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Review

Mononuclear six-coordinated Ga(III) complexes: A comprehensive survey

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Contents

Abstract

Given the commercial availability of ^{68}Ge–^{68}Ga generators, in principle analogous to the worldwide utilized ^{99}Mo–^{99m}Tc generator, it is surprising that few ^{68}Ga agents have been developed beyond basic research toward clinical application. The use of the unconventional ^{68}Ga positron emitter would allow for a cost-effective production of ^{68}Ga radiotracers far from a cyclotron facility. Moreover, the use of ^{67}Ga radiopharmaceuticals for imaging studies, and the application of non-radioactive gallium compounds in the treatment of important disorders, including a number of cancer and infectious diseases, make studies on trivalent Ga coordination chemistry attractive for the design of novel gallium-based drugs. The aim of this review is to survey the reported crystal data of six-coordinated Ga(III) complexes in order to gain information to be used in the design of novel Ga complexes of medicinal interest.

Keywords: Ga(III) octahedral complexes; X-ray crystal structures; Mononuclear Ga(III) complexes; Ga in PET imaging; Ga-based therapeutic agents

Abbreviations: 2Mequin, 2-methyl-quinolin-8-olato (2-methyl-8-oxyquinolinato) (1-); 3eadd, 1,12-bis(2-oxy-3-ethylbenzyl)-1,5,8,12-tetraazadodecane (2-); 3madd, 1,12-bis(2-oxy-3-methoxybenzyl)-1,5,8,12-tetraazadodecane (2-); 4Mepy, 4-methylpyridine; 5madd, 1,12-bis(2-oxy-5-methoxybenzyl)-1,5,8,12-tetraazadodecane (2-); 5dtbsq, 3,5-di-*t*-butyl-1,2-benzosemiquinonato (1-); 6dtbsq, 3,6-di-*t*-butyl-1,2-benzosemiquinonato (1-); [9]aneN$_3$, 1,4,7-triazonane (1,4,7-triazacyclononane); abb[9]aneN$_3$, 1,4,7-tris(2-amino-3,5-di-*t*-butylbenzyl)-1,4,7-triazacyclononane; ac, acetato (1-); acac, 2,4-dioxopentan-3-ido (acetylacetonato) (1-); ad, 1,4,7,10-tetraazadecane; add, 1,5,8,12-tetraazadodecane; aopoz, 2-(2′-oxy-3′-allylphenyl)-2-oxazolinato (1-); apydt, 2-acetylpyridine-4,4-dimethyl-3-thiosemicarbazonato-*N*,*N*,*S* (1-); apzdt, 2-acetylpyrazine-4,4-dimethyl-3-thiosemicarbazonato-*N*,*N*,*S* (1-); bazmp, 2-((2-(9-bromo-7,12-dihydroindolo[3,2-*d*][1]benzazepin-6-yl)hydrazono)methyl)phenolato-*N*,*N*′,*O* (1-); bctrensam, 6^2,16^2,25^2-trioxy-5,7,15,17,24,26-hexaoxo-

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1. Introduction

In a recent review article illustrating therapeutic gallium compounds, L.R. Bernstein ended the introduction with a peculiar observation: "...although we are a bit ahead of Mendeleev when he described gallium before it had been observed, we still have only taken a glimpse into gallium's therapeutic potential" [1]. This statement can certainly be extended to the use of gallium for other medicinal purposes, including, for example, the imaging of tumors, infections and inflammations by means of radioactive gallium agents [2].

Gallium tartrate was the first compound reported to exhibit therapeutic potential against syphilis in rabbit models in 1931 [3]. Twenty years later, the use of radiogallium (initially, ^{72}Ga) was undertaken to treat primary and metastatic bone cancers [4]. From the early 1970s, non-radioactive gallium compounds proved to be efficient in decreasing accelerated bone mineral resorption, lowering associated elevated plasma calcium levels, or inhibiting neoplastic proliferation, becoming the second metal ion, after platinum, to be used in cancer treatment. Several excellent reviews [5–7] cover much of this research and discuss in detail what is known about gallium's biological mechanism of action. We address readers interested in biological and pharmacological aspects of gallium to the above papers; a brief summary of the medicinal applications of gallium agents is reported in Sections 2 and 3.

In this review we instead want to survey the coordination chemistry of gallium, which is still a rather unexplored field.

4,8,11,14,18,23,27-heptaaza-1-azonia-6,16,25(1,3)tribenzenabicylo(9.9.9)nonacosaphane (2-); bfc, bifunctional chelating ligand; bha, benzohydroxamato (1-); bpy, 2,2′-bipyridine; Brobad, 1,10-bis(2-oxy-5-bromobenzyl)-1,4,7,10-tetraazadecane (2-); Brobadd, 1,12-bis(2-oxy-5-bromobenzyl)-1,5,8,12-tetraazadodecane (2-); Brbzitaea, tris((2-(5-bromo-2-oxybenzylidene)amino)ethyl)amine (3-); BuObzitame, 2-(isobutoxy)-1,1,1-tris((2-oxybenzylidene)aminomethyl)ethane (3-); Bupy, 3-*n*-butylpyridine; Bz, benzyl; Bz_2dtc, *N*,*N*-dibenzylcarbamodithioato (*N*,*N*-dibenzyldithiocarbamato) (1-); bzi, 2-oxybenzylidene; c.n., coordination number; cat, benzene-1,2-diolato (catecholato) (2-); cbcyclam, 1,4,8,11-tetraazabicyclo(6.6.2)hexadecane; CCD, Cambridge Crystallographic Database; CD, circular dicroism; cdta, 2,2′,2″,2‴-(cyclohexane-1,2-diyldinitrilo)tetraacetato (4-); cit, 2-oxypropane-1,2,3-tricarboxylato (citrato) (4-); Cl_4cat, 3,4,5,6-tetrachlorobenzene-1,2-diolato (tetrachlorocatecholato) (2-); Clobmpen, *N*,*N*′-bis(5-chloro-2-oxybenzyl)-*N*,*N*′-bis(2-methylpyridyl)ethylenediamine (2-); Cl_2pmamp, 4,6-dichloro-2-(2-pyridylmethylaminomethyl)phenolato-*N*,*N*′,*O* (1-); cpdp, tris(5-(4-cyanophenyl)dipyrrinato (1-); cup, *N*-nitroso-*N*-phenylhydroxylaminato (cupferron) (1-); dbm, 1,3-dioxo-1,3-diphenylpropane-2-ido (dibenzoylmethanato) (1-); DF, desferrioxamine; dbzitmba, tris(2-((2,3-dioxybenzylidene)ammonio)-3-methylbutyl)amine) (3-); dg, 2-deoxyglucose; didmg, *N*,*N*″-diisopropyl-*N*′,*N*′-dimethylguanidinato (1-); dmbziapen, bis(4,6-dimethoxy-2-oxybenzylidene)-*N*,*N*′-bis(2,2-dimethyl-3-aminopropyl)ethylenediamine (2-); dmf, *N*,*N*′-dimethylformamide; dmge, dimethylglycolether-*O*,*O*′; dmop, 1,2-dimethyl-3-oxy-4-pyridinonato (1-); dmtaci, *cis*,*cis*-1,3,5-tris(dimethylamino)-1,3,5-trideoxyinositol; dota, 1,4,7,10-tetraazacylododecane-*N*,*N*′,*N*″,*N*‴-tetraacetato (4-); dota-D-PheNH$_2$, 4,7,10-triacetato-(1-((1-aminocarbonyl-2-phenyl)ethylaminocarbonyl)methyl)-1,4,7,10-tetraazacyclododecane (3-); dota-noc, dota-Nal^3-octreotide; dota-tate, dota-Tyr^3-Thr^8-octreotide; dota-toc, dota-Tyr^3-octreotide; dppdppi, *N*-(P,P-diphenylphosphinoyl)-P,P-diphenylphosphinimidato (1-); dtbzipma, *N*-(2-oxy-3,5-di-*t*-butylbenzylidene)-*N*-(2-pyridylmethyl)amine (1-); dtcat, 3,5-di-*t*-butylcatecholato (2-); dtobmpen, *N*,*N*′-bis(3,5-di-*t*-butyl-2-oxybenzyl)-*N*,*N*′-bis(2-methylpyridyl) ethylenediamine (2-); dtpa, 2,2′,2″,2‴-(carboxylatomethyl)azanediylbis[ethane-2,1-diylnitrilo]tetraacetato (diethylenetriaminepentaacetato) (5-); dtqdtpi, 3,5-di-*t*-butyl-1,2-quinone-1-(2-oxy-3,5-di-*t*-butylphenyl)imine (2-); ebcys, ethylene-bis(L-cysteinato-*N*,*N*′,*O*,*O*′,*S*,*S*′) (4-); ebgly, ethylene-bis((*o*-hydroxyphenylglicinato)*O*,*O*′,*O*″,*O*‴) (4-); edc, ethylenedicysteine; edta, 2,2′,2″,2‴-(ethane-1,2-diyldinitrilo)tetraacetato (ethylenediaminetetraacetato) (4-); EGF, epidermal growth factor; en, ethane-1,2-diamine (ethylenediamine); emop, 1-ethyl-2-methyl-3-oxy-4-pyridinonato (1-); et[9]aneN$_3$, 1,4,7-tris(2-ethanethiolato)-1,4,7-triazacyclononane (3-); Et_2dtc, *N*,*N*-diethylcarbamodithioato (*N*,*N*-diethyldithiocarbamato) (1-); exa, *O*-ethylxanthato-*S*,*S*′ (1-); F_6acac, hexafluoroacetylacetonato (1-); FVB, Friend leukemia Virus strain B; H_2pz, dihydrobis(1-pyrazolyl)borato (1-); HBrobtaea, tris-((5-bromo-2-oxybenzyl)aminoethyl)amine (2-); Hcit, hydrogencitrato (3-); Hdota, hydrogen 1,4,7,10-tetraazacylododecane-*N*,*N*′,*N*″,*N*‴-tetraacetato (3-); Hdmpz, tris-(3,5-dimethyl-1-pyrazolyl)hydridoborato (1-); Hdtqdtpi, 3,5-di-*t*-butyl-2-oxyphenyl-1-(2-oxy-3,5-di-*t*-butylphenyl)imine (1-); Hmib[9]aneN$_3$, 1-(3,5-dimethyl-2-hydroxybenzyl)-4,7-bis(3,5-dimethyl-2-oxy-benzyl)-1,4,7-triazacyclononane (2-); Himepy, *N*-(2-(4-imidazolyl)ethyl)pyridine-2-carboxamido (1-); Hsda[9]aneN$_3$, 1-succinato-4,7-diacetato-1,4,7-triazacyclononane(3-); Hsemim, tris(2-seleno-1-mesityl-3-imidazolyl)hydridoborato (1-); ida, 2,2′-azanediyldiacetato (iminodiacetato) (2-); LEDs, light-emitting diodes; ma, 2-methyl-3-oxy-4H-pyran-4-onato (maltolato)(1-); mbdt, *N*,*N*′-bis((*S*)-1′-methylbenzyl)-2,3-dioxyterephthalamide (1-); mbzitame, 1,1,1-tris((5-methoxy-2-oxybenzylidene)aminomethyl)ethane (3-); mdp, 5-mesityldipyrrinato (1-); MDR, multidrug resistance; Me$_3$[9]aneN$_3$, 1,4,7-trimethyl-1,4,7-triazacyclononane; Me_2bpy, 4,4′-dimethyl-2,2′-bipyridine; Me_2dtc, *N*,*N*-dimethylcarbamodithioato (*N*,*N*-dimethyldithiocarbamato) (1-); mida, methyliminodiacetato (2-); MeOpamp, 6-methoxy-2-(2-pyridylmethylaminomethyl)phenolato-*N*,*N*′,*O* (1-); mmbh, *N*-methyl-4-methylbenzohydroxamato (1-); mobtap, 1,2,3-tris((5-methoxy-2-oxybenzyl)amino)propane (3-); modtc, morpholinocarbamodithioato (morpholinodithiocarbamato) (1-); mpp[9]aneN$_3$, 1,4,7-tris(methylene(phenyl)phosphinato)-1,4,7-triazacyclononane (3-); MRI, magnetic resonance imaging; nbida, *N*-(2-hydroxy-5-nitrobenzyl)iminodiacetato-*N*,*O*,*O*′,*O*″ (3-); NMR, nuclear magnetic resonance; nta, 2,2′,2″-nitrilotriacetato (3-); obtach, *N*,*N*′,*N*″-tris(benzyl-2-oxy)-*cis*,*cis*-1,3,5-triaminocyclohexane (3-); obtame, 1,1,1-tris(((2-oxybenzyl)amino)methyl)ethane (3-); oc, octahedral; OLEDs, organic light-emitting diodes; opbo, 2-(2′-oxyphenyl)-2-benzoxazolato (1-); opoz, 2-(2′-oxyphenyl)-2-oxazolinato (1-); oro, 5-oxyorotato (2-); ox, ethanedioato (oxalato) (2-); pbdp, benzene-1,2-diylbis(dimethylphosphane) (1,2-phenylenebis(dimethylphosphane)); pcdt, pyrrolo-1-carbodithioato (1-); pdta, 2,2′,2″,2‴-(propane-1,2-diyldinitrilo)tetraacetato (4-); PET, Positron Emission Tomography; pfpcor, 3,17-dinitro-5,10,15-tris(pentafluorophenyl)corrolato (3-); Pgp, P-glycoprotein; phen, 1,10-phenanthroline; PIH, piridoxal isonicotinoyl hydrazone; pmop, 1-*n*-propyl-2-methyl-3-oxy-4-pyridinonato (1-); pmtaea, tris(2-(((*N*-pyrrol-2-yl)methylene)amino)ethyl)amine; ppbaba, tris(4-(phenylphosphinato)-3-benzyl-3-azabutyl)amine; py, pyridine; pydc, 2,6-pyridinedicarboxylato-*O*,*O*′ (2-); pymtach, *N*,*N*′,*N*″-tris(2-pyridylmethyl)-*cis*,*cis*-1,3,5-triaminocyclohexane; pyt, pyridine-2-thiolato (1-); quin, quinolin-8-olato (8-oxyquinolinato) (1-); quint, quinolin-8-thiolato (8-quinolinethiolato) (1-); SB, Schiff base; SPECT, Single Photon Emission Computerized Tomography; ta[9]aneN$_3$, 1,4,7-triacetato-1,4,7-triazacyclononane (3-); tach, *cis*,*cis*-1,3,5-triaminocyclohexane; taci, *cis*,*cis*-1,3,5-triamino-1,3,5-trideoxyinositol; taea, tris(2-aminoethyl)amine; tame, 1,1,1-tris(aminomethyl)ethane; tatach, *N*,*N*′,*N*″-triacetato-*cis*,*cis*-1,3,5-triaminocyclohexane (3-); TDDFT, Time-Dependent Density Functional Theory; tddtd, tris(*N*,*N*′-diethyl-2,3-dioxyterephtalamide)diamine (6-); teda, 1,4,7,10-tetraazabicyclo(5.5.2)tetradecane-4,10-diacetato (2-); terpy, 2,2′:6′,2″-terpyridine; teta, 1,4,7,10-tetraazacylotetradecane-1,4,8,11-tetraacetato (4-); thf, oxolane (tetrahydrofuran); tma, 2-methyl-3-oxy-4H-pyran-4-thionato (thiomaltolato) (1-); tmea, tris(2-ethanethiolato)amine (tris(2-mercaptoethyl)amine) (3-); tmop, 1-*p*-tolyl-2-methyl-3-oxy-4-pyridinonato (1-); tpp, 5,10,15,20-tetraphenylporphinato (2-); treniam, *N*,*N*,*N*-tris(2-(3-(methylaminocarbonyl)-2-oxybenzamido)ethyl)amine (3-); trenhopo(tam)$_2$, *N*,*N*′-([(2-([(3-oxy-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)carbonyl]amino)ethyl)imino]diethane-2,1-diyl)bis[2,3-dioxy-N-(2-methoxyethyl)benzene-1,4-dicarboxamide] (5-); trop, 2-oxy-2,4,6-cycloheptatrienone (tropolonate) (1-); trp, trigonal prismatic.

