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The significance of coordination chemistry in the development of anti-cancer peptide-based radiopharmaceuticals

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I. Introduction:

Peptide-based radiopharmaceuticals comprise of three components that include a chelating agent, a radionuclide, and a peptide. Some of the commonly used chelating agents in the development of radiopharmaceuticals include DOTA, DPTA, and DOTATE, amongst others, while some of the commonly available radionuclides used in cancer therapies include iodine-131, samarium-153, strontium-89, yttrium-90, ruthenium-106, palladium-103, cobalt-60, caesium-137 and iridium-192 (Delgado, 1995). On the other hand, one of the commonly used peptides, in this case, is somatostatin and its analogs. The development of peptide-based radiopharmaceuticals is highly dependent on coordination chemistry. In the following sections, the significance of coordination chemistry in the development of anti-cancer peptide-based radiopharmaceuticals is discussed.

Aim:
The Aim of this paper is to explore the role of coordination chemistry in development of radiopharmaceuticals with radio-metals radionuclides in more details.

Synthesis of peptide-based radiopharmaceuticals (characteristics and challenges):

In human bodies, peptides help with the regulation of cellular processes both in the normal and tumor cells. In modern medicine, the development of the radiolabeled peptide analogs has paved the way for the localization as well as the treatment of tumors in vivo. So far the development of radiolabeled peptides of desired affinity properties has been developed through the combination of techniques resulting from advances in coordination chemistry, bioconjugates, solid phase peptide synthesis, organic chemistry, and phage display techniques. Apart from peptides, other biological carriers available for use in therapies include proteins, antibodies, and small

molecules. However, peptides have a significant advantage over all of them because of their high receptor binding affinity, low molecular weights, and their ease of synthesis (Delgado, 1995). They also have good tumor penetration characteristics, favorable pharmacokinetics, and can be modified using bio-conjugation through simple methodologies. Also, their therapeutic value is also enhanced by their high efficacies when applied in low doses and as a result, they cause a shorter spectrum of side effects in comparison to most of the conventional drugs available in the market. The current rising popularity of peptide-based radiopharmaceuticals can be attributed partly to these advantages. With peptide-based radiopharmaceuticals, several strategies are available for the enhancement of radiolabeled peptides' bioavailability. Some of these strategies are the introduction of D-amino acids to the biological active sequence as well as the shortening of the sequence of the natural molecule (Delgado, 1995). For example, radiolabeled RGD peptide may be enhanced by multimerization to improve its affinity for the binding alpha-v-beta-3 receptor. Other pharmacokinetic modifications that may be applied in order to enhance the bioavailability of peptide-based radiopharmaceuticals include PGylation, glycosylation, and the introduction of charged amino acids. Some of the most frequently used elements for the preparation of peptide-based radiopharmaceuticals include radioactive halogens and metals. When labeled with radioactive elements, peptides allow for the targeting of specific molecules for radiotherapy and molecular imaging. Since most metallic radionuclides are capable of forming stable complexes with chelators, it is possible to label peptides with a variety of radionuclides in order to meet specific purposes. Some of the common labeling protocols include the use of bifunctional chelating agents, direct/indirect labeling using prosthetic groups or covalent labeling. Bifunctional chelating agents contain two different moieties that include a

functional group for covalent attachment to peptide and a radio-metal complexing chelating unit. On the other hand, a prosthetic group comprises of bifunctional agents with functional groups for the attachment to the peptide by covalent bonding and a suitable fluorination or radioiodination sites (Delgado, 1995).

Coordination chemistry and macrocyclic/polycyclic chelators:

