57	pot.	25.0	0.1 KCl	108
$LH^{2-} + H^+ = LH_2^-$	8.15	pot.	25.0	0.1 KCl	108
$LH_2^- + H^+ = LH_3$	7.67	pot.	25.0	0.1 KCl	108
$LH_3 + H^+ = LH_4^+$	2.05	pot.	25.0	0.1 KCl	108
$LH_4^+ + H^+ = LH_5^{2+}$	1.07	pot.	25.0	0.1 KCl	108
$Gd^{3+} + L^{3-} = GdL$	18.02	pot.	25.0	0.1 KCl	108

Table 3 (*Continued*)

1,7-dioxa-4,10,13-triazacyclopentadecane-4,10,13-tripropionic acid
N-pr3[15]ane N_3O_2

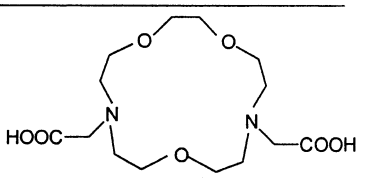
H_3L **C24**



Reaction	LogK	method	T (°C)	medium (mol dm^{-3})	ref.
$L^{3-} + H^+ = LH^{2-}$	8.16	pot.	25.0	0.1 $NaClO_4$	111
$LH^{2-} + H^+ = LH_2^-$	7.14	pot.	25.0	0.1 $NaClO_4$	111
$LH_2^- + H^+ = LH_3$	4.79	pot.	25.0	0.1 $NaClO_4$	111
$Gd^{3+} + L^{3-} = GdL$	11.23	pot.	25.0	0.1 $NaClO_4$	111

1,7-diaza-4,10,13-trioxacyclopentadecane-N,N'-diacetic acid
dacda

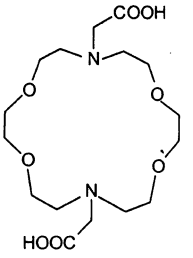
H_2L **C25**



Reaction	LogK	method	T (°C)	medium (mol dm^{-3})	ref.
$L^{2-} + H^+ = LH^-$	9.02	pot.	25.0	0.1 NMe_4Cl	110
$LH^- + H^+ = LH_2$	8.79	pot.	25.0	0.1 NMe_4Cl	110
$LH_2 + H^+ = LH_3^+$	2.95	pot.	25.0	0.1 NMe_4Cl	110
$Gd^{3+} + L^{3-} = GdL$	11.66	pot.	25.0	0.1 NMe_4Cl	110

1,10-diaza-4,7,13,16-tetraoxacyclooctadecane-N,N'-diacetic acid
dacda, K22DA

H_2L **C26**



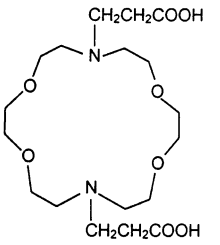
Reaction	LogK	method	T (°C)	medium (mol dm^{-3})	ref.

Table 3 (*Continued*)

$L^{2-} + H^+ = LH^-$	8.45	pot.	25.0	0.1 NMe_4Cl	109
$LH^- + H^+ = LH_2$	7.80	pot.	25.0	0.1 NMe_4Cl	109
$LH_2 + H^+ = LH_3^+$	2.90	pot.	25.0	0.1 NMe_4Cl	109
$Gd^{3+} + L^{3-} = GdL$	11.93	pot.	25.0	0.1 NMe_4Cl	109

1,10-diaza-4,7,13,16-tetraoxacyclooctadecane-N,N'-di-β-propionic acid
K22DP

H_2L **C27**

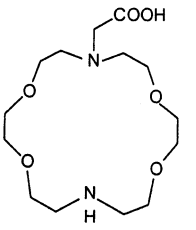


Reaction	LogK	Method	T (°C)	medium (mol dm^{-3})	ref.
$L^{2-} + H^+ = LH^-$	8.97	pot.	25.0	0.1 NMe_4Cl	115
$LH^- + H^+ = LH_2$	8.16	pot.	25.0	0.1 NMe_4Cl	115
$Gd^{3+} + L^{3-} = GdL$	7.02	pot.	25.0	0.1 NMe_4Cl	115

1,10-diaza-4,7,13,16-tetraoxacyclooctadecane-N-acetic acid

K22MA

H_2L **C28**



Reaction	logK	method	T (°C)	medium (mol dm^{-3})	ref.
$L^{2-} + H^+ = LH^-$	8.80	pot.	25.0	0.1 NMe_4Cl	115
$LH^- + H^+ = LH_2$	7.26	pot.	25.0	0.1 NMe_4Cl	115
$Gd^{3+} + L^{3-} = GdL$	7.29	pot.	25.0	0.1 NMe_4Cl	115

[a] Values in parenthesis are standard deviations in the last significant figures.

[b] Method abbreviation are pot. (potentiomeric), sp. (spectrophotometric), ca. (calorimetric), kin. (kinetic), ion exc. (ion exchange), distr. (electrophoretic). Log *K* values with standard devition in parentheses refer to equilibrium constants not previously reported [116,132]

equilibrium constants on the enthalpy values is exponential:

$$\delta(R \log K)/\delta(1/T) = -\Delta H°$$

and

$$\log K = -\Delta H°/2.303RT + \text{const}$$

Therefore, the temperature range explored should be as wide as possible and the equilibrium constants have to be of great accuracy. However, the temperature range of study is limited by the experimental conditions, such as solvent boiling and freezing point, etc. and the assumed constancy of $\Delta H°$ with temperature is less likely to occur the larger the temperature range used. Thus, the dependence of ΔC_p with temperature should be known to correct the enthalpy for its temperature variation, $\delta(\Delta H°)/\delta T = \Delta C_p$.

In conclusion, the direct method is, by far, much more accurate provided that adequate instrumentation (calorimeter) is used.

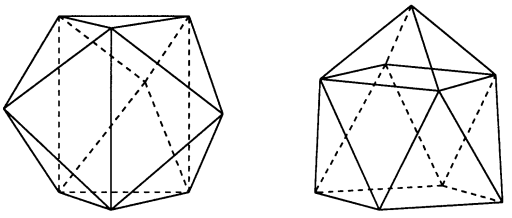
4. General information regarding Gd(III)

The development of the coordination chemistry of the lanthanides (Ln) dates back to about 1950, when the first studies involving the Ln(III) ions in solution were performed for analytical and separation purposes [133–135], but only by the end of the 1970s did Gd(III) become the subject of specific coordination studies, since it was recognized of practical use in MRI investigations [1,4].

Gadolinium is the seventh element of the lanthanide series. The most stable state of lanthanides in their complexes is the Ln(III) ion in which all outer electrons reside in the 4f orbitals. Hence, Gd(III) has a $4f^7$ configuration corresponding to an $^8S_{7/2}$ electronic ground state, all 4f orbitals being singly occupied. Accordingly the Gd(III) ion is colorless and displays a high magnetic moment.

Because of the large number of unpaired electrons, in addition to its especially long electron relaxation time, Gd(III) became of great interest as a contrast medium for MRI.

An important characteristic of lanthanides is the occurrence of the so-called lanthanide contraction, a steady decrease in atomic and ionic size with increasing atomic number. A principal cause of such contraction is the electronic effect of increasing nuclear charge imperfectly screened by 4f electrons. As a consequence of this size contraction the charge density of the Ln(III) ions increases along the series affecting their chemical properties which undergo a gradual change. Nevertheless, this trend is not completely smooth, and there is considerable evidence of discontinuity in various properties around Gd(III). For instance the stability of many Ln(III) complexes increases, along the series, with decreasing ion size (increasing charge density), but the trend is reversed, or discontinuous, at Gd(III). To explain such a 'gadolinium break' the existence of a small LFSE associated with partially occupied 4f orbitals (no stabilizing contributions are expected for high spin f^7 ions) has been suggested, although a change in coordination number from nine to eight,



tricapped trigonal prism capped square antiprism

Fig. 1. Coordination environments of Gd(III) in the hydrated ions $[Gd(H_2O)_8]^{3+}$ [138] and $[Gd(H_2O)_9]^{3+}$ [139].

determined by the ion size contraction and occurring at Gd(III), may also be a major cause of this phenomenon.

Accordingly, there is a general opinion that the number n of water molecules directly bound to the metal in the solvated $[Ln(H_2O)_n]^{3+}$ ion changes with ion size, being nine for the lighter lanthanides and eight for the heavier ones. There is also evidence of the fact that n may vary with ionic strength, increasing with increasing Gd(III) concentration [136,137].

Salts containing both $[Gd(H_2O)_8]^{3+}$ and $[Gd(H_2O)_9]^{3+}$ have been isolated and characterized by X-ray analysis [138,139]. Fig. 1 displays the structure of these hydrated ions as observed in the 4,4′-bipyridyl clathrate of $[Gd(H_2O)_8]Cl_3$ [138] and in $[Gd(H_2O)_9](C_2H_5SO_4)_3$ [139]. The coordination polyhedron of the octaaqua-gadolinium(III) cation is a dodecahedron (Fig. 1(a)), while that of the enneaaqua-gadolinium(III) cation is a tricapped trigonal prism (Fig. 1(b)).

Enneacoordination is the most typical coordination environment of Gd(III) complexes. Based on a repulsive model (VSEPR), the tricapped trigonal prismatic geometry (Fig. 2) generates the most stable stereochemistry for coordination number nine, the capped square antiprismatic geometry (Fig. 2) being slightly less stable [140]. Both coordination geometries are frequently recognized in the crystal structures determined for Gd(III) complexes, although irregular polyhedra are also commonly found, especially when different ligands, or ligands with steric con-

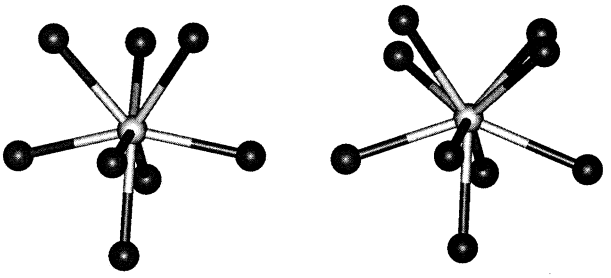


Fig. 2. Coordination polyhedrons in tricapped trigonal prismatic (left) and capped square antiprismatic (right) geometries.

straints, participate in the complex formation. There is some tendency to rationalize these irregular polyhedra in terms of semiregular polyhedra, although unequivocal descriptions of similar coordination environments cannot be made. Thus an enna-coordinated complex may be described well both as distorted tricapped prismatic and as distorted capped square antiprismatic. In such cases the assignment of coordination geometry must be critically evaluated.

5. Acyclic ligands

Equilibrium data ($\log K$, $\Delta H°$ and $T\Delta S°$) for Gd(III) complexation by acyclic polyamino-polycarboxylic ligands are listed in Table 2.

In spite of some discrepancy in the values of the stability constants reported [13–15] for the 1:1 Gd(III) complexes with glycine (**L1**), $\log K = 3.3–4.0$ seems to be acceptable for complexation reactions studied in solution with 0.1 mol dm^{-3} ionic strength (I) at 25–35°C. Such values, when compared with the stability constants reported for the 1:1 complexes of Gd(III) with ammonia [31] and acetate [8–12], are clearly indicative of the chelating nature of glycine. The equilibrium constant for the formation the $[Gd(\mathbf{L1})_2]^+$ complex was also reported ($\log K = 6.5$ for $Gd^{3+} + 2\mathbf{L1}^- = [Gd(\mathbf{L1})_2]^+$, $I = 0.1$ mol dm^{-3}, 25°C) [15]. The reduced difference between the equilibrium constants for the binding of the first and the second ligand molecules is consistent with the high number of coordinative positions available on the metal ion.

Replacement of an amine hydrogen of glycine by a CH_2–COOH group, leads to the iminodiacetic acid (**L2**), whose fully deprotonated form behaves as a tridentate ligand. The presence of an additional carboxylate binding group in **L2** is reflected by a stability increment for the 1:1 complex of about 3 log units [16–18] with respect to **L1**. The stability constants of the 1:2 of **L2** complex were also determined. As previously observed for glycine, also the equilibrium constants for binding of the second ligand of **L2** is considerably high, compared with binding of the first one, in agreement with numerous ligand coordination sites. Potentiometric measurements performed in very alkaline solution with ligand to metal molar ratios up to 10 furnished some evidence of the existence of complexes containing more than two ligand molecules per metal ion, but the errors inherent in measurements performed under these conditions were such that no satisfactory stability constants could be obtained [17]. Hence, the existence of such complexes could not be confirmed nor excluded.