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It turns out that by examining the molecular structures of gallium compounds in use for clinical purposes, all show trivalent Ga in a more or less distorted octahedral (oc) environment. Accordingly, we first decided to focus our work on the, so far, structurally identified mononuclear gallium(III) complexes with coordination number (c.n.) six. However, since the number of such compounds is rather large, we do not discuss here any complexes containing only monodentate ligands. In addition, according to the envisaged medicinal applications of these gallium species in physiological media, we also excluded compounds with direct metal–carbon or metal–hydrogen bonds, because they are expected not to be stable enough or to hydrolyze in such media. On the other hand, volatile organometallic gallium compounds are extensively used in the semiconductor and electronic industry, mainly for the production of binary gallium arsenide (GaAs). The latter is manufactured into optoelectronic devices such as laser diodes, light-emitting diodes (LEDs) and analog integrated circuits [8]. These materials have properties and uses of their own and do not fit with the other compounds presented here.

In the reviewed six-coordinate Ga(III) complexes, the metal environment has a more or less distorted octahedral geometry and presents a closed-shell d^{10} electron configuration, affording an excellent stability to such compounds. Complexes with vacant coordination sites, occuring in less crowded five-coordinate (either square pyramidal or trigonal bipyramidal) and four-coordinate (tetrahedral) species, are more sensitive to nucleophilic attack, especially in physiological media, both for electronic and steric reasons.

After the pioneering use of naked Ga(III) ions (chloride or nitrate salts) mentioned above for the treatment of lymphoma and bladder cancer, and the following applications focused on the positive effects of Ga(III) on bone metabolism [9], it became desirable to devise gallium formulations with the metal surrounded by ligands able to prevent extensive *in vivo* hydrolysis to $[Ga(OH)_4]^-$ and to improve the complex stability. Coordination chemists are thus challenged to design new chelate frameworks, able to stabilize Ga(III) (in a given coordination geometry) in order to prepare bifunctional chelating ligands (bfcs) supporting more sophisticated receptor targeting.

On the other hand, the availability for many years of commercial ^{68}Ge–^{68}Ga generators [10], similar to the ^{99}Mo–^{99m}Tc generator which have allowed the worldwide production of ^{99m}Tc-based radiopharmaceuticals for decades, can trigger the expansion of non-conventional Positron Emission Tomography (PET), using the cost-effective production of ^{68}Ga radiotracers far from a cyclotron facility [10]. If we also consider the wide use of ^{67}Ga ($t_{1/2}$ = 78.27 h, $E\gamma$ = 184.6 keV) for Single Photon Emission Computerized Tomography (SPECT) [11], coordination chemistry studies on gallium compounds appear timely and appropriate in the continuous search for the ideal gallium chelator.

The data substantiating the present review have been extracted from the ISI Web of knowledge (SM) [12]. However, all major chemistry journals have also been independently searched. The metric data reported in Supplementary Information (Tables S1–S7) were obtained from the Cambridge Crystallographic Database (CCD; Version 5.28 of November 2006 + 3 updates [13–15]), even if, in some cases, the CCD values did not agree with published data. Additional metric data and indices describing the coordination geometry around the metal, such as the b and θ indices [16], have been calculated for the 137 reviewed structure determinations.

During the preparation of this work, complexes have been grouped in order of decreasing ligand denticity. Within each group, complexes have been aggregated in subgroups featuring well-known chemical synthons or functionalities, such as ethylenediaminetetraacetate (edta) derivatives, Schiff bases (SB), and so on. The resulting subgroups have been arranged in order of similarity of the coordination sphere, that is, complexes showing, for example, a hexadentate ligand with a donor set of the type N_4O_2, N_3O_3, N_2O_4, have been discussed in this order.

For the sake of clarity, hexadentate compounds that might have been classified within a certain subgroup, but showing unusual donor sets, have been removed from the pertinent subgroup and gathered in a miscellaneous table (Supplementary data, Table S2). The same has been done when discussing mixed-ligand tris-bidentate complexes (Supplementary data, Table S7). In the preparation of the tables we adopted the following criteria: (i) the molecules have been oriented in such a way to present a N_2O_2 equatorial donor set whenever possible; (ii) the pair of mutually *trans* donor atoms (Do) whose Ga–Do bond lengths added up to the highest possible sum have been defined as the axial ligands; (iii) metric data involving monodentate ligands have been omitted.

All the reviewed molecules have been numbered according to their references, so that across the survey the compound number and the reference number are the same. When a single paper reports more structures, like for example, Ref. [35] that describes seven complexes, they have been labeled as [35a], [35b] ... [35g]. Multiple references, like for example Ref. [36] that gathers four papers, represent instead multiple crystallographic determinations of the same compound. In such instances, reported metric data refer to the most recent work. In the tables, the column headed 'Chelate Ligand Donors' shows the set of donor atoms of the polydentate ligands. The latters have been indicated by joining the involved atoms with the symbol '∩'.

The number of the illustrations has been limited by choosing to give emphasis to compounds of medicinal interest or relevant to the discussion of steroisomerism. For clarity, only atoms other than carbon have been labeled, whereas hydrogen atoms and solvent molecules have been omitted. Similarly, the tables report only the chemical formulae of the neutral/charged complexes, without solvent molecules, counter anions or counter cations.

The chemical formulae of all the coordination entities described in this work, whether charged or not, have been written enclosed in square brackets, according to IUPAC recommendations about coordination compounds [17]. However, in the same notations the various ligands have not been written in alphabetical order, rather, priority has been given to the polydentate ligands. As for the ligand names, an effort has been made in order to comply with IUPAC guidelines for the construction and use of ligand abbreviations [17].

2. Gallium-based therapeutic agents

The anticancer properties of gallium were discovered in the early 1970s and since then many investigations have attempted to elucidate its mode of action [7]. Proposed mechanisms invoke the similarity of the ionic radii of Ga^{3+} and Fe^{3+} (0.62 and 0.65 Å, respectively, for c.n. six), electronegativity (1.6 and 1.8, respectively, the Pauling electronegativity values), and hence of chemical behavior, although Ga^{3+} cannot be easily reduced like Fe^{3+}, so it is prevented from participating in redox reactions and likely encounters a different cellular metabolism. These features enable gallium to replace iron in some proteins, the most important being transferrin, which promotes the cellular absorption of Ga^{3+} wherever Fe^{3+} is required, in particular in proliferating cancer cells.

Taking into account the similarity of gallium with iron, a class of aroylhydrazone analogues to piridoxal isonicotinoyl hydrazone (PIH), a transferrin-independent iron chelator which delivers iron to cells in an available form, has been reported and their activity discussed [18]. In order to tune the lipophilicity of gallium-derivates, hexadentate SB ligands featuring a N_4O_2 donor set have been prepared, leading to the complexes [{bis(3-methoxy-2-oxybenzylidene)-*N*,*N*′-bis(3-aminopropyl)-ethylenediamine}gallium(III)]$^+$ and [{bis(4,6-dimethoxy-2-oxy-benzylidene)-*N*,*N*′-bis(3-aminopropyl)ethylenediamine}gallium(III)]$^+$; both molecules showed antiproliferative properties.

Moreover, since the cytotoxic activity of these compounds was against tumor cells modified by the expression of MDR1 P-glycoprotein (Pgp) (that is, in the case of patients presenting multidrug resistance, MDR), they might be probes of MDR1 Pgp-mediated transport activity [19]. However, as pointed out in Section 1 and unlike metals such as platinum(II) and ruthenium(III), the development of anticancer gallium coordination compounds is still in its infancy, so that only very recently the idea of using a bioactive molecule as a Ga carrier has been put into practice. For example, knowledge that α-*N*-heterocyclic thiosemicarbazones are inhibitors of the enzyme ribonucleotide reductase prompted the synthesis of a series of Ga-thiosemicarbazone derivatives. Among these, bis(2-acetylpyridine-4,4-dimethyl-3-thiosemicarbazonato-*N*,*N*,*S*)gallium(III) tetrachlorogallate (KP1089) has proven to have a strong *in vitro* antiproliferative effect against human cancer cell lines.

Following the strategy of chelating gallium to a bioactive molecule, a gallium–paullone derivative, again, a pseudo-octahedral molecule comprising two paullone-like ligands has been recently reported having a high antiproliferative activity *in vitro* [20]. Besides, an anticancer activity has been envisaged, after ultrasound activation, for the complex 7,12-bis(1-decyloxyethyl)Ga(III)-3,8,13,17-tetramethylporphyrin-2,18-dipropionyl diaspartic acid [21].

In addition to the ability of inhibiting the growth of cancer cells, especially in lymphomas and bladder cancer, gallium salts have therapeutic effect in cancer-related hypercalcemia [1]. Until now, the only approved gallium-based drug (citrated gallium nitrate, Ganite^{TM}) is related to this pathology. Despite the data mentioned above, from the late 1990s until 2003, the pharmaceutical production of gallium nitrate was interrupted, and only in the last years have the studies and clinical trials with gallium nitrate as a chemotherapeutic drug gained new impetus.

A serious drawback to the use of gallium nitrate is that its oral administration is hampered by the low intestinal absorption of gallium salts. In order to improve the uptake and stabilize gallium derivatives against hydrolysis, coordination complexes have been developed. Two pseudo-octahedral compounds, namely, tris(8-quinolinato)gallium(III) (KP46), which terminated phase I clinical trials, and gallium maltolate [22], are currently being evaluated in clinical trials as potential oral agents.

Some non-octahedral complexes, such as tetradentate porphyrin derivatives, showed *in vitro* antibacterial activity [21], whereas an amino phenol complex containing a N_4O_2 donor set, [{1,12-bis(2-hydroxy-3-methoxy-5-(quinolin-3-yl)-benzyl)-1,5,8,12-tetraazadodecane}Ga(III)]$^+$, showed selective antimalarial activity against chloroquine-resistant microorganisms [23].

3. Radioactive Ga imaging agents

The three isotopes of gallium with attractive nuclear properties in nuclear medicine are ^{66}Ga, ^{67}Ga and ^{68}Ga. ^{67}Ga is a cyclotron-produced radionuclide, having a γ-emission of 184.6 keV and a relatively long half-life (78.27 h), which is optimal for SPECT detectors. ^{67}Ga has been used as gallium citrate for the imaging of inflammation/infection sites for over 30 years, and to a minor extent in the diagnosis of certain tumor types.

Several studies have demonstrated that, after intravenous administration of gallium citrate (or other weak chelates), ^{67}Ga binds to iron-binding proteins such as transferrin, ferritin and lactoferrin leading to high uptake in the areas where iron generally accumulates [24]. The distribution in different tissues limits the use of such ^{67}Ga derivatives as specific tumor-localizing agents. Thus, efforts have been made to find more robust radiopharmaceuticals by stabilizing coordination compounds with polydentate ligands. In particular, hexacoordinate derivatives containing macrocyclic, like [9]aneN_3, dota, teta or tach-like ligands, have been characterized and tested in biodistribution studies [2].

The other Ga isotopes, ^{66}Ga and ^{68}Ga, are positron emitters and are suitable for the development of alternative, non-conventional PET tracers. For ^{68}Ga, $t_{1/2} = 68$ min, β^+ 89%, β_{max} 1.899 MeV, whereas for ^{66}Ga, $t_{1/2} = 9.49$ h, β^+ 56%, β_{max} 4.153 MeV, γ 44%, 1.039 and 2.572 MeV. ^{66}Ga is attractive for tumor imaging due to its relatively long half-life that is suitable for PET imaging over an extended time period after radiopharmaceutical administration. ^{68}Ga is obtained from a long-lived parent nuclide, ^{68}Ge ($t_{1/2} = 270.8$ d), which can be adsorbed onto SnO_2 or TiO_2 solid phases from which ^{68}Ga can be selectively eluted. Currently, generators are available from at least two companies, Cyclotron Co., Obninsk (Russia) and Eckert & Ziegler, Berlin (Germany). Several authors have described methods of preparing high specific activity Ga radiopharmaceuticals from these generators. The chance of operating far from a cyclotron

facility, and the long half-life of the parent ^{68}Ge, which allows the generator a lifetime of 1–2 years, makes the use of ^{68}Ga also economically attractive [10,11].

Despite its interesting features and the availability, for many years, of ^{68}Ga generators, movement towards the clinical use of ^{68}Ga-labeled target-specific agents has begun only recently. Taking advantage of the chemical similarity of Group 13 gallium and indium, a large number of polydentate ligands have been designed for the application with radioactive Ga and ^{111}In [2]. Two requirements are needed for using Ga(III) and In(III) complexes as radiopharmaceuticals: stability to hydrolysis to avoid the formation of insoluble [M(OH)$_3$] species, and kinetic inertness to exchange with transferrin favored by the large formation constants of these M(III)-transferrin compounds (log K_1 for Ga = 20.3; In = 18.7) and high plasma concentration of the protein. Hence, extensive studies on the thermodynamic stability of Ga(III) and In(III) complexes comprising polyaminopolycarboxylate, hydroxyaromatic, macrocyclic and amine-thiol type have been carried out providing a rational platform for the development of gallium and indium radiopharmaceuticals.

For example, among Ga-labeled small molecules, cationic and lipophilic hexadentate bis(salycilideneiminate) compounds have been tested as myocardial imaging agents. More recently, some chelate frameworks, selected on the basis of their ability to form thermodynamically stable complexes with Ga (and other trivalent ions) [25], have been functionalized to generate the 'so-called' bifunctional chelating ligands (bfcs) useful in the field of (radio)metal-labeled receptor-targeting agents. Bfcs consist of a chelate able (i) to coordinate the radiometal on one side, and (ii) to conjugate biomolecules or peptides through an appropriate functional group on the other side [26].

An illustrative example of bfc toward gallium is the potentially octadentate dota ligand which utilises the tetraaza macrocycle and only two carboxylate groups for the metal coordination and one carboxylic pendant function for the conjugation with the biomolecule.

To date, the agents most studied for imaging tumors overexpressing somatostatin receptors are, by far, the Ga-labeled octreotide derivatives, that is, ^{68}Ga-dota-toc, ^{68}Ga-dota-tate and ^{68}Ga-dota-noc (dota-noc, dota-tate and dota-toc for, dota-Nal^3-octreotide, dota-Tyr^3-Thr^8-octreotide and dota-Tyr^3-octreotide, respectively) [2].

Other examples of potential gallium tracers are: ^{68}Ga-dota-EGF (EGF for epidermal growth factor) for visualization of EGF receptor expression in tumors, ^{68}Ga-dota-albumin as blood-pool marker and ^{68}Ga-dota-bombesin analogue for gastrointestinal tumors [27]. Besides dota, other polydentate ligands have been used as bfc, such as [9]aneN$_3$ (especially if thiol-derivatized) [28], teta or dtpa derivatives. By using desferrioxamine (DF) as bfc, a series ^{68}Ga-, ^{67}Ga- and ^{66}Ga-labeled DF folate as potential folate-receptor-targeted radiopharmaceuticals has been prepared for tumor imaging [29].

Although thermodynamic studies have established the superior stability of six-coordinated over four- and five-coordinated N$_2$S$_2$-type Ga complexes [25], coordinatively unsatured tetrahedral or trigonal bipyramidal species continue to be investigated [30]. Examples include ^{68}Ga derivatives of ethylenedicysteine (edc), like edc-guanine and edc-dg (dg = 2-deoxyglucose), that have been tested in animals for the imaging of different kind of tumors [30], and [^{68}Ga(tmea)L] species (tmea = tris(2-mercaptoethyl)amine, L = water or a secondary amine ligand) prepared in aqueous solution at room temperature.

