Chemistry and bifunctional chelating agents for binding ^{177}Lu

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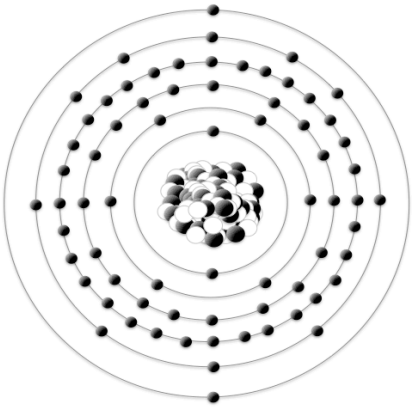
Graphical abstract



Abstract

A short overview of fundamental chemistry of lutetium and of structural characteristics of lutetium coordination complexes, as relevant for understanding the properties of lutetium-177 radiopharmaceuticals, is presented. This includes basic concepts on lutetium electronic structure, lanthanide contraction, coordination geometries, behavior in aqueous solution and thermodynamic stability. An illustration of the structure and binding properties of the most important chelating agents for the Lu^{3+} ion in aqueous solution is also reported with specific focus on coordination complexes formed with linear and macrocyclic polydentate amino-carboxylate donor ligands.

INTRODUCTION

Lutetium (Lu) is a chemical element classified as a rare-earth metal and last member of the lanthanide series of the periodic table [1, 2]. Natural lutetium exists in two isotopic forms, namely the stable ^{175}Lu (natural abundance, 97.41%) and the long-lived β- and γ-emitting radioactive isotope ^{176}Lu (half-life = 3.78×10^{10} years; natural abundance, 2.51%). This isotope is used for radiometric dating. Besides these two natural isotopes, 56 artificial radioisotopes have been produced including 23 nuclear isomers with mass numbers ranging from 150 to 184. Below mass number 175, the main decay mode is by electron capture, but some

unstable isotopes may also emit protons and α particles. Above mass number 176, the common decay mode is through β-emission. Most of these radioisotopes have half-lives in the millisecond-to-minute range [3], and some of them may have potential interest for medical applications (Table 1). In particular, lutetium-177 is currently considered as one of the most promising radioisotopes for radionuclide therapy of cancer.

Table 1. Some important radioisotopes of lutetium with half-life > 1 hour

Nuclide	Half-life	Decay	%Decay
^{169}Lu	36.06 h	EC[(a)], β^+	99.3, 0.7
^{170}Lu	2.01 h	EC[(a)], β^+	99.8, 0.2
^{171}Lu	8.24 d	EC[(a)]	100
^{172}Lu	6.70 d	EC[(a)]	100
^{173}Lu	1.37 y	EC[(a)]	100
^{174}Lu	3.31 y	EC[(a)]	100
^{174m}Lu	142 d	EC[(a)], IT[(b)]	99.4, 0.62
^{176m}Lu	3.63 h	EC[(a)], β^-	99.9, 0.095
^{177}Lu	6-73 d	β^-	100
^{177m}Lu	160.4 d	IT[(b)], β^-	78.3, 21.7
^{179}Lu	4.59 h	β^-	100

[(a)] EC = electron capture.
[(b)] IT = isomeric transition.

Using a few fundamental concepts of inorganic chemistry [4], a qualitative picture of the most distinctive chemical properties of the element lutetium can be simply conceived. This representation may provide some deeper understanding of the chemical rationale underlying common solutions currently employed in the preparation of ^{177}Lu radiopharmaceuticals including the use of specific chelating agents and challenges related to the stability of the final radiolabelled compounds.

Lutetium atom has 71 electrons distributed among different energy levels. Electrons occupying the highest and outermost energy levels are responsible of its chemical reactivity. For lutetium these electrons are arranged in the configuration $4f^{14}5d^{1}6s^{2}$, where integer numbers indicate the various energy levels, italic represents letters the type of energy level and superscripts are the number of electrons occupying that level. When entering a chemical reaction, a lutetium atom usually loses its two outermost 6*s*-electrons and the single 5*d*-electron. This leaves 14 electrons in the *f* level and yields a resulting 3+ charged ion. As dictated by the

