Inorganic Chemistry

Forum Article

pubs.acs.org/IC

Preface for the Forum on Metals in Medicine and Health: New Opportunities and Approaches to Improving Health

Debbie C. Crans*,† and Thomas J. Meade*,‡

†Department of Chemistry and Cell and Molecular Biology Program, Colorado State University, Fort Collins, Colorado 80523, United States

‡Department of Chemistry, Molecular Biosciences, Neurobiology, Biomedical Engineering and Radiology, Northwestern University, Evanston, Illinois 60208-3113, United States

Inorganic Chemistry, a discipline that embraces the entire periodic table, has an important role in human health that is sometimes neglected. Surprisingly, potential drugs that are classified as "inorganic" are not readily translated to the clinic despite the fact that one inorganic drug, cisplatin and its derivatives, are among the most effective anticancer agents known.[1,2] In a time of increasing development of drug resisitance, the metal-based drugs offer an alternative, as described in detail in this *Inorganic Chemistry* Forum.

Recent work has led to a deeper understanding of the structures and mechanisms of metalloproteins and other biologically active metal complexes.[3,4] As a result, the time is fast approaching when new generations of inorganic complexes will profoundly impact human health. The reluctance to develop and employ metal-based drugs can be overcome by both industry and academia so that potential opportunities are not overlooked. The resistance to using other metal-based drugs for a range of diseases[5,6] may limit potential options and underlies the fact that the carboplatin remains one of the few metal-based drugs in clinical use.[1,2]

Metals play an important role in a number of diagnostic techniques. Molecular imaging frequently employs metal-based agents as probes to enhance contrast at the subcellular and whole animal level.[7,8] Recent advances in this area have led to the development of theranostics, which can function for both diagnosis and therapy.[9,10] The mechanisms of metal-based drugs are quite different from those employed by traditional organic-based drugs. Commonly, the metabolism of organic drugs involves the generation of CO_2 and/or predictable carbon-based decomposition products.[11] In contrast, the metabolism of metal-based therapeutics generates multiple and variable metal compounds resulting from hydrolysis and redox reactions of the original metal complex.[11,12] This is profoundly important because the metabolism of the original metal complex may result in other active metal-containing materials that, in turn, may demonstrate high persistence and differences in cellular and organ localization as well as the potential to impact other off-target pathways.[11]

This *Inorganic Chemistry* Forum features contributions in several important areas of metals in medicine with the goal of highlighting the scope and providing specific examples that have been realized in this field. This issue describes historic topics in the field and includes contributions in nontraditional areas employing inorganic drugs.

The first contribution of the volume is from the Lippard group focusing on platinum complexes.[13] Cisplatin was the first platinum derivative found to have anticancer activity, and its success initiated the development of entirely new classes of these compounds.[1,13,14] The search for an even more effective complex continues using traditional structure−activity relationships as well as other nontraditional methods particularly with regard to delivery systems. These studies are put in the context of contributions by the Lippard group for the past decades, characterizing the mode of action of several both platinum(II) and platinum(IV) compounds. In addition, recent studies from the Lippard laboratory on monofunctional platinum(II) and platinum(IV) complexes are highlighted in this contribution.[13]

The second contribution by Sessler and co-workers describes the pentaaza expanded porphyrins, coined Texaphyrins, developed for combined chemotherapy and radiation therapy.[15] Such complexes have led to clinical breakthroughs in the controlled treatment and cure of patients having several cancers. This manuscript describes studies exploring stable texaphyrin complexes with a variety of metal cations, including gadolinium and other lanthanides, bismuth, and lead developed for different applications in anticancer therapy.[15] Gadolinium texaphyrin functionalized magnetic nanoparticles are investigated as multimodal magnetic resonance imaging contrast agents and as constructs with reactive oxygen species (ROS)-induced sensitization and concurrent hyperthermia.