4. Structural overview on Ga(III) mononuclear complexes with c.n. six

4.1. Hexadentate ligands

In this section are outlined the data presented in Supplementary data, Tables S1 and S2, referring to the Ga complexes in which the metal is wrapped by an hexadentate ligand. Supplementary data, Table S1 lists 27 structure determinations [31–54] divided in six subgroups (i–vi). Subgroup (i) gathers all the [Ga(edta)]$^-$ complexes. The eight entries differ because of the counter cation (alkali metals, ammonium, nitron or pyridinium salts) and of the number of co-crystallized solvation water molecules (1–4). We note here that similar considerations apply also to the other cases in which multiple structure determinations of the same complex have been described in the tables.

In all the complexes reported, the edta molecule coordinates to the metal in the simplest of its binding modes, that is, by using all of its donor atoms, so that in the resulting octahedral environment the equatorial positions are held by a N$_2$O$_2$ donor set. However, the atoms belonging to such donor set show some departure from the equatorial mean plane. The measured deviations range between 0.14 and 0.19 Å, and they are such that the four atoms lie, alternatively, above and below the plane, almost by the same amount, a motif that has been found in all the structure determinations reviewed.

On the contrary, the Ga atom itself does not deviate too much from the mean plane, its departure being at most 0.03 Å. The apical positions above and below the plane are occupied by the remaining two acetate oxygen atoms, which, together with the metal atom, define an O$_{ax}$–Ga–O$_{ax}$ angle (O$_{ax}$ for oxygen in an apical position) also measuring the extent of distortion from an ideal geometry (from 171.6° to 177.3°).

Subgroups (ii–iv) are, in a way, similar because they all include Ga complexes showing an aza-cyclic chelate. The latter is 1,4,7-triazacyclononane in subgroup (ii) ([9]aneN$_3$ type), *cis*,*cis*-1,3,5-triaminocyclohexane in subgroup (iii) (tach type), and 1,4,7,10-tetraazacyclododecane in subgroup (iv) (dota type).

In these subgroups, the Ga coordination sphere is either of the N$_3$O$_3$ or the N$_4$O$_2$ type. Accordingly, in all these molecules the O$_{ax}$–Ga–O$_{ax}$ angle is replaced by the N$_{ax}$–Ga–O$_{ax}$ one in [9]aneN$_3$ and tach subgroups, and by the N$_{ax}$–Ga–N$_{ax}$ one in the dota subgroup.

Besides, while all hexadentate edta complexes are anionic and hydrophilic, the majority of the complexes in these three subgroups are neutral and lipophilic. Only two are cationic: [Ga(Hmib[9]aneN$_3$)]$^+$ [37] and *cis*(*O*,*O*)-[Ga(teda)]$^+$ [44] (Fig. 1). For these last two, an application such as a heart perfusion agent could be envisaged, mimicking the current clinical

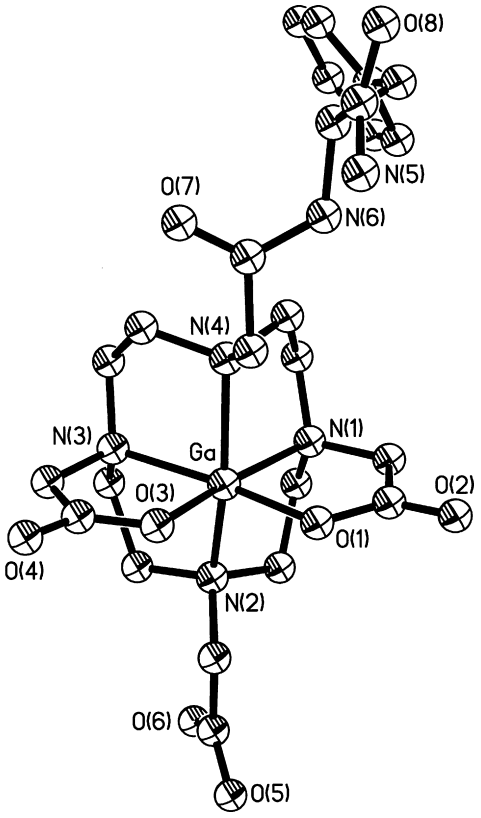

Fig. 1. The molecular structure of *cis*(*O*,*O*)-[Ga(dota-D-PheNH$_2$)] [43].

use of monocationic, lipophilic ^{99m}Tc-Myoview^{TM} or ^{99m}Tc-Cardiolite^{TM} in SPECT imaging.

In the complexes belonging to the [9]aneN$_3$ and tach subgroups (N$_3$O$_3$ donor set), the ligand wraps around the metal in such a way that the three nitrogen atoms and the three oxygen atoms are facially arranged. Besides, most of these molecules show a regular or approximate C_3 axis of symmetry, with the exception of [Ga(Hsda[9]aneN$_3$)] [39] (Fig. 2), which has been designed with a pendant carboxylate group for additional coupling with bioactive molecules.

In subgroups (ii–iv), the amount of the octahedral distortion as measured by the deviation from the pertinent mean plane of the atoms holding the equatorial positions appears to be more or less of the same order than that observed in the edta subgroup (range between 0.01 and 0.16 Å), with the notable exception of the already mentioned *cis*(*O*,*O*)-[Ga(teda)]$^+$ [44], where the four atoms deviate by as much as 0.26 Å. These rather high values are due to the steric constraint imposed by the insertion of an additional ethylene bridge into the 1,4,7,10-tetraazamacrocycle, and gallium itself deviates more from the equatorial plane (up to 0.12 Å) than previously observed in subgroup (i).

As for the bond distances, there is little variation across the subgroups (ii–iv), the clearest difference between subgroup (i) and subgroups (ii–iv) being the angle that the two apical donor atoms define with Ga. This parameter oscillates between 164.8° and 176.4° and the narrowing, compared with the edta subgroup, can be due to the geometric constraints imposed by the chelating macrocycles.

SB type ligands are gathered in subgroup (v). These complexes are again characterized by a N$_3$O$_3$ donor set, in which the three nitrogen atoms and the three oxygen atoms are facially arranged around the metal, featuring a more or less regular C_3 axis of symmetry. All complexes are neutral and lipophilic, like *fac*-[Ga(mbzitame)] [45], which was the first potential gallium radiopharmaceutical to be structurally characterized (Fig. 3).

The arrangement of the polydentate ligand resembles that found in the tach subgroup, and in fact the metric data are rather similar, although Ga–N$_{eq}$ distances appear a little shorter (0.01–0.03 Å) than in subgroup (iii). The degree of octahedral distortion also seems to match that found in the [9]aneN$_3$ and tach subgroups. In fact, the angle defined by the two apical donors and Ga is always about 171°, the atoms holding the equatorial positions deviate from the mean plane in a narrow range

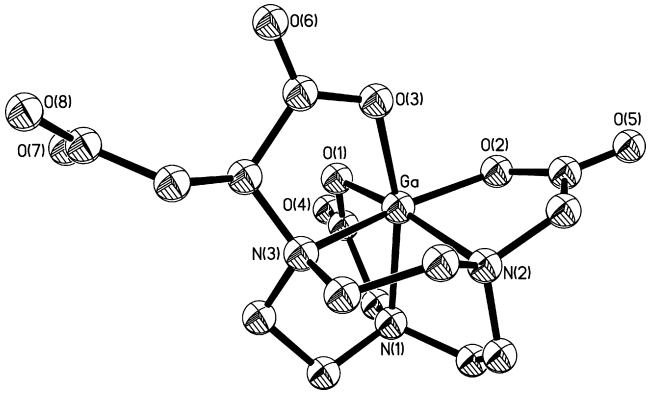

Fig. 2. The molecular structure of [Ga(Hsda[9]aneN$_3$)] [39].

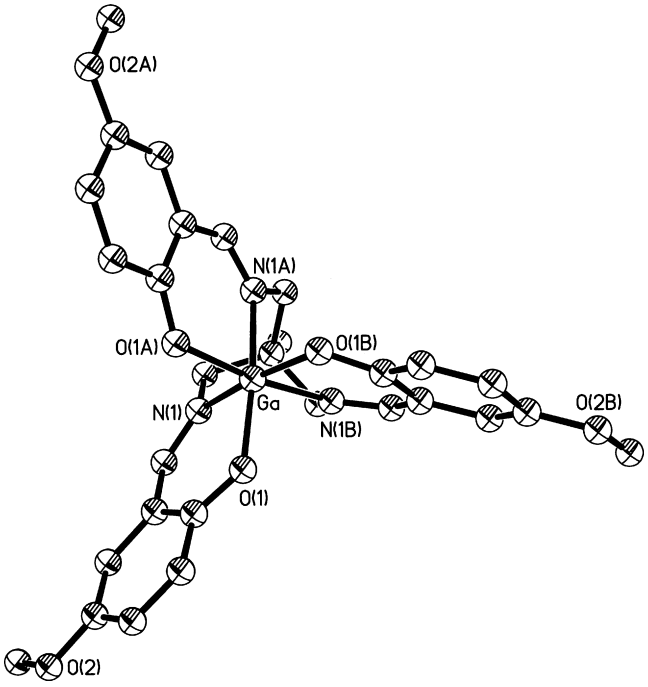

Fig. 3. The molecular structure of *fac*-[Ga(mbzitame)] [45].

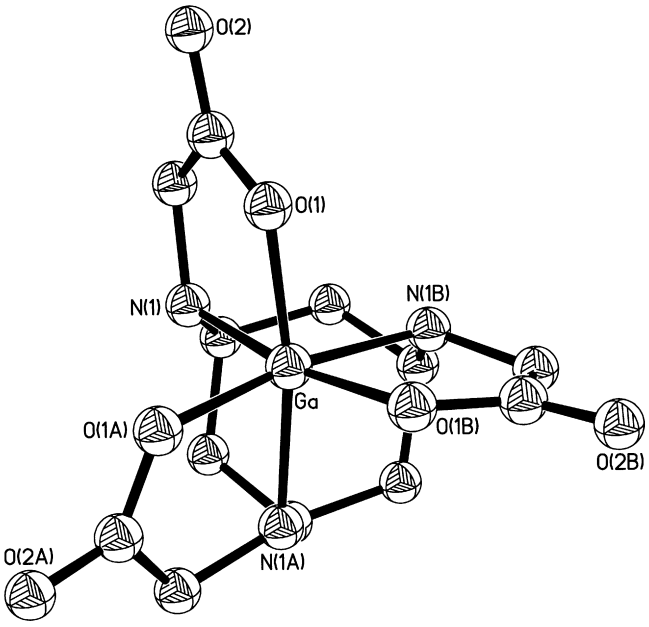

Fig. 4. The molecular structure of [Ga(tatach)] [41].

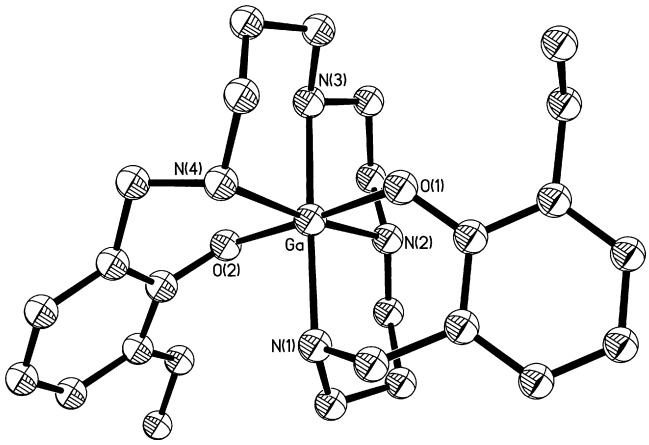

Fig. 5. The molecular structure of the cation *trans*(*O*,*O*)-[Ga(3eadd)]$^{+}$ [52].

(from 0.08 to 0.10 Å), and the Ga itself does not deviate by more than 0.08 Å.

The facial arrangement of the nitrogen and oxygen donors in compounds having a N_3O_3 donor set offers another opportunity for measuring the degree of octahedral distortion by introducing two further parameters, the 'twist' ϕ and the 'tilt' τ angles. ϕ is the torsion angle defined by one nitrogen donor, the centroid of the N_3 face, the centroid of the O_3 face and the oxygen donor closest to the above nitrogen (average of the three possible values); τ is the dihedral angle between the N_3 and O_3 planes. For an ideal octahedron, the N_3 and O_3 faces would be exactly staggered, with $\phi = 60^\circ$ and $\tau = 0^\circ$.

In Supplementary data, Table S1, these parameters show a different behavior; the τ angle varies between 0.0° and 2.6°, with the unique exception of complex *fac*-[Ga(Brbzitaea)] [47], where $\tau = 6.4^\circ$. On the contrary, ϕ shows more variation, spanning a range of about 18°. The greatest departures from the ideal value of 60° are shown by [Ga(Hsda[9]aneN_3)] [39] (44.4°), [Ga([9]aneN_3)] [36] (47.5°) and [Ga(tatach)] [41] (48.4°) (Fig. 4), where the Ga atom is coordinated by rather small and sterically constrained aza chelate ligands.

The amine phenol subgroup (vi) gathers seven entries, which are all monocationic complexes showing the N_4O_2 donor set. Compounds [48–50], that is, *cis*(*O*,*O*)-[Ga(Brobad)]$^{+}$, *cis*(*O*,*O*)-[Ga(Clobmpen)]$^{+}$ and *cis*(*O*,*O*)-[Ga(HBrobtaea)]$^{+}$, are different from the others in the subgroup because of the orientation assumed by the negatively charged oxygen donors (*trans* in all the remaining compounds).

We remind here our decision to preserve (see Section 1) an N_2O_2 equatorial donor set whenever possible. In the above mentioned *cis* compounds, this choice implies that the Ga–N_{eq} distances listed in Supplementary data, Table S1 are longer than the corresponding Ga–N_{ax} ones. The range of Ga–N_{eq}, Ga–O_{eq} distances in *trans* compounds is in good agreement with that found in the edta subgroup, while the Ga–O_{eq} bond lengths found in the *cis* compounds are the shortest (range: 1.854–1.914 Å) in Supplementary data, Table S1.

In all these compounds the metal environment is distorted octahedral, although the distortion appears to be more pronounced in the *cis* rather than in the *trans* compounds. Thus, the deviation from the equatorial mean plane of the donor atoms is greater for *cis* (range for N, O: 0.05–0.18 Å; range for Ga: 0.02–0.03 Å) than for *trans* molecules (range for N, O: 0.04–0.06 Å; range for Ga: 0.01–0.08 Å). The same is true for the N_{ax}–Ga–N_{ax} angle, which is always greater than 175° in *trans* complexes and always smaller than this value in *cis* compounds, being as narrow as 160.7° in *cis*(*O*,*O*)-[Ga(HBrobtaea)]$^{+}$ [50]. The minor degree of octahedral distortion of the *trans* complexes might be related to the dimensions of the rings formed by the ligands upon coordination. In fact, while *trans* compounds form one five-membered and four six-membered rings, *cis* compounds form two six-membered and three five-membered rings.

The complexes *trans*(*O*,*O*)-[Ga(3eadd)]$^{+}$, *trans*(*O*,*O*)-[Ga(3madd)]$^{+}$, *trans*(*O*,*O*)-[Ga(5madd)]$^{+}$ [52–54] (Fig. 5) possess antimalarial activity, whereas *trans*(*O*,*O*)-[Ga(Brobadd)]$^{+}$ [50], whose metric data are in close agreement with those of the other *trans* compounds, was investigated as a putative radiopharmaceutical.

Supplementary data, Table S2 is a miscellaneous table, whose purpose was to gather eleven gallium complexes [55–64] showing unusual hexadentate ligands having previously unseen N_6, O_6, $N_2O_2S_2$, N_3S_3 donor sets, together with the already encountered N_2O_4, N_3O_3, N_4O_2 ones.

All these entities are distorted octahedral complexes, and in some cases the departure from an ideal geometry becomes evident. The charged status of the listed compounds is also heterogeneous, so that Supplementary data, Table S2 gathers three anionic, three cationic and five neutral compounds. Although charged compounds have already been seen, ionic compounds in Supplementary data, Table S1 are always singly charged, whereas in Supplementary data, Table S2 we also find multiply charged compounds such as *fac*-[Ga(pymtach)]$^{3+}$ [55] and [Ga(tddtd)]$^{3-}$ [61].