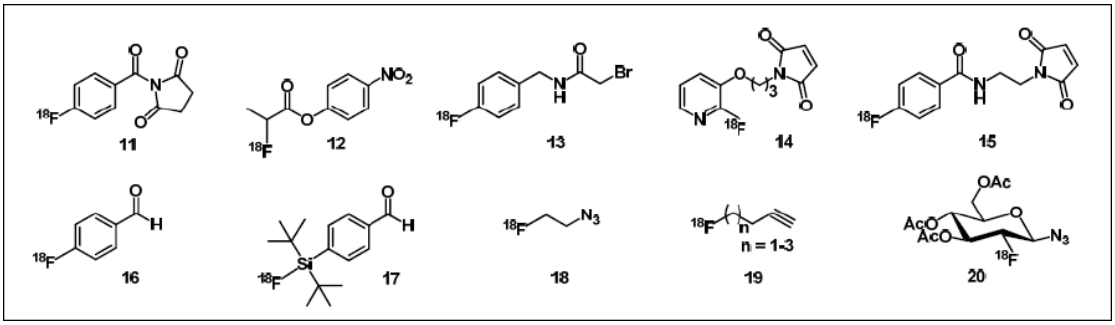
Macrocyclic chelators can be synthetic or natural, and they comprise of donor atoms in they cyclic backbones. The donor atoms may also be incorporated in the substituents attached to the macrocyclic backbones. Macrocyclic chelating agents have not less than three donor atoms and at least nine atoms in their rings. The formation of metal complexes with macrocyclic chelating agents happens through coordinate bonds. In general, macrocyclic chelators coordinate strongly with metallic ions whose size have the best match for the cavity of the ring resulting from complexation, and thus forming the best complementary pair (Jamous, Haberkorn, and Mier, 2013). Through this complementarity, the largest bond energies present when all the donor atoms have been utilized fully. As a result, the macrocyclic agent would have a peak selectivity size which determines the size of the metal that best fits the ring cavity leading to the macrocyclic effect – the phenomenon in which small metal ions would fall through the cavity, while the large ones would be too large to be accommodated (Delgado, 1995). The macrocyclic effect as a behavior is determined by investigating the stability constants ratios of the macrocyclic ligand complexes to the analogous acyclic ligands of the same binding sites sets, in a given solvent, in a given cation and at a given temperature (Jamous, Haberkorn, and Mier, 2013). The macrocyclic effect of these cyclic polyaminopolycarboxylic ligands is the basis for the radiometallation of peptides with such radiometals as Cu^{2+}, Y^{3+}, Lu^{3+}, In^{3+}, and Ga^{3+} in order to improve the radiopharmaceuticals' pharmacokinetics. One of the common macrocyclic chelating agents used in complexation of radiometals is DOTA. The synthesis of DOTA involves a reaction of chloroacetic acid with cyclen 50 under alkaline conditions, in water. DOTA complexes have significantly high stabilities making them suitable chelators for different therapeutic and diagnostic applications (Jamous, Haberkorn, and Mier, 2013). Additionally, DOTA is also a favorable bifunctional chelating agent for use when preparing most of the therapeutic lanthanide radiopharmaceuticals, besides the preparation of stable

complexes with trivalent and divalent radionuclides, for example, 64/67Cu, 86/90Y, and 67/68Ga. The coordination chemistry of DOTA allows for the formation of several species of DOTA-based bifunctional chelators after attaching biomolecules to the DOTA-unit (Delgado, 1995). Such new species of DOTA-based bifunctional chelators formed after the attachment of the biomolecules to DOTA-unit included DOTA-derivatives, active DOTA esters, and protected DOTA forms.

DOTA-active esters are prepared by the activation of at least one carboxylic groups, and they are used for the optimization of DOTA-conjugated biomolecules synthesis. Some of such DOTA-conjugated biomolecules include the active ester DOTA-NHS and the DOTA-phenolic active esters (Jamous, Haberkorn, and Mier, 2013). Coordination chemistry also plays an important role when synthesizing Chelator-peptide conjugates. One of the commonly used methods of synthesizing Chelator-peptide conjugates is post-conjugation. This strategy involves first synthesizing protected peptide on a solid phase and the subsequent conjugation of a bifunctional chelating agent to the resin bound peptide (Delgado, 1995).

Development of iodine-labeled peptide radiopharmaceuticals:

Peptides used in cancer treatment may be lined with radioiodine via conjugation or electrophilic substitution. In this case, such side chains of the peptide as histidine or tyrosine provide the possibility of high-efficiency electrophilic radioiodine aromatic substitution under mild conditions. This is the direct approach to linking peptides with radioiodine. On the other hand, conjugation of the peptide with radioiodine is used when direct labeling is impossible. In this approach, a radioiodinated prosthetic group is utilized for the conjugation with such functional groups of the peptide as amine, thiol, and aminooxy (Jamous, Haberkorn, and Mier, 2013). Another group of peptide-based radiopharmaceuticals used in cancer treatment and that utilizes coordination chemistry during its development is fluorine-labeled peptide radiopharmaceuticals. When labeling peptides with radiofluorine, direct labeling by nucleophilic substitution is impossible because the reaction requires the elevated temperature to induce radiofluorination and thus destroying the peptidic biomolecules. As a result, the conjugation of fluorine to peptides remains as the only remaining option where 18-fluorine-labeled prosthetic groups are used to bind to such functional groups as an alkyne, hydrazine, azide groups, amine, and aminooxy.

