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Recent development in lanthanide coordination compounds for biomedical imaging applications

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In dedication to Prof. Thomas C. W. Mak's achievements in structural inorganic chemistry and coordination chemistry, as well as his longevity in chemical researches.

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ABSTRACT

In this mini-review, we present some recent development of lanthanide complexes in biomedical imaging, in particular MRI, optical imaging and multi-modal imaging probes. Through a few examples, we shall look at the fascination and the drive of researchers worldwide to thrive for further discoveries using lanthanide coordination compounds.

1. Introduction

Biomedical imaging encompasses a wide range of techniques and processes, creating images of the human body for clinical purposes and the study of medical sciences. Some of the best known techniques are magnetic resonance imaging (MRI), optical imaging, nuclear medicine, ultrasonography, and tomography. Of course, these techniques often requires the use of contrast or imaging agents, and the unique properties of lanthanides and their coordination complexes make them prime candidates as such agents. It is a well-known fact that the 4f orbitals is lower in energy compared to the 6s, 5s, and 5p orbitals, and as such the 4f electrons are well-shielded by electrons in those orbitals and rarely participate in bonding or reactions. The resulting electronic configurations of lanthanide cations (generically [Xe] $4f^n$, $n = 0$–14) are often the main reason for their suitability to perform as a contrast or imaging agent, and can translate to a large number of well defined electronic states where transition can occur upon excitation and relaxation [1]. In their own ways, the special electronic configurations and the related energy levels contribute to the applications of lanthanide complexes in MRI and optical imaging.

1.1. Magnetic resonance imaging

On average, water makes up 57% of the total body weight [2]. When the body is subjected to a static magnetic field inside a scanner, the protons in the body water would align with the direction of the applied field. A radio frequency pulse is then applied to the aligned protons to change their magnetisation alignment briefly (resonates), returning to the original alignment when this electromagnetic field is switched off (relax), creating a changing magnetic flux that in turn yields a changing voltage in the receiver coils to give the signal. This forms the basis of MRI, and is one of the most important *in vivo* imaging techniques to date. MRI contrast agents can drastically alter the water protons' relaxation time, in turn enhancing visibility during MRI [3]. Currently, gadolinium-based contrast agents are the most commonly used in medical diagnosis today, with ten different complexes approved by either the European Medicine Agent (EMA) or the U.S. Food and Drug Administration (FDA). For example, *Magnevist* and *Dotarem* are among the most popular. Gd(III) is an excellent ion for contrast agents because of its seven unpaired electrons (electronic configuration: [Xe] $4f^7$), making it highly paramagnetic. This in turn produces the coupling of a large magnetic moment with long electron spin relaxation time [4]. As a positive contrast agent, Gd-based complexes can shorten the longitudinal relaxation time (T_1), brightening areas where the agents are taken up. More recently, europium(II)- [5] and

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dysprosium(III)-based [6] complexes have also been investigated as potential contrast agents for MRI.

1.2. Optical imaging

Optical imaging, particularly bioluminescence imaging, plays an important role in the understanding of the structural and functional properties of living systems in biology and medicine. Most basically, optical imaging involves the staining of the area or cells of interest with a staining or imaging agent, whereby it would emit ultraviolet (UV), visible, or near infrared (NIR) radiation upon excitation at a suitable wavelength. The emission would then be observed through various methods. Although there are other staining agents like organic luminophores and semiconductor quantum dots, their inherent flaws meant they are not heavily applied in medicine [7]. Due to their unique luminescence properties, including long wavelength emissions, sharp line-like bands and relatively long excited state lifetimes, lanthanides become an important choice as an imaging agent in optical imaging [8]. The physical interpretations of these properties are well documented, but generally they hinge on the 4f electrons in lanthanides. The energy levels of the 4f orbitals are influenced by several interactions depending on whether the lanthanide ion concerned is a free ion or coordinating. These include Coulombic interactions (electron–electron repulsion), spin–orbit coupling, and crystal field splitting. As one can see from Fig. 1, the energy difference between levels varies greatly. This inevitably leads to a large number of possible electronic transitions, for example, $^5D_0 \rightarrow {}^7F_4$ or $^5D_3 \rightarrow {}^7F_1$, which all leads to different emissions. Although not all such transitions are luminescent, there are plenty for chemists to play with.