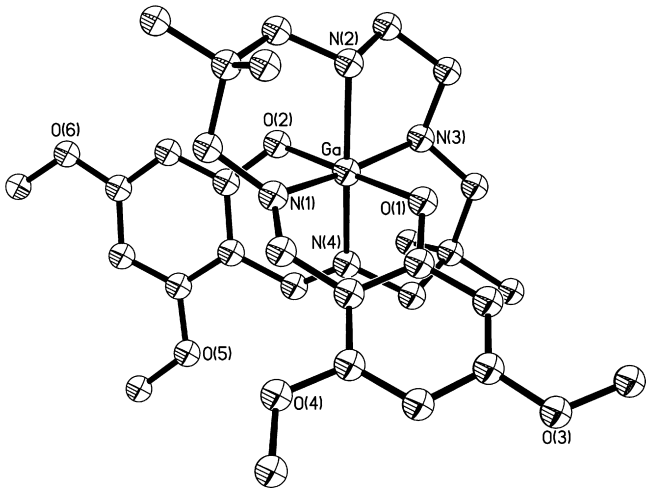

Fig. 6. The molecular structure of the cation *trans*(*O*,*O*)-[Ga(dmbziapen)]$^{+}$ [57].

As an example of the unusual nature of these compounds, the cationic *trans*(*O*,*O*)-[Ga(dmbziapen)]$^{+}$ complex [57] (Fig. 6), is a SB type compound featuring the N_4O_2 donor set. This complex has shown significant myocardial uptake in animal studies.

Bond distances and angles compare reasonably with those of Supplementary data, Table S1, apart from sulfur-containing compounds. In this perspective, the sulfur donor is scarcely represented in a landscape largely dominated by the N and O atoms. Interestingly, in *cis*(*S*,*S*)-[Ga(ebcys)]$^{-}$ [63] and *fac*-[Ga(et[9]aneN_3)] [64] the sulfur donor belongs to a mercapto group, which is not 'soft' in the hard/soft acid base sense, but rather shows a borderline behavior by forming stable complexes with the 'hard' gallium metal.

By omitting metal–sulfur data, the Ga–N_{eq} and Ga–O_{eq} distances range from 2.014 to 2.149 Å and from 1.885 to 1.975 Å, respectively. The corresponding intervals in Supplementary data, Table S1 are 2.046–2.183 and 1.854–1.954 Å, denoting a shift towards longer Ga–O_{eq} distances. The intervals for Ga–N_{ax} and Ga–O_{ax} distances in Supplementary data, Table S2 are 2.014–2.220 and 1.917–2.102 Å, respectively, comparing with 2.072–2.189 and 1.912–1.997 Å in Supplementary data, Table S1.

As for the amount of octahedral distortion, all the reported X_{ax}–Ga–Y_{ax} angles (X_{ax}, Y_{ax} for the donor atoms occupying the apical positions) are smaller than 175° and five (out of 11) complexes have X_{ax}–Ga–$Y_{ax} < 170°$. This compares in Supplementary data, Table S1 with about one half of the compounds having X_{ax}–Ga–Y_{ax} angle smaller than 175° and only 6 (out of 27) compounds for which X_{ax}–Ga–$Y_{ax} < 170°$. The narrowest angle in Supplementary data, Table S2 is 159.4° for [Ga(tddtd)]$^{3-}$ [61], compared with 160.7 for *cis*(*O*,*O*)-[Ga(HBrobtaea)]$^{+}$ [50] in Supplementary data, Table S1. In [Ga(tdtd)]$^{3-}$ the metal is coordinated by a macrobicyclic catechol cryptand that enforces a marked distortion on the octahedral geometry.

The equatorial donor atoms deviate in the range 0.03–0.28 Å (0.01–0.26 Å in Supplementary data, Table S1). The compounds in which the equatorial donor atoms deviate more are *fac*-[Ga(pymtach)]$^{3+}$ [55], [Ga(ebgly)]$^{-}$ [60] and, again, [Ga(tddtd)]$^{3-}$ [61], with the latter showing the largest departures. In these cases the gallium atom and the ligand form, upon coordination, three five-membered rings, a situation somehow resembling that found in the edta complexes and in *cis*(*O*,*O*)-[Ga(teda)]$^{+}$ [44], all showing five five-membered rings.

Another way for appreciating the amount of octahedral distortion is by means of the above defined ϕ and τ parameters. In Supplementary data, Table S2 we have three complexes showing either a N_3O_3 or N_3S_3 donor set in which the donor atoms of the same type are facially arranged around the metal. Besides, we also have N_6- and O_6-compounds in which there are two sets of three equivalent nitrogen atoms (or oxygen atoms) for which the parameters can be calculated. Finally, although the nature of the ligand would not support this approach, we also decided to calculate the ϕ and τ indices also for [Ga(tddtd)]$^{3-}$, because it is a distorted complex whose symmetry allows to identify two opposing O_3 faces.

As already seen in Supplementary data, Table S1, the behavior of the two parameters is different. The τ index ranges between 0.0 and 4.3° in *fac*-[Ga(mobtap)] [59]. In the complex *fac*-[Ga(bctrensam)]$^{+}$ [62b], where the Ga atom is also chelated by a macrocycle, there are two independent molecules in the unit cell, with mean τ of 3.0°, the second largest value in the table. The ϕ values vary from 34.1° in the already mentioned [Ga(tddtd)]$^{3-}$ [61] to the nearly ideal 59.9° in *fac*-[Ga(obtame)] [58], spanning about 26°. By omitting [Ga(tddtd)]$^{3-}$, the spanned range reduces to 15°, similar to that found for the complexes listed in Supplementary data, Table S1 (18°).

4.2. Pentadentate or tetradentate ligands

The 11 structure determinations [35d–35g, 65–70] whose metric data are reported in Supplementary data, Table S3 refer to the few Ga(III) complexes in which the octahedral coordination sphere is filled by a pentadentate plus a monodentate ligand ('5+1') or a tetradentate plus two monodentate ligands ('4+$(1)_2$' or '4+1+1' type). The limited number of these entities, especially if compared with the population of other sections of this review, indicates a greater propensity of Ga for hexadentate '6+0', bistridentate '3+3', tris-bidentate '2+2+2' coordination rather than for the '5+1', '4+$(1)_2$' arrangements.

Like Supplementary data, Table S2, this is also a miscellaneous list, in which about half of the reported entries are edta complexes. The presence of one or two monodentate ligands completing the coordination environment of the metal makes it difficult to compare the metric data with those of the previous section. As for the charge status, about half of these compounds are anionic, only one is cationic and the remaining are neutral. All the reported entities are distorted octahedral complexes.

As noted above, the subgroup gathering '5+1' complexes is homogeneous in that the polydentate ligand is always edta. Interestingly, the data in Supplementary data, Table S3 for these compounds show some divergence from the values found for the corresponding subgroup (i) in Supplementary data, Table S1, notably, with respect to the Ga–N_{eq} and Ga–O_{eq} parameters. In fact, most of the Ga–N_{eq} bond lengths reported in

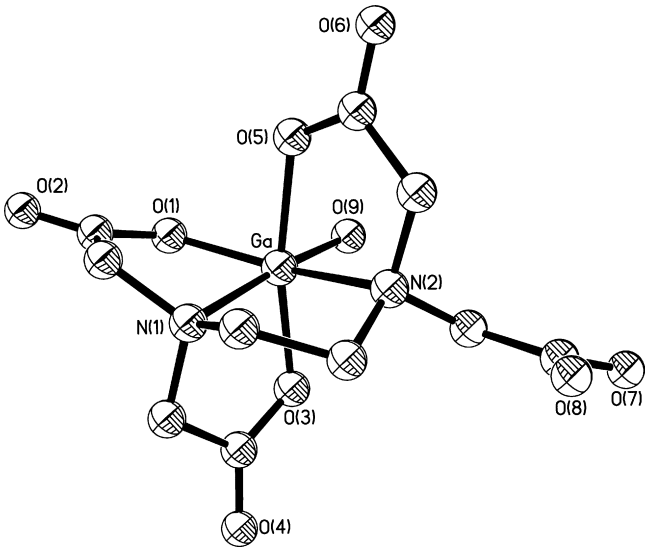

Fig. 7. The molecular structure of [Ga(Hedta)(OH_2)] [35d].

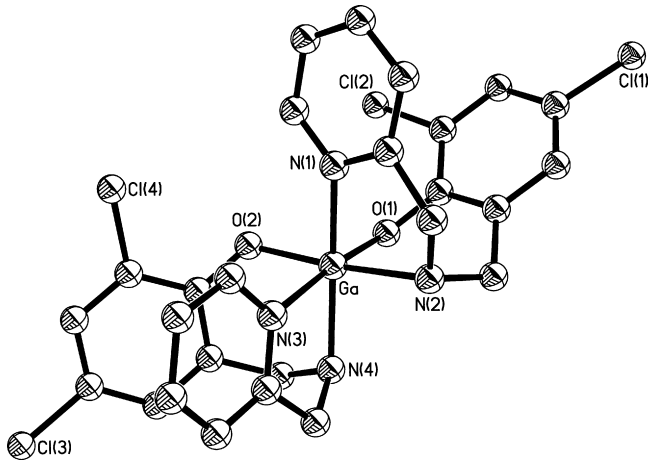

Fig. 8. The molecular structure of the cation *unsym*,*fac*-[Ga(Cl_2pmamp)$_2$]$^+$ [75a].

Supplementary data, Table S3 are longer (0.01–0.08 Å) than the longest Ga–N_{eq} distance in Supplementary data, Table S1. On the other hand, although the Ga–O_{eq} bond lengths for '5+1' and '6+0' edta complexes both span a similar and very narrow range, the latter are shifted towards slightly longer (0.02 Å) bonds in '5+1' compounds.

The two subgroups show also different values of the angle involving the gallium atom and the two apical oxygen atoms (interaxial angle). In Supplementary data, Table S3, the angle is always narrower than 175° (average 170.4°), whereas in Supplementary data, Table S1 it becomes smaller than 175° only in two structure determinations (average 175.6°). The structure determination of [Ga(Hedta)(OH_2)] [35d] somehow resumes the above mentioned features, and can be taken as representative of this subgroup (Fig. 7).

The situation for '4+($1)_2$' complexes is more diverse and a proper comparison with the previously reviewed compounds is more problematic. This is exemplified by the absence of the X_{ax}–Ga–Y_{ax} parameter, always dependent on a monodentate ligand, which leaves only the ΔGa, Δeq values for a rough estimate of octahedral distortion. The Ga–N_{eq} and Ga–O_{eq} bond lengths in this subgroup are, respectively, shorter and longer than those seen overall in the previous section. The variation is more apparent for Ga–N_{eq} distances than for Ga–O_{eq} ones, while, on the contrary, the Ga–O_{ax} data overlap those of already reviewed compounds. The shortest Ga–N_{eq} bond lengths in Supplementary data, Table S3 are those of the macrocyclic complexes [Ga(tpp)pyCl] [65] and [Ga(pfpcor)(py)$_2$] [66] (1.909–2.016 Å), and this reflects the constraints imposed by these special ligands.

However, if we omit the data involving planar macrocyclic ligands, the Ga–N_{eq} distances in this subgroup vary between 2.070 and 2.132 Å, a range compatible with those of Supplementary data, Tables S1 and S2. As a final remark, we note that the Ga–O_{eq} span a wider range than those found in the previous section (0.19 Å *vs.* 0.10 Å), and the two extremes of the range are found in the same structure determination, that of *mer*-[Ga(nbida)(OH_2)$_2$] [68] (1.884 and 2.077 Å).

4.3. Tridentate ligands

The structure determinations of the 25 gallium complexes [71–90] showing at least 1 tridentate ligand are listed in Supplementary data, Table S4. The table is organized into three subgroups, gathering (i) homoleptic bis-tridentate, (ii) heteroleptic bis-tridentate and (iii) mono-tridentate complexes.

Most of the X-ray reports describe bis-tridentate Ga(III) complexes, since subgroup (iii) accounts for only four structures. Besides, the four heteroleptic compounds in subgroup (ii) have been so defined mainly because the charge status of the two tridentate ligands differ by one unit (1-/2- or 3-/4-). Accordingly, the sole 'truly' heteroleptic complex is *fac*-[Ga(taci)$_2$]$^{3+}$ [85], in which the two taci ligands adopt the *O*,*O*,*O* and the *N*,*N*,*N* binding modes, respectively. Taken all together, the 21 reported homoleptic and heteroleptic complexes make the bis-tridentate '3+3' arrangement the third most represented in this review, after the '2+2+2' (48) and the '6+0' (38) types.

All the entities described in Supplementary data, Table S4 are octahedral complexes, showing, in most cases, little or no distortion. The tridentate ligands bind to the metal either facially or meridionally, with *fac*-compounds accounting for about 2/3 of the total. Among *fac*-complexes, the *sym*,*fac* arrangement largely predominates over the *unsym*,*fac* one, which is represented only by *unsym*,*fac*-[Ga(Cl_2pmamp)$_2$]$^+$ [75a] and *unsym*,*fac*-[Ga(ida)$_2$]$^-$ [77]. Interestingly, replacing the Cl_2pmamp ligand with the similar MeOpamp one [75b] again stabilizes the more common *sym*,*fac* arrangement (Figs. 8 and 9).

As usual, the N and O donors are the most represented, accounting for 48.7% and 44.7% of the total in this section (S = 2.7%, Se = 4.0%). The coordination sphere is usually filled by a single donor or it is shared by two donors in the 2:1 ratio (N_6, O_6, Se_6, N_2O_4, N_4O_2, N_4S_2). In bis-tridentate complexes, a 1:1 ratio between two donors is seen only in the already mentioned *fac*-[Ga(taci)$_2$]$^{3+}$ [85], showing the N_3O_3 set, as well as in the few mono-tridentate entities (N_3O_3, N_3X_3, X = halide ligand).

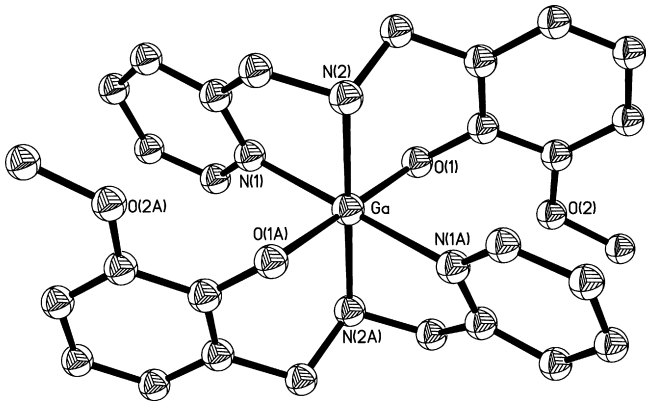

Fig. 9. The molecular structure of the cation *sym*,*fac*-[Ga(MeOpamp)$_2$]$^+$ [75b].

As for the charge status of the compounds, it is heterogeneous. There are twelve cationic, eight anionic and five neutral complexes. Most of these molecules are singly charged, but there are also three polycationic and four polyanionic entities. The most interesting feature of the molecules described in this section is that about half of them have been thoroughly investigated for their relevance in medicinal chemistry. This is particularly true for citrates, such as *sym*,*fac*-[Ga(Hcit)$_2$]$^{3-}$ [80], aminophosphinates [82], inositol derivatives [85], thiosemicarbazones [22,83] and compounds similar to, or derived from natural products, like the paullone derivative *mer*-[Ga(bazmp)$_2$]$^+$ [74] (Figs. 10 and 11).

With respect to the metric data of Supplementary data, Table S4, maintaining the N_2O_2 equatorial donor set required us sometimes to classify as axial, metal-to-donor bond distances shorter than the equatorial ones. In the complexes showing the N_6, O_6 or Se_6 donor sets, where the donor set criterion obviously did not apply, the 'highest possible sum' of mutually *trans* Ga–donor bond lengths was used instead to identify the axial ligands.