Functionalization of the amine group of **L2** has been carried out by insertion of CH_3, CH_2–CH_2–OH, CH_2–CH_2–O–CH_3, CH_2–benzene and CH_2–(*o*-phenol) groups leading to the **L3**–**L7** ligands, respectively. All these ligands in their fully deprotonated forms bind Gd(III) forming stable complexes with 1:1 and 1:2 stoichiometry. The stability constants reported for the 1:1 complexes [19–22,25,26,32] indicate important modifications of the ligand binding properties brought about by the different substituents. Actually, while the insertion of methyl and benzyl groups (**L3**, **L6**) does not significantly affect the complex stability, stability increases of

about 1, 2, and 6.5 log K units were found for **L5** (CH_2–CH_2–O–CH_3), **L4** (CH_2–CH_2–OH), and **L7** (CH_2–(*o*-phenol)), respectively, indicating very good coordination properties of phenolate oxygens towards Gd(III), a lower, although appreciable, binding ability of alcoholic oxygens, and modest coordination properties of ethereal ones. Evidently coordination of the **L7** ligand to the metal ion is favored by the presence of an additional negative charge produced by deprotonation of the phenol group.

The 1:2 complexes of these ligands also display considerable stability, both in an absolute sense and relative to the 1:1 species, the stability trend observed for the 1:1 complexes (**L3** ≈ **L6** < **L5** < **L4** ≪ **L7**) being maintained for the 1:2 ones.

These observations suggested that even in the case of the ligand **L7**, containing a bulky CH_2–(*o*-phenol) group, no steric hindrance occurs between the two ligands in the 1:2 complex, in spite of the fact that eight coordination sites are occupied by the ligand molecules on the metal ion [25].

L7 also forms monoprotonated 1:1 and diprotonated 1:2 complexes in which the phenol groups are protonated. Comparative analysis of the equilibrium constants for the formation of **L7** and **L2** complexes with all lanthanide ions from Y(III) to Lu(III) suggested that **L7** is likely to behave as a tridentate ligand, the protonated phenol group not being involved in the coordination [25]. The second stepwise stability constant of the diprotonated 1:2 complex ($K = [Gd(HL)_2^-]/[GdHL^+][HL^{2-}]$) is higher by 0.59 log K units than the first constant. This situation is very unusual, since the second stepwise stability constant does not generally exceed the first one, and it is not observed for any other complex of **L7** with metal ions different from lanthanides. This peculiarity was ascribed to hydrogen bonding between the free phenol group of each ligand molecule and the other ligand molecule in the 1:2 complex.

Substitution of the amine hydrogen of the iminodiacetic acid **L2** by a CH_2–COOH group generates the nitrilotriacetic acid **L8**, characterized by a symmetrical tripod structure containing four potential donor groups. **L8** forms Gd(III) complexes with both 1:1 and 1:2 stoichiometry. The equilibrium constants for the formation of these complexes [27–31,116] are significantly higher than those found for the analogous complexes of **L2**, in accordance with the involvement of all four donor groups in the coordination to the metal ion.

The enthalpy change for the formation of the 1:1 complex was first estimated by following the dependence of the stability constant with temperature [27]. In spite of the fact that no significant variations of the log K value were found, within the presumed experimental errors, at the various temperatures considered in the range 15–40°C, no unequivocal trend in log K values was observed; a $\Delta H°$ value of 4.3 kJ mol^{-1} was calculated and reported. The enthalpy change for the same complexation reaction was later measured by means of a microcalorimetric technique which furnished a reliable value of -3.9 kJ mol^{-1} [28]. The small, but favorable, enthalpic contribution indicates that the stability of the 1:1 complex of Gd(III) with **L8** is mostly determined by the largely favorable entropic term ($T\Delta S° = 59.5$ kJ mol^{-1}), which can be ascribed to the strong desolvation produced by the charge

neutralization accompanying the complexation reaction. No microcalorimetric enthalpy changes for the formation of the 1:2 complex are available.

Several derivatives of nitrilotriacetic acid (**L9**–**L14**) were considered for Gd(III) complexation in solution [24,32,33]. These ligands do not contain additional donor groups and hence, similarly to **L8**, they are expected to behave at most as tetradentate ligands. Stability constants for both 1:1 and 1:2 complexes were reported for **L10**–**L12** and **L14**. In the case of the benzyl derivative **L9** only the equilibrium constant for the addition of one ligand molecule to the 1:1 complex was reported [32]. Only the stability constant of the 1:1 complex was reported for **L13**, although electrophoretic measurements also revealed the formation of the 1:2 complex [24]. The coordination properties of these molecules [24,32,33] are very similar to that of the parent ligand **L8**, apart from the modest increase of complex stability found for the methyl derivative **L10** and the stability decrease reported for the complexes of **L14** containing a 2-propyl substituent [33]. For all these ligands the equilibrium data for the formation of the 1:1 and 1:2 Gd(III) complexes are consistent with the involvement of all donor atoms in the coordination to the metal ion.

As far as complexes of the previous tripod **L8**–**L14** ligands with the whole series of lanthanide(III) ions are concerned [24,27–33], it is noted that the difference between the first and the second stepwise stability constants for the formation of 1:1 and 1:2 species is rather small and remains nearly constant across the series, as expected for complexes in which there are no particular steric effects as the size of the metal ion decreases. In other words, two such ligand molecules do not suffer significant steric hindrance in the 1:2 complexes of lanthanide, including Gd(III).

A similar consideration was also reported for the ligand **L15** which can be considered another **L8** derivative, ideally obtained by removing a hydrogen atom of each of two methylene groups of **L8** and incorporating these two groups into a piperidine ring [34]. **L15** form 1:1 and 1:2 Gd(III) complexes of slightly lower stability than **L8**. Examination of molecular models of these two ligands indicated that **L15** should be more suited for coordination to the metal ion and, hence, the lower stability was ascribed to the lower basicity of the nitrogen donor atoms of **L15** [34].

Another aminotricarboxylic ligand (**L16**) not having a tripod structure was considered for Gd(III) complexation [23]. The 1:1 complex (the only complex reported) displayed reduced stability with respect to those of nitrilotriacetic acid **L8** and all its tripod-like derivatives.

A large number of aminocarboxylic ligands used for Gd(III) complexation are based on the ethylendiamine structure. In **L17** an acetic residue has been inserted on each amine nitrogen of ethylenediamine, giving rise to a diaminodiacetic ligand able to bind the metal ion via the formation of three five-membered chelate rings. Complexes with both 1:1 and 1:2 metal to ligand stoichiometry were found [88]. The stability of both species is intermediate with respect to the analogous complexes formed by the monoaminodiacetic ligand **L2** and the monoaminotriacetic ligand **L8**, indicating that the formation of a five-membered N–Gd–N chelate ring contributes to a lower extent than five-membered N–Gd–O(carboxylate) chelate rings to the stability of the Gd(III) complexes.

The enthalpy changes, and the derived entropies, for the formation of both 1:1 and 1:2 **L17** complexes were microcalorimetrically determined on the basis of equilibrium constants extrapolated at 1.0 mol dm^{-3} ionic strength [89] from values obtained at 0.1 mol dm^{-3} [88]. The complexation reactions are favored by both enthalpic and entropic contributions, the latter being predominant in accordance with the large desolvation determined by the charge neutralization occurring upon metal ion interaction with the negatively charged ligand. The greater charge neutralization occurring in the first complexation stage determines a larger entropic contribution. On the other hand, since desolvation is an endothermic process, the enthalpy change for the formation of the 1:1 complex is lower than that found for the 1:2 species.

Three derivatives of ethylenediamine containing three acetic substituents and one methyl (**L18**), or benzyl (**L19**) or hydroxyethyl (**L20**) group, respectively, were studied for analytical assay of lanthanides and for their separation by ion exchange [28,44–46,60,61,66]. These ligands have been found to only form 1:1 complexes with lanthanide(III) ions including Gd(III). The stability constants for such Gd(III) complexes indicate a similar binding ability of the pentadentate ligands **L18** [60,61] and **L19** [66,116], while **L20** bearing an additional alcoholic oxygen donor atoms displays a larger propensity to bind this metal ion [28,44–46]. Since pentadentate chelation of lanthanide(III) ions by **L18** was assessed by ^{1}H-NMR measurements [90], the larger stability of the Gd(III) complex with **L20** can be ascribed to the involvement of the alcoholic oxygen in the coordination. The hexadentate coordination of **L20** is supported by the more favorable enthalpy change measured for the Gd(III) complex of this ligand [28] with respect to the **L18** complex [61]. Both enthalpic and entropic contributions are favorable to the formation of these complexes the entropic one being largely dominant.

It is noteworthy that the stability constants for the formation of the Gd(III) complexes with **L18** and **L19** are only 1–1.5 log units higher than the stability constants reported for the 1:1 complex with the nitrilotriacetic acid **L8** which contains only one amine group. This observation suggests that the stability of such complexes is principally determined by the number of carboxylate groups, the amine groups furnishing a minor contribution.

On the contrary, a significant stability enhancement ($\Delta\log K = 4.37$; 25°C, $I = 0.1$ mol dm^{-3}, stability constants potentiometrically determined) is observed when the Gd(III) complex of **L18** [60] is compared with the complex of EDTA (**L21**) [116] which contains an additional acetate group. Such stability enhancement has been interpreted as proof of the hexadentate chelation of Gd(III) by EDTA in solution. This coordination behavior of **L21** has been confirmed in the solid state by the crystal structure of the $Na[Gd(\mathbf{L21})(H_2O)_3]$ compound containing the $[Gd(\mathbf{L21})(H_2O)_3]^-$ complex anion in which the Gd(III) ion displays a coordination number nine, being coordinated to two nitrogen and four oxygen atoms of **L21** and three oxygen atoms of water molecules [117] (Fig. 3). It seems reasonable that such a structure is retained in solution. Hence, complexation of Gd(III) in aqueous solution by **L21** is expected to occur through the replacement of six water molecules in the aqua ion $[Gd(H_2O)_9]^{3+}$ by six donor atoms of the ligands. A similar reaction

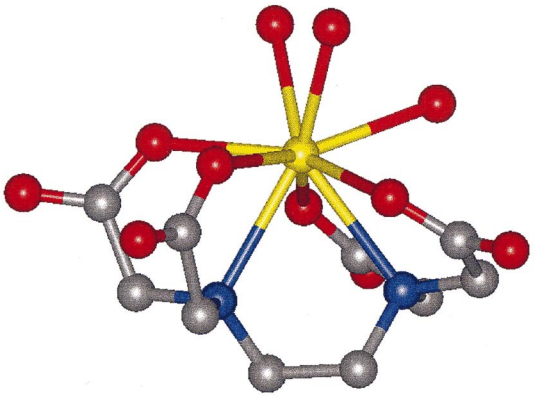


Fig. 3

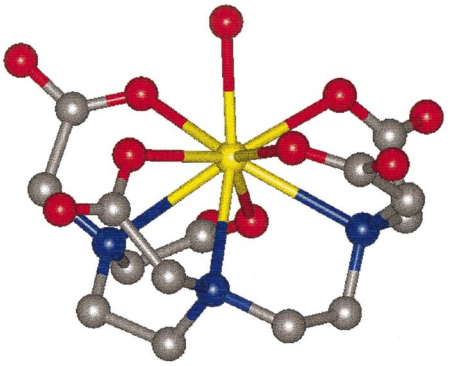


Fig. 4

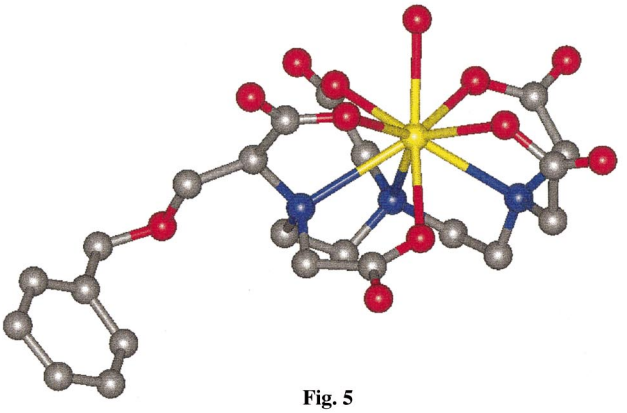


Fig. 5

Fig. 3. Crystal structure of $[Gd(\mathbf{L21})(H_2O)_3]^-$ (**L21** = EDTA) [117]. Gd, yellow; N, blue; O, red; C gray.
Fig. 4. Crystal structure of $[Gd(\mathbf{L55})H_2O]^{2-}$ (**L55** = DTPA) [93]. Gd, yellow; N, blue; O, red; C gray.
Fig. 5. Crystal structure of $[Gd(\mathbf{L56})H_2O]^{2-}$ (**L56** = BOPTPA) [83]. Gd, yellow; N, blue; O, red; C gray.

is accompanied by an important desolvation of the reacting species due both to the release of six water molecules from the first solvation sphere of the metal ion and the general mobilization of solvent molecules determined by the charge neutralization accompanying complex formation. Accordingly complexation of Gd(III) by **L21** is promoted by a largely favorable entropic contribution, the enthalpic one also being favorable although of minor importance [28].

