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Permalink

<https://escholarship.org/uc/item/5vg5q337>

Journal

Inorganic Chemistry, 53(4)

ISSN

0020-1669

Authors

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Publication Date

2014-02-17

DOI

10.1021/ic500099n

Peer reviewed

Preface for the Forum on Imaging and Sensing: Probing and Utilizing the Elements of Life for Studying and Improving Health and Society

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The periodic table represents the heart of Inorganic Chemistry and a roadmap for the contributions of our discipline to health and society. Indeed, all living organisms require a diverse array of metals and other elements of life to thrive in their given environments, and misregulation of these same elements can contribute to aging, disease, and pollution of our surroundings. At the same time, the intrinsic and unique properties of elements across the periodic table can be elucidated and harnessed to create new ways to help understand and treat aging, disease, and environmental damage. Nowhere is this nexus of inorganic chemistry and biology better illustrated than in the field of molecular imaging, which broadly probes and utilizes the elements of life for the betterment of health and society. Coordination chemists, materials and solid-state chemists, and bioinorganic chemists alike work together to play important roles in shaping this emerging, multidisciplinary area of science, joined by the unique ability of inorganic chemists to create new molecules and materials that fully utilize all areas of the periodic table.

This Forum features a collection of articles that survey recent research advances in Inorganic Chemistry approaches to molecular imaging and sensing. As shown by these contributions, chemists are developing new tools that either exploit the fundamental properties of elements across the periodic table in monitoring healthy or disease states or target metal-based signaling and stress pathways to study the basic biology of inorganic species. The sheer diversity of elements and their biomedical and environmental applications offers a rich field that remains insufficiently explored.

The first contribution of this volume is in the rapidly growing area of metal sensing, where inorganic chemists are making notable contributions in the detection of endogenous and exogenous metal-ion pools in biological and environmental settings.^{1–3} Such chemical tools are essential to gaining a greater understanding of how natural metal stores and their mismanagement contribute to health, disease, and the environment and have far-reaching implications in basic research and translational diagnostic applications. The Forum Article by Cho, Kim, and co-workers describes the development of two-photon fluorescent probes for monitoring metals in live tissues.⁴ The use of coordination chemistry principles for selective metal-ion recognition, combined with fluorophores that possess high two-photon absorption cross sections, allows for new reagents that are capable of being used in thin, optically transparent sections as well as thicker specimens such as tissue and whole organisms.

In addition to molecular strategies for biological metal detection, the unique properties of transition-metal coordina-

tion compounds themselves can be exploited for molecular imaging applications. Nam, You, and Cho present an inorganic strategy for phosphorescence sensing of biological metal ions by exploiting the photophysical properties of cyclometalated iridium complexes.⁵ Such systems avoid autofluorescence and scattered light via time-gated imaging and are more photostable than many conventional organic fluorophores. In another application of transition-metal chemistry for molecular imaging, Hamachi and co-workers describe recent progress in coordination-chemistry-based protein-labeling methods and their use in fluorescence imaging and functional analysis of cellular proteins.⁶ Indeed, such bioorthogonal chemistry has largely been the purview of organic reactions,⁷ but the diversity of elements and reactions that inorganic chemistry brings offers an underdeveloped area of research at the chemistry/biology interface. The fact that simple polycarboxylate and poly-imidazole cassettes can be utilized for the site-specific incorporation of metal-based fluorescent tags in complex cellular settings presages the generality and versatility of this approach.