The data indicate that bis-tridentate complexes do not generally show a marked distortion of the octahedron. In fact, the X_{ax}–Ga–Y_{ax} angle ranges from 157.5° (imposed by chelation)

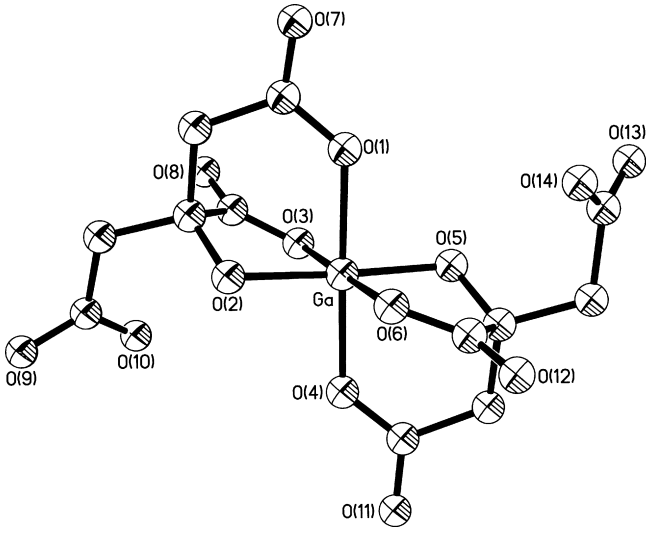

Fig. 10. The molecular structure of the anion *fac*-[Ga(Hcit)$_2$]$^{3-}$ [80].

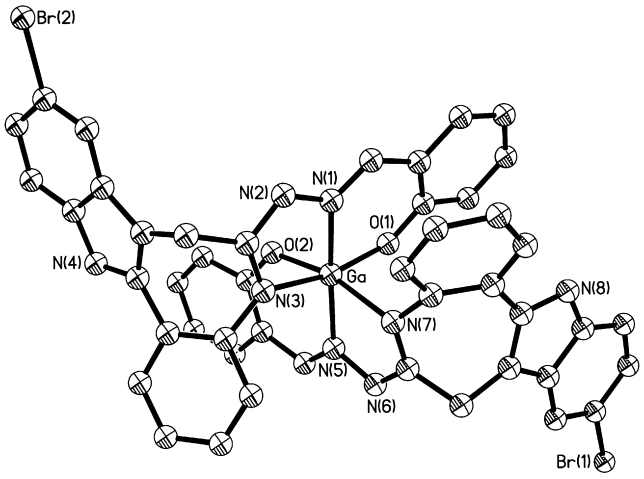

Fig. 11. The molecular structure of the cation *mer*-[Ga(bazmp)$_2$]$^+$ [74].

in *mer*-[Ga(pydc)$_2$]$^-$ [78] to 180.0° (imposed by symmetry), for example, in *fac*-[Ga(dmtaci)$_2$]$^{3+}$ [79], and it is narrower than 170° only in five cases.

Similarly, the departure of the Ga atom from the main coordination plane varies from 0.00 to 0.13 Å, an interval comparing well with those seen previously, and again, the highest value is seen in a [9]aneN$_3$ type compound, *fac*-[Ga(Me$_3$[9]aneN$_3$)Br$_3$] [89]. The Δeq values, instead, vary from 0.00 (by symmetry) up to 0.41–0.42 Å in the thiosemicarbazone derivatives *mer*-[Ga(apydt)$_2$]$^+$ [83] and *mer*-[Ga(apzdt)$_2$]$^+$ [22] (Fig. 12). Not considering the thiosemicarbazone chelates, the top of the range goes down to 0.26 Å in the rather sterically demanding paullone derivative *mer*-[Ga(bazmp)$_2$]$^+$ [74].

As for the distances within the coordination sphere, the Ga–N_{eq}, Ga–VI_{eq} (VI = O, S or Se donor) bond lengths vary

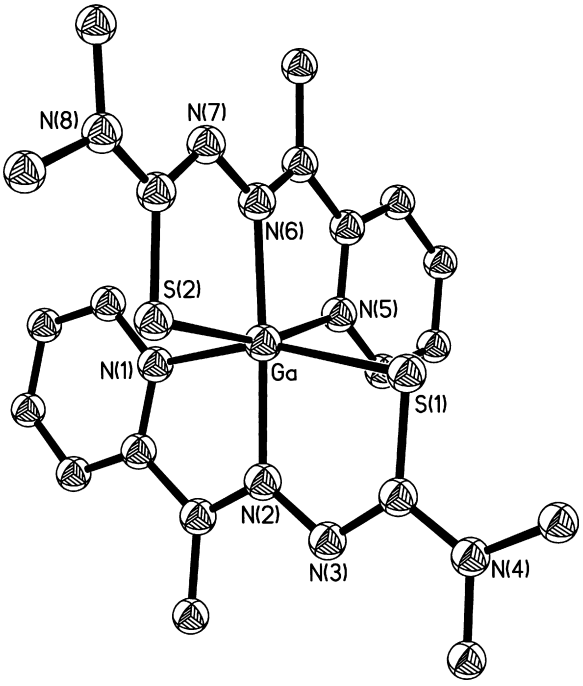

Fig. 12. The molecular structure of the cation *mer*-[Ga(apydt)$_2$]$^+$ [83].

between 1.961 and 2.180 Å and between 1.881 and 2.594 Å, respectively, where the wide range spanned by the Ga–VI_{eq} distance is due to the long Ga–Se bond in *fac*-$[Ga(Hsemim)_2]^+$ [84]. The second longest Ga–VI_{eq} bond is 2.373 Å for Ga–S in *mer*-$[Ga(apydt)_2]^+$ [83], while by omitting heavier Group 16 elements the range of Ga–VI_{eq} distances reduces to 1.881–2.004 Å, close to that seen for unusual hexadentate ligands in Supplementary data, Table S2. Finally, the Ga–N_{ax} bond distances vary from 2.004 to 2.190 Å, whereas the Ga–VI_{ax} ones (reported only for bis-tridentate complexes) range from 1.948 up to 2.597 Å, a range similar to that found for the same parameter in Supplementary data, Table S2.

In most of the '3+3' complexes described here, the two tridentate ligands are facially arranged around the metal. This stimulated us to evaluate the octahedral distortion in *fac*-complexes by calculating the 'twist' (ϕ) and 'tilt' (τ) indices. However, in bis-tridentate complexes the opposing triangular faces are those defined by the two independent ligands, for which, unlike the '6+0' hexadentate ligands, there is no straightforward relationship between the vertices of the two triangles. Accordingly, we decided to measure, for each vertex of a given triangular face, the two torsion angles involving the same vertex, the centroid of the face, the centroid of the opposing face and the two closest vertices of the opposing face. Among the six measured dihedrals, the one deviating most from the ideal 60° has been defined as the twist angle for these compounds, and named ϕ'. The tilt parameter did not need redefinition; however, for consistency the latter has been named τ' in describing '3+3' compounds.

The ϕ' and τ' indices do not deviate too much from their ideal values. This was somewhat expected, since in general the two tridentate ligands are flexible entities, and it appears to be especially true for ϕ', which deviates at most by 6.0°. With respect to τ', it ranges from 0.0° to 1.8°, except for *unsym*,*fac*-$[Ga(Cl_2pmamp)_2]^+$ [75a] and for *unsym*,*fac*-$[Ga(ida)_2]^-$ [77]. In the former, $\phi' = 5.6°$ and $\tau' = 7.7°$, while in the latter $\phi' = 6.0°$ and $\tau' = 17.8°$.

An attempt has also been made to evaluate octahedral distortion in *mer*-complexes, by defining a further parameter, the angle ε. ε is the dihedral angle between the mean planes passing through the donor atoms of each of the two tridentate ligands. Ideally, ε equals 90°, and like ϕ' and τ' above, it also shows little variation. In the seven *mer*-complexes reported in Supplementary data, Table S4, the relevant departures of ε from 90° have been found only in *mer*-$[Ga(dtbzipma)_2]^+$ [73] and *mer*-$[Ga(bazmp)_2]^+$ [74], where ε is 86.7° and 86.8°, respectively.

4.4. Bidentate ligands

In this section we examine the structure determinations in which Ga(III) is complexed by three bidentate ligands, the '2+2+2' group, whose pertinent metric data are listed in Supplementary data, Tables S5 and S6. Supplementary data, Table S5 accounts for the 38 structure determinations of homoleptic tris-bidentate complexes [91–123] showing a unique donor type. The latter have been further collected according to the coordination sphere, so that subgroups (i–iii) gather compounds with N_6, O_6 or S_6 donor set, respectively. The remaining ten structures listed in Supplementary data, Table S6 are homoleptic tris-bidentate complexes [124–132] showing two donor atom types in the 1:1 ratio, for which the coordination sphere is of the N_3O_3, N_3S_3 or O_3S_3 types. Overall, the O, N and S donor atoms account, respectively, for 58.3, 24.0 and 17.7% of the total in the two tables.

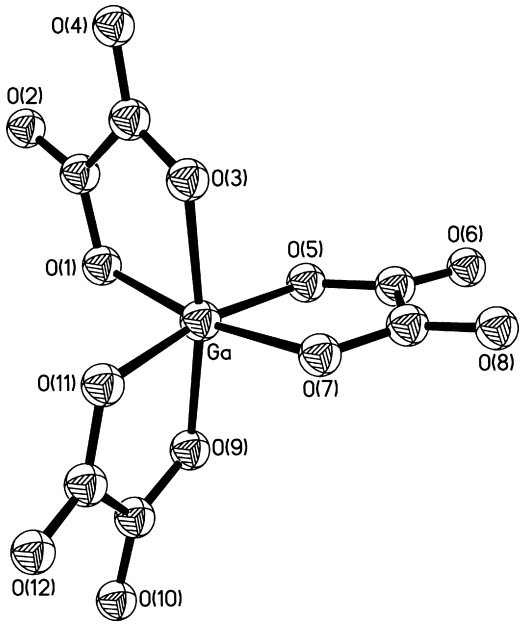

Fig. 13. The molecular structure of the anion $[Ga(ox)_3]^{3-}$ [97].

Besides of being of chemical interest, the '2+2+2' complexes have also been investigated for their potential applications in material science or nuclear medicine. The neutral dipyrrinato complexes $[Ga(mdp)_3]$ [96a] and $[Ga(cpdp)_3]$ [96b], as well as the gallate(III) anions of the type $[Ga(ox)_3]^{3-}$ [97] (Fig. 13) are important in the realization of high-frequency LEDs, diode lasers and in the elucidation about superstructures of donor packing arrangements of charge transfer salts, an issue investigated again in the case of $[Ga(ox)_3]^{3-}$ [99].

Sometimes, an identical compound has been considered by material scientists for the preparation of OLEDs as well as for its application in medical imaging. This has been the case for $[Ga(quin)_3]$, which was investigated by Welch for its potential in diagnostic nuclear medicine as early as 1988 [127] (Fig. 14).

The work of Welch has been pursued in the last 20 years by many other investigations involving tris-bidentate Ga derivatives. The chelating groups more appealing towards medical applications are β-diketonates like $[Ga(acac)_3]$ [102] (Fig. 15), 3-hydroxy-4-pyridinones [105–109], catecholates [112,113] and dithiocarbamates [119–121].

Notably, the 3-hydroxy-4-pyridinone moiety is almost isosteric with the maltolate one, and in fact both these ligands coordinate gallium in a three-fold propeller arrangement. They form stable, water-soluble compounds whose lipophilicity, a biologically relevant property, can be modified by means of

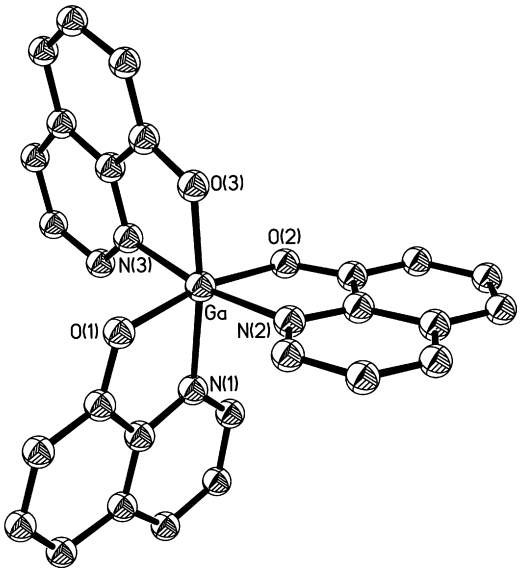

Fig. 14. The molecular structure of *mer*,*cis*-[Ga(quin)$_3$] [127].

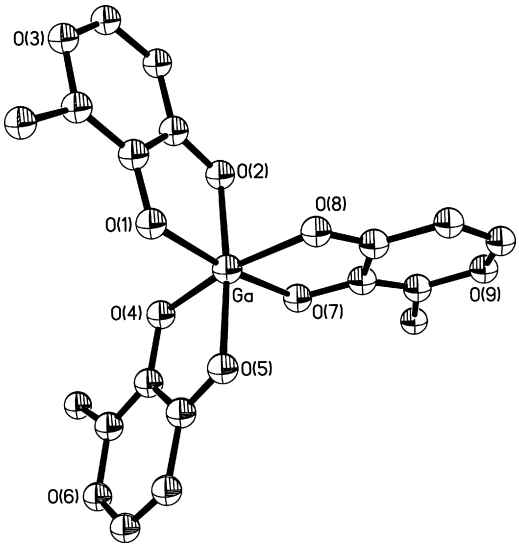

Fig. 16. The molecular structure of [Ga(ma)$_3$] [110].

appropriate substitutions to the molecular mainframe. The *in vivo* biodistribution of the corresponding complexes might thus also be modulated as needed, as it has been demonstrated by the studies of Orvig and co-workers about 3-hydroxy-4-pyridinones [105–107,109].

Maltolate complexes such as [Ga(ma)$_3$] [110] (Fig. 16) have met renewed interest in recent years because of their proposed oral delivery, showing promise in cancer treatment. These observations stimulated further investigations on similar thiomaltolate derivatives like *fac*-[Ga(tma)$_3$] [132] (Fig. 17).

Other families of ligands which might become of clinical interest are those comprising oxazoline and pyridinethiolate derivatives. The chelating mainframe of oxazolines is also somehow similar to the one of maltolate and their Ga complexes have been proposed like putative iron chelators. The biodistribution behavior of the Ga–pyridinthiolate complexes suggested instead their application like hepatobiliary imaging agents [129,130].

The coordination environment of the metal in '2+2+2' complexes is always octahedral, although in some cases it is markedly distorted. The deviations have been evaluated by means of the metric parameters, as well as by means of the b and θ indices proposed by Kepert [16]. A discussion about the facial or meridional arrangement of the donors about the metal center is easier when the bidentate ligands show two different donor atoms (Supplementary data, Table S6).

Unlike '3+3' complexes above, in these complexes the *mer*-arrangement largely dominates over the *fac*-one. The latter appears only in two compounds having the S donor in the coordination sphere, that is, *fac*-[Ga(pyt)$_3$] [130] (Fig. 18) and *fac*-[Ga(tma)$_3$] [132].

The charge status of the molecules is different from that of the compounds so far reviewed, in that 72.9% of the structure determinations reported in Supplementary data, Tables S5 and

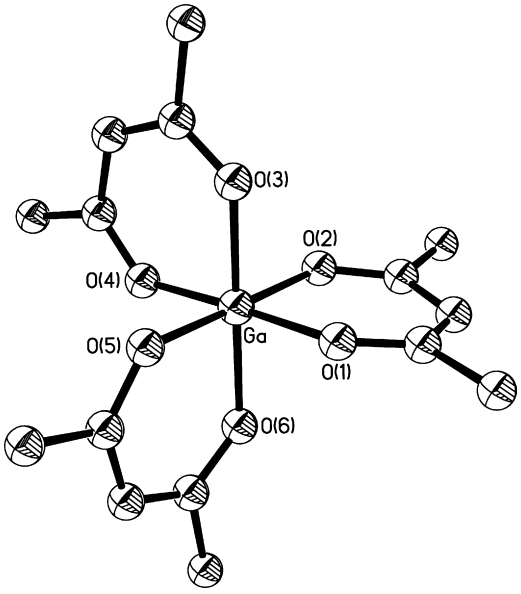

Fig. 15. The molecular structure of [Ga(acac)$_3$] [102].