Studies carried out by Cohen and co-workers describe zinc(II)-dependent inhibitors of metalloproteins in clinical use.[16] Metalloproteins constitute a large fraction of proteins that are a rich source of potential therapeutic targets. Cohen presents studies identifying novel metal binding groups as a strategy for the development of new drugs. Studies using human carbonic anhydrase II are used as a model system to provide a systematic evaluation of how the coordination environment of a catalytic metal ion affects the binding of the inhibitors. The protein environment is found to affect the metal-binding group, causing dramatically enhanced inhibition. These studies provide insight on how metal coordination influences inhibitor binding, and these findings can be used to design new therapeutics which target zinc(II)-dependent metalloproteins.[16]

While the main topic of this issue is metals in medicine and health, other inorganic compounds including metalloids are a rapidly growing class of agents for the treatment of disease. O'Halloran and co-workers address the anticancer activity of

Special Issue: Metals in Medicine and Health

Received: September 16, 2013
Published: November 4, 2013

small-molecule and nanoparticle forms of arsenic.[17] This contribution reviews the use of arsenic compounds for the treatment of disease over a period of 3000 years. The recent interest in this class of agents has been fueled by the discovery that dilute aqueous solutions of arsenic trioxide are now part of the frontline treatment of acute promyelocytic leukemia.[18] Over 100 clinical trials involving inorganic arsenic or organoarsenic compounds are currently open, and new generations of both inorganic and organometallic arsenic compounds are under development. This review describes the aqueous and biological chemistry of arsenic(III), nanoparticle formulations, biological mechanisms, and discoveries of new compounds that contain robust arsenic−platinum bonds and that show promising biological response.[17]

Because coordination complexes undergo hydrolysis, redox reactions, ligand coordination, and geometric isomerization reactions and different biological activity is observed with different complexes, biotransformations are important to the action of the metal complexes and must be considered. Speciation, which is the specific form of a metal complex, is therefore critical for understanding bioavailability, transport, activity, and excretion of metal-containing compounds.[19,20] Classical solution chemists define speciation in terms of composition and molecular formula.[20] More broadly, the chemical speciation definition has been extended by the IUPAC commission to include composition, concentration, and oxidation state.[19,20] However, inorganic and coordination chemists generally use an even broader definition of speciation. The manuscript by Crans and co-workers reviews this area and specifically describes vanadium- and iron-based systems where speciation is important.[21] The antidiabetic action of vanadium compounds and their modes of action in biology are described. The changes in coordination chemistry impact their action, uptake, and biodistribution, describing how metal-based drugs are fundamentally different from organic drugs.[11] In the case of the essential metal iron, they describe how speciation dictates the metal's involvement in biological pathways. For example, when not carefully regulated, excess iron can lead to the formation of ROS.[22,23] Specifically, the reaction of iron(2+) with hydrogen peroxide was recently demonstrated to take place only below pH 3, and at neutral pH, an iron(IV) species is produced.[22,23] This contribution highlights the speciation of both iron and vanadium bioinorganic chemistry and their biological action.[21]

It is well-known that metals play a significant role in diagnostics.[9,24−26] A wide range of magnetic resonance imaging agents have been developed for a number of applications in basic science and clinical investigations. The manuscript by Meade and co-workers describes a new class of probes that upon internal rearrangement change from low relaxivity (dark) to high relaxivity (bright) upon complexation with zinc(II).[27] The relaxation properties of these complexes are a consequence of the change in the coordination environment about the gadolinium(III) center that results in a change in the number of water molecules coordinated to the lanthanide. Variable-temperature ^{13}C NMR studies were used to determine how the distance between the gadolinium(III) and the zinc(II)-binding domain affects the coordination environment about the lanthanide. Optimizing the physical properties of the probes suggests that only one acetate group is necessary to effectively restrict water access, achieving a sufficiently low relaxivity state in the absence of zinc(II).[27]

Visualizing DNA in cells and tissues by attaching magnetic nanoparticles or gadolinium ions to DNA binding fluorochromes is described by Josephson and co-workers.[28] By imaging these metals administered in a form that have been developed to target DNA by fluorochromes, one can visualize the DNA that is a mediator of dead cell clearance, a component of coagulation reactions, and an immunogen in the autoimmune disease Lupus. This group has imaged DNA using a DNA binding magnetic nanoparticle by both magnetic resonance and surface fluorescence imaging techniques.[28]

Metal ions have important roles in biology as electrolytes, structural and functional activities in proteins, and other cellular structures.[29−33] Metalloproteins constitute a large fraction of proteins that are potentially viable targets for drug development. Specifically transition-metal ions such as iron and copper are critical to the function of metalloproteins by having key structural and functional roles[29−31] Both iron and copper are reactive metal ions and are carefully regulated to prevent excess metal ions in the cell.