Several of the articles in this series describe the use in biological assays of the unique long fluorescence lifetimes of several of the lanthanides. These lifetimes, of course, are a consequence of the highly forbidden electronic transitions for metal ions such as Tb³⁺ and Eu³⁺. Thus, the issue is how one can effectively use antenna ligands to excite the complexed lanthanide and preserve its long fluorescence lifetime.⁸ While lanthanide complexes, in general, will usually be less bright than organic fluorophores, the long lifetime means that time resolution can substantially enhance the signal-to-noise ratio of the corresponding signal and hence give rise to a large increase in the sensitivity of the measurement and hence potentially enable bioassays. The article by Hildebrandt and co-workers⁹ begins with a nice review of the history of what is now called Förster resonance energy transfer and its application and subsequent use. Most of these applications are in areas of biochemistry, molecular biology, and some pure chemistry uses in which intermolecular interactions as a function of the distance are crucial issues. The article focuses on fluorescence resonance energy transfer (FRET), with the donors being luminescent lanthanide labels and the acceptors being semiconductor quantum dots. The combination of long-lived luminescence donors (with fixed and very sharp emission

Special Issue: Imaging and Sensing

Received: January 15, 2014

Published: February 7, 2014

lines) with quantum dot acceptors (with broad and tunable absorbances) gives a large variability of the emitted wavelength for the FRET pair. It also creates an extraordinarily large distance for the FRET pair coupling of up to 20 nm. Hildebrandt and co-workers summarize the large number of current commercial applications of this kind of technology and describe innovative approaches to potential new applications. While the long-term stability of quantum dot bioconjugates has remained a problem for commercial quantum-dot-based assay kits, the work has demonstrated new applications for cellular imaging using this technology.

The use of lanthanide-based imaging agents in live cells is the topic of the paper by Miller and co-workers.¹⁰ They have used cell-penetrating peptides conjugated to a terbium donor to enable cellular uptake of the terbium fluorescence source. In one case, the terbium complex is linked to trimethoprim, a target for half of the protein pair to be imaged. The other half is the FK506 binding protein, which is itself conjugated to green fluorescent protein. The result is that, for a pair of proteins whose interaction is the subject of interest, the fluorescent source is on one protein and the FRET acceptor is on the second. Miller and co-workers have shown that they can achieve high signal-to-noise data using time gating with this combination. The importance of understanding protein–protein interactions in live cells and the ability to monitor these processes adds substantial significance to this capability. The commercial applications of luminescent lanthanide complexes in FRET assays are the topic of the paper by Mathis and co-workers.¹¹ Gérard Mathis has been a pioneer in the introduction of lanthanide complexes for sensing biological applications, and for many years, CisBio, the company with which he and his co-workers are associated, has developed high-throughput screening assays for large pharmaceutical companies. The Forum Article presents a history of the development of CisBio's technology and a synopsis of the latest technology being developed. Prominent new targets are G-protein coupled receptors, also called seven transmembrane receptors. These are involved with a signaling cascade within cells. The group has developed functional assays to monitor these signaling cascades, based on a monoclonal antibody labeled with fluorescent donor and which recognizes a FRET pair molecule that incorporates a red-emissive acceptor dye. The combination of what is called the SNAP technology¹² with the lanthanide fluorescent agents has developed a new line of assay technology that CisBio calls Tag-lite. This also provides new capabilities in monitoring protein–protein interactions.

A general feature of most of the metal-based assays described in this collection is that they incorporate bifunctional chelating agents. This means that, while the molecule can strongly bind a metal ion, it has a remaining linking arm that can be conjugated to a targeting molecule such as an antibody. The article by Gunnlaugsson, Comby, and co-workers¹³ describes lanthanide-functionalized luminescence probes as well as lanthanide-functionalized nanoparticles for luminescence imaging and magnetic resonance imaging (MRI), respectively. They describe the functionalization of gold nanoparticles with molecules that can complex gadolinium and hence act as MRI enhancement agents. Such hybrid compounds increase the rotational correlation time as well as potentially confer other desirable properties on the functionalized nanoparticle. The chelators are derivatives of diethylenetriaminepentaacetic acid (DTPA) or 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) with a linker arm designed to attach to a gold

surface. Derivatives of DOTA and DTPA have been the standard MRI enhancement agents in the clinic for the last nearly 30 years and are in very wide use. However, their application is limited by the sensitivity, which, in turn, is in large part limited by the fast tumbling time of the small molecules. Combining the MRI and luminescent components of this research, Gunnlaugsson, Comby, and co-workers are examining the development of bimodal imaging agents, utilizing both these signaling techniques, which differ so greatly in their intrinsic sensitivity and potential applications.