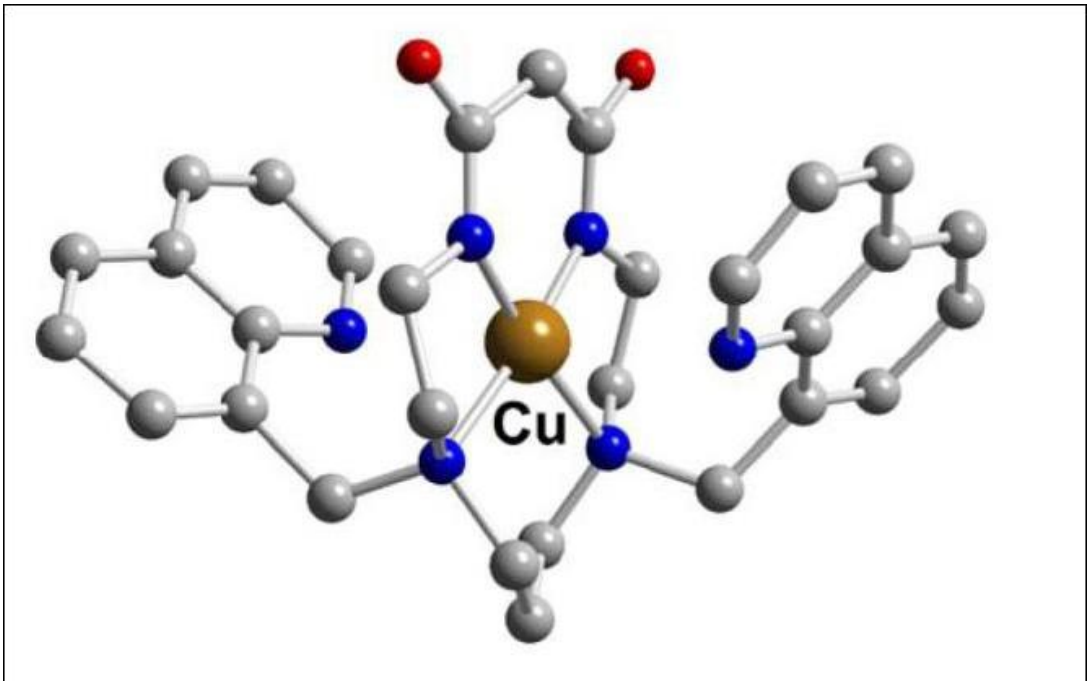


chemical structures of some of the prosthetic groups used in peptide fluorination.

Most 18-Fluorine labeled radiopharmaceuticals have high lipophilicity and as a result, they have a low tumor and unspecific liver uptake (Jamous, Haberkorn, and Mier, 2013). Moreover, one of the most widely used radiolabeled peptide radiopharmaceuticals is 99mTc. 99mTc is frequently used for diagnostic applications, and it offers rich labeling chemistry, and it has ideal nuclear physical properties. 99mTc-complexes used in most radiopharmaceuticals have an oxidation state of +V, and they are prepared from chemically inert generator whose oxidation state is +VII. The preparation involves reduction of the generator using such reducing agents as Zinc, phosphines, SnCl2 and Na2S2O4 in the presence of a suitable ligand. Generally, the preparation of peptide-based radiopharmaceuticals using 99mTc applies the post-conjugation labeling strategy where a bifunctional chelating agent is first attached to the peptide by covalent bonds. This step is then followed by the reduction of 99mTcO4- with Sn(II) before being completed by the chelating agent. In the end, this scheme results in the formation of technetium complexes whose structure and oxidation states depend on ligands, ligands and the reducing agent (Jamous, Haberkorn, and Mier, 2013). If the tetradentate bifunctional chelating agent used in this case is based on mercaptoacetyltriglycine, N3S or N2S2, and the ligand is tetraamine, the resultant complexes are octahedral. The advantage of using N4 cores is that it allows for the formation of hydrophilic Tc-complex without the structural influence of isomerism. Another component used when coupling technetium to peptides is hydrazinonicotinic acid (HYNIC), which acts either as a monodentate or a bidentate ligand. In both cases, the complete coordination of the core of the [Tc]-HYNIC is achieved only after the addition of such acids as nicotinic acid, tricine or EDDA. 99mTc is may also be linked to peptides by combining organometallic [99mTc(CO)3] with the core through the 99mTc carbonyl approach.