Ferritin is a protein that accumulates and stores iron as caged Fe_2O_3 and represents a target of the future, as described in the contribution by Theil.[34] Ferritins contribute to the normal iron flow by maintaining the iron concentration, sequestering iron from invading pathogens, and preventing oxidative stress functions by converting iron and dioxygen to internal iron minerals.[35] Eukaryotic ferritins provide a strategy for iron chelation because nucleation channels between active sites and the mineral growth cavity affect the biomineral crystallinity of the FeO core. The relatively low mineral order facilitates rapid iron turnover and the physiological role of liver ferritin as a general iron source for other tissues. Concepts for future regulation of ferritin structure/function/genetics include (i) mini-ferritin/Dps protein active sites, (ii) ferritin protein nanocage pores, (iii) a ferritin mRNA noncoding riboregulator, and (iv) ferritin cages as nanovessels to deliver medical or sensor cargo.

The Faller and Hureau team describe aggregation of amyloid-β (Aβ) by self-assembly into oligomers or amyloids as a central event in Alzheimer's disease.[36] Coordination of copper and zinc to Aβ occurs in vivo and modulates the peptide aggregation process. Analysis of the impact of copper(II) and zinc(II) on the aggregation of Aβ reveals some general trends: (i) zinc(II) and copper(II) at high concentrations compared to Aβ have a tendency to promote amorphous aggregation (precipitation); (ii) metal ions affect the kinetics of Aβ nucleation aggregation; (iii) the impact is metal-specific; (iv) copper(II) and zinc(II) affect the concentrations and/or the type of aggregation intermediates formed; (v) the binding of metal ions changes both the structure and the charge of Aβ.[36] The overall charge decrease at physiological pH and increases the overall driving force for aggregation altough they may favor precipitation over fibrillation. In contrast, the induced structural changes seem more relevant for amyloid formation.

Sadler and co-workers provide a contribution in which future challenges in the area of Metals in Medicine are identified.[37] Specifically, they focus on the challenge of combating platinum resistance and treating cancers not previously sensitive to platinum compounds. These compounds deviate from the traditional platinum compounds in that they form different lesions on DNA and, most importantly, they appear to exert their activity through multimodal mechanisms. One approach reviewed is the potential of using redox modulators to increase the potency of the metal complexes. For example, organo-

metallic ruthenium(II), osmium(II) arene, and iridium(III) cyclopentadienyl complexes can achieve nanomolar potency toward cancer cells when administered in combination with the redox modulator L-buthionine sulfoxime.[37] This type of approach is dependent on the biotransformations and articulates the importance of speciation. The authors highlight the need for future global strategies to support research on the design of such new approaches.

As demonstrated in this collection of articles, research in the area of metal-based diagnostics and drugs is undergoing significant growth. This rich area of research naturally reaches across the aisles of many disciplines, and advances in inorganic coordination chemistry are driving this growth. Drug discovery teams in industry and academia are embracing nontraditional approaches regarding this topic, and society is set to exploit the wealth of knowledge about metal coordination chemistry for translation into clinical medicine.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: Debbie.Crans@ColoState.edu.

*E-mail: tmeade@northwestern.edu.