The paper by Lewis and co-workers¹⁴ describes the application of radioactive metal ions for potential biomedical imaging. While this is a field with a history of several decades, positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are in wide use in the clinic and so this continues to provide an incentive for the development of new technologies. Because PET imaging is largely dominated by the use of ¹⁸F, the group first asked the following important question: “Why use a metallic radioisotope?” The answer they provided, which is an answer that applies to all of the papers in this collection in one way or another, is that the use of metals, as radioisotopes, provides flexibility, modularity, and other useful properties. In particular, using metal radioisotopes means that bifunctional chelates that are selective or strongly bind the particular radioisotope can enable the target to be identified when conjugated to a targeting agent such as an antibody. This opens tremendously the range of potentially useful radioisotopes and enables increased lifetime or easier forms of production of the radioisotope. One of the highlighted reagents is a copper-based complex that has already had a significant impact in cancer PET imaging. This paper concludes with an extremely valuable look ahead that provides both the scientific and societal requirements for full utilization of both diagnostic and therapeutic radioisotopes.

In addition to molecular coordination chemistry, materials and nanoscience also have an important role to play in the advancement of molecular imaging technologies. Nocera and co-workers document the use of inorganic quantum dots as chemosensing scaffolds that exploit the general “3Rs”: recognition, relay, and report scheme.^{15,16} By combining the high optical brightness and photostability of nanocrystal emitters with analyte-responsive dyes, these laboratories have devised a series of noninvasive chemosensors for biological applications. In particular, these quantum dot–dye conjugates have shown utility in characterizing tumor microenvironments by measuring the chemical properties of acidity, hypoxia, and glucose levels. Another versatile family of molecular materials for molecular imaging applications are metal–organic frameworks (MOFs), which are a class of hybrid materials self-assembled from organic bridging ligands and metal ion/cluster connecting points.^{17–20} Because of the modularity of building blocks, such reticular chemistry offers an infinite array of new materials for a variety of applications, including molecular imaging. Lin and co-workers discuss the development of MOFs as chemical sensors and imaging contrast agents.²¹ They first describe how size and shape control can be tailored in such porous pockets and issues that need to be addressed to make practical reagents. The second part of their Forum Article focuses on the design and applications of nanoscale MOFs (NMOFs) as imaging contrast agents, exploiting their high cargo loading, size and shape tunability, and intrinsic biodegradability. Specific examples of NMOFs for MRI, X-ray

computed tomography, and optical imaging are used to highlight the utility of NMOFs in these endeavors.

Biomolecule systems offer additional platforms for molecular imaging with intrinsic compatibility with living systems. In the context of metal detection, protein-based reporters have been the classic motif for cellular and animal imaging, particularly for calcium and zinc.^{22,23} In their timely Forum Article, Lu and Xiang describe DNA-based systems as alternative metal detection scaffolds.²⁴ Through both rational design and combinatorial selection, a number of metal-ion-dependent DNazymes as well as metal-ion-binding DNA structures with high specificity have been developed. The generality of this approach is illustrated by the wide range of fluorescent, colorimetric, electrochemical, and Raman-based detection schemes. Moreover, the translation of such sensors into “dipstick tests”, portable fluorimeters, computer-readable disks, and widely available glucose meters has led to the translation of such DNA-based reagents into point-of-care diagnostics and online environmental monitors.

To close, we hope that these Forum Articles will introduce readers to how inorganic chemists can contribute to the burgeoning opportunities in molecular imaging, where they can study the fundamental roles of metals and other elements in biology as well as exploit the intrinsic properties of elements in the periodic table to develop new reagents for research and diagnostics. With more chemical and physical tools applied to molecular imaging, Inorganic Chemistry is poised to push the frontiers of this emerging and exciting field. We thank all of the authors for their valuable time and insight into their respective areas of expertise.

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Notes

The authors declare the following competing financial interest(s): K.N.R. has a financial interest in Lumiphore Inc., whose reagent use is described in some of the articles.

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