The stability constant of the Gd(III) complex with **L21** has been determined in numerous studies by means of different methods under different experimental conditions, the log K values obtained vary in the range 16.28–17.7 [28,35–42].

EDTA (**L21**) has proven particularly useful for metal ion coordination, and a large number of ligand modifications have been developed in attempts to enhance its binding ability. According to the aim of this review, we will consider here only those **L21** derivatives that have been employed for Gd(III) complexation [28,35,43,47,48,50–59,62–65,68–73,77–80,116]. Hence, three kinds of modifications will be considered: (i) insertion of substituents on the ethylenic chain connecting the two nitrogen atoms (**L22**–**L34**); (ii) insertion of substituents on the carbon atoms connecting the carboxylate groups to the nitrogen atoms (**L35**–**L38**); and (iii) elongation of the chain connecting the two nitrogen atoms (**L39**–**L48**). In (i) and (ii) the modifications considered do not change the set of donor atoms of **L21**, while modifications of type (iii) involve, in some cases, the use of ethereal oxygen atoms, which may act as donors, to elongate the chain. The insertion of amine and/or carboxylate groups will not be considered modifications of EDTA (**L21**), even when the structural features of EDTA can be recognized after the modification, since such insertions give rise to different polyamino-polycarboxylic ligands.

Polarographic measurements performed at 20°C revealed that mono-substitution of type (i), performed by insertion of $-(CH_2)_nCH_3$ ($n = 0$–3, 5; **L22**–**L26**) or $-(CH_2)_mCH(CH_3)_2$ ($m = 0$, 1; **L27**, **L28**) groups enhances the coordinating ability of the ligand, the stability increase being almost independent of the substituent structure, as shown by the small difference in stability between the Gd(III) complexes of **L22**–**L28** (log $K = 18.21$–18.56) [48,54–57]. An inductive effect of the substituents and preorientation of donor atoms determined by the groups inserted has been invoked to account for the stability enhancement observed.

In contrast a similar ligand functionalization obtained by insertion of a phenyl group (**L29**) does not produce a significant modification of the ligand binding properties toward Gd(III) [62]. Similar results were observed for the ligand **L30** containing two methyl groups on the same carbon atom of the ethylenic chain [53].

Interesting results were obtained by functionalization of both carbon atoms of the ethylenic chain connecting the two amine groups in the EDTA structure, by using methyl and phenyl substituents. Such functionalization gave rise to *meso* and DL isomers of **L31** (2,3-diaminobutane-*N*,*N*,*N*′,*N*′-tetraacetic acid) and **L32** (1,2-diphenylethylenediamine-*N*,*N*,*N*′,*N*′-tetraacetic acid) which display very different coordination properties. While *meso*-**L31** does not show significant modification of the binding ability (log $K = 16.51$–17.03; 20°C, $I = 0.1$ mol dm^{-3}) with respect to EDTA, the Gd(III) complex of DL-**L31** exhibits an apparent increase in stability

(log $K = 18.64–18.84$; 20°C, $I = 0.1$ mol dm^{-3}) [58,59]. An even more evident stability enhancement was found for the Gd(III) complex of DL-**L32** (log $K = 20.29$; 25°C, $I = 0.1$ mol dm^{-3}) [116], in contrast to the large stability loss observed for the *meso*-**L32** complex (log $K = 11.66$; 20°C, $I = 0.1$ mol dm^{-3} [47]. The different behavior of the *meso* and DL isomers was accounted for, in the case of **L31**, by considering the conformational strain imposed by the proximity of the two adjacent methyl groups in the chelated ethylenediamine moiety of the *meso* complex [59]. The same argument can be applied to **L32**, since a greater conformational strain, and a consequent stability loss, is expected to occur in the complex of *meso*-**L32**, owing to the presence of the bulkier phenyl groups. On the other hand the greater stability of the DL-**L32** complex seems to be determined by a greater ligand preorganization.

Actually **L21** does not contain the donor atoms in the most appropriate orientation for complexation, since the two $N(CH_2COOH)_2$ groups can freely rotate around the central ethylenic chain. A better preorientation of the set of donor atoms in EDTA (**L21**) was achieved by incorporating the ethylenic chain of EDTA in a cyclohexane ring, obtaining the *trans*-1,2-diaminocyclohexane-*N*,*N*,*N*′,*N*′-tetraacetic acid (**L33**), in which the cyclohexane ring forces the $N(CH_2COOH)_2$ groups to maintain an appropriate arrangement for coordination. Successfully, **L33** displays enhanced coordinating ability, the stability constant of its Gd(III) complexes being higher, by more than one order of magnitude, than those of the **L21** complex [28,35,50–52].

The enthalpy change for complexation of Gd(III) by **L33** was estimated by determining the complex stability constants at three different temperatures in the range 20–39.9°C [50]. The thermodynamic parameters obtained indicate that the formation of this complex is determined by a very large entropic contribution ($T\Delta S° = 131$ kJ mol^{-1}) the enthalpic one being unfavorable ($\Delta H° = 24$ kJ mol^{-1}). While a more favorable entropic contribution is expected for **L33** in the formation of the Gd(III) complex with respect to **L21** ($T\Delta S° = 70$ kJ mol^{-1} [28]) due to the greater preorganization of the former ligand for coordination, an enthalpy loss of about 47 kJ mol^{-1} is rather surprising considering the strict analogy with **L21** ($\Delta H° = -22.9$ kJ mol^{-1}[28]). Such a difference in the enthalpic contribution, not commented on by the authors [28], must be critically evaluated considering that thermodynamic data for **L21** were microcalorimetrically measured while those for **L33** derive from the determination of equilibrium constants at only three, very close temperatures (see Section 4).

Another EDTA derivative (**L34**), very similar to **L33**, but containing a cyclopentane ring instead of the cyclohexane one, was considered for Gd(III) complexation. The unique stability constant reported for the **L34** complex demonstrates that, also in this case, the greater preorganization of the ligand imposed by the structural modifications made to EDTA gives rise to a significant increase (by about one log K unit) of complex stability [63].

Modifications of type (ii) were made in order to study the effect of alkyl substituents, in the position α to the carboxylate groups of EDTA (**L21**), on the coordination properties of this ligand [64,65]. For this purpose both *n*-alkyl

(**L35**–**L37**) and *iso*-alkyl (**L38**) substituents were considered. Equilibrium data obtained at 20°C, $I = 0.1$ mol dm^{-3}, indicate that, while the presence of two methyl groups (**L35**) does not significantly modify the stability constants of the Gd(III) complex ($\log K = 17.0$) with respect to that of **L21**, although a modest stability decrease can be recognized [65], a moderate to marked stability loss is found when two ethyl or *n*-propyl (**L36**, **L37**; $\log K = 16.48$, 16.60) or two *iso*-propyl substituents (**L38**; $\log K = 13.47$) are considered [64]. This is due to the steric hindrance for chelation brought about by such substituents.

Regarding the type (iii) EDTA (**L21**) modifications, first of all let us consider the simple elongation of the $N(CH_2)_nN$ chain connecting the two nitrogen atoms ($n = 2$ for EDTA), achieved by increasing the number of methylene groups. Ligands **L39**, **L42**–**L44** ($n = 3$–6) were considered for Gd(III) complexation in solution [43,68,69,72,73]. In spite of the rather different experimental conditions employed in the determination of the thermodynamic parameters for Gd(III) complexation with such ligands and EDTA, some interesting features can be identified. First of all the complex stability undergoes marked decreases of about 3.5 log units on passing from EDTA ($n = 2$) to **L39** ($n = 3$) and from **L39** to **L42** ($n = 4$), while considerably smaller variations are observed for the longer ligands **L43** ($n = 5$) and **L44** ($n = 6$). Secondly, the complexes with the longer ligands ($n = 4$–6) display a marked tendency to undergo protonation, while similar behavior is not observed for EDTA and **L3**, the equilibrium constants for proton binding being typical of amine groups. Finally, the formation of 1:1 complexes with **L39** and **L42** are promoted by largely favorable entropic contributions, the enthalpic ones being unfavorable. The stability loss observed with increasing separation of the two amine groups is clear evidence of the fact that six- and seven-membered chelate rings are increasingly less suitable than five-membered ones for fitting the coordination sphere of a metal ion, such as Gd(III), which forms complexes with high coordination numbers. Commonly, large chelate rings reduce the interaction of the amine groups with the metal ion favoring the cleavage of the coordinative N–Gd(III) bonds and the formation of protonated complexes. On the other hand, the insertion of additional methylene groups is less effective for large than for small chelate rings, representing, in proportion, a smaller structural modification for larger chelate rings. The weakening of the metal to ligand interaction, observed upon increasing the length of the $N(CH_2)_nN$ chain, is consistent with the observed loss of complexation enthalpy, the reactions of Gd(III) with **L39** ($n = 3$) and **L42** ($n = 4$) being endothermic in contrast with the exothermic reaction of EDTA ($n = 2$). On the other hand, a weaker metal to ligand interaction determines a smaller entropy loss by the ligand in the complexation reaction, the desolvation processes becoming of greater importance in determining a favorable entropic contribution.

Functionalization of the propylenic chain in **L39** by inserting two methyl groups (**L40**) further reduces the stability of the Gd(III) complex [70], while the introduction of an alcoholic group (**L41**) does not modify the coordinating ability of the ligand towards this metal ion [71]. Although **L41** could act as heptadentate ligand, it seems [71] that its backbone is not sufficiently flexible for this to happen with

Gd(III). Enhancement of stability, and heptacoordination, is otherwise expected for the complex of **L41** in very alkaline solution where the hydroxyl proton is released [71], but no equilibrium data are available in this respect.

A marked stability enhancement of the Gd(III) complex is otherwise observed when the central CH_2 group of the $N(CH_2)_5N$ chain in **L43** is replaced by an oxygen atoms leading to **L45** [78,79]. The **L45** complex is even more stable than the corresponding EDTA complex. The greater stability is ascribable to the involvement of the ethereal oxygen in the coordination to the metal ion, which gives rise to the formation of an additional five-membered chelate ring with respect to EDTA. The higher stability of five-membered chelate rings with respect to larger ones can be further noted by considering the ligands **L46**, in which a CH_2–COOH function of **L45** is replaced by a longer $(CH_2)_2COOH$ arm, and **L47**, containing two propylenic chains instead of ethylenic ones. In spite of the moderately different experimental conditions employed for the determination of the stability constants of the Gd(III) complex with **L46** [80], an apparent loss of stability is observed when this complex, containing one six-membered chelate ring, is compared with the **L45** complex, and a further stability decrease is found for **L47**, whose complex contains two six-membered chelate rings [77]. Evidently the increment of ligational ability of donor atoms, expected as a consequence of the inductive effect due to the additional methylenic groups, is largely overcome by the chelate ring effect. Also in these cases the weakening of the metal–ligand interaction facilitates the formation of protonated species [77,80].

Further extension of the chain connecting the two amine groups in **L45** by inserting a $(CH_2)_2O$ moiety generates **L48**, in which eight potential donor groups might form seven five-membered chelate rings. In spite of the possibility to form an additional five-membered chelate ring, the Gd(III) complex of **L48** displays a lower stability, by about one log K unit, than that with **L45** [78]. The origin of this stability loss was not elucidated. It seems reasonable, however, that when the number of donor atoms in a ligand is close to the maximum coordination number of the metal ion, in particular for high coordination numbers, the ligand must be accurately tailored to achieve a proper fit of the metal coordination sites. **L48**, which is not the product of a specific molecular design, might have a less adequate structure than **L45** for coordination to Gd(III). Nevertheless, in the absence of structural information it is not possible to obtain conclusive opinions in this respect.

Another group of ligands (**L49**–**L53**) employed for Gd(III) complexation [74–76] derives ideally from diethylenetriamine ($H_2N(CH_2)_2NH(CH_2)_2NH_2$). All these ligands contain four acetate residues on the terminal amine groups, while the central nitrogen bears different substituents (**L49**, ethyl; **L50**, *n*-octyl; **L51**, phenyl; **L52**, benzyl; **L53**, hydroxyethyl) and potentially can form only five-membered chelate rings. The stability constant reported for the Gd(III) complex with **L49** ($\log K = 17.79$; 25°C, $I = 0.1$ mol dm^{-3}) is very similar to the stability constant of the EDTA complex. This is evidence of the fact that the presence of further amine groups, leading to the formation of an additional five-membered chelate ring of ethylenediamine type, does not significantly contribute to complex stability. On the other

hand, the nature of the central substituent affects the stability of the Gd(III) complex. **L49** forms the most stable complex among this group of ligands, the trend of decreasing stability for the other complexes being ascribable [74–76] to different inductive effects and steric hindrance of the central substituents. These two contributions can be antagonistic in determining the complex stability, as in the case of **L50** for which the greater inductive effect of the octyl group is expected to enhance the binding ability of the central amine group, with respect to **L49** bearing an ethyl group, but the bulky octyl residue hampers the ligand leading to a less stable complex.