The role of coordination chemistry of radiometals used in peptide-based radiopharmaceuticals*:*

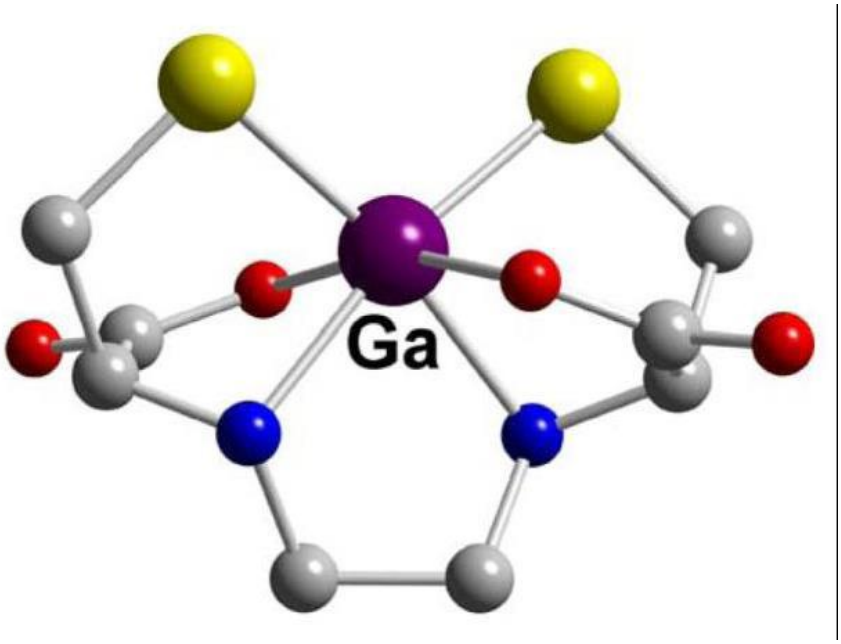
Some of the commonly used radionuclides in the development of peptide-based radiopharmaceuticals include Cu, Y, Ga, In, and Zr. Copper(II) radio-ion is the most common of radioactive copper ions present in aqueous solutions. It has been found to have a high plasticity of coordination geometry making it suitable for complexation with multiple chelating agents. Copper(II) radiation's coordination number ranges from 4 through 6, with geometries of octahedral, trigonal bypyramidal, square planar and square pyramidal. AS a result, the square-planar geometry is exploited to design tetradentate chelating agents that complement the high affinity of this geometry where the common donor set comprise two charge-neutralizing anionic oxo, thiolato or amido sites combined with imino or amino nitrogen (Wadas, Wong, Weisman and Anderson, 2012). The coordination numbers of copper(III) radioions are also the driving force behind the use of cyclic hexadentate chelators where they allow the Cu(II)-EDTA to interact with Cu(II) ions along one O-Cu-O axis in a tetragonally-distorted N2O4 octahedron. Coordination number five of copper(II) radioions is also exploited to develop five-coordinate Cu(II) complexes, for example, bispidine (3,7-diazabicyclo[3.3.1]nonane). Coordination chemistry is also credited for the formation more inert Cu(II) complexes in 14-membered N2S2 macrocycle compared to other ring sizes. In this complexes, and thus allowing carboxymethyl arms to be appended and complexed with 64Cu(II) and C(II). Another aspect that indicates the role of coordination chemistry in the development of peptide-based radiopharmaceuticals from Cu(II) ions is the radio-copper chelation potential (Wadas, Wong, Weisman and Anderson, 2012). In this regard, some chelating agents form more stable complexes with radio-copper regardless of the size of the ring. For example, dioxocyclan has been observed to have highly stable complexes because of the influence of their distorted square-planar coordination geometry.



A distorted square-planar coordination geometry

The coordination chemistry of Gallium (III) also influences the development of peptide-based radiopharmaceuticals in several ways. In the aqueous state, the most prevalent oxidation state of gallium is +3 (Wadas, Wong, Weisman and Anderson, 2012). The ion has a coordination number of 4-6 and an ionic radius of 47-62 pm, and a *pKa* of 2.6 when hydrated. Accordingly, it has a very strong affinity for hydroxide ions and therefore at high pH it tends to demetallate from the complex to form gallate anion (Ga(OH)4-. The coordination properties of gallium (III) ions are responsible for the interaction of the metal with tetrahydrate ligands and hexadentate ligands in peptide-based radiopharmaceuticals involving radio-gallium. In tetradentate ligands, such iminodiacetic acid derivatives as tetradentate o-hydroxybenzyl provide NO3 donor set in order to complete the distorted octahedral coordination around two cis-coordinated water molecules and Ga(III) in their centers. Additionally, the small size of Ga(III) as well as its low coordination number causes the formation of a distorted square pyramidal GaCl complex after a reaction between GaCl and a bis (aminothiolate) N2S2. With regard to hexadentate ligands, a reaction between N2O2S2 donor sites