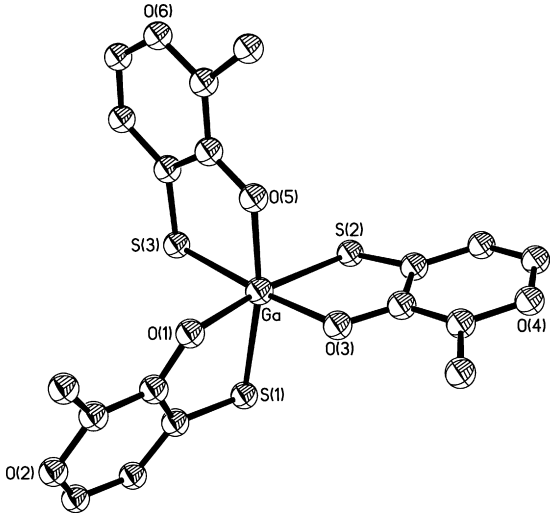

Fig. 17. The molecular structure of *fac*-[Ga(tma)$_3$] [132].

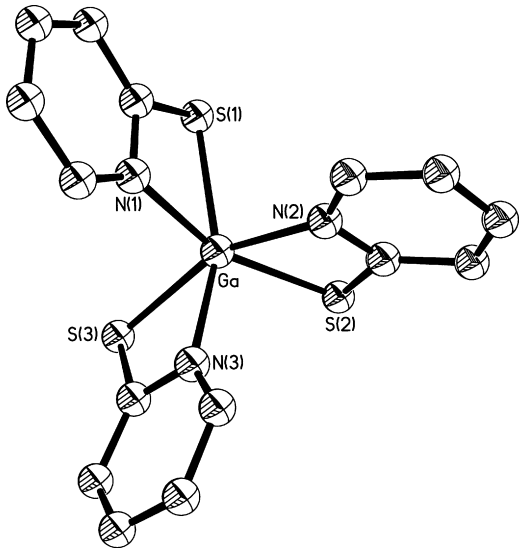

Fig. 18. The molecular structure of *fac*-[Ga(pyt)$_3$] [130].

S6 and 100% of the complexes in Supplementary data, Table S6 are neutral entities. Of the remaining, five are cationic species and eight are anionic.

The departure of the '2+2+2' compounds from an ideal octahedron has been assessed by looking first at the values of ΔGa, Δeq and of the interaxial angle (Do_{ax}–Ga–Do_{ax} and X_{ax}–Ga–Y_{ax} in Supplementary data, Tables S5 and S6, respectively), and then by means of the indices *b* and *θ*. ΔGa values vary between 0.00 and 0.13 Å, a range similar to those seen in Supplementary data, Tables S1–S4. The same applies to the Δeq values, ranging from 0.01 to 0.34 Å. Unlike in previous sections, instead, the interaxial angle is smaller than 175° in about 77% of the structure determinations and it is smaller than 170° in about 50% of the cases.

The largest departures from ideality have been found in the guanidinato complex [Ga(didmg)$_3$]$^{3+}$ [95], for which the angle is 154.7°. Very narrow interaxial angles, about 20° away from 180°, have also been found in sulfur-containing molecules, like the dithiocarbamato, the carbodithioato and the ethylxanthato derivatives [Ga(Et_2dtc)$_3$] [119], [Ga(pcdt)$_3$] [122] and [Ga(exa)$_3$] [123]. In these compounds, the interaxial angles are 158.0°, 159.5° and 162.9°, respectively. Similar values have been found also in the pyridinethiolato *fac*-[Ga(pyt)$_3$] [130] and in the quinolinethiolato *mer*-[Ga(quint)$_3$] [131], for which the pertinent values are 159.1° and 165.5°, respectively.

The inspection of the *b* and *θ* indices confirmed that these complexes are heavily distorted. For a regular octahedron, $b = \sqrt{2} = 1.414$ and $\theta = 30°$. Most of the structure determinations in this section show *b* values in the range $\sqrt{2} \pm 10\%$, except for the compounds having a S_6 coordination sphere [119–123], in which $b = 1.20$, the already mentioned *fac*-[Ga(pyt)$_3$] [130], in which $b = 1.14$ and the guanidinato compound [Ga(didmg)$_3$]$^{3+}$, [95] where *b* reaches its minimum at 1.06. In all these compounds, the low *b* values are due to the very narrow 'bite' angle of the chelate ligands, which upon coordination forms a four-membered ring made by Ga, an sp^2 carbon and two identical donor atoms (N or S).

Since the C–N, Ga–N bond lengths in the guanidinato ligand are shorter than the corresponding C–S, Ga–S distances in the other compounds, the N–Ga–N 'bite' angle of the guanidinato is forcedly narrower. The values assumed by the *θ* index in the same compounds are also different. In the guanidinato complex [95] $\theta = 31.2°$, not too far from the ideal 30°, whereas in compounds showing the S_6 coordination sphere *θ* is always equal or close to 20°. This is true also for the pyridinethiolato [130], where $\theta = 18.8$, but not for the other sulfur-containing complexes in Supplementary data, Table S6. *mer*-[Ga(quint)$_3$] [131] shows $b = 1.31$ and $\theta = 24.4°$, while for *fac*-[Ga(tma)$_3$] $b = 1.34$ and $\theta = 25.6°$.

By omitting the compounds discussed above, *θ* ranges from 19.9° to 30.6°. The lower value is found in [Ga(cup)$_3$] [115], which also shows a very narrow interaxial angle of 163.2°; the higher value pertains to the β-diketonato complex [Ga(acac)$_3$] [102]. A comparison of the Do_{ax}–Ga–Do_{ax} and of the *θ* values reported in Supplementary data, Tables S5 and S6 indicates that the two entities are correlated and allows the following empirical relation to be established:

$$Do_{ax}\text{–Ga–}Do_{ax}\ (°) = 1.67\theta + 129.2.$$

With respect to the other metric data, they do not seem markedly different from those presented in the previous sections, whereas the Ga–S distances deserve a comment. Ga–S_{eq} and Ga–S_{ax} bond lengths vary between 2.331 and 2.464 Å and between 2.391 and 2.487 Å, respectively. Although in both cases the spanned range is rather wide (0.13 and 0.10 Å, respectively), by examining each compound one at a time, the equatorial and axial distances involved do not appear to be dramatically different. However, a comparison with the other sulfur-containing molecules reveals that in '2+2+2' compounds the longest Ga–S bond found in the unique O_3S_3 complex *fac*-[Ga(tma)$_3$] [132] (2.487 Å) is about 0.11 Å longer than any other bond reviewed in the previous sections.

The landscape of reviewed mononuclear six-coordinated Ga(III) compounds is completed by the 13 structure determinations listed in Supplementary data, Table S7, that gathers either [Ga(bidentate)$_3$] '2+2+2' and [Ga(bidentate)$_2$(unidentate)$_2$] '2+2+(1)$_2$' compounds [133–143]. The '2+2+2' molecules listed here do not fit those in Supplementary data, Tables S5 and S6 because they are heteroleptic complexes. Of the 10 '2+2+(1)$_2$' compounds, eight are homoleptic molecules, in which a bidentate ligand has been replaced by two identical monodentate donors, and two are heteroleptic complexes showing different bidentate ligands. The table also includes the unique example of a [Ga(bidentate)(unidentate)$_4$] '2+(1)$_4$' compound.

The metric data listed in Supplementary data, Table S7 are obviously miscellaneous, and a comparison with those of the previous section is sometimes difficult, also because the parameters involving monodentate donors have been omitted. Accordingly, these data will be only shortly commented.

With respect to charge, seven of the listed molecules are cationic compounds and five are neutral, whereas there is only one monoanionic complex, *trans*-[Ga(oro)$_2$(dmf)$_2$]$^-$ [140]. The cationic compounds are all singly charged, except for the

cis-[Ga(Me$_2$bpy)$_2$(OH$_2$)$_2$]$^{3+}$ [137c]. As usual, the N and O donors dominate, representing 42.3 and 38.5% of the total, respectively, with halide ligands accounting for 16.7%. The sulfur donor appears only in the Et$_2$dtc ligand of the unique [Ga(4Mepy)$_2$(Et$_2$dtc)Cl$_2$] '2+(1)$_4$' complex [143].

The geometry of the listed compounds can be either *cis* or *trans*. In the '2+2+(1)$_2$' complexes the *cis* geometry is more represented (7:3), whereas the two neutral '2+2+2' compounds, which have both in common a chelating acetate, show the *cis* arrangement when the N∩N bidentate ligand is a pyrazolylborate [133] and the *trans* one when N∩N is a benzoxazolate [134]. Curiously, the three *trans* '2+2+(1)$_2$' compounds are also representative of all the possible charge conditions, since *trans*-[Ga(acac)$_2$(thf)$_2$]$^+$ [138] is cationic, *trans*-[Ga(dtcat)(5dtbsq)(Bupy)$_2$] [142] is neutral and the above mentioned *trans*-[Ga(oro)$_2$(dmf)$_2$]$^-$ [140] is anionic.

The octahedral distortion shown by the complexes listed in Supplementary data, Table S7 has been estimated also by calculating Kepert's *b* parameter. With the exception of the two already mentioned '2+2+2' complexes, *b* values range from 1.25 to 1.36, that is, $\sqrt{2} \pm 12\%$. The average *b* value is 1.27, slightly smaller than 1.31 shown by the complexes in Supplementary data, Tables S5 and S6, indicating that these 'mixed' compounds might suffer from a little more distortion. The acetate complexes *cis*-[Ga(H$_2$pz)$_2$(ac)] and the *trans*-[Ga(opbo)$_2$(ac)] are peculiar. In these complexes, the *b* values referring to the N∩N ligands are the highest in Supplementary data, Table S7 (1.42 and 1.40, respectively), whereas those referring to the O∩O ligands are the lowest (1.03 and 1.02, respectively).

During the preparation of this paper, the authors have periodically checked the literature for newly published structural determinations of Ga(III) complexes, thus becoming aware of six more X-ray crystal structure reports fitting with the focus of the present review [144–149].

The first paper [144] illustrates the synthesis and the structure characterization of potassium hydrated salts of [Ga(cdta)]$^-$ and [Ga(pdta)]$^-$, which are '6+0' complexes. The two compounds show an octahedral coordination in which Ga is bound by tetraanionic hexadentate ligands similar to edta in a N_2O_4 donor set. As usual, the metal environment is only slightly distorted, especially in the case of [Ga(pdta)]$^-$. Another distorted octahedral '6+0' complex is the cationic *cis*(*O*,*O*)-[Ga(dtobmpen)]$^+$ [145], in which, however, the metal is bound by a dianionic amine phenol-type ligand in a N_4O_2 coordination environment. The resulting complex is a close analogue of the already reported *cis*(*O*,*O*)-[Ga(Clobmpen)]$^+$ [49] mentioned in Section 4.1.

Two more reports describe the crystal structures of the neutral tris-bidentate '2+2+2' complexes of gallium with dibenzoylmethane, [Ga(dbm)$_3$] [146] and with the iminocatecholato ligand tris(2-((2,3-dioxybenzylidene)ammonio)-3-methylbutyl)-amine), [Ga(dbzitmba)$_3$] [147]. In both cases, the O_6 coordination environment about the metal is again distorted octahedral, with the ligands assuming the same three-fold propeller arrangement previously described in this section. The paper by Yang et al. [146] also highlights the luminescent properties of the three polymorphs of [Ga(dbm)$_3$] relevant towards the preparation of new OLEDs.

The work by Jurchen and Raymond [148] is meant to explore the preparation, solution behavior and coordinating ability towards trivalent metal cations of a series of derivatives of a versatile hexadentate donor, among which the heteroleptic '2+2+2' trenhopo(tam)$_2$ ligand (trenhopo(tam)$_2$ = *N*,*N*'-([(2-([(3-oxy-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)carbonyl]amino)ethyl)imino]diethane-2,1-diyl)bis[2,3-dioxy-*N*-(2-methoxyethyl)benzene-1,4-dicarboxamide]). The reported structure of its anionic gallium complex [Ga(trenhopo(tam)$_2$)]$^{2-}$ is defined to be pseudo-octahedral, with the ligand assuming the expected tripodal geometry.

In the last work [149], finally, the authors describe the synthesis and characterization of some hiterto unknown gallium phosphane and arsane derivatives, among which three '2+2+(1)$_2$' compounds of the pbdp ligand (pbdp = 1,2-phenylenebis(dimethylphosphane)), that is, [Ga(pbdp)$_2$X$_2$]$^+$ (X = Cl, Br, I). Such distorted octahedral complexes are the first examples of six-coordinated Ga in a phosphane complex.

5. Stereoisomers

Some aspects dealing with geometric isomers (diastereoisomers) have already been taken into account in the previous sections, like, for example, *mer*- *vs*. *fac*-coordination in bis(tridentate) '3+3' complexes, or *cis*(*O*,*O*) *vs*. *trans*(*O*,*O*) arrangement in complexes containing symmetric hexadentate ligands. In addition to diastereoisomers, in the following section we would like to make some comments about (i) optical isomers (enantiomers), (ii) conformers involving ethylene diamine (en) chains and (iii) isomers arising from the presence of stereogenic centres, usually C or P atoms, in the outer coordination sphere.

The chirality of Ga octahedral coordination compounds can be described in accordance with the IUPAC recommendations for the nomenclature of inorganic chemistry [17] by means of the skew-line convention (*vide infra*) or by using a specific notation, referred to as the *configuration index*: for example, *OC*-6-21-*C* or *OC*-6-1′2-*A*. Such notation allows one first to distinguish between diastereoisomers (from the two consecutive digits) and then to determine the absolute configuration about the metal as clockwise (*C*) or anticlockwise (*A*).

On these grounds, the structurally authenticated compound [Ga(dmbziapen)]$^+$ [57] can be described, for illustrative purposes, with the annotations *OC*-6-1′3′-*C* or *OC*-6-1′3′-*A* (Fig. 19).