As already observed ligand rigidity is of major importance in determining the binding ability of polyamino-polycarboxylic ligands, especially when the ligands contain a large number of donor groups and a metal ion such as Gd(III), having many coordination sites, is considered. As matter of fact, ligand rigidity may have opposite effects on complex stability, since it furnishes a favorable contribution when the ligand is well-preorganized to bind the metal ion, but an unfavorable one when the ligand needs to rearrange its conformation for coordination. In the last case, one or more donor atoms could be unable to coordinate.

The last effect seems to be at the origin of the loss of complex stability observed when a carboxylic group is inserted in the ethylenic chain of EDTA to form **L54** [67]. On the contrary **L54** might have been expected to form more stable complexes than EDTA due to the presence of a further donor group. Nevertheless, the additional donor group would determine, upon complexation, the formation of interlaced, more strained chelate rings, increasing the energetic cost required for ligand orientation. From an energetic point of view it might be less expensive not to involve all the donor groups in complexation.

A ligand of great importance for the development of Gd(III) coordination chemistry, has been the penta-acetic derivative of diethylenetriamine **L55** (DTPA). The Gd(III) complex of DTPA was the first contrast agent used for human MRI study, and it has been the only contrast agent available for clinical diagnostics for many years.

This ligand forms a very stable Gd(III) complex whose stability constant has been determined by several authors under rather different experimental conditions [18,28,36,81,82,116]. Log K values ranging from 22.2 to 23.1 were obtained by means of potentiometric and spectrophotometric methods in 0.1 mol dm^{-3} solutions of electrolytes containing both tetramethylammonium or K^+ ions at 20/25°C [18,36,81,82,116]. A lower value ($\log K = 20.73$) was obtained at the same temperature in solutions containing 0.5 mol dm^{-3} $NaClO_4$, in which extensive Na^+ complexation takes place [28]. The equilibrium constants for complex protonation taking place in very acidic solutions were reported in a single paper [81]. Also evidence for the formation of complex species with 2:1 metal–ligand stoichiometry was reported, but the relevant stability constants were not determined [82].

The large stability enhancement observed when the **L55** complex is compared with those of **L49**, a similar ligand also containing a diethylentriamine backbone but having only four acetic groups, is strongly indicative of the involvement of all

donor atoms in the coordination to Gd(III) via the formation of seven five-membered chelate rings. Such a coordination mode was observed in two crystal structures containing $[Gd(\mathbf{L55})H_2O]^{2-}$ [93] and $[Gd_2(\mathbf{L55})_2]^{4-}$ [118], respectively.
Both structures display similar coordination environments of the metal ion (Fig. 4) constituted by three nitrogen and six oxygen atoms. The coordination geometry could be described by either a highly distorted square antiprism, with one of the square planes capped by the oxygen atom of the exogenic ligand, or by a distorted tricapped trigonal prism. The second geometry, however, seems to better describe the coordination environment of the metal ion. In $[Gd(\mathbf{L55})H_2O]^{2-}$ one oxygen atom in the coordination polyhedron belongs to the coordinated water molecule, while in the centrosymmetric $[Gd_2(\mathbf{L55})_2]^{4-}$ the corresponding position for each Gd(III) ion is occupied by an oxygen atom of a bridging carboxylate group of the adjacent complex unit. No evidence about the formation of a similar 2:2 complex in solution has been so far reported, and hence it appears that the solid state structure of the complex depends on the nature of the counter ions in the crystal lattice [118]. In solution, independent of the counter ion, the complex is expected to have a structure very similar to that shown by $[Gd(\mathbf{L55})H_2O]^{2-}$ in the solid state, in which a water molecule is directly bound to the nine-coordinated metal ion. This water molecule, being in rapid exchange with the bulk solvent, allows an efficient relaxation enhancement of solvent protons determining the effectiveness of this complex as an MRI contrast agent.

The enthalpy change for the complexation reaction of Gd(III) with **L55** was first estimated ($\Delta H° = -31$ kJ mol^{-1}) by determining the complex stability constant at different temperatures with solutions containing 0.1 mol dm^{-3} KNO_3 [81] This enthalpic contribution was later measured by means of a microcalorimetric method in 0.5 mol dm^{-3} $NaClO_4$ [28]. The result indicates that both favorable enthalpic ($\Delta H° = -47.5$ kJ mol^{-1}) and entropic ($T\Delta S° = 71$ kJ mol^{-1}) terms contribute to the high stability of the complex. The entropic change furnishes the major contribution also revealing that in the case of **L55** desolvation plays a fundamental role in the complexation of Gd(III).

The success encountered by the Gd(III) complex of **L55** as a contrast agent for MRI, stimulated the development of modifications of **L55** in search of new ligands with high tissue and/or organ specificity. For example, $[Gd(\mathbf{L55})H_2O]^{2-}$ does not enter cells and is excreted almost exclusively by the kidney. In order to obtain a contrast agent that would enter hepatocytes and which could be excreted in the bile, several Gd(III) complexes with polyamino-polycarboxylic ligands carrying various substituents were considered [91]. Among these compounds the Gd(III) complex with **L56** (BOPTA), containing a β-benzyloxy-α-propionic (CH_2OCH_2–benzene) residue on a lateral arm, proved useful for the imaging of liver and myocardium in animals [92] in addition to its effectiveness in all applications requiring extracellular agents.

The equilibrium constant determined for the **L56** complex ($\log K = 22.58–22.61$; 20/25°C, $I = 0.1/0.15$ mol dm^{-3}) [49,83,116] reveals that the insertion of the CH_2OCH_2–benzene substituent does not modify the binding ability toward Gd(III)

of the parent **L55** ligand. Thermodynamic parameters for the coordination of Gd(III) indicate that the similar stability of **L56** and **L55** complexes is determined by a sort of enthalpic/entropic compensation, since the less favorable enthalpic contribution measured for the **L56** complex ($\Delta H° = -21$ kJ mol^{-1}) is counterbalanced by a more favorable entropic term ($T\Delta S° = -108$ kJ mol^{-1}) [49]. It seems likely that such compensation is due to a larger desolvation occurring upon formation of the **L56** complex, probably determined by the presence of the lipophilic substituents, since, as suggested by the crystal structure of the [Gd(**L56**)H_2O]$^{2-}$ complex (Fig. 5) [83], **L56** and **L55** are expected to have very similar binding features in their Gd(III) complexes. Actually the coordination environment of Gd(III) in [Gd(**L56**)H_2O]$^{2-}$ is quite similar to that observed in the **L55** complex (Fig. 4), in terms of ligand arrangement, bonding distances, and coordination geometry [83]. Also in this case it seems that a tricapped trigonal prismatic geometry fits the coordination environment of Gd(III) better than a square capped antiprismatic one.

In order to increase the specificity of the **L56** complex, **L57**, an **L56** isomer in which the lipophilic residue has been moved to the central nitrogen of DTPA (**L55**), **L58** and **L59**, containing two and three such lipophilic residues, respectively, were tested for Gd(III) complexation [116]. The stability constants determined for the complexes with **L57**–**L59** are quite similar to the constant obtained for the **L56** complex. Nevertheless, although the specificity of these complexes increases with increasing number of lipophilic residues, their toxicity exceeds clinical advantages. Similar situations were found for other DTPA derivatives such as **L60**, **L61**, **L62** and **L63**, containing –CH_2–benzene–OCH_2CH_3, –CH_2OCH_2–cicloesane, *O*-(4-hydroxyphenyl)-3,5-diiodo-L-tyrosine, *O*-(4-hydroxyphenyl)-L-tyrosine residues, respectively, in spite of the considerable stability displayed by their Gd(III) complexes [116].

L64 is a close analogue of **L55**; its structure is formally obtained by inserting a methylenic (CH_2) group in the central acetic arm of **L55**. As a consequence of such ligand modification **L64** can bind Gd(III) forming six five-membered and one six-membered chelate rings, instead of the seven five-membered ones formed by **L55**, manifesting a loss of complex stability of at least four log *K* units [85]. As observed for previous ligands, the increment of binding ability of the central carboxylate group, expected as a consequence of the greater inductive effect determined by the additional methylenic group, is largely overcome by the chelate rings effect.

In an attempt to enhance the coordination ability of **L55** towards Gd(III), a propionic acid residue was attached to the methylenic carbon of the central acetic arm, leading to **L65**. In spite of the additional binding group, the Gd(III) complex with this ligand displayed a lower stability, by about one log *K* unit [116], than the analogous complex with the parent **L55** ligand. On the contrary it could have been expected that the formation of the additional six-membered chelate ring would increase, although modestly, complex stability, but, as already found for other

ligands, the formation of interlaced chelate rings seems to be responsible for the lower binding ability.

Conversely, a remarkable enhancement of complex stability is achieved with the ligand **L66**, constituted by six acetic pendent functionalities attached to a triene (triethylenetetraamine) structure [86,87]. This ligand, which contains ten potential donor groups arranged in manner to form nine five-membered chelate rings, is able to fulfil the coordination environment of Gd(III) justifying the very high complex stability. It is to be noted that Gd(III) complexation by this ligand is largely promoted by the high negative charge (6-) of its fully deprotonated form, which gives rise, on the other hand, to the formation of highly charged complexes characterized by high osmolality. Such a characteristic seems to be responsible for the rather high toxicity of the Gd(III) complex with **L66**, which prevented its applicability as an MRI contrast agent [86].

In spite of the fact that only equilibrium data have been reported for the 1:1 complex with **L66**, the compound $K_4[Gd_2(H\mathbf{L66})_2] \cdot 14H_2O$ was crystallized from aqueous solution [119]. This product contains two monoprotonated ligand molecules forming the binuclear complex $[Gd_2(H\mathbf{L66})_2]^{4-}$ in which each Gd(III) ion is coordinated by three nitrogen atoms and four carboxylate oxygen atoms of a ligand molecule and by two carboxylate oxygens from the other one, defining a tricapped trigonal prism coordination polyhedron (Fig. 6) [119].

6. Cyclic ligands

The thermodynamic parameters determined for the formation of Gd(III) complexes with macrocyclic polyaminopolycarboxylic ligands are listed in Table 3.

Most of these ligands are based on the cyclic structure of cyclen (1,4,7,10-tetraazacyclododecane) [94–103,111–113,36,49,116]. The use of this building block for the preparation of such ligands is justified by the fact that this cyclic moiety can bind to metal ions forming five-membered chelate rings which, as already observed, are of particular stability for complexes of metals with high coordination numbers such as Gd(III).

Three ligands (**C1**, **C2**, **C3**) containing two, three, and four acetate groups attached to the nitrogen atoms of cyclen have been of basal importance in the development of a large number of Gd(III) chelators.

In **C1** (DO2A) the two pendent carboxylate groups are located on opposite nitrogen of the cyclen ring. The stability constant of the Gd(III) complex with this ligand is surprisingly high ($\log K = 19.1$, 19.4; 25°C, $I = 0.1$ [102]) if compared with that of the analogous complex with EDTA (**L21**) (Table 2), which is lower by about two $\log K$ units. Actually **C1** employs four amine nitrogens and only two carboxylate groups to bind the metal ion, while EDTA uses four carboxylate groups and two nitrogen atoms. The greater binding ability of **C1** can be ascribed to the cyclic nature of the ligand backbone which induces a preorganized arrangement of binding sites. Along with the high thermodynamic stability the Gd(III)

complex with **C1** displays considerable inertness in both formation and acid catalyzed dissociation reactions [102], as commonly observed for polyamine macrocycles.

Insertion of a further acetate group on a **C1** nitrogen gives rise to **C2**, commonly known as DO3A. Although two rather different equilibrium constants for the formation of the Gd(III) complex ($\log K = 21.0$ [36] and $\log K = 22.02$ [49,113]) were obtained, by different methods under equal experimental conditions, the enhancement of binding ability brought about by the additional acetate groups is apparent. The involvement of all donor groups of **C2** in the coordination to Gd(III) was confirmed in the solid state by the crystal structure of the $\{[Gd(\mathbf{C2})]_3 \cdot Na_2CO_3\} \cdot 17H_2O$ compound containing three crystallographically independent [Gd(**C2**)] units displaying essentially the same structure and conformation [120]. Each enneacoordinated Gd(III) is bound to the four nitrogens and an oxygen from each carboxylate arm of the ligand, as well as to two oxygens of the carbonate anion acting as a tris-bidentated ligand (Fig. 7). The macrocyclic rings adopt a C corner (square) [3333] conformation with carbon atoms at the corner positions, the carboxylate groups pointing to the same side of the ring. In solution it is expected that two water molecules replace the carbonate oxygens in the metal ion coordination sphere.