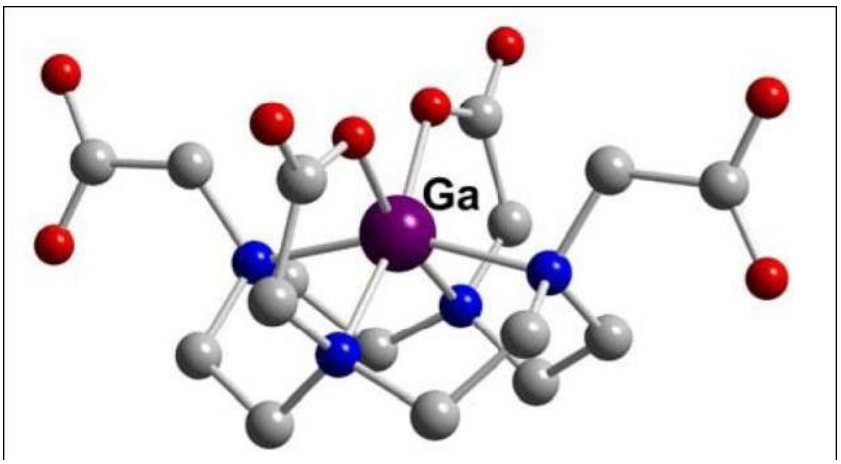
and N,N'-ethylene-di-L-cysteine (an acyclic hexadentate chelator)results to the formation of a stable complex if Ga(III) is added to the mixture (Wadas, Wong, Weisman and Anderson, 2012). This complex has a distorted octahedral structure that has two carboxylate O's in *trans*- arrangement.



A very stable complex of Gallium (III) and N,N'-ethylene-di-L-cysteine.

Coordination Chemistry of Gallium (III) is also the cause of high stability of several other complexes from such chelates as 1,4,7-triazacylononane (NOTA), and DOTA. NOTA, in addition to it relatives, forms highly stable complexes with Ga(III) as a result of the formation of coordinate bonds as demonstrated by the envelopment of the cation by distorted octahedral N3O3 (Wadas, Wong, Weisman and Anderson, 2012). This complex is significantly inactive, and thus it can survive acidic conditions for extended periods.

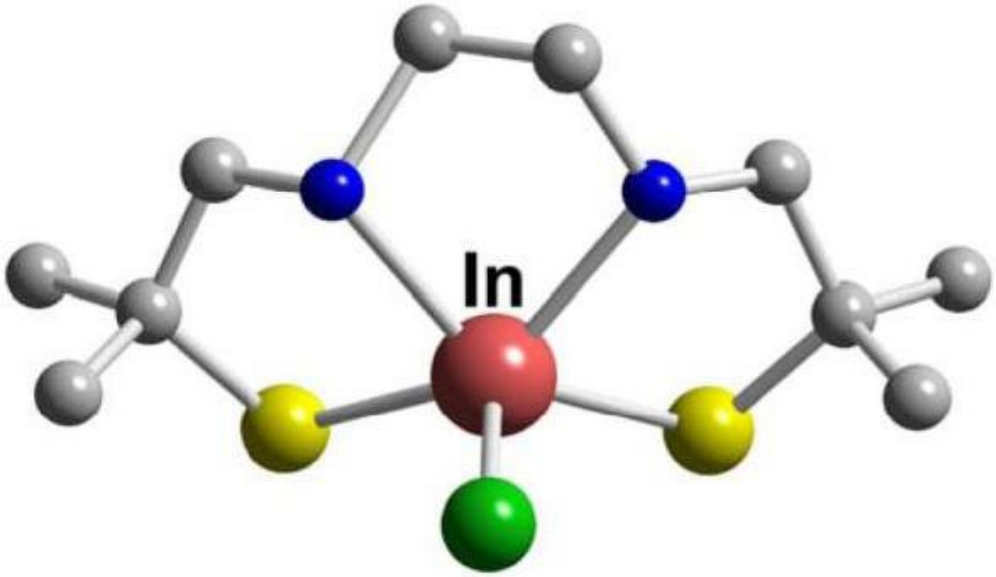
Fig 37: stable Ga-NOTA complex. On the other hand, the 6-coordination sphere of Ga(III) is saturated by octadentate (DOTA) to form complexes of two different structures, namely di- and monoprotonated structures that are similar to the distorted octahedron coordination of four macrocyclic N's and two cis-carboxylates *(Wadas, Wong, Weisman and Anderson, 2012).*



Ga-DOTA complex

Another radiometal whose coordination chemistry influences the development of peptide-based radiopharmaceuticals is indium (III). Indium is like gallium in that its stable oxidation state is