rules of quantum chemistry, the *f* level with 14 electrons constitutes a completely filled electronic shell, thus forming a closed external core surrounding the ion. This almost spherical layer of electrons feels the strong attraction of the high nuclear charge (+71), which forces the electron to move at a speed closer to that of light. In accordance with the principles of the theory of relativity, an object moving faster concomitantly increases its mass and, therefore, electrons in the outer shell of Lu^{3+} ion (and, generally, all along the lanthanide series) are more massive than in other series of the Periodic Table. The mass increase brings about a significant drop of electron energy and, consequently, a further stabilization of the external *f* electrons that become less prone to form chemical bonds with other elements. This relativistic effect [5, 6] determines a dramatic shrinking of the atomic volume, an effect commonly called 'lanthanide contraction'. As a consequence, lutetium has the shortest ionic atomic radius among the lanthanide series. A small radius combined with a 3+ ionic charge generates a strong local electric field that constitutes the other most important factor regulating the chemical behavior of the Lu^{3+} ion in conjunction with *f* shell energy stabilization. The net result of all these concomitant effects is that the chemistry of Lu^{3+} is largely dominated by ionic interactions and its complexes are usually ionic in character, thus formed with ligands having hard donor coordinating atoms such as negatively charged oxygen, nitrogen or halogenides (a hard donor is shortly defined as a low-polarizable coordinating atom [7]). Another important consequence of the compact spherical distribution of electron density in the outermost *f* level is that there is no significant effect of ligand field interaction with 4*f* electrons (a ligand field effect is simply described as the stabilization of the energy levels of a metal ion through the bonding interaction with the coordinating ligands [8]), and the coordination number and geometry around the Lu^{3+} ion are mainly determined by the fitting of the ionic size of the metal ion with the spatial distribution of ligand's donor atoms. As a result, the molecular shapes of Lu^{3+} complexes are less defined and a few molecular arrangements more complex than octahedral geometry are possible (Table 2). Since there is no ligand field effect, complexes of Lu^{3+} with monodentate ligands are kinetically labile and multidentate, chelating ligands are commonly used to yield stable complexes. Presumably, these chemical traits may also explain the observed biological distribution of the Lu^{3+} ion in living organisms. In fact, lutetium does not exhibit any interaction with some specific protein and, therefore, any evident biological role. Yet, it is found in very small amounts also in humans, concentrating particularly in bones and, to a lesser extent, in liver and kidneys.

Table 2. Coordination number of lutetium in selected compounds

Complex	Coordination number	Complex	Coordination number
Lu_2O_3	6	$[LuCl_3(THF)_3]^{(c)}$	6
LuF_3	9	$[Lu(NO_3)(terpy)]^{(d)}$	9
$LuCl_3$	6	$[Lu(H_2O)_8]^{3+}$	8
$LuBr_3$	6	$\{Lu[N(SiMe_3)_2]_3\}^{(e)}$	3
LuI_3	6	$[Lu(\eta^2\text{-}NO_3)_2(Ph_3PO)_4]NO_3$	8
$[Lu(acac)_3(H_2O)]^{(a)}$	7	$[Lu(DOTA)(H_2O)]^+$	9
$[Lu(EDTA)(H_2O)^{2-}]^{(b)}$	8	$[Lu(DTPA)(H_2O)]$	9

(a) acac = acetylacetone (Pentane-2,4-dione)
(b) EDTA = ethylenediaminetetraacetic acid
(c) THF = tetrahydrofuran
(d) terpy = terpyridine
(e) Me = CH_3

In summary, despite lutetium does not exhibit a large variety of chemical properties among the lanthanide series, the strong ionic character of the Lu^{3+} ion (ionic potential) allows the formation of robust aggregates with specific ligands having sufficient stability in aqueous solution, which is the ubiquitous solvent for the preparation of injectable radiopharmaceuticals. Because of its favorable nuclear characteristics, ^{177}Lu might be superior to many other therapeutic radionuclides, but the clinical use of this radioisotope is still in its infancy and the breath of its applications remain to be seen. In the following sections, the simple model outlined above will be employed to review the most common reactions that may occur in aqueous solution, and the type of coordinating ligands able to form lutetium complexes having sufficient stability to be used as therapeutic agents.

BIFUNCTIONAL CHELATORS FOR ^{177}Lu

Reactions in aqueous solution

Assuming the proposed ionic model for the Lu^{3+} ion, it is easy to predict its usual fate in aqueous solution. The high electric field of this ion will strongly attract the dipolar water molecules, which surround it from the oxygen side. In turn, the high electrostatic attraction may cause one proton to be removed from a water molecule, thus yielding one hydroxyl ion (OH^-). When there exist three OH^- groups around the ion, the resulting neutral aggregate $Lu(OH)_3$ can precipitate as a tiny solid powder that in water usually takes the form of a colloidal particle. Unfortunately, due to the high electric field, colloidal hydroxide precipitation can occur also in strong acidic conditions (pH < 3) where, usually, water deprotonation is less likely. Actually, along the lanthanide series, the ion Lu^{3+} is the most affected by colloid formation since the onset of hydroxide precipitation occurs at the

lowest pH value as compared to the other lanthanides (see Fig. **1** and Table 3) [10]. In fact, the aqueous solubility of $Lu(OH)_3$ is 0.5×10^{-6} mol dm^{-3} at 25 °C, the lowest value within the series (Table 2). This constitutes the most common drawback affecting the preparation of ^{177}Lu radiopharmaceuticals and nicely accounts for the need to store Lu^{3+} aqueous solutions under very acidic conditions (pH < 3) to avoid colloidal formation.