As displayed by the crystal structure of $\mathbf{C2} \cdot H_2SO_4$, the metal-free ligand has almost the same arrangement as that adopted in the Gd(III) complex [36]. Such preorganization is primarily encouraged by the stability of the [3333] conformation of the macrocycle which defines a rigid binding cavity with well defined size.

Most likely such characteristics of both free ligand and Gd(III) complex are retained in solution. The rigidity and preorganization of the ligand justify the formation of the very stable and kinetically inert metal complex.

Evidence of metal complex protonation was obtained by mixing [Gd(**C2**)] solution with H^+ solution allowing the determination of the relevant protonation constant ($\log K = 2.1$) [141]. In such experiments rapid proton binding is followed by a slow dissociation reaction of the complex and hence, from this experimental evidence it is not possible to establish if the protonated complex is actually a thermodynamically stable species or just an intermediate species formed in the acid catalyzed dissociation of the complex. As a matter of fact, the formation of this species was not observed in any experiment developed to perform the speciation of the Gd(III)/**C2** system at equilibrium, although on the base of the reported stability constant such a protonated complex should have been present in most of the sample solutions employed. Nevertheless, as presented later, different authors found similar protonated species for Gd(III) complexes with analogous ligands.

DOTA (**C3**), the ligand containing an acetate group linked to each nitrogen atom of cyclen, is probably the best known macrocyclic ligand used for Gd(III) complexation, and it is surely the macrocyclic ligand which up to now has been the subject of the largest number of studies concerning the determination of equilibrium constants for Gd(III) complexation [36,49,96–101,113]. As a matter of fact, the

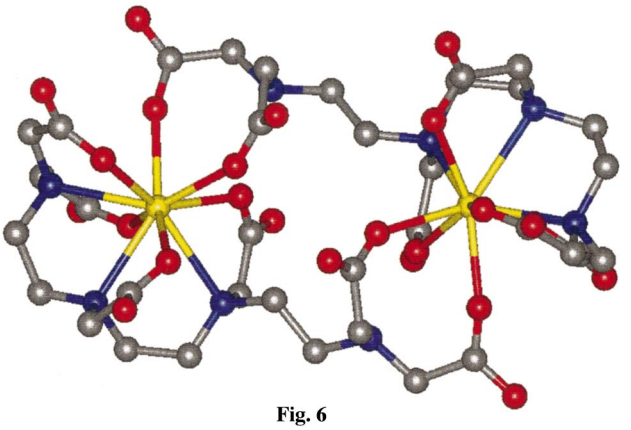


Fig. 6

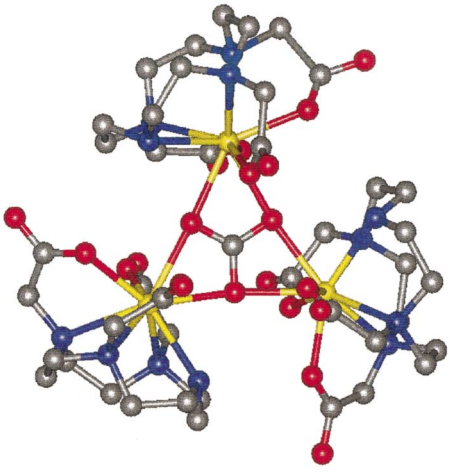


Fig. 7

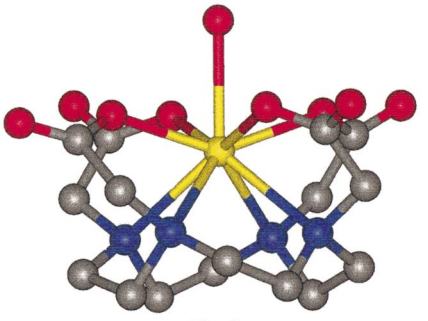


Fig. 8

Fig. 6. Crystal structure of $[Gd_2(H\mathbf{L66})_2]^{4-}$ (**L66** = TTHA) [119]. Gd, yellow; N, blue; O, red; C gray.
Fig. 7. Crystal structure of $\{[Gd(\mathbf{C2})]_3(CO_3)\}^{2-}$ (**C2** = DO3A) [120]. Gd, yellow; N, blue; O, red; C gray.

Fig. 8. Crystal structure of $[Gd(\mathbf{C3})H_2O]^{-}$ (**C3** = DOTA) [121]. Gd, yellow; N, blue; O, red; C gray.

Gd(III) complex of DOTA has been one of the first contrast agents (DOTAREM) used in diagnostic MRI. Notwithstanding that, the values reported for the equilibrium constant for the formation of the Gd(III) complex with DOTA span a considerable range ($\log K = 22.1–28.0$) only part justified by the different methods and experimental conditions employed. Nevertheless, if the values determined in solutions with 0.1 mol dm^{-3} ionic strength, in the absence of alkali metal ions, by means of batchwise methods employing auxiliary (competitive) ligands at 25.0°C are considered, a $\log K$ of 25.0 ± 0.3 seems acceptable. This value compares well with $\log K = 24.0$ [98] determined in 0.1 mol dm^{-3} KCl if K^+ complexation is taken into account.

Such values indicate that an increment of complex stability of about three $\log K$ units corresponds to the insertion of a fourth acetate group in the **C2** structure.

As shown by the crystal structure of $Na[Gd(\mathbf{C3})] \cdot 5H_2O$ the metal ion is linked to the four nitrogen atoms of the cyclic ring and to an oxygen atom of each carboxylate groups completing the enneacoordinated environment by a water molecule which caps the square antiprismatic arrangement of the other eight coordinated atoms (Fig. 8) [121]. Also in this case the macrocycle adopts a C corner [3333] conformation with the carboxylate groups pointing to the same side of the ring. Similarly to **C2**, **C3** also displays well-suited conformation for Gd(III) binding.

Such a compact structure is likely maintained in solution, where the ligand is expected to occupy eight coordination sites of the metal ion forming four N–Gd–N and four N–Gd–O(carboxylate) five-membered chelate rings which confer very high stability to the complex.

Several studies indicate the formation of the monoprotonated [Gd(H**C3**)] complex in acidic solutions, but rather different equilibrium constants were obtained in spite of the similarity of experimental conditions [96,98,141].

In order to confer additional rigidity, and possibly a greater preorganization to **C3**, the ligand **C4** containing an α-methyl group in each acetate arm, was considered. In addition the inserted groups are expected to enhance the binding ability of carboxylate groups by an inductive effect. Such modification, however, produces a loss of complex stability of about one $\log K$ unit [116], suggesting that the principal effect of the α-methyl groups is, presumably, a reduction of ligand preorganization for Gd(III) complexation.

The secondary amine groups of **C1** have been functionalized by insertion of hydroxyethyl residues (CH_2CH_2OH) leading to **C5**, a ligand containing eight potential binding groups. The stability constant of the Gd(III) complex with this ligand ($\log K = 21.1$) [102], which is about two $\log K$ units higher than that of the corresponding **C1** complex, suggests the involvement of the alcoholic oxygens in metal ion coordination.

C2 has also been subjected to analogous functionalization by attachment of a hydroxyethyl residue to the unique secondary nitrogen. The **C6** ligand, obtained by this way, displays at most a modest enhancement of complex stability ($\log K = 22.3$ [103]) with respect to **C2**.

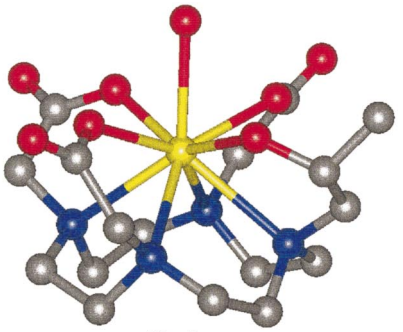


Fig. 9

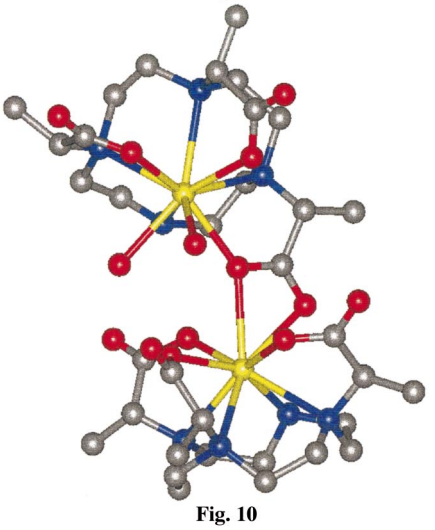


Fig. 10

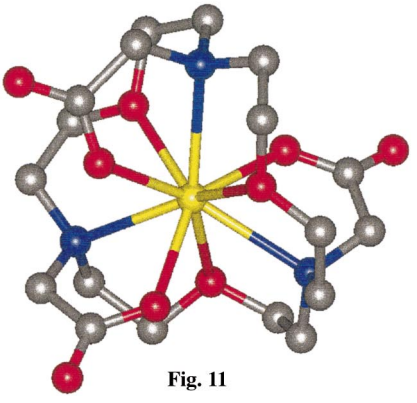


Fig. 11

Fig. 9. Crystal structure of [Gd(**C7**)H_2O] (**C7** = HP-DO3A) [36]. Gd, yellow; N, blue; O, red; C gray.
Fig. 10. Crystal structure of [Gd_2(**C12**)$_2$(H_2O)$_2$] (**C12** = DO3MA) [104]. Gd, yellow; N, blue; O, red; C gray.
Fig. 11. Crystal structure of [Gd(**C23**)] (**C23** = *N*-ac$_3$[18]aneN_3O_3) [123]. Gd, yellow; N, blue; O, red; C gray.

The poor stabilization produced by the hydroxyethyl groups for both **C5** and **C6** complexes can be ascribed to the low stability displayed by six-membered chelate rings in Gd(III) complexes.

A greater stabilization effect is otherwise observed [36,113] for the complex with a very similar ligand (**C7**) containing a methyl group in the α-position with respect to the alcoholic group of **C6**. This ligand, commonly referred to as HP-DO3A, displays coordination features quite similar to those of DOTA (**C3**), as visualized by the crystal structure of [Gd(**C7**)H_2O] (Fig. 9) [36]. The asymmetric unit of this compound contains two independent complexed molecules in which the macrocycle has the typical C corner [3333] conformation. Four nitrogen and four oxygen atoms (one from each arm) are coordinated to the embedded Gd(III) ion, the ninth, apical position of the capped square antiprismatic coordination environment being occupied by the water molecule. The nitrogen atoms are coplanar within experimental error, while the coordinated oxygen atoms define another plane. The Gd(III) ion is sandwiched between these almost parallel planes. The Gd–O(alcoholic) distances are comparable to the Gd–O(carboxylate) ones indicating good ligational properties for this alcoholic oxygen.

Actually the stability of the Gd(III) complex with **C7** is very similar to that of the DOTA complex, although two rather different log K values have been reported for the **C7** complex log $K = 23.8$ [36], log $K = 24.5$ [113]). Such a high stability of the **C7** complex, compared to that of the **C6** one, has to be ascribed to the additional methyl group present in **C7**, which enhances, by its electron donating properties, the binding ability of the alcoholic oxygen atom, and increases for steric reasons the preorganization of the hydroxypropyl arm toward metal ion chelation.

The high stability of this complex, together with its inertness toward metal ion release and its low toxicity determined the applicability of this compound as contrast agent (PROHANCE) for MRI diagnostics.

Evidence for the acidic dissociation of [Gd(HP-DO3A)] ($pK_a = 11.36$) was obtained by means of potentiometric titration of the complex in alkaline solution [112], although no definitive proof was obtained regarding the nature of the dissociating group, since it is impossible to discriminate, by means of the potentiometric method, between ligand dissociation at the alcoholic residue and metal ion hydrolysis.

Equilibrium constants for complex protonation were also determined, but the values reported, obtained by different methods under similar experimental conditions, are quite different [112,115].

Another ligand (**C8**) quite similar to **C7**, containing the methyl group in β- instead of in α-position with respect to the alcoholic oxygen donor, was studied for Gd(III) complexation [103]. Unfortunately a meaningful comparison between the binding ability of the two ligands toward Gd(III) cannot be drawn due to the different log K values reported for the **C7** complex [36,113]. Nevertheless, the **C8** complex displays a very high stability (log $K = 23.9$) [103] denoting that the ligand is well-suited for Gd(III) complexation.