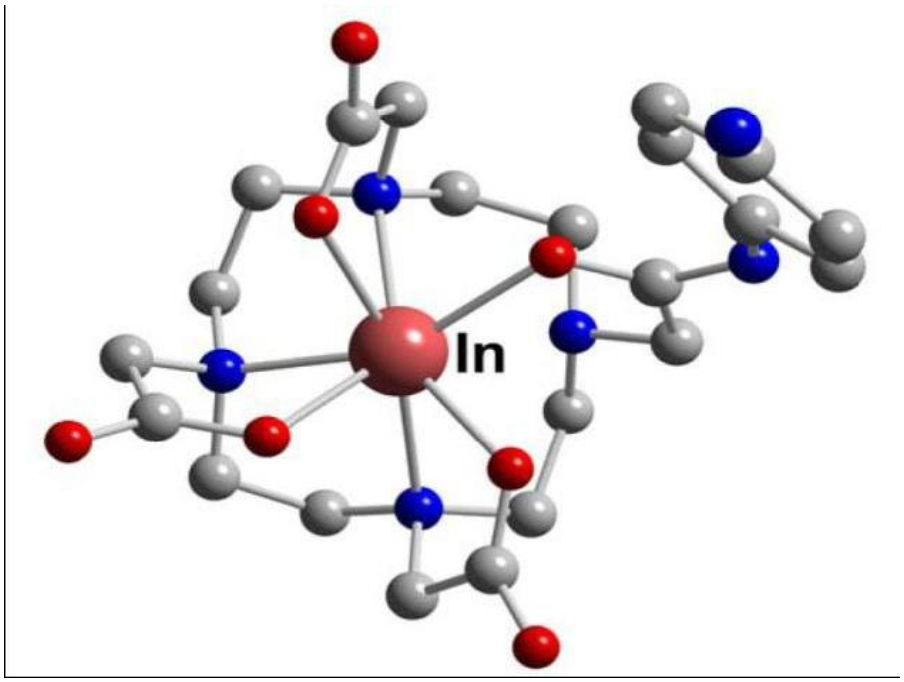
+3. However, its coordination number is 4-8, and its atomic radius is 62-92 pm. Coordination chemistry of indium also influences the development of peptide-based radiopharmaceuticals through its interaction with tetradentate and hexadentate chelating agents to influence the stability of the entire radiopharmaceutical Wadas, Wong, Weisman and Anderson, 2012). One of the tetradentate chelating agents complex with Indium(III) is InCl-bis(aminothiolate). This structure is 5-coordinate, and it interacts with an axial chloride in a near square pyramidal version. This complex is stable in aqueous acetonitrile solutions.



InCl-bis complex

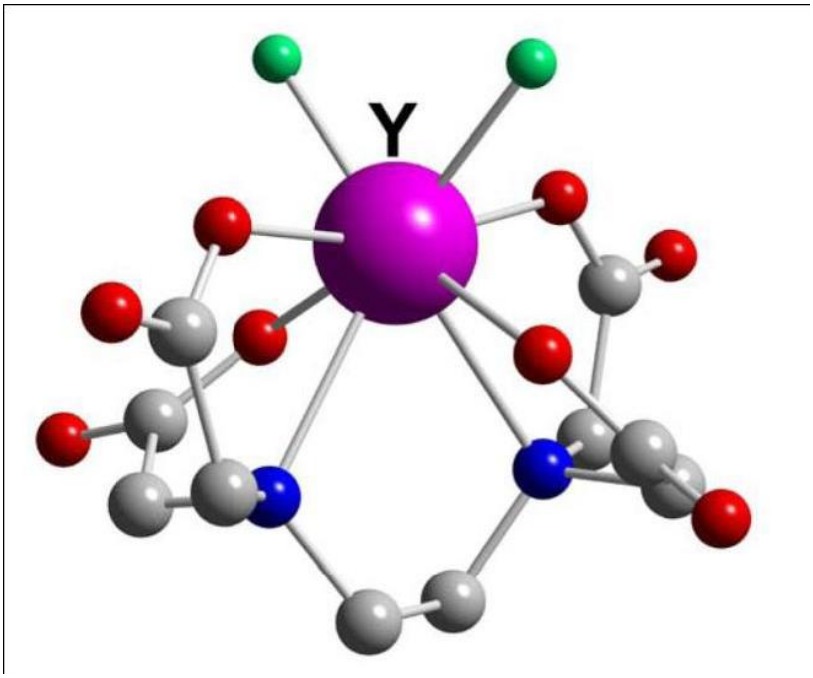
On the other hand, the interaction of indium with hexadentate, heptadentate and octadentate chelators results in the formation of a distorted octahedral Indium(III) complex that has carboxylate donors at its axial sites. For example, when EDTA or DTPA interact with indium the product is a thermodynamically stable structure. In this case, interactions with EDTA results in the formation of 7-coordinate In-EDTA that includes an hexadentate chelator and has a pentagonal bipyramidal geometry. On the other hand, the In-DTPA complex has about 7- and full 8-coordination by the chelator, and it has a distorted pentagonal bipyramidal as well as square antiprismatic geometries, respectively. Another chelator whose complexation with indium influences the structure and stability of peptide-based radiopharmaceuticals is DOTA Wadas, Wong, Weisman and Anderson, 2012)

. One of the derivatives of DOTA that has been studied in relation to the stability of peptide-based radiopharmaceuticals is DTA-AA, which has a twisted square antiprismatic geometry. Other coordination features present in this complex include the O4 and N4 coordination planes.