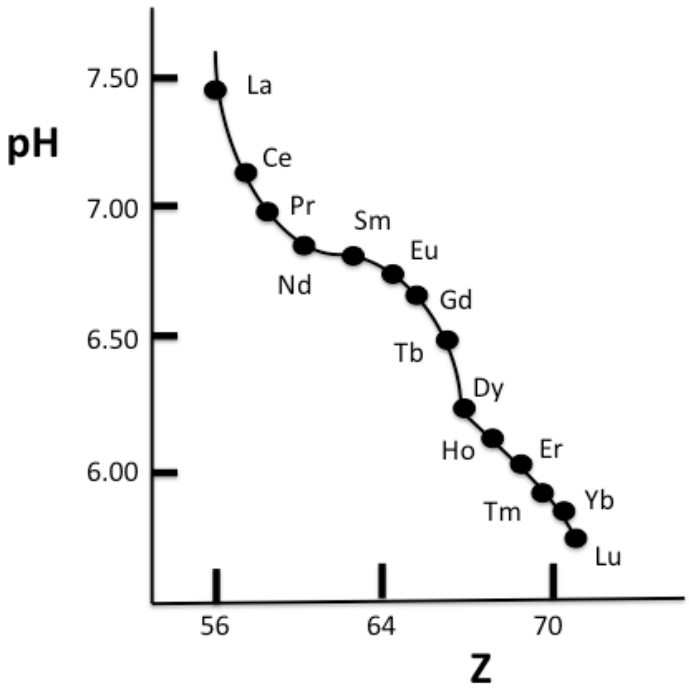


Fig. (1). Values of pH at the onset of precipitation of neutral lanthanide hydroxides in aqueous solution [6].

Table 3. Solubility of lanthanide hydroxides

Lanthanide	pK_{sp}	pH* ([Ln^{3+}] = 0.1 M)	pH* ([Ln^{3+}] = 0.01 M)	Solubility [mol/dm^3 × 10^6]
La	18.7	8.1	8.43	8.0
Ce	19.5	7.8	8.17	4.0
Pr	19.4	7.89	8.20	4.2
Nd	20.4	7.53	7.87	1.8
Sm	20.9	7.37	7.70	1.1
Eu	21.1	7.30	7.63	0.8
Gd	21.3	7.23	7.57	0.9
Tb	21.4	7.20	7.53	-
Dy	21.5	7.17	7.50	-
Ho	22.0	7.00	7.33	-
Er	22.5	6.83	7.17	0.7
Tm	23.2	6.60	6.93	0.6
Yb	23.3	6.57	6.90	0.5
Lu	23.4	6.53	6.87	0.6

* Highest pH value at which hydroxide precipitation does not yet occur at the given metal concentration.

It turns out that competition with OH^- groups is the major hurdle that should be overcome during the preparation of a ^{177}Lu radiopharmaceutical in aqueous solution. To address this point, the usual strategy is to design a suitable bifunctional chelating agent (BFC) able to bind the radiometal ion with a higher strength than OH^- groups. By definition, a bifunctional ligand (Fig. **2**) is made of two parts, namely a chemical binding site (chelator) for the radiometal and a pharmacophore imparting the biological specificity to the resulting radiolabelled compound (conjugate complex). A chemical linker is also required to connect the binding site to the pharmacophore in the final BFC [11−13]. Typically, chelators are derivatized with reactive functional groups that can be covalently coupled (conjugated) to targeting biological vectors (*e.g.*, drugs, peptides, nucleotides, antibodies). Examples of bioconjugation approaches are (a) standard coupling reaction between a carboxylic acid and a primary amine in the presence of a coupling reagent, (b) coupling reactions between activated esters of tetrafluorophenyl (TFP) or N-hydroxysuccinimide (NHS) and a primary amine, (c) thiourea bond formation between an isothiocyanate and a primary amine and (d) thioether bond formation between a maleimide and thiol [11−14].

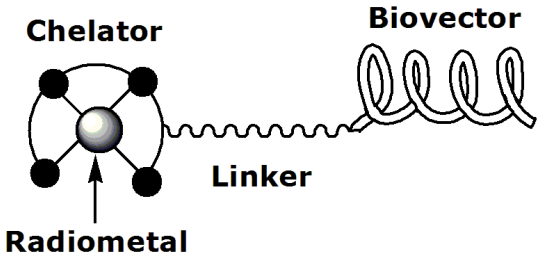
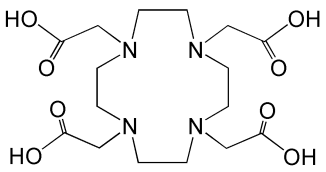
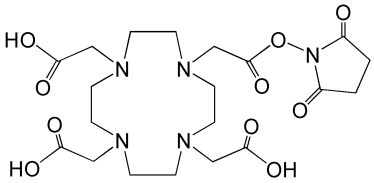


Fig. (2). Schematic drawing of the structure of a bifunctional chelator (BFC).

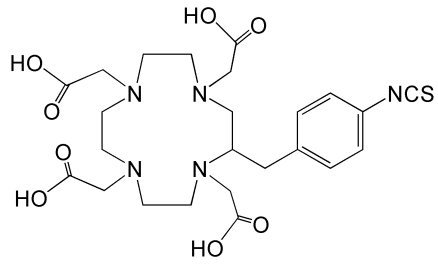
The next step is to identify the most appropriate class of binding ligands for the Lu^{3+}ions. Given the results of the ionic model, possible selections are rather limited and usually point to the use of ligands able to establish a strong ionic interaction with the metallic ion and, concomitantly, wrap it within a cage of coordinating atoms. The use of monodentate ligands is impractical because of the ubiquitous competition with OH^- groups in water, which always exhibit the highest formation constants for the corresponding hydroxides. Moreover, with monodentate ligands it is not possible to take advantage of the so-called 'chelating effect' (see below), which is typical for polydentate ligands. For these reasons, polycarboxylates appended to either a carbon or nitrogen backbone, as illustrated in Fig. **3**, are widely employed as chelating systems for the preparation of ^{177}Lu radiopharmaceuticals [11−15]. These ligands are broadly classified as acyclic and cyclic chelators. Their advantages can be understood from both thermodynamic and kinetic arguments as explained in the following paragraph.