A greater binding ability of the α-hydroxypropyl arms with respect to hydroxyethyl ones is otherwise indicated by the stability of the Gd(III) complex with **C9**,

the analog of **C5** in which the two hydroxyethyl arms have been replaced by hydroxypropyl ones, the stability increase amounting to about 1.5 log K units [102].

Considering the contribution that alcoholic oxygen donors can furnish to complex stability, the two ligands **C10** and **C11** have recently been studied [113]. **C10** can be considered a **C2** (DO3A) derivative containing three arms in which both acetate and hydroxyethyl features can be recognized, while **C11** contains an additional α-hydroxypropyl arm linked to the secondary nitrogen atom of **C10**. In spite of the high number of donor atoms present in both ligands, **C10** and **C11** display considerably lower binding properties toward Gd(III) ($\log K = 18.82$ and 19.4, respectively [113]) than DO3A. The observed loss of stability has been ascribed to the steric hindrance of the bulky functionalities of **C10** and **C11** which determines a more strained, less stable, coordination environment of the metal ion [113]. Both ligands contains a surplus of donor atoms for Gd(III) complexation. Apparently, the complex stability depends to a very low extent on the presence of the additional α-hydroxypropyl group [113], probably due to the surplus of donor atoms born by the ligands.

Another DO3A derivative (**C12**) containing α-methyl groups in the arms was employed for Gd(III) complexation to demonstrate the effect of additional rigidity on complex stability [104]. The stability constant ($\log K = 25.3$) reported for the **C12** complex is considerably higher than the constant previously obtained for the analogous complex with the unmethylated DO3A (**C2**) ligand, in agreement with enhanced ligand preorganization, and enhanced donating properties of carboxylate oxygens produced by the inductive effect of the methyl groups. As previously observed for **C4**, the insertion of α-methyl groups has an opposite effect on the stability of the DOTA (**C3**) complex. Such different behavior is rather surprising, but a critical evaluation is not possible in the absence of independent confirmation of the equilibrium constants determined for **C4** and **C12** complexes, and of structural information for both complexes.

In the case of **C12**, the Gd(III) complex was isolated in the solid state as $[Gd_2(\mathbf{C12})_2(H_2O)_2]$ and its crystal structure was solved by X-ray analysis [104]. In this compound two crystallographically-independent complex units are joined to form a binuclear species (Fig. 10). The unit consisting of $[Gd(\mathbf{C12})(H_2O)_2]$ links the other one, [Gd(**C12**)], through two of its carboxylate groups acting as bridging elements between the metal ions. In each unit an oxygen atom from each carboxylate group and the four essentially coplanar nitrogen atoms are coordinated to the embedded metal ion. In addition to these seven 'internal' ligating atoms of **C12**, two other 'external' oxygen atoms complete the enneacoordinate environment. One of the 'external' oxygen atoms lies approximately in the plane defined by the three coordinated carboxylate oxygens, while the other one occupies an apical position over this plane. In the $[Gd(\mathbf{C12})(H_2O)_2]$ unit the 'external' oxygens are from the linked water molecule, while in [Gd(**C12**)] they are from the bridging carboxylate groups. In both complex units the macrocycle adopts a distorted quadrangular C corner [3333] conformation.

The formation of a similar dimetallic species was not observed in solution where the complex is expected to exist in the form of $[Gd(\mathbf{C12})(H_2O)_2]$ [104].

Another derivative of **C2** containing a pendent arm bearing three hydroxy groups, **C13**, was considered for Gd(III) complexation [112]. Two of these alcoholic groups are in the same position of the alcoholic group in **C7** (HP-DO3A) which can coordinate by forming five-membered chelate rings, while the third one would form a six-membered one upon complexation. In spite of this abundance of donor atoms, the stability of the Gd(III) complex with **C13** is considerably lower than that of the corresponding complex with **C7**, being closer to that of the complex with the unsubstituted **C2** ligand. These differences were interpreted by assuming that the coordination of the bulky residue containing the three alcoholic groups is sterically hindered [112]. Actually these alcoholic groups might coordinate to Gd(III) giving rise to interlaced chelate rings, whose formation, as observed for previous cases, does not favor the complex stability.

Upon consideration of the effectiveness for in vivo applications as a contrast agent in MRI diagnostics of the Gd(III) complex with **L56**, the DTPA (**L55**) analogue containing a β-benzyloxy-α-propionic (CH_2OCH_2–benzene) residue on a lateral arm, several macrocyclic ligands (**C14**–**C16**) based upon 1,4,7,10-dodecaaza-cyclododecane (cyclen) and containing β-benzyloxy-α-propionic functionalities were developed [116]. **C14** and **C15,** containing three such residues, potentially dispose of the same sets of donor atoms of DO3A (**C2**) and HP-DO3A (**C7**), respectively, but form complexes of lower stability with respect to the latter ligands. Steric hindrance to coordination determined by the bulky substituents seems to be at the origin of the observed stability loss. In the case of **C14** only the stability constant of the monoprotonated complex was determined, due to the low solubility of the unprotonated species. A relatively low stability was also found for the Gd(III) complex with **C16**, a **C12** analog containing only one β-benzyloxy-α-propionic substituent. Owing to their intrinsic toxicity, the Gd(III) complexes of **C14**–**C16** are not useful as contrast agents for in vivo MRI applications.

Tetraazacycloalkanes larger than cyclen, such as 1,4,7,10-tetraazacyclotridecane and 1,4,8,11–tetraazacyclododecane (cyclam) were used as basal structure for the preparation of polyamino-polycarboxylic ligands containing four acetate side arms. These ligands, **C17** (TRITA) and **C18** (TETA), can be considered simple modifications of DOTA (**C3**) obtained by replacing one or two ethylenic chains of the macrocyclic ring by propylenic ones. Such modifications that, in principle, do not seem very important from a structural viewpoint, determine a drastic loss of binding ability. A decrease in complex stability by about five log K units ($\log K =$ 24.0, 19.17, 13.77 for **C3**, **C17** and **C18**, respectively) as the dimensions of the macrocyclic ring increase, was found by batchwise potentiometric experiments employing auxiliary ligands (0.1 mol dm^{-3} KCl at 25.0°C) [98]. Such stability loss can be ascribed to the formation of one and two six-membered chelate rings in the complexes of **C17** and **C18**, respectively.

Protonation of the complexes with **C17** and **C18** is much easier than for the **C3** complex, the protonation constant increasing with decreasing complex stability, in agreement with the lower overall interaction of the ligand with the metal ion.

A considerably higher stability constant of the **C18** complex ($\log K = 15.75$) was obtained at 80°C (1 mol dm^{-3} NaCl) by means of pH-metric titrations, since at this temperature the complexation reaction was found to be sufficiently fast [106].

Other polyamino-polycarboxylic ligands employed for Gd(III) complexation were obtained by appending five (**C19**) and six (**C20**) acetic groups to the macrocycles 1,4,7,10,13-pentaazacyclopentadecane and 1,4,7,10,13,16-heptaazacyclooctadecane, respectively. Complexation of Gd(III) by **C19** and **C20** is much faster than for the other polyamino-polycarboxylic ligands based upon tetraazamacrocycles, and hence determination of the corresponding stability constants was possible by means of common pH-metric titration methods, provided equilibration times lasting from 10 to 60 minutes, depending on the ligand and the pH range, were allowed after each titrant addition [107]. These ligands, which contain a surplus of donor atoms with respect to the common coordination numbers of Gd(III), can bind the metal ion forming five-membered chelate rings. In spite of this, the stability constants obtained for **C19** ($\log K = 15.88$) and **C20** ($\log K = 22.95$) at 25°C (0.2 mol dm^{-3} $NaNO_3$) [107] demonstrate a reduced tendency to form Gd(III) complexes, with respect to the homologous ligand **C3** (DOTA) containing four amine and four acetate groups. In the case of the **C19** complex the loss of stability is very large, while for the **C20** one it is much less pronounced. Hence, the increased ligand size does not favor the coordination of Gd(III), although the larger ligand **C20** which is more flexible seems to adapt better to the metal ion. As far as the possible use of similar complexes for in vivo application is considered, the very high basicity of the ligands in the multiple protonation steps determines a deleterious competition between the binding of Gd(III) and H^+ ions, weakening the metal to ligand interaction at physiological pH. As a matter of fact, the Gd(III) complex with **C20** undergoes protonation to form a diprotonated species at physiological pH. The equilibrium constant for the binding of the metal ion to the diprotonated form of **C20** ($\log K = 17.26$) [107] indicates the marked loss of ligand binding ability brought about by protonation.

Three other ligands (**C21**–**C23**) based upon macrocyclic frames of increasing size were obtained by implanting three carboxylic arms on the oxaazamacrocycles 1-oxa-4,7,10-triazacyclododecane, 1,7-dioxa-4,10,13-triazacyclopentadecane and 1,7,13-trioxa-4,10,16-triazacyclooctadecane. The equilibrium constants for Gd(III) complexation with these ligands were determined by means of common pH-metric titrations (0.1 mol dm^{-3} KCl, 25.0°C) adopting long equilibration times (up to 40 min.) for each titration point. In the case of **C21**, due to the large value of the equilibrium constant, the use of an auxiliary ligand (EDTA) was necessary [108]. The stability constants obtained ($\log K = 21.6$, **C21**; $\log K = 17.23$, **C22**; $\log K = 18.2$, **C23**) display the same trend previously observed for **C3**, **C19** and **C20**. When the size of the macrocycle increases from a 12- to a 15-membered ring there is a drop in stability in spite of the introduction of an additional donor atom in the ring. On the other hand, another increase of the ring size with the introduction of a further oxygen atom to form a 18-membered ring brings a slight increase of the

stability constant. To explain this behavior it was suggested that the first increase of the ring size leads to a ligand which cannot place all the donor atoms in the correct position for coordination, but the larger ligand, which is more flexible, seems to adapt better to the size of the metal ion and to bring the donor atoms near to the metal ion [108]. The crystal structure of the [Gd(**C23**)] complex indicates that, at least in the solid state, **C23** is able to involve all its donor atoms in the coordination to Gd(III) forming a complex in which no particular stain is observed [123]. The structure (Fig. 11) reveals that the Gd(III) complex has a propeller conformation, the metal ion being bound to three nitrogen and three oxygen atoms of the macrocycle and to an oxygen atom of each acetate group in an enneacoordinate environment.

In spite of the fact that **C22** completes the coordination sphere of Gd(III) and the complex does not have a coordinated water molecule, it was found that the complex in solution provides a moderate enhancement of water proton relaxation [108].

Replacement of the acetic groups in **C22** with propionic acid residues (**C24**) provides a marked decrease in the Gd(III) complex stability [111]. Such large stability loss (6 log K units) is to be ascribed to the lower stability of the six-membered chelate rings formed by **C24** with respect to the five-membered ones formed by **C22**. Furthermore, molecular mechanics calculations suggested that lengthening of the substituents on the side arms from acetic acid to propionic acid may bring stronger hindrance to access of the carboxylate donor atoms to the coordinated metal cations [111].

Two ligands containing only two acetic side arms linked to 15-membered N_2O_3 or to a 18-membered N_2O_4 macrocyclic rings, **C25** and **C26** respectively, were considered for Gd(III) complexation. As expected these ligands form rather weak complexes ($\log K = 11.66$ and 11.93, respectively) [109,110], less stable that the complexes formed by the tricarboxylate analogues **C22** and **C23**.

A further decrease in complex stability was observed by lengthening the ring substituents on the side arms of **C26** from acetic to propionic acid ($\log K = 7.02$ for **C27**) or by eliminating a side arms from **C26** ($\log K = 7.29$ for **C28**) [115].

Estimations of the Gd(III) complexation constants with some triacetic derivatives of triazamacrocycles (1,4,7-triazacyclononane-*N*,*N*′,*N*′-triacetic, 1,4,7-triazacyclononane-1,4,7-tris(2-methylacetic), 1,4,7-triazacyclodecane-*N*,*N*′,*N*′-triacetic, 9-methyl-1,4,7-triazacyclodecane-*N*,*N*′,*N*′-triacetic, 9,9-dimethyl-1,4,7-triazacyclodecane-*N*,*N*′,*N*′-triacetic acids), performed by using a proton relaxivity technique, have also been reported [142,143]. Unfortunately the particular methodology and the experimental conditions employed for the determination of such stability constants do not allow a fully profitable comparison with the stability constants determined for the other macrocyclic ligands. Nevertheless, it seems that the triazamacrocyclic ligands offer a less stable coordination environment than tetraazamacrocyclic ones independently of the number (2, 3, 4) of carboxylate groups present in the last ligands. An increasing binding ability seems to occur upon enlargement from nine- to ten-membered macrocyclic rings, while methylation of both pendant arms and ring carbon atoms reduces the complex stability.