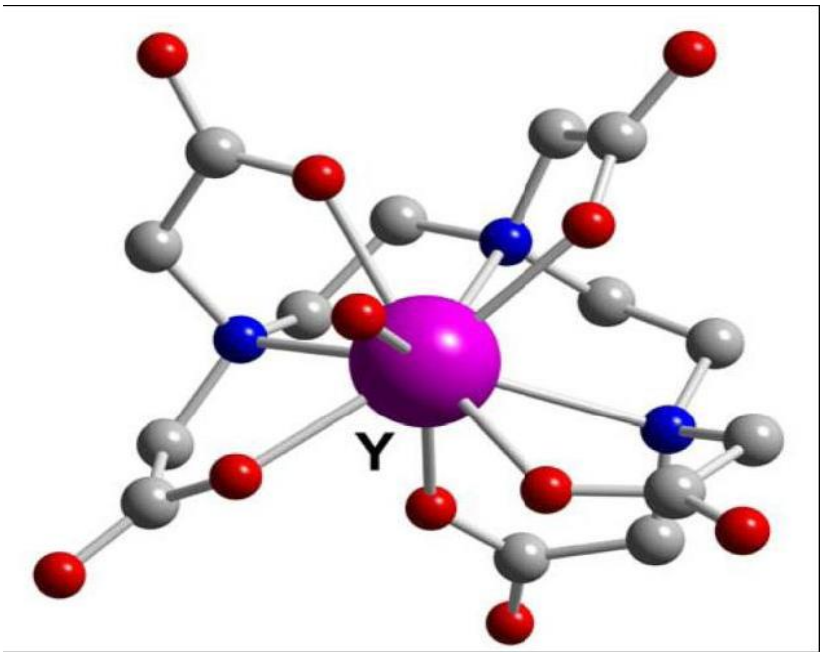


In-DOTA-AA complex

With regard to yttrium(III) ions, some of the extensively studied chelating agents include DTPA, EDTA, Tris(carbamoylmethyl) derivative (NOTAM) DOTA and DOTATOC, amongst others. Both DPTA and EDTA have significantly stable complexes with Y(III), where YF2-EDTA exists as a dodecahedron while Y-DPTA exists as a 9-coordinate comprising of a monocapped anti-prismatic geometry (Wadas, Wong, Weisman and Anderson, 2012). In both YF2-EDTA and Y-DPTA, the 9-coordinate has a distorted tricapped trigonal prismatic geometry in which a coordinated solvent molecule and octadentate chelator exists.

