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BIOLOGICAL AND BIOMEDICAL APPLICATIONS OF THE LANTHANIDES COMPOUNDS: A MINI REVIEW

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Lanthanide complexation chemistry has been studied intensively and progress has been stimulated by applications as bioactive probes for magnetic resonance, luminescence, in drug delivery and in cancer therapy. Trivalent lanthanide ions (III) form complexes with various organic molecules and supramolecular assemblies have been carried out in the solid and solution state which is of great importance scientifically, biologically and commercially. The design of organic ligands in the optimization of the specific properties (optical, luminescence, paramagnetic, biological) of the lanthanide complexes for biomedical applications received more attention in the last decades. Found on the physical and spectral properties, lanthanides have numerous applications, such as fluorescent probes in biological assays. The major aim of this mini-review is to present recent research of novelty lanthanides compounds with biological and biomedical applications.

Keywords: lanthanide, complexes, biological applications.

INTRODUCTION

Lanthanides occupy unique positions in the periodic table and they exhibit interesting properties variability. In the last decades, it has been explored extensively that lanthanides have an important role in several biochemical reactions and their utility as structural and functional probes in understanding structures conformations and characteristics of biomolecules was acknowledged[1,2].

The lanthanide research conducted proved that they have a great variety of applications like medical diagnostics and treatments, material sciences, industry and agriculture.

Nanotechnology is as well a promise of significant improvement in human health in the field of medical applications such as drug delivery and development of fluorescent tags in biomolecular sensing, imaging and for cancer diagnosis and therapy[3-6].

Their outstanding properties recommend them as excellent, fluorescent dyes and contrast agents in medical research, spectroscopic probes, sensors and lasers. Lanthanide compounds have magnetic, catalytic and optic properties and are also used in biological applications as biosensors[7]. The approach has proved an extremely successful one and it is largely responsible for the sustained interest in lanthanide biochemistry.

Another important property is their luminescence and photophysical behavior that underlines their application as imaging agents in the visible region and recently demonstrated in the near-IR as well[8-10].

This work wants to be a link between the properties and the unique functionality of lanthanides complexes which were recently developed and successfully applied in different branches of biological science.

STRUCTURE AND PROPERTIES OF THE LANTHANIDE COMPOUNDS

Ln is the generic symbol of lanthanide elements. The particular electronic configuration is responsible for the constancy of lanthanide physical-chemical properties such as the oxidation state, the redox potentials and the ionic radii[11]. The importance of the coordination chemistry of the lanthanide elements is dominated by the trivalent ions that all lanthanides form. Lanthanides ions exhibit a coordination number ranging from as low

as 3 and as high as 12, depending on the steric demand of the ligand[12]. Lanthanide complexes typically have coordination numbers of 7–12 and have a rapid rate of ligand exchange in solution. The trivalent lanthanide ions are hard acceptors, making them ideal for forming complexes with ligands containing oxygen donor. They have a strong affinity for water and the chelating ligands preferred are monodentate ligands as it is difficult for them to displace water molecules from the inner coordination sphere. Thus, common complexes of lanthanide ions often contain diketones or other polydentate oxygen donor ligands [13].

The geometry of the Ln^{III} complexes is determined by steric factors rather than electronic ones. As a consequence, the Ln^{III} complexes of the same ligand are all isostructural. Due to their small size, Ln^{III} ions are considered to have a high positive charge density so that they behave as hard Lewis acids. Accordingly, they strongly coordinate ligands having highly electronegative donor sites (hard Lewis bases), in the order: $F^- > HO^- > H_2O > NO_3^- > Cl^-$[14].

The new complexes obtained from hydrated nitrate salt of lanthanide^{III} (Ln = Er, Ho, Tb, Gd) or yttrium^{III} (Y) with the ligand di-2-pyridyl ketone-p-Cl-benzoylhydrazone (DpkClBH), afforded air stable solid compounds, that were characterized by different techniques and it was proposed the general structure: $[Ln(DpkClBH)_2(NO_3)_2]\ NO_3 \cdot nH_2O$, (n = = 2, 1, 1, 1, 1.5 for Ln = Y, Gd, Tb, Ho, Er, respectively) [15]. There were also reported and characterized new Ln complexes with stoichiometry: $Ln(4\text{–}bpy)_{1.5}(CCl_3COO)_3\ nH_2O$, where Ln^{III}= Pr, Sm, Eu, Gd, Tb, n=1 for Pr, Sm, Eu and n=3 for Gd, Tb [16].