7. Concluding remarks

Gd(III) is a typical hard metal ion and consequently it interacts preferentially with ligands bearing hard donor groups, such as carboxylate, while it demonstrates lower tendency to form complexes with softer ligands like amines. Nevertheless, polyamino-polycarboxylic ligands, containing both such functional groups, form very stable complexes with this metal ion. The stability of these complexes, however, is strictly connected with the chelating nature of the ligands, with the size of the chelate rings, and the mutual arrangement of all chelate rings in the complexes. Actually the most stable Gd(III) complexes are formed by those ligands which are able to bind the metal ion via five-membered chelate rings. The stability of chelate rings largely depends on the metal ion size. Small cations tend to have low coordination numbers and to form six-membered chelate rings, while larger cation, having higher coordination numbers, prefers five-membered ones. The most stable (less strained) five-membered chelate rings are expected, and found, for those complexes in which bond lengths and angles between the metal ion and the donor atoms forming the chelate rings are about 2.5 Å and 70°, respectively [144]. The structural parameters observed for the crystal structure of Gd(III) complexes with polyamino-polycarboxylic ligands are consistent with these values, the bond angles commonly being slightly smaller than 70°. Hence, five-membered chelate rings produce the most appropriate binding bites in the tricapped trigonal prismatic and the capped square antiprismatic coordination geometries of the Gd(III) complexes with this type of ligands. Actually, ligands based on ethylenediamine moieties and containing acetate pendent groups give rise to the most stable Gd(III) complexes. However, loss of complex stability is generally observed when the carbon atoms of the ethylenediamine moieties, or the methylene carbon of the acetate groups, carry further coordinating functionalities, even if only five-membered chelate rings are formed, the stability loss being ascribable to a more strained conformation imposed by the resulting interlaced chelate rings to the ligand in the complex.

Such coordinative features are displayed by both acyclic and macrocyclic ligands. The latter ligands, however, manifest the typical complex stability enhancement generally observed for macrocyclic ligands with respect to the acyclic counterparts. The particularly high thermodynamic stability of the macrocyclic complexes, coupled with their kinetic inertness toward metal ion release, have focused the interest of almost all research teams involved in the study of metal-containing contrast agents.

As observed above, polyamino-polycarboxylic ligands contain donor groups with different affinity for the hard Gd(III) ion. The amine groups are not expected to be very inclined to bind this metal ion, especially in water, while a much easier replacement of water molecules in the Gd(III) coordination sphere is achieved by carboxylate groups. Most likely the first interaction of Gd(III) with the negatively charged carboxylate groups produces sufficient dehydration of the

metal ion to promote successive coordination of the amine groups. Accordingly, several complexation stages have been observed in the coordination reactions involving Gd(III) and polyamino-polycarboxylic ligand, especially with macrocyclic ligands, of which the final and slowest one corresponds to the coordination of the last amine nitrogen.

Interesting considerations can be drawn regarding the enthalpic and entropic contributions to complex stability. For this purpose only $\Delta H°$ and $T\Delta S°$ values obtained by calorimetric measurements will be considered, in agreement with the cautionary suggestions reported in Section 3. Up to now, only enthalpy changes for the complexation of Gd(III) with acyclic polyamino-polycarboxylic ligands have been reported, since complexation reactions with macrocyclic ones are too slow to be followed by using the calorimeters presently available. For all the systems studied by means of calorimetry, it has been found that the complexation reactions are promoted by largely favorable and dominant entropic contributions. On the contrary the enthalpy changes display different behavior: they are favorable for complexation reactions involving ligands, such as **L17**, **L18**, **L20**, **L21**, **L55** and **L56**, which form five-membered chelate rings, and unfavorable with ligands (**L39**, **L42**) forming larger chelate rings. The binding of carboxylate groups to Gd(III) is a reaction between hard species and hence it is a process, predominantly determined by electrostatic forces, in which dehydration of reactants plays a fundamental role. Consequently, such reactions are expected to be accompanied by unfavorable enthalpic ($\Delta H° > 0$) and favorable entropic ($T\Delta S° > 0$) contributions. On the other hand, coordination of softer amine nitrogens should involve some covalency, and take place, as said above, after a preliminary coordination of carboxylate groups, when the charge of the metal cation has been partly neutralized and consistent dehydration of reactants has already occurred. Hence, coordination of amine groups is expected to furnish a favorable enthalpic contribution, which appears, in the case of **L17**, **L18**, **L20**, **L21**, **L55** and **L56**, to overcome the unfavorable enthalpic contribution determined by the coordination of carboxylate groups, the overall entropic contribution remaining favorable for all systems studied. The unique cases of unfavorable complexation enthalpy changes are observed for ligands forming chelate rings larger than five-membered ones. As commented at the beginning of this section, the formation of such large chelate rings in Gd(III) complexes generates a considerable decrease in complex stability, due to increased conformational strain. Most likely this strain, and the consequent mismatching between metal ion orbitals and nitrogen donor lone pairs, determines the observed enthalpy loss.

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References

[1] R.B. Lauffer, Chem. Rev. 87 (1987) 901.
[2] S.H. Koenig, R.D. Brown, Prog. NMR Spectrosc. 22 (1990) 487.
[3] K. Kumar, M.F. Tweedle, Pure Appl. Chem. 65 (1993) 515.
[4] J.-C.G. Bünzli, G.R. Choppin (Eds.), Lanthanide Probes in Life, Chemical and Earth Sciences, Elsevier, Amsterdam, 1989.
[5] J.-M. Lehn, D.D. Macnicol, J.L. Atwood, J.E. Davies, D.N. Reinhoudt, F. Vögtle (Eds.), Comprehensive Supramolecular Chemistry, vol. 10, Pergamon, Oxford, 1996 (Chapter 17).
[6] D.H. Carr, J. Brown, G.M. Bydder, H.-J. Weinmann, U. Speck, D.J. Thomas, I.R. Young, Lancet 1 (1984) 484.
[7] (a) Drugs Future 14 (1989) 290. (b) Drugs Future 19 (1994) 293. (c) Drugs Future 21 (1996) 315. (d) Drugs Future 16 (1998) 1001.
[8] R.S. Kolat, J.E. Powell, Inorg. Chem. 1 (1962) 293.
[9] E. Ohyoshi, Anal. Chem. 57 (1985) 446.
[10] K. Bukietynska, A Mondry, Polyhedron 3 (1984) 31.
[11] A. Sonesson, Acta Chem. Scand. 13 (1959) 1437.
[12] A. Sonesson, Acta Chem. Scand. 12 (1958) 165.
[13] P.R. Reddy, V.B.M. Rao, Inorg. Chim. Acta 125 (1986) 191.
[14] Z. Konteatis, H.G. Brittain, J. Inorg. Nucl. Chem. 43 (1981) 1675.
[15] E.E. Kriss, Ukr. Khim. Zh. 31 (1965) 153.
[16] S. Verma, M. Saxena, Ind. J. Chem. 27A (1988) 1068.
[17] L.C. Thompson, Inorg. Chem. 1 (1962) 490.
[18] R. Harder, S. Chaberek, J. Inorg. Nucl. Chem. 11 (1959) 197.
[19] N.M. Dyatlova, V.Ya. Temkina, Yu.F. Belugin, O.Yu. Lavrova, L.E. Bertina, F.D. Ozefovich, N.N. Kalmykova, E.P. Zhirov, Russ. J. Inorg. Chem. 10 (1965) 612.
[20] L.C. Thompson, J.A. Loraas, Inorg. Chem. 2 (1963) 594.
[21] V. Jokl, J. Majer, H. Scharff, H. Kroll, Mikrochim. 1–2 (1966) 169.
[22] L.C. Thompson, B.L. Shafer, J.A. Edgar, K.D. Mannila, Lanthan. Actin. Chem. 71 (1967) 169.
[23] A.I. Kapustnikov, Yu.M. Kozlov, I.P. Gorelov, J. Gen. Chem. USSR 52 (1982) 578.
[24] S. Lubkeova, P. Balgavy, E. Fuleova, V. Novak, M. Svicekova, I. Valaskova, J. Majer, Chem. Papers 39 (1985) 317.
[25] I. Yoshida, F. Sagara, K. Ueno, Bull. Chem. Soc. Jpn. 62 (1989) 2296.
[26] G. Makhmeeva, V. Gontar, et al., Zhur. Neorg. Khim. 25 (1980) 855.
[27] T. Moeller, R. Ferrus, Inorg. Chem. 1 (1962) 49.
[28] (a) T.F. Gritmon, M.P. Goedken, G.R. Choppin, J. Inorg. Nucl. Chem. 39 (1977) 2021. (b) G.R. Choppin, M.P. Goedken, T.F. Gritmon, J. Inorg. Nucl. Chem. 39 (1977) 2025.
[29] G. Schwarzenbach, R. Gut, Helv. Chim. Acta 39 (1956) 1589.
[30] G. Anderegg, Helv. Chim. Acta 43 (1960) 825.
[31] L.D. Pettit, IUPAC Stability Constants Database, Academic Software, Otley, UK, 1993.
[32] R. Hering, W. Kruger, G. Kuhn, Z. Chem. 2 (1962) 374.
[33] E. Riecanska, J. Mayer, A. Bumbalova, Chem. Zvesti 28 (1974) 768.
[34] L.C. Thompson, S.K. Kundra, Inorg. Chem. 7 (1968) 338.
[35] G. Schwarzenbach, R. Gut, G. Anderegg, Helv. Chim. Acta 37 (1954) 937.
[36] K. Kumar, C.A. Chang, L.C. Francesconi, D.D. Dischino, M.F. Malley, J.Z. Gougoutas, M.F. Tweedle, Inorg. Chem. 33 (1994) 3567.
[37] E.J. Wheelwright, F.H. Spedding, G. Schwarzenbach, J. Am. Chem. Soc. 75 (1953) 4196.
[38] E. Wheelwright, F. Spedding, US Atomic Energy Commission, ISC-637, 1955.
[39] R. Betts, O. Dahlinger, Can. J. Chem. 37 (1959) 91.
[40] G. Popa, E. Jercan, Ann. Univ. Bucur. Chim. 18 (1969) 71.
[41] A.E. Martell, R.M. Smith, Crit. Stab. Constant 1 (1974) 205.
[42] A.E. Martell, R.M. Smith, Crit. Stab. Constant 6 (Suppl. 2) (1989) 97.
[43] J.E. Powell, M.W. Potter, H.R. Burkholder, E.D.H. Potter, P.K. Tse, Polyedron 1 (1982) 277.