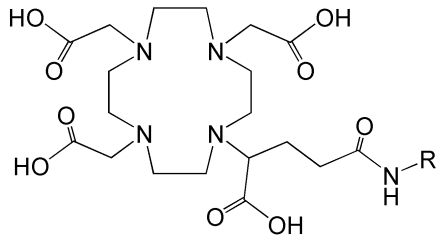
1,4,7,10-tetraazacyclodecane-1,4,7,10-tetraacetic acid (DOTA)



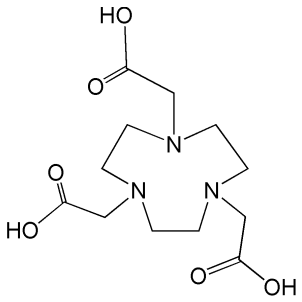
DOTA-NHS-ester



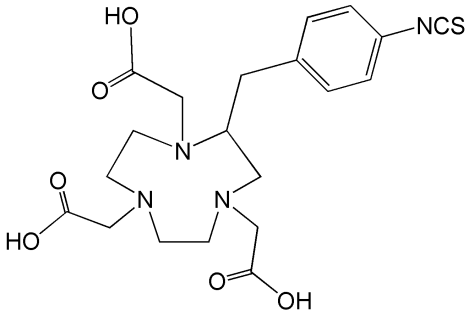
p-SCN-Bn-DOTA



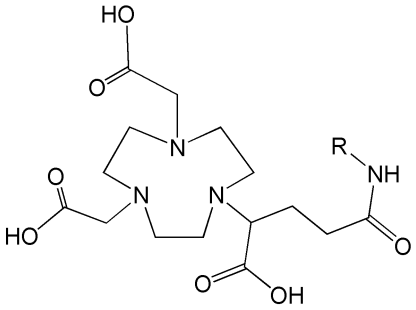
DOTAGA, R = NHS ester, amide



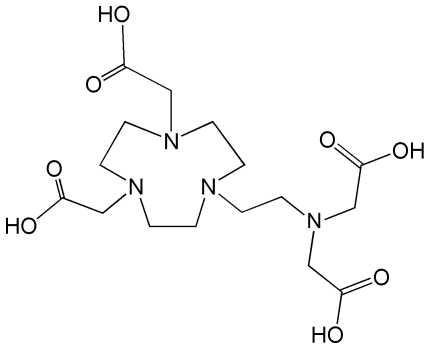
1,4,7-triazacyclononane-1,4,7-triacetic acid
(NOTA)



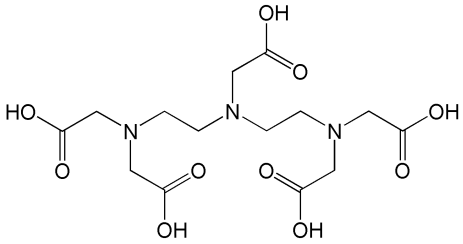
p-SCN-Bn-NOTA



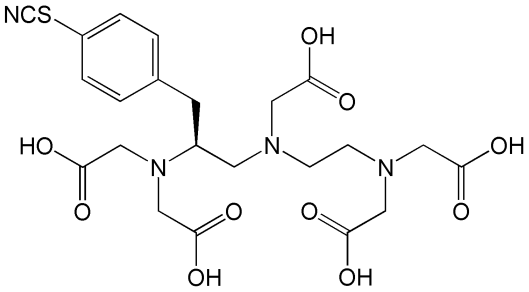
NODAGA
(R = NHS-ester, amide)



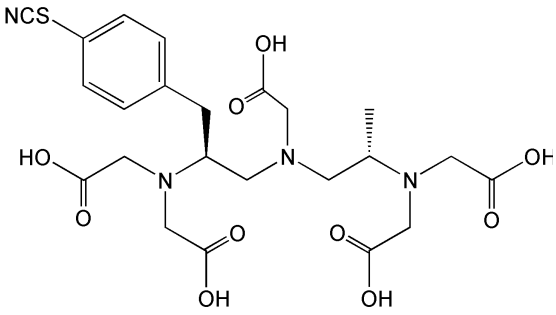
{4-[2-(bis-carboxymethylamino)-ethyl]-7-carboxymethyl-[1,4,7]-triazonan-1-yl}-acetic acid (NETA)



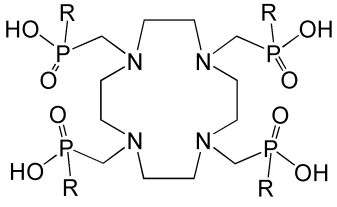
diethylenetriaminepentaacedic acid (DTPA)



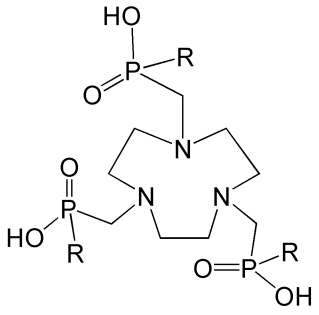
p-SCN-Bn-1B-DTPA



p-SCN-Bn-1B4M-DTPA



1,4,7,10-tetraazacyclodecane-1,4,7,10-tetra(R)ester phosphinic acid (DOTRP)



1,4,7-teriazacyclononane-1,4,7-tri(R)ester phosphinic acid (NORP)

Fig. (3). Drawings of the structure of some of the most widely employed chelating systems for coordination to ^{177}Lu.