POTENTIAL FLUORESCENCE OF LANTHANIDE COMPLEXES

One of the inconveniences when performing steady-state fluorescence measurements is that some biological fluids or serum are also fluorescent. To increase the sensitivity of the assays long-lived fluorophores like lanthanides can be used. Their role in the biochemical process is underlined by new experimental methods. Time-resolved detection which can be defined as a delay between excitation and emission detection can minimize the fluorescence interference and it is used for a highly sensitive detection of various biological molecules.

Certain life science applications take advantage of the unique fluorescence properties of lanthanide ion complexes (Ln^{III} chelates or cryptates). Their special properties like long fluorescence lifetime, large Stoke shifts and sharp emission band differentiate them from common use fluorophores (*e.g.*, fluorescein, allophycocyanin, phycoerythrin and rhodamine).

Among the biomedical application of the lanthanide chelates we find nuclear magnetic imaging (MRI)[17], radiotherapy, cytotoxicity and pharmacokinetic studies, specific DNA or RNA cleavage[18,19].

The complex of $[LaL_2(H_2O)_2(NO_3)_3]_n$ where L=1–phenyl-2 (morpholinyl)ethanol was reported exhibiting fluorescence properties with a very good Stoke shift. The high fluorescence emission intensity recommends it for a new marker that could potentially inhibit the monoaminooxidase activity (MAO) [20].

A recent photoluminescence studies on a new Eu^{III} ofloxacin complex shows the differences between the complex and ligand underlined by both lanthanide ion and ofloxacin. The complex is a fluorescent pH indicator whose excitation extend to visible range[21].

Furthermore, the progress made in pharmaceutical screening led to intense research in enzymatic activity with fluorescent probe. The method is robust, inexpensive and it's used for enzymes inhibitors screenings, enzymatic conversion *monitoring and establishing the enzymatic activity* [22].

LUMINESCENCE OF LANTHANIDE COMPLEXES

The ligand is the one that enchances the lanthanide luminescence through a complex mechanism in three steps. It begins with the absorbance of the excitation light by the ligand, continues with the transfer of the absorbed energy to the lanthanide ion and finally the ion emits light[23].

One of the factors that influence the luminescent spectral features is the state in which they are carried out. Two extremes were identified, the gas and the liquid state and the intermediate the solid state. The differences are marked by the energy transfers, the energy of the emission bands, the presence of the crystal field and the bandwidth [23,24]. A series of lanthanide complexes (Ln = La to Lu) with 2,2′-bipyridyl-6,6′-dicarboxamide ligands was

reported with photophysical properties in the solid state at 77 and 300 K. Eu and Tb presented an intense red and green luminescence[25].

The long-lived (milliseconds timescale) excited states of the lanthanide ions provide the Ln^{III} complexes intense luminescence, making possible applications ranging from biomedical to sensing areas and optical imaging [8,9,23].

In order to use lanthanide chelates in bioanalytical application a chemical labelling step is required because they can't be genetically encoded[26,27]. Lanthanide complexes, polyamino-carboxylates or macrocyclic complexes, are attached to a specific antibody and luminescence from the emitting ion is detected after the biochemical reaction is completed, either in a two-step procedure or with a one-step. Studies on immunohistochemical detection of human kallikrein 2 and a prostate specific antigen used Eu^{3+} and Tb^{3+} chelate-labeled antibodies[28].

Another trending study presents luminescent nanoparticles and lanthanides have the advantage of a minimal concentration quenching[29]. The incorporation of lanthanides intonanoparticles increase the specificity and binding capacity. Upconversion luminescence detection in nucleic microarrays was reported with specifically designed upconverting phosphors of composition Y_2O_2S: (Yb,Er).