[44] T. Moeller, R. Ferrus, J. Inorg. Nucl. Chem. 20 (1961) 261.
[45] J.E. Powell, J.L. Mackey, Inorg. Chem. 1 (1962) 418.
[46] F.H. Speeding, J.E. Powell, E.J. Wheelwright, J. Am. Chem. Soc. 78 (1956) 34.
[47] J. Lucansky, V. Novak, M. Svicekova, E. Dvorakova, J. Majer, Proceedings of the 9th Conference on Coordination Chemistry, Mikrochim. Acta Bratislava, 1983, p. 265.
[48] H.M.N.H. Irving, J.P. Conesa, J. Inorg. Nucl. Chem. 26 (1964) 1945.
[49] A. Bianchi, L. Calabi, L. Ferrini, P. Losi, F. Uggeri, B. Valtancoli, Inorg. Chim. Acta 249 (1996) 13.
[50] T. Moeller, T.M. Hseu, J. Inorg. Nucl. Chem. 24 (1962) 1635.
[51] E. Merciny, J. Fuger, Anal. Chim. Acta 160 (1984) 87.
[52] A.E. Martell, R.M. Smith, Crit. Stab. Constant 6 (Suppl. 2) (1989) 105.
[53] V. Novak, J. Lukansky, et al., Chem. Zvesti 32 (1978) 32.
[54] V. Novak, J. Lukansky, J. Majer, Chem. Zvesti 22 (1968) 721.
[55] V. Novak, J. Lukansky, J. Majer, Chem. Zvesti 22 (1968) 733.
[56] V. Novak, J. Lukansky, M. Svicekova, J. Majer, Chem. Zvesti 28 (1974) 324.
[57] J. Majer, P. Butvin, V. Novak, M. Svicekova, E. Fuleova, I. Valaskova, J. Novak, Chem. Zvesti 33 (1979) 742.
[58] V. Novak, M. Svicekova, J. Majer, Chem. Zvesti 19 (1965) 817.
[59] H. Irving, K. Sharpe, J. Inorg. Nucl. Chem. 33 (1971) 217.
[60] J.E. Powell, D.A. Johnson, H.R. Bukholder, S.C. Vick, J. Chromatogr. 87 (1973) 437.
[61] E.N. Rizkalla, G.R. Choppin, W. D'Olieslager, Inorg. Chem. 25 (1986) 2327.
[62] V. Novak, E. Dvorakova, M Svicekova, et al., Chem. Zvesti 23 (1969) 330.
[63] V. Simeon, Arh. Hig. Rada Toksikol. 19 (Suppl. 1) (1968) 99.
[64] V. Novak, E. Dvorakova, M Svicekova, J. Majer, Chem. Zvesti 23 (1969) 861.
[65] A.E. Martell, R.M. Smith, Crit. Stab. Constant 1 (1974) 226.
[66] J.H. Miller, J.E. Powell, Inorg. Chem. 17 (1978) 774.
[67] Yu.M. Mozlov, V.A. Babich, Russ. J. Inorg. Chem. 25 (1980) 1574.
[68] F. L'Eplattenier, G. Anderegg, Helv. Chim. Acta 47 (1964) 1792.
[69] G. Anderegg, K. Wenk, Helv. Chim. Acta 54 (1971) 216.
[70] V. Novak, M. Svicekova, E. Dvorakova, I. Valaskova, J. Majer, Chem. Zvesti 35 (1981) 481.
[71] J.E. Powell, D.R. Ling, P. Tse, Inorg. Chem. 25 (1986) 585.
[72] G.R. Choppin, J.L. Brock, Inorg. Chim. Acta 109 (1985) 99.
[73] E. Brucher, R. Kiraly, Z. Varga, Magy. Chem. Foly. 81 (1975) 339.
[74] P.K. Tse, J.E. Powell, Inorg. Chem. 24 (1985) 2727.
[75] V.F. Vasil'eva, O.Yu. Laurova, N.M. Dyatlova, V.G. Yashunskii, J. Gen. Chem. USSR (Engl. Transl.) 36 (1966) 1720.
[76] V.F. Vasil'eva, O.Yu. Laurova, N.M. Dyatlova, V.G. Yashunskii, J. Gen. Chem. USSR (Engl. Transl.) 38 (1968) 468.
[77] P.K. Tse, J.E. Powell, M.W. Potter, H.R. Burkholder, Inorg. Chem. 23 (1984) 1437.
[78] J.L. Mackey, M.A. Hiller, J.E. Powell, J. Phys. Chem. 66 (1962) 311.
[79] A.E. Martell, R.M. Smith, Crit. Stab. Constant 1 (1974) 263.
[80] J.E. Powell, D.R. Ling, Inorg. Chem. 24 (1985) 2967.
[81] T. Moeller, L.C. Thompson, J. Inorg. Nucl. Chem. 24 (1962) 499.
[82] V. Krumina, K. Astakhov, S. Barkov, Zhur. Phys. Khim. 43 (1969) 1196.
[83] F. Uggeri, S. Aime, P.L. Anelli, M. Botta, M. Brocchetta, C.de Haen, G. Ermondi, M. Grandi, P. Paoli, Inorg. Chem. 34 (1995) 633.
[84] A. Muhler, H.J. Weinmann, Acad. Radiol. 2 (1995) 313.
[85] V.F. Vasil'eva, O.Yu. Laurova, N.M. Dyatlova, V.G. Yashunskii, J. Gen. Chem. USSR (Engl. Transl.) 36 (1966) 688.
[86] G. Sosnovsky, N.U.M. Rao, Eur. J. Med. Chem. 23 (1988) 517.
[87] Y. Masuda, T. Nakamori, E. Sekido, Nippon Kagaku Kaishi 2 (1978) 204.
[88] L.C. Thompson, J. Inorg. Nucl. Chem. 24 (1962) 1083.

[89] I. Grenthe, G. Gardhammar, Acta Chem. Scand. A 28 (1974) 125.
[90] P.B. Baisden, G.R. Choppin, B.B. Garrett, Inorg. Chem. 25 (1986) 2327.
[91] E. Felder, F. Uggeri, L. Fumagalli and G. Vittadini, Paramagnetic Chelates Useful for MRI Imaging, US Patent No. 4, 916, 246, April 10, 1990; IT 19236A, Jan 30, 1986.
[92] F. Cavagna, M. Daprà, F. Maggioni, C. de Haën, E. Felder, Magn. Reson. Med. 22 (1991) 329.
[93] H. Gries, H. Miklautz, Physiol. Chem. Phys. Med. NMR 16 (1984) 105.
[94] E.T. Clarke, A.E. Martell, Inorg. Chim. Acta 190 (1991) 27.
[95] R. Delgado, J.J. Frausto da Silva, Talanta 29 (1982) 815.
[96] J.F. Desreaux, Bull. Cl. Sci. Acad. Belg. 64 (1979) 814.
[97] W.P. Cacheris, S.K. Nickle, A.D. Sherry, Inorg. Chem. 26 (1987) 958.
[98] E.T. Clarke, A.E. Martell, Inorg. Chim. Acta 190 (1991) 37.
[99] S. Aime, P.L. Anelli, M. Botta, F. Fedeli, M. Grandi, P. Paoli, F. Uggeri, Inorg. Chem 31 (1992) 2422.
[100] X. Wang, T. Jin, V. Comblin, A. Lopez-Mut, E. Merciny, J.F. Desreux, Inorg. Chem 31 (1992) 1095.
[101] E. Tòth, E. Brücher, Inorg. Chim. Acta 221 (1994) 165.
[102] J. Huskens, D.A. Torres, Z. Kovacs, J.P. André, C.F.G.C. Geraldes, A.D. Sherry, Inorg. Chem. 36 (1997) 1495.
[103] K. Kumar, T. Jin, X. Wang, J.F. Desreux, M.F. Tweedle, Inorg. Chem. 33 (1994) 3823.
[104] S.I. Kang, R.S. Ranganathan, J.E. Emswiler, K. Kumar, J.Z. Gourgoutas, M.F. Malley, M.F. Tweedle, Inorg. Chem. 32 (1993) 2912.
[105] J.F. Desreaux, E. Merciny, M.F. Locin, Inorg. Chem. 20 (1981) 987.
[106] M.F. Locin, J.F. Desreux, E. Merciny, Inorg. Chem. 25 (1985) 2646.
[107] M. Kodama, T. Koike, A.B. Mahatma, E. Kimura, Inorg. Chem. 30 (1991) 1270.
[108] R. Delgado, Y.S. Ramunas, A.E. Martell, Inorg. Chem. 32 (1993) 3320.
[109] C.A. Chang, M.E. Rowland, Inorg. Chem. 22 (1983) 3866.
[110] C.A. Chang, V.E. Ochaya, Inorg. Chem. 25 (1986) 355.
[111] K.-Y. Choi, Y.-I. Lee, H.S. Kil, D.-W. Kim, Y.S. Chung, C.-S. Kim, C.-P. Hong, W. Sim, Microchem. J. 53 (1996) 180.
[112] E. Tòth, R. Kiràly, J. Platzek, B. Radüchel, E. Brücher, Inorg. Chim. Acta 249 (1996) 191.
[113] A. Bianchi, L. Calabi, C. Giorgi, P. Losi, P. Paoli, P. Rossi, B. Valtancoli, M. Virtuani, J. Chem. Soc. Dalton Trans. (2000) 697.
[114] C.A. Chang, Y.-H. Chen, H.-Y. Chen, F.-K. Shieh, J. Chem. Soc. Dalton Trans. (1998) 3243.
[115] C.A. Chang, P.H.-L. Chang, V.K. Manchanda, S.P. Kasprzyk, Inorg. Chem. 27 (1988) 3786.
[116] Unpublished results.
[117] L.K. Templeton, D.H. Templeton, A. Zalkin, H.W. Ruben, Acta Crystallogr. Sect. B 38 (1982) 2155.
[118] M.B. Inoue, M. Inoue, Q. Fernando, Inorg. Chim. Acta 232 (1995) 203.
[119] C. De-Fu, Y. Wei-Chun, W. Rui-Yao, J. Tian-Zhu, Acta Chim. Sin. 55 (1997) 672.
[120] C.A. Chang, L.C. Francesconi, M.F. Malley, K. Kumar, J.Z. Gougoutas, M.F. Tweedle, Inorg. Chem. 32 (1993) 3501.
[121] J.-P. Dubost, J.-M. Leger, M.-H. Langlois, D. Meyer, M. Schaefer, C.R. Acad. Sci. Paris 312 (1991) 349.
[122] S.I. Kang, R.S. Ranganathan, J.E. Emswiler, K. Kumar, J.Z. Gougoutas, M.F. Malley, M.F. Tweedle, Inorg. Chem. 32 (1993) 2912.
[123] D. Chen, P.J. Squattrito, A.E. Martell, A. Clearfield, Inorg. Chem. 29 (1990) 4366.
[124] H.-J. Weinmann, R.C. Brasch, R.C. Press, G.E. Wesbey, Am. J. Roentgenol. 142 (1984) 619.
[125] M.F. Tweedle, H.G. Brittain, W.C. Eckelman, in: C.L. Partain, et al. (Eds.), Magnetic Resonance Imaging, second ed., W.B. Saunders, Philadelphia, 1987.
[126] M.F. Tweedle, G.T. Gaughan, J. Hagan, P.W. Wedeking, P. Sibley, L.J. Wilson, D.W. Lee, Int. J. Rad. Appl. Instrum. B 15 (1988) 31.
[127] A.D. Watson, J. Alloy Comp. 207/208 (1994) 14.
[128] G. Vittadini, E. Felder, P. Tirone, V. Lorusso, Invest. Radiol. Suppl. 23 (1988) S246.
[129] M.C. Gennaro, S. Aime, E. Santucci, M. Causà, C. De Stefano, Anal. Chim. Acta 233 (1990) 85.

[130] G.E. Jackson, S. Wynchank, M. Woudenberg, Magn. Reson. Med. 16 (1990) 57.
[131] W.P. Cacheris, S.C. Quay, S.M. Rocklage, Magn. Reson. Imag. 8 (1990) 467.
[132] Potentiometric and calorimetric data not published before and reported in this paper were obtained by following the general procedures adopted for similar systems and described in Ref. [113]. A brief description of the experimental procedure is reported below. All pH-metric measurements employed for the determination of protonation and complexation constants were carried out in solutions, containing the reported electrolyte, at 298.1 ± 0.1 K, by a combined Ingold 405 S7/120 electrode, calibrated with a hydrogen concentration probe. Empirical corrections were applied for the non-Nernstian response of the glass electrode below pH 2.5 and above pH 10.5. At least three measurements (about 100 data points for each) were performed for each system in the pH ranges 2.0–12 for ligand protonation and 2.5–10.5 for complexation experiments. The ligand concentration [L] was about 1×10^{-3} mol dm^{-3} in all measurements while the metal ion concentration in the complexation experiments was 0.8[L]. Complexation reactions of Gd^{3+} with cyclic ligands are slow. For this reason out-of-cell experiments were performed, in which 30–40 individual solutions corresponding to single points of conventional titrations were stored in a thermostat at 298.1 ± 0.1 K, and their pH was periodically controlled to ensure the achievement of equilibrium conditions. For all cyclic ligands the use of EDTA as an auxiliary ligand was necessary due to the very high value of the equilibrium constants to be determined. The enthalpy changes were determined by means of microcalorimetric titrations performed with an automated system composed of a Thermometric AB thermal activity monitor (model 2277) adopting the experimental conditions employed in the corresponding potentiometric measurements.
[133] F.H. Spedding, A.F. Voight, E.M. Gladrow, N.R. Sleight, J. Am. Chem. Soc. 69 (1947) 2777.
[134] F.T. Fitch, D.S. Russell, Can. J. Chem. 29 (1951) 363.
[135] R.C. Vickery, J. Chem. Soc. (1952) 4357.
[136] H. Kanno, J. Hiraishi, J. Phys. Chem. 86 (1982) 1488.
[137] G. Johnson, H. Wakita, Inorg. Chem. 24 (1985) 3047.
[138] M. Bukowska-Strzyzewska, A. Tosik, Acta Crystallogr. Sect. B 38 (1982) 265.
[139] R.E. Gerkin, W.J. Reppart, Acta Crystallogr. Sect. C 40 (1984) 781.
[140] D.L. Kepert, Coordination Numbers and Geometries, in: G. Wilkinson (Ed.), Comprehensive Coordination Chemistry, vol. 1, Pergamon Press, Oxford, 1987.
[141] K. Kumar, C.A. Chang, M.F. Tweedle, Inorg. Chem. 32 (1993) 587.
[142] E. Brucher, S. Cortes, F. Chavez, A.D. Sherry, Inorg. Chem. 30 (1991) 2092.
[143] E. Brucher, S.L. Stefan, D.R. Allen, A.D. Sherry, Radiochim. Acta 61 (1993) 207.
[144] A.E. Martell, R.D. Hancock, Metal Complexes in Aqueous Solution, Plenum Press, New York, 1996.