REFERENCES

(1) Jung, Y. W.; Lippard, S. J. *Chem. Rev.* **2007**, *107*, 1387−1407.
(2) Reedijk, J. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 3611−3616.
(3) Berg, J. M.; Shi, Y. G. *Science* **1996**, *271*, 1081−1085.
(4) Nam, W. *Acc. Chem. Res.* **2007**, *40*, 522−531.
(5) Valko, M.; Rhodes, C. J.; Moncol, J.; Izakovic, M.; Mazur, M. *Chem. Biol. Interface* **2006**, *160*, 1−40.
(6) Hosler, J. P.; Ferguson-Miller, S.; Mills, D. A. *Annu. Rev. Biochem.* **2006**, *75*, 165−187.
(7) Ramogida, C. F.; Orvig, C. *Chem. Commun.* **2013**, *49*, 4720−4739.
(8) McNaughton, R. L.; Reddi, A. R.; Clement, M. H. S.; Sharma, A.; Barnese, K.; Rosenfeld, L.; Gralla, E. B.; Valentine, J. V.; Culotta, V. C.; Hoffman, B. M. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 15335−15339.
(9) Major, J. L.; Meade, T. *Acc. Chem. Res.* **2009**, *42*, 893−903.
(10) Ryu, J. H.; Koo, H.; Sun, I.-C.; Yuk, S. H.; Choi, K.; Kim, K.; Kwon, I. C. *Adv. Drug Delivery Rev.* **2012**, *64*, 1447−1458.
(11) Willsky, G. R.; Halvorsen, K.; Godzala, M. E., III; Chi, L.-H.; Most, M.; Kaszynzki, P.; Crans, D. C.; Goldfine, A. B.; Kostyniak, P. J. *Metallomics* **2013**, DOI: 10.1039/C3MT00162H.
(12) Crans, D. C.; Schoeberl, S.; Gaidamauskas, E.; Baruah, B.; Roess, D. A. *J. Biol. Inorg. Chem.* **2011**, *16*, 961−972.
(13) Johnstone, T. C.; Wilson, J. J.; Lippard, S. J. *Inorg. Chem.* **2013**, DOI: 10.1021/ic400538c.
(14) Reedijk, J. *Chem. Rev.* **1999**, *99*, 2499−2510.
(15) Preihs, C.; Arambula, J. F.; Magda, D.; Jeon, H.; Yeo, D.; Cheon, J.; Siddik, Z. H.; Sessler, J. L. *Inorg. Chem.* **2013**, DOI: 10.1021/ic400226g.
(16) Martin, D. P.; Hann, Z. S.; Cohen, S. M. *Inorg. Chem.* **2013**, DOI: 10.1021/ic400295f.
(17) Swindell, E.; Hankins, P.; Chen, H.; Miodragovic, D.; O'Halloran, T. *Inorg. Chem.* **2013**, DOI: 10.1021/ic401211u.
(18) Zhu, J.; Chen, Z.; Lallemand-Breitenbach, V.; de The, H. *Nat. Rev. Cancer* **2002**, *2*, 1−9.
(19) Templeton, D. M.; Ariese, F.; Cornelis, R.; Danielsson, L. G.; Muntau, H.; Van Leeuwen, H. P.; Lobinski, R. *Pure Appl. Chem.* **2000**, *72*, 1453−1470.
(20) Kiss, T.; Odani, A. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1691−1702.
(21) Crans, D. C.; Woll, K. A.; Prusinskas, K.; Johnson, M. D.; Norkus, E. *Inorg. Chem.* **2013**, DOI: 10.1021/ic4007873.
(22) Batainch, J.; Pestovsky, O.; Bakac, A. *Chem. Sci.* **2012**, *3*, 1594−1599.
(23) Pestovsky, O.; Bakac, A. *J. Am. Chem. Soc.* **2004**, *126*, 13757−13764.
(24) Aime, S.; Castelli, D. D.; Crich, S. G.; Gianolio, E.; Terreno, E. *Acc. Chem. Res.* **2009**, *42*, 822−831.
(25) Raymond, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 4050−4050.
(26) Sherry, A. D.; Wu, Y. K. *Curr. Opin. Chem. Biol.* **2013**, *17*, 167−174.
(27) Matosziuk, L. M.; Leibowitz, J. H.; Heffern, M. C.; Macrenaris, K. W.; Ratner, M. A.; Meade, T. J. *Inorg. Chem.* **2013**, DOI: 10.1021/ic400681j.
(28) Cho, H.; Guo, Y.; Sosnovick, D.; Josephson, L. *Inorg. Chem.* **2013**, DOI: 10.1021/ic400404g.
(29) Darensbourg, M. Y.; Lyon, E. J.; Smee, J. J. *Coord. Chem. Rev.* **2000**, *206*, 533−561.
(30) Gray, H. B.; Winkler, J. R. *Annu. Rev. Biochem.* **1996**, *65*, 537−581.
(31) Karlin, K. D. *Science* **1993**, *261*, 701−708.
(32) Supuranm, C. T. *Nat. Rev. Drug Discovery* **2008**, *7*, 168−181.
(33) Szpunar, J. *Analyst* **2005**, *130*, 442−465.
(34) Theil, E. *Inorg. Chem.* **2013**, DOI: 10.1021/ic400484n.
(35) Theil, E.; Behera, R. K.; Tosha, T. *Coord. Chem. Rev.* **2013**, *257*, 579−586.
(36) Faller, P.; Hureau, C.; Berthoumieu, O. *Inorg. Chem.* **2013**, DOI: 10.1021/ic4003059.
(37) Romero-Canelon, I.; Sadler, P. J. *Inorg. Chem.* **2013**, DOI: 10.1021/ic400835n.