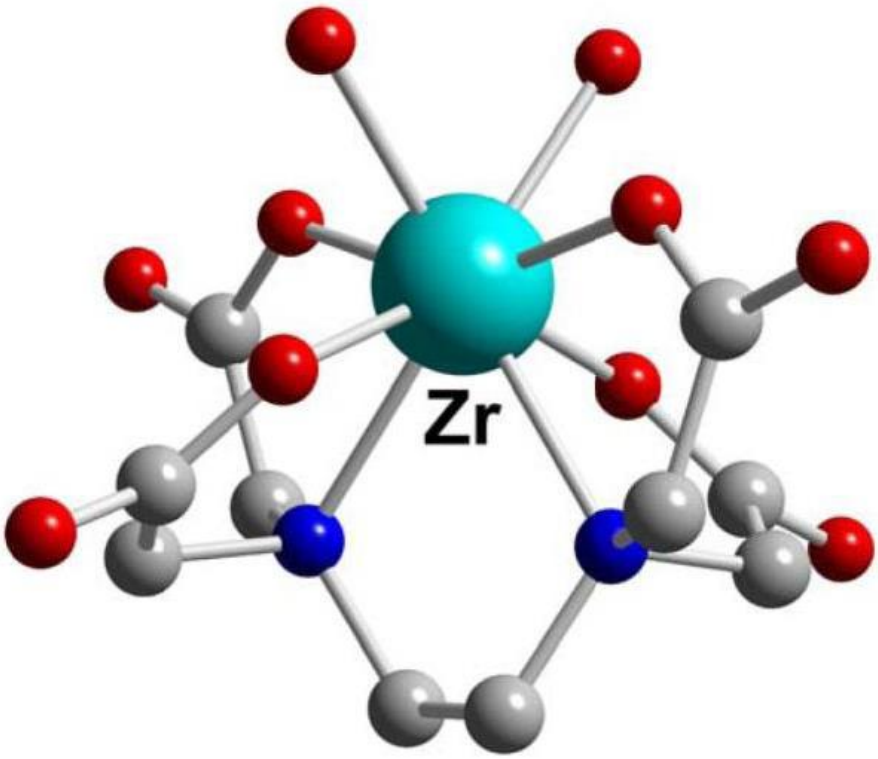


YF2-EDTA complex



Y-DPTA complex

Also, the coordination chemistry of zirconium has been seen to influence the stability of complexes used in peptide-based radiopharmaceuticals. Zirconium ion is highly positively charged, and it has a small radius of 59-89 pm for coordination number 4-9. It also has an extreme hardness leading to high stability constants of DPTA and EDTA complexes (Wadas, Wong, Weisman and Anderson, 2012). The complex of Zr and EDTA forms a dodecahedral geometry while the complex of Zr-DPTA complex forms a full envelopment of Zr(IV).



Zr-EDTA complex

Coordination chemistry of radiometals & The concept of matched-pair radiometals:

In some cases, some radionuclides have both the imaging and the therapeutic values. For example, some iodine radioisotopes are useful for imaging as well as therapy, which makes them ideal matched-pairs. Usually, the concept of matched-pair emerges from the ability of some radiometals to emit both particulate forms of energy (alpha and beta particles) and gamma radiations, which allow for their use both as therapeutic and imaging agents (theranostic agent) (Giblin, Veerendra, and Smith, 2005). In basic terms, matched-pair radiometals are radionuclides with value for imaging as well as therapy, and thus they can be utilized for molecular imaging as well as therapeutic agents. Coordination chemistry of radiometals also extends the concept of

matched pairs further as different radionuclides may be used together for imaging as well as therapy after linking them to suitable ligands to form complexes. In this case, radionuclides any two radionuclides of a single element that may not be applied as theranostic agents may be coordinated through a bifunctional chelator and tethering them to the biologically active molecule for targeting in order to deliver a theranostic performance. The application of matched pair radiometals in theranostics may be demonstrated by several examples. One of the examples of the application of this concept in theranostics is the use of 99mTc/188Re (Ricardo, Kumar and Wiebe, 2015). In this matched pair strategy, 99mTc provides diagnostic information by Single Photon Emission Computed Tomography (SPECT), which demonstrate the availability of the receptors on the primary as well as the metastatic tissue, while 188Re is administered as a therapeutic agent for diagnosed problem. Such a concept as the one indicated in this approach; the target receptor guides the administration of the treatment agent. In addition, the diagnostic radiopharmaceutical allows for the pre-screening of receptor-positive patients before the administration of the therapy in order to characterize such aspects as the receptor density, drug pharmacokinetics as well as the patient dosimetry and ultimately reduce or eliminate the unsuccessful radiotherapeutic regimens. In this case, the therapeutic value of Re-188 is contributed by its attractive physical characteristics (Gamma emission =155keV, half-life = 16.94 hours and maximum beta particles release = 2.12MeV) and its widespread available for use. Other radioisotopes of rhenium that are available for radiotherapy include Re-186, which emits gamma photon of 137KeV, beta emission of 1.07MeV and a half-life of 3.7 days. However, Re-186 has a lower specific activity compared to Re-188, and this limits its usefulness as a radiotherapy agent. Another example of the successful application of the matched pair concept is the use of In-111 and Y-90 (Ricardo, Kumar and Wiebe, 2015). In this case, 111In-Octreotide is administered in the body as a somatostatin tracer to localize the somatostatin receptors expressed by neuroendocrine tumors in order to guide the treatment of the target tumor with Y-90 radiopharmaceuticals. Elements of

theranostic significance have been explored widely in the recent years from 2000, and the value of the theranostic matched pairs is outlined in the following paragraph. The concept of matched pair is aimed at using a radiotherapeutic as well as an imaging analog of similar pharmacokinetic and biodistribution characteristics in order to allow for the prior estimation of dosimetry as a tool for sound clinical decisions (International Atomic Energy Agency, 2009).

II. Conclusion:

In the history of radiotherapy practices, the use of matched pairs has been rare, but the approach has been gaining popularity since 2000 due to the need to predict outcomes of different therapies as well as avoid irrelevant as well as expensive treatments. These have been the reasons behind the concerted development of matched pair radiotherapy treatment techniques. However, the matched pair concept is limited by several factors. For example, although In-111 has in history been used, as an imaging surrogate, along with Y-90, the former does not offer effective quantitative prediction because the two metals do not have the same coordination chemistry. On the other hand, the use of Tc along with Re-186/188 is also limited by the low image able emissions of Re-186/188, which limits the ability of technetium images to determine the dosimetry of Re isotope (International Atomic Energy Agency, 2009).

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