Another two lanthanides doped nanostructures with Lu_2O_3 and $KLu(WO_4)_2$ were synthesized and were reported for high chemical stability. The compounds offer favourable incorporation of Ln^{III} ions and high absorption and emission cross section.

It was reported that depending on the chemical environment of the ion, the shape of the spectra may differ substantially. The presence of contaminant functional groups OH^- and CO_3^{2-}, absorbed on the surface of nanostructures modifies the luminescence dynamics of Ln^{III} ions [12].

In order to enhance the MRI contrast agent and luminescence properties a series of nucled acid delivery polymers wich contain certain oligoethylene amines were protonated at physiological ph gadolinium and terbium [30].

Another two efficient ligands, analogues of the dipicolinate (H_2dpa) ligand were synthesized for being an attractive alternative. The tridentate pyridine- tetrazolate ligands were used for lanthanide coordination and presented emission in both visible and the near-IR with unusually high luminescene [31].

New research referring as Lanthanide upconversion nanophosphors (UCNPs) show unique upconversion luminescence are used in a significant number of potential bio-applications. Their biosafety is important and has attracted significant attention. The association between the chemical and physical properties of UCNPs and their bio-distribution, excretion, and toxic effects has recently been presented in a review [32].

LANTHANIDES SIMILARITY TO CALCIUM

Lanthanides properties are most pertinent to their biochemical interactions, and special attention is given to their similarities to Ca^{II}, as this form the basis for many of the biochemical studies which employ lanthanides. The strategy of substituting Ca^{II} by Ln^{III} ions in biological systems has been proved valuable because of the irony whereby Ca^{II}, biologically one of the most important metal ions, is chemically one of the least informative.

Lanthanides ions (especially La^{III} and Gd^{III}) have a significant and unique effect in physiological process. This was observed in human and animal cell and plants. The similarity between the lanthanides and calcium is observed in terms of ionic radii, the coordination preference for higher coordination numbers, binding behaviour and underlines their use as probes in biological reactions. A review[33] presents data on the effects of lanthanides on membrane ions transport, the function of receptors and microsome electron transport chains, especially of the cytochrome P450, which is an oxidant in these systems.

The biological chemistry of lanthanides also includes a new metal-based drug, lanthanum carbonate, which was approved as a phosphatebinder for the treatment of hyperphosphatemia[34]. Considering that La^{III} and Ca^{II} possess analogous ionic radii (La^{III} 0.86–1.22 Å *vs.* Ca^{II} 1.1.4 Å), donor atom preferences (O>N>S) and coordination numbers (CN = 6–9) the lanthanides can imitate calcium. This similarity allows La^{III} metal ions to exchange with Ca^{II} ions in bone when the bone remodeling cycle is altered so that the proliferation of osteoblasts (cells that regenerate bone) is stimulated and the

differentiation of osteoclasts (cells that break down bone) is impeded [35].

BIOLOGICAL EVALUATION OF LANTHANIDES ACTIONS

The lanthanides can be mediators in a wide range of degenerative disease based on their antioxidant properties and their role as ROS (reactive oxygen species) scavenger. Various Ln complexes show potential photocytotoxicity in cancer cells. Ln complexes show photo-induced DNA cleavage activity and photocytotoxicity for their applications in PDT[36].

They are potentially hazardous to human health and there is a need to clarify the effects of these elements on tissues. The effect of hydrophobicity and charge on the cell viability and cell association of lanthanide metal complexes was studied on terbium luminescent probes feature a macrocyclic polyaminocarboxylate ligand (DOTA) in which the hydrophobicity of the antenna and that of the carboxyamide pendant arms are independently varied. It was confirmed that the most lipophilic macrocyclic polyaminocarboxyalamide complexes exhibit low cellular association[37].

Another recent study presents three novel La^{III} complexes which have been synthesized using a Schiff base ligand (bis(N-salicylidene)-3-oxapentane-1,5-diamine H_2L) and then characterized. The ligand and its Ln^{III} complexes bind to DNA in a groove binding mode and the Ln^{III} complexes have the preferable ability to scavenge hydroxyl radical and superoxide radical. Their antioxidant activity was demonstrated in vitro[38].