Thermodynamic and kinetic considerations

For biological applications, kinetic inertness and thermodynamic stability of metal-chelator conjugates are relevant factors [11]. Generally, it is held that acyclic chelator complexes are less kinetically inert than macrocyclic complexes of comparable thermodynamic stability. Similarly, acyclic chelators typically have faster metal-binding kinetics compared with their macrocyclic analogues because of the requirement for the metal to enter into the macrocyclic cavity. Unfortunately, there exist many common misconceptions in this simple model, the most apparent being that the metal ion does not enter the ring cavity as nicely demonstrated by X-ray structural characterization (see below) [16, 17]. According to experimental evidence, the role of the macrocyclic ring is not in encapsulating the trivalent ion, but simply to sustain the pendant carboxylic functional groups, thus favoring their binding to the metal. This behavior is ubiquitous for all trivalent ions commonly used in nuclear medicine (Ga^{3+}, Y^{3+}, In^{3+} and Lu^{3+}) [15, 17] and, therefore, makes less fundamental the distinction of ligands illustrated in Fig. **3** between acyclic and cyclic chelators.

The following considerations may help to further clarify this argument. Evidently, the role of negative oxygen atoms in polycarboxylate ligands is to provide a strong ionic interaction with the ionic metallic core. The strength of this interaction should be sufficiently high to compete with that generated by OH^- groups. This is a key factor contributing to the decrease of the enthalpy of formation that, in turn, leads to a decrease of the free energy of the reaction (at constant volume and temperature, a negative free energy indicates a thermodynamically favored process). In this context, it is important to understand the role played by the ligand backbone structure (cyclic or acyclic) bearing the carboxylate groups. In simple terms, it helps to achieve some ligand preorganization by bringing all negatively charged coordinating atoms in the proximity of the positively charged ion. This ordering effect has an unfavorable impact on the free energy of the reaction because it causes a decrease of entropy. Since macrocyclic chelators possess inherently constrained geometries and partially pre-organized binding sites, for these ligands entropy loss is less significant than for acyclic chelators that usually require more extensive geometrical reorientation to arrange donor atoms for coordination with the metal ion. However, the decrease in entropy is largely balanced by the opposite effect caused

by the removal of water molecules composing the hydration cage surrounding the positive ion. In addition, the characteristic strong electrostatic interaction between the Lu^{3+} ion and negatively charged oxygen atoms greatly enhance the enthalpic factor, thus yielding an overall decrease of the free energy of the reaction. The favorable thermodynamic situation is nicely reflected by the high values of the stability constants of Lu^{3+} complexes with both open chain and macrocyclic polycarboxylate ligands (Table 4).

Table 4. Stability constants (*K*) for lanthanides Ln^{3+} complexes with

Log *K*							
Ion	NTA	EDTA	DTPA	NOTA	DOTA	DO3A	DOTMP
La^{3+}	10.36	15.50	19.48	13.5	22.9	-	27.6
Ce^{3+}	10.83	15.98	20.5	13.2	23.4	19.7	27.7
Pr^{3+}	11.07	16.40	21.07	13.3	23.0	-	27.4
Nd^{3+}	11.26	16.61	21,60	13.1	23.0	-	27.3
Sm^{3+}	11.53	17.14	22.34	13.9	23.0	-	28.1
Eu^{3+}	11.52	17.35	22.39	14.3	23.5	20.69	28.1
Gd^{3+}	11.54	17.37	22.46	14.5	24.7	21.02	28.8
Tb^{3+}	11.59	17.93	22.71	15.1	24.2	-	28.9
Dy^{3+}	11.74	18.30	22.82	15.2	24.8	-	-
Ho^{3+}	11.90	18.60	22.78	15.2	24.5	-	29.2
Er^{3+}	12.03	18.85	22.74	15.4	24.4	-	29.6
Tm^{3+}	12.22	19.32	22.72	15.4	24.4	-	29.5
Yb^{3+}	12.40	19.51	22.62	15.6	25.0	-	29.5
Lu^{3+}	12.49	19.83	22.44		25.4	23.0	29.6

[a] DO3A = 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid.
[b] DOTMP = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylenephosphonic acid.

The outlined chemical mechanism may help also to clarify the impact of the coordination process on the kinetics of the reaction. More precisely, in order to present the coordinating atoms to the metallic center, the ligand backbone has to undergo some structural rearrangement, which usually requires some stretching and deformation of the chemical bonds. Obviously, for an open chain ligand this adjustment is relatively easier to perform than for a cyclic ligand where structural constrains are higher. It comes, therefore, as an obvious consequence that labeling reactions employing cyclic ligands commonly requires higher temperatures. As mentioned above, there exist a number of misconceptions that did not

contribute to clarify this matter. The most popular argument underpins that the additional thermal energy is necessary to allow the metal ion entering the ring of the macrocyclic ligand. For this reason, the ionic radius should fit well within the ring size of the macrocycle. However, X-ray diffraction studies on the crystal structure of a macrocyclic Lu^{3+} complex with DOTA [16] clearly revealed that the metal ion does not enter the macrocyclic cavity. Instead, the cyclic ligand forms a kind of 'hat' on the top the ion (Fig. **4**) from which the pendant carboxylate arms extend and bind to the metal in a square antiprismatic geometry. In conclusion, heating is required for warping the macrocyclic structure that should adapt itself to the geometry of the coordination site. Concurrently, this distortion allows the nitrogen atoms within the macrocyclic ring to achieve the most favorable arrangement for binding the metal ion.