OC-6 indicates an octahedral compound with coordination number six (to be distinguished, for example, from a trigonal prismatic (trp) one, whose annotation would be *TPR*-6). The coordinating atoms are then numbered according to the Cahn, Ingold and Prelog (CIP) priority rules [150]. The essence of these rules is that the donor atoms attached to the metal are compared to one another. The comparison is made on the basis of atomic number. Once the donors have been compared, the priority numbers are assigned as follows: (i) identical donors have the same rank; (ii) the donor(s) with highest priority is(are) assigned the priority number 1; those with the next priority, 2, and so on; (iii) the presence of polydentate ligands may require

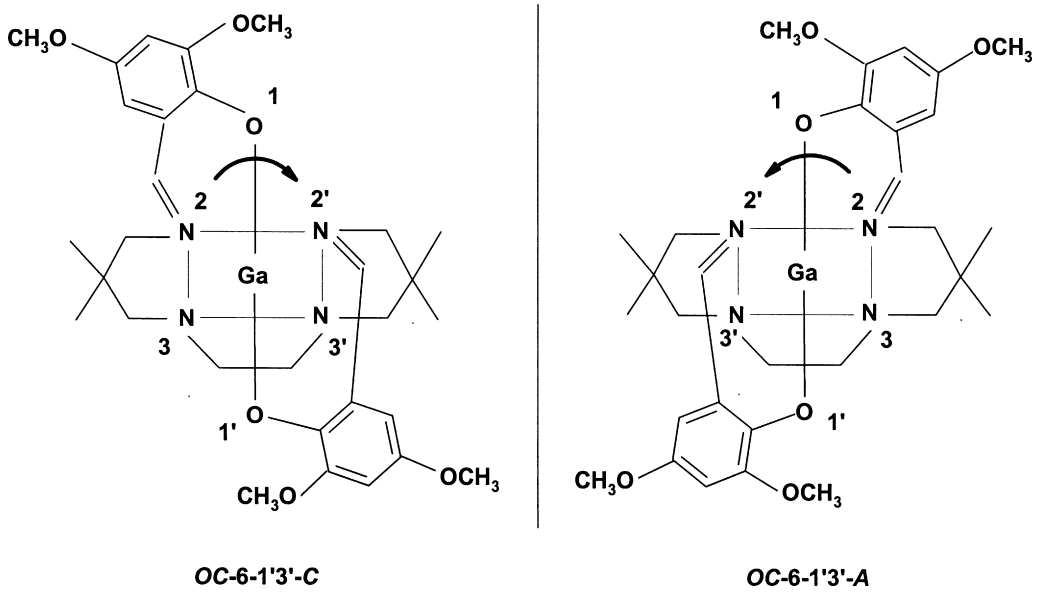

Fig. 19. The *OC*-6-1′3′-*C* (left) and *OC*-6-1′3′-*A* (right) arrangements of *trans*(*O*,*O*)-[Ga(dmbziapen)]$^+$.

the use of primes on some of the numbers in the configuration index. The primes are used to indicate either that donor atoms are not part of the same polydentate ligand as those that have unprimed priority numbers (for example, two identical tridentate ligands), or that the donor atoms belong to different parts of a polydentate ligand that are related by symmetry (for example, symmetric hexadentate ligands). A primed number has a lower priority (that is, a higher numerical value) than the corresponding unprimed one.

Donor 1 and its *trans*-coordinated donor of lowest priority (if more than one donor having priority number 1 are present) define the reference axis of the octahedron, whereas the four remaining donors define the equatorial plane. In the case of [Ga(dmbziapen)]$^+$, the two digits 1′ and 3′ are, respectively, the priority number of the atom ($O_{phenolate}$) *trans* to the highest priority number atom 1 (another $O_{phenolate}$), and the priority number of the atom (N_{amine}) that is *trans* to the highest priority number atom 2 (N_{imine}) of the equatorial plane (Fig. 19).

The absolute configuration (*C* or *A*) about the metal is then determined by moving from the highest priority number atom 2 (N_{imine}) on the equatorial plane towards the subsequent priority number atom 2′ (N_{imine}) on the same plane. If the path turns clockwise the annotation is *C*, otherwise *A*.

5.1. Bidentate and tridentate ligands

As already specified in Supplementary data, Tables S5–S7, tris(bidentate) '2+2+2' Ga complexes with dissymmetric bidentate ligands can adopt both meridional and facial geometries of the donor atoms. In addition, with both symmetric and dissymmetric ligands optical isomers also form. In this case, enantiomers are distinguished by means of the skew-line convention [17].

In octahedral complexes, the donor atoms of each ligand are connected by means of thick lines wrapping the edges of the coordination octahedron, and the two enantiomers are unambiguously identified by the symbols Δ and Λ. Fig. 20 illustrates the pictorial representation of the Δ and Λ configurations of homoleptic tris(bidentate) complexes, such as $[Ga(en)_3]^{3+}$, $[Ga(ox)_3]^{3-}$, $[Ga(Et_2dtc)_3]$ and $[Ga(ma)_3]$, containing both symmetric (*e.g.* en, ox, dtc) or dissymmetric (ma) bidentate ligands.

Among the 62 reviewed crystal structure determinations of bis(tridentate) and tris(bidentate) Ga complexes, only eight (Table 1) exhibit a non centrosymmetric space group allowing the absolute configuration about the metal center to be determined. In these cases, the Λ isomers are more represented than the Δ ones (6:2 ratio).

The two optically resolved Λ $[Ga(en)_3]^{3+}$ complexes differ by the conformation of the en chain, as it emerges from the related (δδδ) and (δδλ) descriptors (Fig. 21). In this connection, a very detailed study on the origin of optical activity (Δ *vs.*

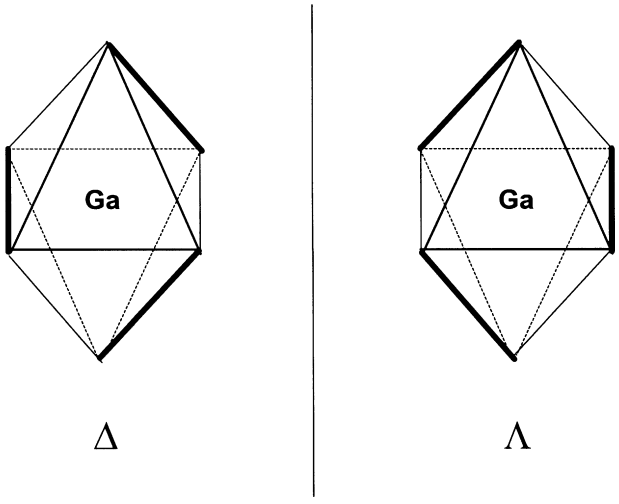

Fig. 20. The skew-line Δ (left) and Λ (right) configurations of homoleptic tris(bidentate) type complexes.

Table 1
Optical isomers

Compound	Absolute configuration†	δ/λ Notation*	Ref.
(i) Hexadentate ligands			
$[Ga(edta)]^-$	*OC*-6-2′1′-*C*	δ	[32], [33a][a], [35a,35b,35c]
	OC-6-2′1′-*A*	λ	[33a][a], [33b], [34]
cis(*O*,*O*)-$[Ga(teda)]^+$	*OC*-6-3′3-*C*	λ[b], $\lambda_{ob}\ \delta_{lel}\ \lambda_{ob}\ \delta_{lel}$	[44]
fac-[Ga(mbzitame)]	Δ		[45]
trans(*O*,*O*)-$[Ga(Brobadd)]^+$	*OC*-6-1′3′-*C*	λ	[51]
trans(*O*,*O*)-$[Ga(5madd)]^+$	*OC*-6-1′3′-*C*	λ	[54]
fac-[Ga(pmtaea)]	Λ		[56]
cis(*S*,*S*)-$[Ga(ebg)]^-$	*OC*-6-3′3-*A*	λ	[63]
(ii) Tetradentate ligands			
cis-$[Ga(cbcyclam)Cl_2]^+$	*OC*-6-2′2-*C*	λ[b], $\delta_{lel}\ \delta_{lel}$	[67]
(iii) Bidentate ligands			
$[Ga(en)_3]^{3+}$	Λ	δ δ δ	[91]
$[Ga(en)_3]^{3+}$	Λ	δ δ λ	[92]
$[Ga(bpy)_3]^{3+}$	Λ		[94]
$[Ga(didmg)_3]^{3+}$	Λ		[95]
$[Ga(mbdt)_3]^{3-}$	Λ		[112]
$[Ga(5dtbsq)_3]$	Δ		[116]
fac-$[Ga(pyt)_3]$	Δ		[130]
cis-$[Ga(dmge)_2Cl_2]^+$	Λ		[138]

(†) Denoted according to the *C*/*A* system, when applicable, or according to the skew-line reference system; (*) conformation assumed by the en fragment(s), where present; [a]two independent molecules in the unit cell making an enatiomeric pair. The same situation is also shown by the complexes *sym*,*fac*-$[Ga(MeOpamp)_2]^+$ [75b] (configuration index *OC*-6-1′2′) and *fac*-$[Ga(tma)_3]$ [132]; [b]the notation refers to the 'en' bridging fragment of the macrocycle.

Λ) and δ and λ conformation in tris-diamine metal complexes, corroborated by Time-Dependent Density Functional Theory (TDDFT) applied to circular dicroism (CD) spectra, has recently been published [151].

Although there are reported examples of chromatographic separation of Δ/Λ mixtures of tris(bidentate) metal complexes supported by CD and NMR investigations on the two separate enantiomeric forms [152], studies on the impact of an optically pure tris(bidentate) gallium species in different biological substrates have not been reported yet. Investigations in this field may be appropriate, especially in the case of tris(quin) complexes [124–128] to eventually enhance their cytotoxic efficacy.

The number of possible steroisomers for homoleptic bis(tridentate) '3+3' compounds increases on replacing symmetric ligands with dissymmetric ones. Although both meridional and facial geometries are theoretically accessible, complexes of the $[Ga(A\cap A\cap A)_2]$ type, where A is an identical donor atom, adopt invariably the facial coordination, irrespective of the nature of the donor atom. Examples include N [72], O [79,82] and Se [84]. For symmetry reasons, complexes of this kind do not generate enantiomers. Complexes of the $[Ga(A\cap B\cap A)_2]$ type can instead assume three different geometries: *mer*-, *sym*,*fac*- and *unsym*,*fac*- [16], all of which have been observed and all containing O∩N∩O ligands (*mer*- [78,86], *sym*,*fac*- [76a,76b] and *unsym*,*fac*- [77]; Fig. 22). While *mer*- and *sym*,*fac*-compounds do not generate enantiomers for symmetry reasons, the unique *unsym*,*fac*-compound [77] crystallizes in the centrosymmetric *Pbcn* space group, not allowing the attribution of the absolute configuration.

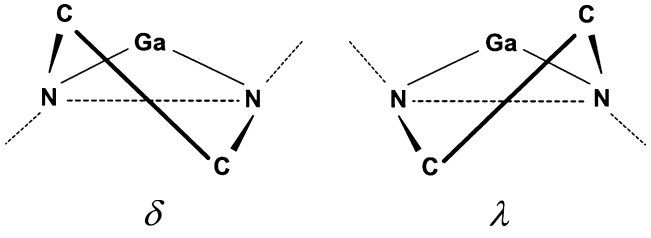

Fig. 21. The δ (left) and λ (right) conformations of en.

Likewise, the reported complexes of the types $[Ga(A\cap B\cap C)_2]$, $[Ga(A\cap A'\cap B)_2]$ or $[Ga(A\cap A'\cap A'')_2]$ (A, A′, A″ for three donor atoms of same atomic number but different environment) show *mer*-, *sym*,*fac*- and *unsym*,*fac*-arrangements. The first has been found, for example, in compound [71], the second in compound [75a] and the last in bis(citrate) species [81a,81b,81c]. In these cases, the metal becomes chiral, and a pair of enantiomers is expected for each geometry (Fig. 23).

Unfortunately, all the reviewed crystal structures of bis(tridentate) Ga-complexes exhibit a centrosymmetric space group, thus precluding the determination of the absolute configuration around the metal. As reported for tris(bidentate) Ga complexes, chromatographic separation of *C*/*A* mixtures of bis(tridentate) '3+3' Ga species have not been performed yet and, consequently, no reports on the biological behavior of an optically pure agent are available so far. As above, investigations in this field may be attractive, especially in the case of bis(thiosemicarbazone) complexes.

5.2. Hexadentate ligands

An excellent recent study by Green and co-workers [153] begins to address some of the unanswered questions regarding

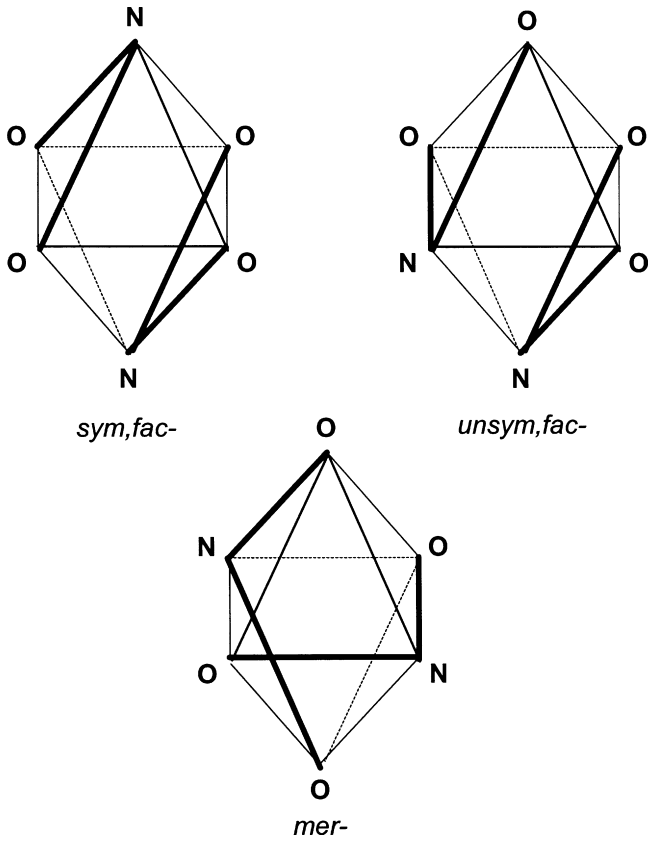

Fig. 22. The *sym,fac-* (top left), *unsym,fac-* (top right) and *mer-* (below) geometries for a complex of the [Ga(O∩N∩O)$_2$] type.

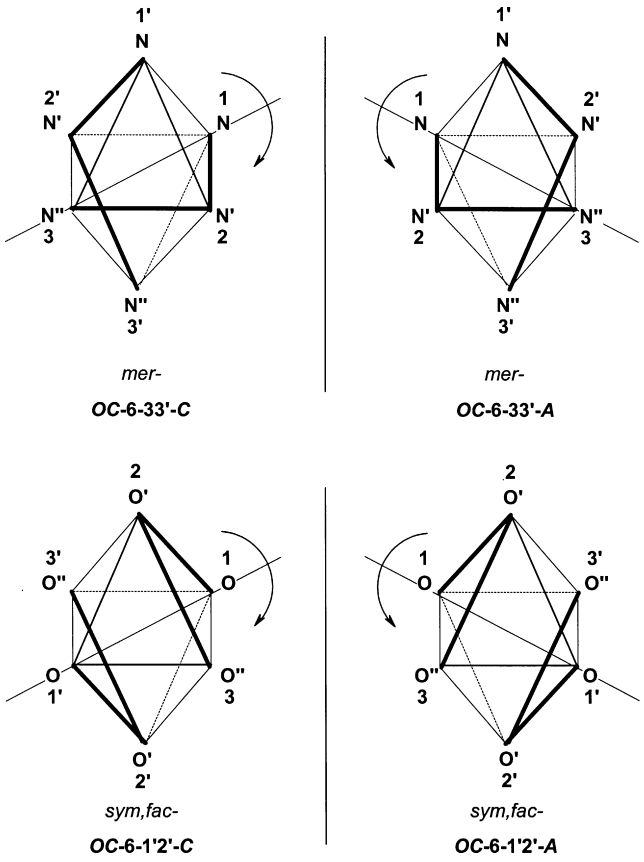

Fig. 23. Top: the *OC*-6-33′-*C* (left) and *OC*-6-33′-*A* (right) arrangements for a *mer-* complex of the type [Ga(N∩N′∩N″)$_2$], like *mer*-[Ga(Himepy)$_2$]$^+$ [71]; bottom: the *OC*-6-1′2′-*C* (left) and *OC*-6-1′2′-*A* (right) arrangements of a *sym-fac-* complex of the type [Ga(O∩O′∩O″)$_2$], like *sym,fac*-[Ga(cit)$_2$]$^{5-}$ [81a].

the interaction of optically pure gallium species in biological substrates. Lipophilic, monocationic ^{68}Ga(III) complexes of linear hexadentate SB ligands (Supplementary data, Table S1) in which the oxygen donor atoms of the two terminal phenolate groups are *trans* to each other are chiral, due to the clockwise or anticlockwise arrangement of the ligand about the metal center (Fig. 19). The two stereoisomers can be resolved by means of chiral HPLC and are 'stable', in the sense that they do not interconvert into one another.