The lanthanide chelate application as contrast agents is used in clinical investigation of cerebrospinal diseases and in the general function evaluation of the central nervous system. Chelated lanthanide complexes shift reagent aided ^{23}Na NMR spectroscopic analysis is used in cellular, tissue and whole organ systems [39].

The synthesis and physical properties of new lanthanide complexes with the anionic form of the bioactive ligand 5-methyl-1,2,4-triazolo[1,5-a]pyrimidin-7(4H)-one (HmtpO), named $[Ln(mtpO)_3(H_2O)_6]\cdot 9H_2O$ (Ln^{III} =La, Nd, Eu, Gd, Tb, Dy, Er) was reported (Caballero & al., 2014). The high activity on the *in vitro* antiproliferative activity against parasite (*Leishmania spp*. and *Trypanosoma cruzi*) and their low cytotoxicity against host cell lines show a great potential for this type of compounds to become a new generation of highly effective and non-toxic antiparasitic agents to fight some diseases.

TOXICOLOGICAL ASPECTS

The progress made in the sphere of lanthanides biological application initiated their toxicology evaluation.

Due to their low aqueous solubility, the lanthanides have a low availability in the biosphere and are not known to naturally form part of any biological molecules. Compared to other chemical elements, non-radioactive lanthanides are classified as having low toxicity. They may present an accumulation risk which may affect their metabolic processes. Lanthanides can affect numerous enzymes activity. In neurons, Ln ions regulate the transport and release of synaptic transmitters and block some membranes receptors[33].

Cancer treatment can include photosensitizer drugs and light, through photodynamic therapy (PDT), where the cytotoxicity and the photoactivated DNA cleavage activity can be observed. Non-macrocyclic lanthanide complexes are lately presenting photocytotoxicity in cancer cells, and also photochemotherapeutic applications are being taken into consideration for future researches.

Early toxicology studies on rats showed that lanthanides chlorides (cerium, europium, ytterbium) tend to accumulate mainly in the liver, bones and spleen. In the liver they will interact with proteins, affect enzymes activity and physiological function leading to morphological changes[40].

In rat organs, cerium and praseodymium have shown hepatotoxic effects such as jaundice, steatosis and increased aminotransferases. The toxic effects of gadolinium include mineral deposits in capillary, liver and spleen necrosis, gastric mucosa demineralization and thrombocytopenia. Cerium is responsible for magnesium deficit, which may be a cause of cardiac fibrosis that could lead to cardiomyopathy. Gadolinium chloride form, $GdCl_3$, is a selective inhibitor of phagocytosis in liver macrophages and at the same time contributes to the selective elimination of these cells, because it blocks the channels, competing with calcium

membrane. This competition is explained by the fact that the radii of the crystal gadolinium is similar to that of calcium. Other lanthanides have a protective liver effect. However, the toxic effect of the lanthanides may be a combination of hepatotoxic action of the active metabolite generated by the microsomal metabolism and the effects of lanthanum ions, which is, the selective blocking of the cells by the calcium channels. A study of the thyroid cells has determined that the lanthanide ions are calcium antagonists[33,41,42].

Long term exposure to lanthanides could cause pneumoconiosis in human and inhalational or intratracheal exposure in animals had been proven to cause acute pneumonitis with neutrophil infiltration in the lung[43]. Many toxicology studies are still conducted and their main purpose is to establish the mechanisms mediating the effects of lanthanides on cellular functioning.

CONCLUSIONS

Lanthanide complexes researches are steadily growing underlined by their unique set of properties such as optical, luminescence, fluorescence and magnetic.

This recommends them for modern technology and biomedical applications thus the scientific community explore their behaviour at academic and practical levels. Recent pharmaceutical progress recognizes their therapeutic utility and success in medicinal applications. The aim of this review is to contribute to the enhancement of novelty research and to the development of new Ln complexes especially with biological applications.

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