Another thing worthy of note is that since f–f transition is partially forbidden, the lifetimes of the excited states tend to be long, as much as six times as long as organic luminophores in fact [9]. This of course means an extended luminescence lifetime, and an extended period for effective observations. When coupled with a suitable chelates and/or an activator/receptor, lanthanide coordination compounds can be tuned to the needs of an individual.

1.3. Bio-compatibility

Even though the topic of bio-compatibility has been covered in many textbooks or reviews alike, it will be briefly discussed here due to its importance when designing a potential imaging agent. As with any other types of medicine that is potentially administered into a live body, there are certain criteria that the lanthanide complex must adhere to other than having the suitable physical chemical properties: (1) being water soluble; (2) kinetic inertness and thermodynamic stability at biological environments; (3) low cytotoxicity, lanthanide ions themselves are toxic to human body; (4) specific targeting, while not interfering with any biochemical processes; (5) can be excreted within a number of hours after administration. Arguably, bio-compatibility poses the biggest challenge in the design of imaging agents today.

1.4. Basic design of contrast/imaging agent

One common feature found in lanthanide MRI contrast agents and optical imaging agents is the use of a chelating ligand, which is used to enhance the chemical stability of the lanthanide complexes, and in turn prevent the release of the metal ion when applied. Considering that lanthanide ions are hard Lewis acids, ligands containing hard atoms (N or O, etc.) are favoured. For example, cyclen (1,4,7,10-tetraazacyclododecane) and its derivatives are often the ligand of choice for this propose. In terms of complexes built for MRI, the chelating ligand is regularly octa- or hepta-coordinated. This leaves space in the inner coordination sphere for water molecule(s) to be directly attached to the lanthanide centre, whereby rapid exchange of water molecule(s) between the complex and the surrounding environment can occur – a process that affects the relaxation time of all solvent protons. Conventionally, this exchange is vital as MRI images are directly related to the relaxation times of such protons, and the exchange rate need to be rapid as relaxivity is inversely proportion to the mean residence time of water molecule in the first coordination sphere (τ_M) [10]. Ligand can also be used to influence the tumbling rate of the molecular species, and the related rotation correlation time (τ_R). Similar to τ_M, relaxivity is inversely proportional to τ_R. As such,

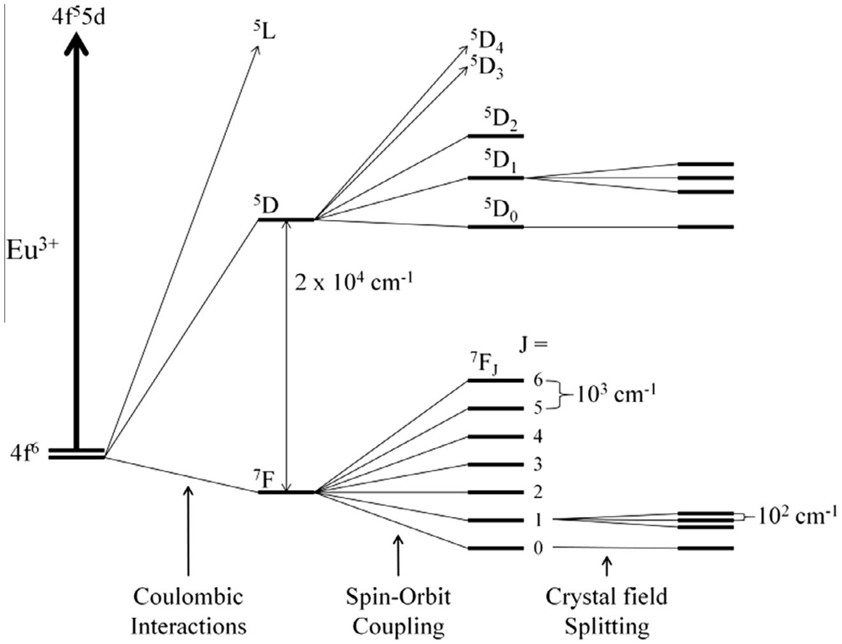

Fig. 1. A simple energy level diagram of an Eu^{3+} ion.