In this connection, the contribution of Green and co-workers [150] has shown that biodistribution of the *C* and *A* isomers of [^{67}Ga(dmbziapen)]$^+$ in MDR1a/b knock-out mice and Friend Leukemia Virus (FVB, strain B) wild-type control animals revealed that the two forms show different plasma protein binding and that the *C* isomer appears to have a MDR1 Pgp-independent pathway for hepatobiliary excretion that is not available for the *A* isomer [153].

This experimental evidence indicates that knowledge of the chirality at the metal is of crucial impact when Ga(III) octahedral compounds are designed for potential use in medicine. Table 1 gathers 14 examples of Ga complexes wrapped by a hexadentate ligand for which the absolute configuration has been assigned *via* X-ray crystal structure determination. All eight [Ga(edta)]$^-$ compounds are described by the *OC*-6-2′1′ notation (Fig. 24), whereas the absolute configuration is *C* in five complexes, and *A* in the others.

The absolute configuration *A* has been assigned also to the *cis*(*S*,*S*)-[Ga(ebcys)]$^-$ complex containing the branched $S_2O_2N_2$ hexadentate ligand [63]. Here, the usual N, O donor set of edta- or SB-type ligands has been enriched by the presence of S, which may have a role in tuning the stability of the resulting complex. In terms of diastereoisomers, only the *cis(S,S)* species, described by the *OC*-6-3′3 notation, has been experi-

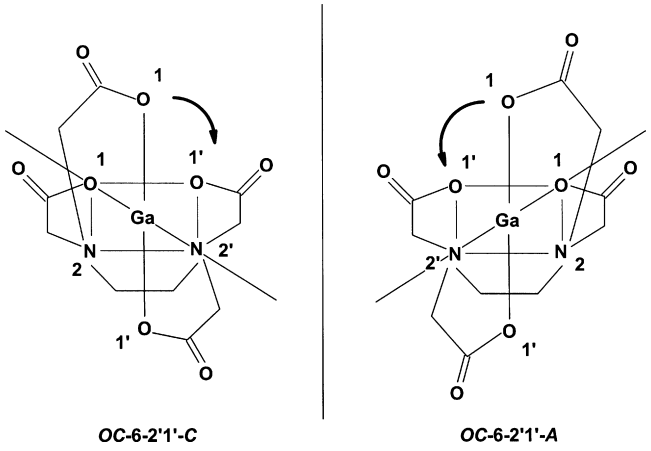

Fig. 24. The *OC*-6-2′1′-*C* (left) and *OC*-6-2′1′-*A* (right) reported arrangements for [Ga(edta)]$^-$ compounds.

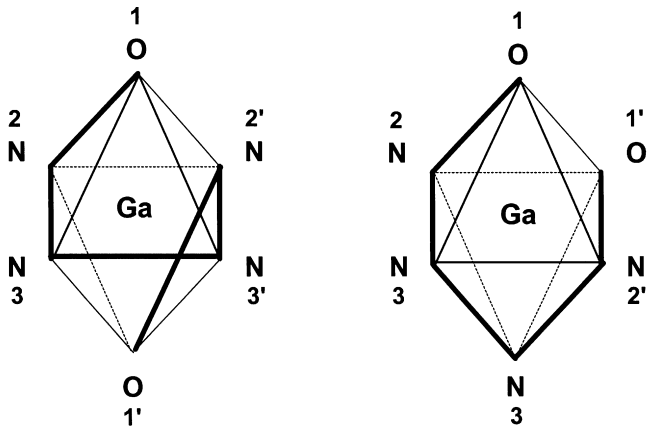

Fig. 25. The difference between the *trans*(*O*,*O*)-[Ga(Brobadd)]$^+$ [51] (left) and *cis*(*O*,*O*)-[Ga(Brobad)]$^+$ [48] (right) complexes is clearly underlined by their skew-line representation.

mentally observed in the solid state, in agreement with molecular mechanics calculations that predicted lower strain energies of the *cis*-form compared to the *trans*-one.

Of course, *cis*(*O*,*O*) and *trans*(*O*,*O*) complexes (Table 1) have different configuration indexes, that is, *OC*-6-1′3′ and *OC*-6-3′3, respectively. Sometimes, these stereoisomers are easily recognized using the skew-line representation, as illustrated in Fig. 25 for the complexes *trans*(*O*,*O*)-[Ga(Brobadd)]$^+$ [51] and *cis*(*O*,*O*)-[Ga(Brobad)]$^+$ [48]. Only the former complex had the absolute configuration *C* crystallographically assigned.

As for tris(bidentate) species, the family of Ga(III) complexes containing an hexadentate ligand derived from the [9]aneN$_3$ (tacn) skeleton functionalized with three methylcarboxylate pendant arms can also be represented using the Δ/Λ description.

As depicted in Fig. 26, the coordination of this hexadentate ligand is best described by the two opposite triangular faces arising from the triaza ring and the three carboxylate oxygen atoms. Upon coordination, each carboxylate arm describes a right-handed or a left-handed helix, which corresponds to the Δ or Λ configuration, respectively. The Δ or Λ configurations

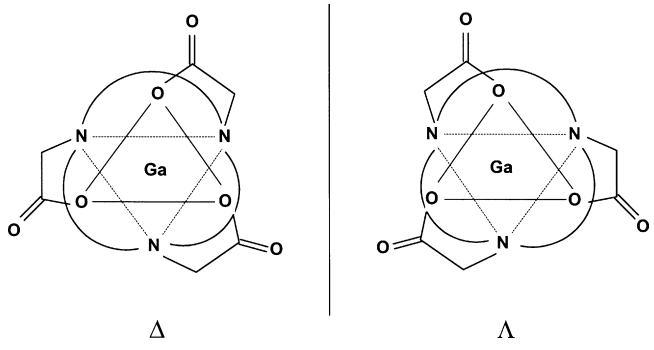

Fig. 26. The skew-line Δ (left) and Λ (right) representation of an hexadentate ligand in which the [9]aneN$_3$ skeleton has been functionalized with three methylcarboxylate pendant arms.

have been crystallographically assigned only in the case of the two *fac*-complexes [45] and [56] (Table 1).

Further source of chirality in octahedral Ga(III) complexes arises from the presence of stereogenic C or P atoms in the outer coordination sphere of the metal. For example, in the representative C_3-symmetric [9]aneN$_3$-type complex [38] the three equivalent phosphinate P become chiral upon coordination of the hydroxyl O. As pointed out by the authors, two diastereoisomers may result from the cooperative binding of all six ligand donor atoms, both of which are chiral (*i.e*. *RRR*/*SSS* and *RSR*/*SRS*). However, a single chiral stereoisomer forms (*RRR* at each stereogenic phosphorus center), and the en fragments within the [9]aneN$_3$ ring adopt the δ_{lel}, δ_{lel}, δ_{lel} arrangement [151].

6. Conclusions

The first crystal structure determination by means of X-ray diffraction of an octahedral Ga(III) complex, the tris(acetylacetonato)gallium(III) [102], dates back to 1926. After this work, and until 1980, only three more X-ray studies, on these species, were published: [90] in 1970, [135] in 1972 and [119] in 1976. After such a stunted opening, since 1981 the number of solid-state investigations of mononuclear Ga(III) complexes including polydentate ligands has known a rapid increase and is still experiencing a flourishing period (see Fig. 27). In fact, during the period 2006-spring 2007, 21 additional structure determination have been reported.

The interest is not only due to the clinical relevance of some coordination compounds, but also to the discovery that Ga(III) oxalates and quinolinolates have excellent properties as electroluminescence materials utilized for the construction of light-emitting diodes (OLEDs) [56,96,115,124,125].

The trend illustrated in Fig. 27 parallels to some extent the rise in the world production of gallium over the last part of the twentieth century, owing to the increased demand for GaAs and GaN in components for electronic devices. In fact, according to

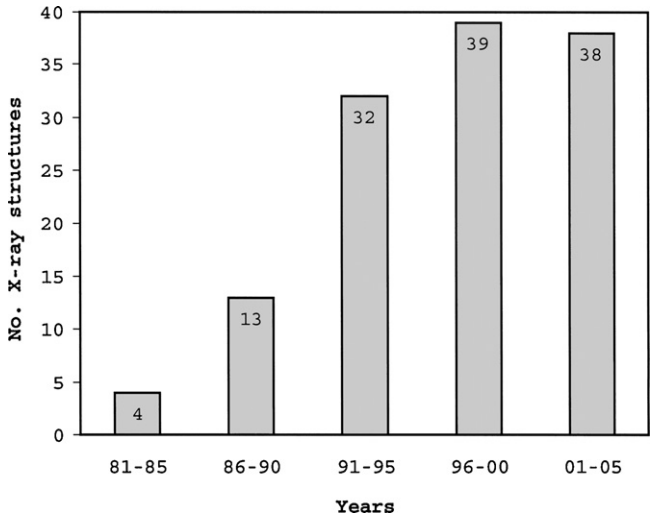

Fig. 27. Number of Ga reported crystal structures reported in the review *vs*. year of publication (1981–2005); each column refers to a 5-year period.

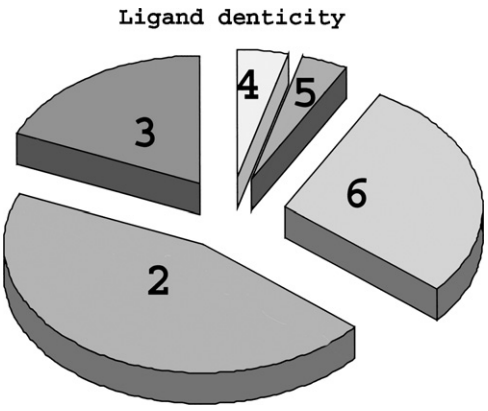

Fig. 28. A pie chart representing the percentage of Ga(III) complexes showing at least one bi- (2), tri- (3), tetra- (4), penta- (5) or hexadentate (6) ligand.

the information released in 2007 by the United States Geological Survey, the world production of primary "crude" Ga in the 5-year terms indicated in Fig. 27 was of about 130, 190, 250 and 400 tonnes, respectively [154].

The world gallium market is expected to be worth about five billion US dollars by the year 2008, the total amount being divided as follows: 42% for LEDs, laser diodes, photodetectors, solar cells; 48% for integrated circuits; 10% for research and development, special alloys and medical uses. Correspondingly, our survey focused on gallium complexes of medicinal interest covers about 5% (135 out of 2740) of the total number of Ga crystal structure determinations.

With respect to the denticity of the ligands coordinated around the gallium metal, a hexa-, penta-, tetra-, tri- or bidentate ligand appears in 28.1%, 3.7%, 4.4%, 18.5% and 45.2% of the reviewed complexes, respectively (Fig. 28), indicating that penta- and tetra-dentate ligands appear to be less suitable frameworks for the preparation of six-coordinate Ga-complexes.

All the surveyed complexes invariably adopt a more or less distorted octahedral geometry, with no evidence of formation of trigonal prismatic arrays. In agreement with the acidic character of the Ga^{3+} ion, O (51.4%) and N (38.8%) are by far the most preferred donors and taken together account for more than 90% of total entries, followed by S (5.6%). The percent weight of the N donor increases ongoing from complexes bearing bidentate ligands (29.6%) to complexes bearing tridentate (44.3%) and hexadentate (45.0%) ligands. In the complexes showing hexadentate ligands, sp^3 N_{amine} are largely predominant (79.8%) over sp^2 N (N_{imine} = 12.8%; N_{py} = 7.4%). The situation is almost reversed in bis(tridentate) complexes, in which sp^2-type N are preferred (68.9%) over sp^3-type N (31.1%). The presence of the planar sp^2-type N justifies the occurrence of the meridional geometry in several bis(tridentate) complexes, whereas the need of more flexibility for hexadentate ligands in order to fill all the sites of the octahedron is in agreement with the increased number of sp^3-type N. Among hexadentate ligands, those generating combinations of five- and six-membered rings upon coordination are favored. This evidence is in accordance with the thermodynamic data reported by Hancock and Martell [25,63]. For example, gallium complexes containing triaza-macrocycles of the [9]aneN_3 (tacn) type, comprising phenolate pendant groups able to form six-membered rings, display the highest stability constants ($\log K_1$ in the range 40.5–45.6). Instead, complexes including the same triaza macrocycle with pendant groups generating five-membered rings (acetate or ethanethiolate residues) show lower stability ($\log K_1$ of 30.1 and 34.2 for [Ga(ta[9]aneN_3)] [36] and [Ga(et[9]aneN_3)] [64], respectively). Similarly, Ga-dota complexes, also forming only five-membered chelating rings, exhibit an even lower $\log K_1$ value of 21.3, indicating that the steric constraints imposed by the coordination of a tetraaza macrocycle markedly decreases the stability of the resulting complexes. Nevertheless, dota-based bfcs, borrowed from the extensive chemistry of other M(III) agents used in magnetic resonance imaging (MRI), are actually the unique examples available for receptor targeting studies based on Ga-complexes.

Complexes bearing macrocyclic ligands confirm the trend of stability dictated by the size of the chelate ring. In any case, the insertion of thiolate groups in the coordination framework leads to extremely stable complexes, as illustrated by the class of $N_2S_2O_2$-diamine dithiolate dicarboxylate complexes ($\log K_1$ in the range 31.5–41.0).

Most of the research focused on medicinal gallium chemistry has been performed in North America. In the last three decades, coordination chemists have been working on the preparation of kinetically inert complexes, trying to overcome the poor bioavailability of the citrated Ga nitrate (Ganite^{TM}), so far the unique FDA-approved gallium drug. Coordination of O-based ligands (*e.g.* citrate or maltolate) improved to some extent the biological properties of gallium agents, but they still remain labile towards transferrin transchelation. The introduction of N in the coordination donor set, coupled with the strong chelation effect imposed by a polydentate (*i.e.* hexadentate) framework, finally generated complexes stable towards hydrolysis and also kinetically inert enough to drive the biodistribution in accordance to their physico-chemical properties, such as overall charge, size and hydrophilicity/lipophilicity balance.

The increased *in vivo* inertness of these agents allowed the preparation of the corresponding complexes containing radioactive Ga isotopes (^{67}Ga and ^{68}Ga for SPECT and PET imaging, respectively). In this connection, non-radioactive monocationic Ga complexes with linear hexadentate SB ligands have shown antiproliferative and antimalarial properties, whereas their radioactive counterparts have been proposed for myocardial PET imaging and for tumor imaging to assess MDR1 Pgp transport function.

The availability of the ^{68}Ge–^{68}Ga generator is stimulating the expansion of non-conventional ^{68}Ga PET, as it allows for a cost-effective production of ^{68}Ga radiotracers far from a cyclotron facility. Moreover, the use of sophisticated dota-based bifunctional chelators, coordinated to the Ga^{3+} ion and conjugated with appropriate peptides (*e.g.* somatostatin), opens an avenue for the imaging of tumors [155]. Semi- and fully-automated radiopharmaceutical synthesis devices for the standardized and reproducible synthesis of ^{68}Ga-dota-conjugated peptides are now available for both research and clinical trials [156].

In spite of the manifold use of these gallium compounds for medicinal purposes, studies on the interaction of pure enan-

tiomeric forms (defined by the Δ/Λ or *C*/*A* descriptors) with a variety of substrates have appeared only recently. Different plasma protein binding and MDR1 Pgp-independent pathways for hepatobiliary excretion of pure *C* and *A* enantiomers of $[^{67}Ga(dmbziapen)]^+$ in control animals have been detected [153], suggesting that more sophisticated investigations are needed to establish the potential activity of Ga agents.

In this connection, *C* and *A* isomers (or Δ/Λ mixtures) could be separated by chiral column chromatography and isolated as optically pure species. The absolute configuration around the metal could be assigned in the solid state by X-ray crystal structure determination, and confirmed in the solution state by circular dichroism and/or NMR studies. The determination of the enantiomeric purity by ^1H NMR spectroscopy is becoming an easy and routine task in the presence of chiral shift reagents, which rearrange an enantiomer into a diastereoisomer [157].

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ccr.2007.12.001.

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