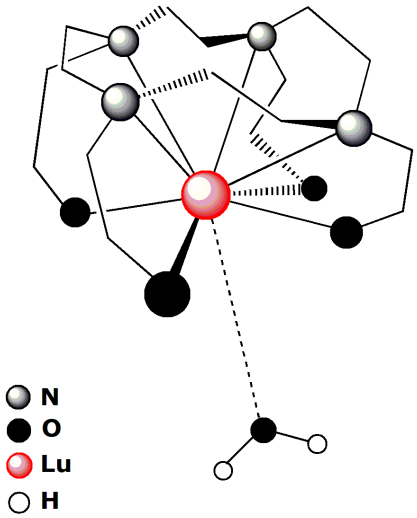


Fig. (4). Schematic drawing of the arrangement of coordinating atoms of DOTA bound to the Lu^{3+} ion as determined by X-ray crystallography [12]. It is apparent, on the top of the structure, the characteristic 'hat' formed by the ring of the four nitrogen atoms of the macrocyclic ligand.

Properties of some common BFCs

DOTA

The macrocyclic ligand 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid (DOTA) is one of the most important chelators for radiometal chemistry [18, 19], and is widely employed for the preparation of metallic radiopharmaceuticals, including ^{111}In, ^{177}Lu and ^{90}Y (Fig. **3**). Potentially, it is an octadentate coordinating ligand binding the metal through the four nitrogen atoms in the macrocyclic ring and the four deprotonated oxygen atoms of the pending carboxylic groups (N4O4-type ligand). With lanthanides, DOTA preferentially forms 8–9 coordinate complexes in square antiprismatic or monocapped square antiprismatic geometries. The lutetium analog crystallizes as the salt $Na[Lu(DOTA)(H_2O)]\cdot 4H_2O$ forming a triclinic unit cell. The molecular structure of

this complex comprises all four nitrogen atoms and four oxygen atoms coordinated to Lu^{3+} with an oxygen donor from water, which acts as the capping ligand. The N4 and O4 donor sets form two separate planes acting as square bases at the top and bottom of the Lu^{3+} atom. The twist angle of the two planes is 39°. The N4 plane is placed above the Lu^{3+} ion by 1.586 Å, whereas the O4 plane is separated from the metal center by 0.732 Å. These structural data clearly show that the Lu^{3+} ion does not enter the macrocyclic cavity, but it is simply sandwiched between the two N4 and O4 planes [16].

For the synthesis of BFCs, some common bifunctional DOTA derivatives utilize one of the carboxylic acid arms for conjugation of the bioactive vector required to impart specific targeting properties to the final radiopharmaceutical. This approach effectively blocks one of the coordinating carboxylate groups, thus potentially weakening the stability of the resulting coordination arrangement (for example, DOTA-NHS-ester in Fig. **3**). To avoid disrupting the original coordination sphere of the chelator, derivatives like *p*-SCN-Bn-DOTA (Fig. **3**) have been synthesized. In this system, conjugation of the bioactive vectors occurs through the carbon backbone and side-arm functionalization. As a result, these bifunctional DOTA derivatives retain their maximum potential denticity (octadentate) as well as the same thermodynamic stability and kinetic inertness of the primitive DOTA.

Recently, a new class of DOTA ligands where the pendant carboxylic groups are replaced by functional groups derived from phosphinic acid [−P(=O)(OH)R ,where R = organic functional group] have been reported (Fig. **3**) [20, 21]. These new ligands show peculiar coordination characteristic as compared to conventional DOTA derivatives and are currently under extensive investigation for the design and preparation of novel radiopharmaceuticals.

Despite the slow kinetics of formation, DOTA remains the most widely employed BFC for the preparation of ^{177}Lu radiopharmaceuticals. A DOTA derivative that could radiolabel at room temperature is actively pursued, but no conclusive results have been reported so far.

NOTA

The macrocycle 1,4,7-triazacyclononane-1,4,7- triacetic acid (NOTA) is a hexadentate chelating ligand (Fig. **3**) that can potentially bind the metal atom through the three nitrogen atoms in the macrocyclic ring and the three deprotonated oxygen atoms of the pending carboxylic groups (N3O3-type chelator) [12, 15]. In comparison with DOTA, the smaller size of NOTA usually demands a lower amount of energy to achieve the deformation of the macrocyclic ring necessary to accommodate the binding of the six coordinating donor atoms within the most favorable structural arrangement. For this reason, NOTA exhibits faster radiolabeling kinetics, albeit the lower number of coordinating atoms in the N3O3 system does not allow a complete saturation of the coordination sphere of the Lu^{3+} ion, a fact that may threaten the stability of the final lutetium complex. This may become even more problematic when one pending carboxylate group of NOTA is used for tethering a pharmacophore, thus leaving only five donor atoms for coordination to the metal. To address this issue, the modified NOTA chelator {4-[2-(bis-carboxymethylamino)-ethyl]-7-carboxymethyl-[1,4,7]-triazonan-1-yl}-acetic acid (NETA) has been synthesized by incorporating an additional carboxylate group into a lateral pending arm (Fig. **3**). NETA possesses fast radiolabeling kinetics closer to those of acyclic chelators, as well as

a higher degree of stability imparted by the macrocyclic framework.

Due to its reduced dimensions and lower coordination number, NOTA seems more suitable for binding smaller trivalent ions like Ga^{3+}. Actually, the Ga(III)-NOTA complex exhibits an exceptional stability [22, 23]. In many publications, this result is still attributed to the effective encapsulation of the Ga^{3+} ion within the macrocyclic cavity despite the outstanding experimental evidence provided by X-ray crystallography [17] showing that the metal ion is far out from the N3 ring. A simpler and, presumably, more satisfactory explanation can be obtained by considering that Ga^{3+} complexes always prefer an almost ideal octahedral coordination and NOTA binding capacity perfectly fits within this arrangement. Conversely, due to its electronic characteristics, Lu^{3+} favors expanded coordination geometries, which cannot be fully satisfied by the insufficient coordination properties of DOTA.

As mentioned for DOTA-type ligands, new derivatives of NOTA with appended phosphinate groups have been recently reported and are actively investigated as potential replacement of common NOTA ligands with the usual three lateral carboxylate moieties (Fig. **3**) [24].

DTPA

Diethylenetriaminepentaacetic acid (DTPA) belongs to the first generation of acyclic chelators used in radiopharmaceutical chemistry, and like most acyclic chelators it can easily coordinate to many radiometal ions at room temperature [12, 13]. It is an aminopolycarboxylic acid consisting of a diethylenetriamine backbone with five pending carboxylate arms. As a result, it is potentially an octadentate ligand wrapping the metallic center through the three nitrogen atoms and the five deprotoned oxygens of the carboxylate groups (N3O5-type ligand).

Since DTPA has been employed for the preparation of a large number of radiopharmaceuticals with different radioisotopes, ranging from ^{99m}Tc and ^{111}In to lanthanides, there exists a bulk amount of data on the stability and inertness of these products both in solution and in biological medium. Analysis of these experimental results does not always allow obtaining a comprehensive and precise picture of all factors involved in generating the observed chemical and biological behavior. This suggests that only through a careful evaluation of experimental results collected from labeling studies of a specific DTPA-derived BFC with a selected radioisotope, it can be recognized whether the resulting conjugate could be efficiently employed as radiopharmaceutical. An example of this uncertainty is provided by the observed difference in stability between DTPA complexes of Lu^{3+} and Y^{3+}. As a potential octadentate ligand, DTPA can almost completely saturate the coordination sphere of Lu^{3+} and Y^{3+} ions. However, DTPA forms a complex with Y^{3+} that appears more stable than the corresponding Lu^{3+} complex despite similar values of the Shannon eight-coordinated ionic radii [25] of these ions (Lu^{3+}, 111.7 pm; Y^{3+}, 115.9 pm). Evidently, other important parameters are involved in determining the observed results that are yet difficult to measure or calculate.

Despite this uncertainty, attempts to solve some shortcomings of DTPA have lead to design novel derivatives such as 1B4M-DTPA (Fig. **3**). 1B4M-DTPA is a bifunctional DTPA derivative that contains a single methyl group on one of its ethylene backbones. It is maintained that this addition can increase the rigidity of the carbon backbone, thus improving the stability of the resulting metallic conjugate.

CONCLUSIONS

In this minireview on Lu^{3+} chemistry, an illustration and critical analysis of a few widely accepted general concepts commonly inspiring the design of BFCs for ^{177}Lu labeling has been undertaken. It has been shown that polycarboxylate ligands still remain the most effective option for the development of a BFC suitable for binding ^{177}Lu and forming a radioconjugate with sufficient stability in aqueous solution and under biological conditions. This conclusion is largely supported by the strong ionic character of chemical bonds formed by Lu^{3+} ion that usually demand negatively charged hard donor atoms like oxygen for stable coordination. The conceptual picture underlying the supposed difference between acyclic and cyclic polyaminocarboxylic ligands has been also discussed along with its weakness and common misconceptions. In particular, the conventional view maintaining that cyclic ligands impart higher kinetics inertness to the resulting radioconjugate as a consequence of the encapsulation of the metallic ion within the cyclic cavity has been challenged on the ground of well-established results from X-ray crystallography. These data clearly show that the trivalent ion is not hosted into the ring cavity, which simply forms a plane standing above it. According to this view, the diversity between acyclic and cyclic polyaminocarboxylate ligands becomes less sharply defined and can be simply related to their different ability in achieving a preorganization of the coordinating donor atoms around the metallic center, thus promoting complex formation.

REFERENCES

[1] Greenwood, N.N.; Earnshaw, A. *Chemistry of the Elements*, 2nd ed; Elsevier Butterworth-Heinemann: Oxford, UK, **1997**; pp. 1227−1249.

[2] Cotton, S. *Lanthanide and Actinide Chemistry*, John Wiley & Sons, Ltd.: Colchester, UK, **2006**.

[3] Audi, G.; Wapstra, A.H.; Thibault, C.; Blachot, J.; Bersillon, O. The NUBASE evaluation of nuclear and decay properties. *Nuclear Physics A*, **2003**, *729*, 3–128.

[4] Huheey, J.E.; Keiter, E.A.; Keiter, R.L. *Inorganic Chemistry: Principles of Structure and Reactivity*, 4th edition, **1993**, Harper-Collins, New York, USA.

[5] Seth, M.; Dolg , M; Fulde, P.; Schwerdtfeger, P. Lanthanide and actinide contractions: relativistic and shell structure effects. *J. Am. Chem. Soc.*, **1995**, *117* (24), 6597–6598.

[6] Pitzer, K.S. Relativistic effects on chemical properties. *Acc. Chem. Res.*, **1979**, *12*, 271–276.

[7] Pearson, R.G. Chemical hardness and density functional theory. *J. Chem. Sci.*, **2005**, *117*, 369–377.

[8] Schläfer, H. L.; Gliemann, G. *Basic Principles of Ligand Field Theory*, Wiley Interscience: New York, **1969**.

[9] Pitzer, K.S. Relativistic effects on chemical properties. *Acc. Chem. Res.*, **1979**, *12*, 271–276.

[10] Evans, C.H. *Biochemistry of the Lanthanides*, Plenum Press, New York, **1990**.

[11] Liu, S. Bifunctional coupling agents for radiolabeling of biomolecules and target-specific delivery of metallic radionuclides. *Adv. Drug. Delivery. Rev.*, **2008**, *60*, 1347−1370.

[12] Price, E.W.; Orvig, C. Matching chelators to radiometals for radiopharmaceuticals. *Chem. Soc. Rev.*, **2014**, *43*, 260−290. DOI: 10.1039/c3cs60304k.

[13] Zeglis, B.M.; Lewis, J.S. A practical guide to the construction of radiometallated bioconjugates for

positron emission tomography. *Dalton Trans.*, **2011**, *40*, 6168−6195.

[14] Ramogida, C.F.; Orvig, C. Tumour targeting with radiometals for diagnosis and therapy. *Chem. Commun.*, **2013**, *49*, 4720−4739.

[15] Cutler, C.S.; Hennkens, H.M.; Sisay, N.; Huclier-Markai, S.; Jurisson, S:S. Radiometals for combined imaging and therapy. *Chem. Rev.*, **2013**, *113*, 858−883.

[16] Aime, S.; Barge, A.; Botta, M.; Fasano, M.; Ayala, J.D.; Bombieri, G. Crystal structure and solution dynamics of the lutetium(III) chelate of DOTA. *Inorg. Chim. Acta* **1996**, *246*, 423−429.

[17] Wadas, J.W.; Wong, E.H.; Weisman, G.R.; Anderson, C.J. Coordinating radiometals of copper, gallium, indium, yttrium, and zirconium for PET and SPECT imaging of disease. *Chem. Rev.*, **2010**, *110*, 2858−2902.

[18] Viola-Villegas, N.; Doyle, R.P. The coordination chemistry of 1,4,7,10-tetraazacyclododecane-N,N′, N″,N‴-tetraacetic acid (H_4DOTA): Structural overview and analyses on structure–stability relationships. *Coord. Chem. Rev.*, **2009**, *253*, 1906−1925.

[19] Stasiuk, G.J.; Long, N.J. The ubiquitous DOTA and its derivatives: the impact of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid on biomedical imaging. *Chem. Commun. (Camb).*, **2013**, *49*, 2732−2746.

[20] Campello, M.P.C.; Sara Lacerda, S.; Santos, I.C.; Pereira, G.A.; Geraldes, C.F.G.C.; Kotek, J.; Hermann, P.; Vaneˇk, J.; Lubal, P.; Kubícˇek, V.; Tóth, É.; Santos, I. Lanthanide(III) complexes of 4,10-bis(phosphonomethyl)-1,4,7,10-tetraazacyclododecane-1,7-diacetic acid (trans-H6do2a2p) in solution and in the solid state: structural studies along the series. *Chem. Eur. J.* **2010**, *16*, 8446– 8465.

[21] Notni, J.; Šimeček, J.; Wester, H.J. Phosphinic acid functionalized polyazacycloalkane chelators for radiodiagnostics and radiotherapeutics: unique characteristics and applications. *ChemMedChem.*, **2014**, *9*, 1107−1115.

[22] Clarke, E.T.; Martell, A.E. Stabilities of the Fe(III), Ga(III) and In(III) chelates of N,N',N''-triazacyclononanetriacetic acid. *Inorg. Chim. Acta* **1991**, *181*, 273−280.

[23] Moore, D.A.; Fanwick, P.E.; Welch, M.J. A novel hexachelating amino-thiol ligand and its complex with gallium(III). *Inorg. Chem.* **1990**, *29*, 672−676.

[24] Šimeček, J.; Schulz, M.; Notni, J.; Plutnar, J.; Kubíček, V.; Havlíčková, J.; Hermann, P. Complexation of metal ions with TRAP (1,4,7-triazacyclononane phosphinic acid) ligands and 1,4,7-triazacyclononane-1,4,7-triacetic acid: phosphinate-containing ligands as unique chelators for trivalent gallium. *Inorg. Chem.* **2012**, *51*, 577−590.

[25] Shannon, R.D. Revised effective ionic radii and systematic studies of interatomic distances in halides and chalcogenides. *Acta Cryst.*, **1976**, *A32*, 751−757.