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Rhodium at the Chemistry-Biology Interface

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As a rare element with no known natural biological function, rhodium has a limited history in biological chemistry and chemical biology. However, rhodium complexes have unique structure and reactivity attributes, and chemists have increasingly used these attributes to probe and perturb living systems. This brief review focuses on recent advances in the use of rhodium complexes in biological contexts, including medicinal chemistry, protein science, and chemical biology. In particular, we highlight both structure- and reactivity-driven approaches to biological probes, and discuss how coordination environment affects molecular properties in a biological environment.

Introduction

Transition-metal complexes find widespread use at the interface of chemistry and biology.[1] The properties that make transition-metal chemistry so versatile and compelling for chemists also allow novel functions in a biological environment. To name just a few, transition-metal complexes have a variety of coordination numbers, predictable and unique 3D structures, rich and tuneable redox properties, diverse ligand exchange kinetics and thermodynamics, and broad-ranging chemical reactivity.

Rhodium is a non-biological precious metal, and has been relatively little-used in biological or medicinal contexts. However, rhodium complexes have desirable attributes for use in a complex biological milieu: rhodium complexes at all common oxidation states (0, +1, +2, +3,) display low oxophilicity and, consequently, broad functional-group tolerance and aqueous stability.[2–4] This functional-group tolerance is key to the growth of rhodium in catalytic organic synthesis[5] and in emerging fields such as metal-organic frameworks.[6,7] As with most transition metals, the development of rhodium-based methods in biological environments lags behind their use in organic chemistry, but biological applications of rhodium have a surprisingly long history. Interactions of rhodium ions with the protein casein were first reported in 1958,[8] and soon thereafter rhodium(II) complexes were studied as antitumor agents or enzyme inhibitors.[9,10] More recent studies of rhodium in biological contexts have allowed a much clearer understanding of structure and activity. This article highlights key recent developments in rhodium chemistry for biological applications.

It is instructive to divide rhodium complexes for biological applications into two broad categories (1) coordinatively saturated, exchange-inert complexes at the Rh^{III} oxidation state—in which rhodium plays a structural role—and (2) Rh^{II} complexes, which contain open coordination sites or weakly-held ligands—in which ligand exchange chemistry plays a key role in biological function. This distinction has created two quite different approaches to addressing biological problems. Dimetallic Rh^{II} complexes with facile ligand-exchange kinetics provide perhaps the most diverse possibilities for addressing biological problems, since ligand structure allows tuning of ligand-binding energetics. But at the same time, exchange labile complexes create challenges of biological lifetime, off-target effects, and often opaque mechanisms of action. The stability of closed-shell Rh^{III} complexes, on the other hand, minimizes ambiguity about active species and facilitates X-ray analysis of protein–metal assemblies, for example. While stable Rh^{III} complexes do participate in electron-transfer and other outer-shell phenomenon, applications of these complexes have, to date, focussed on simple non-covalent protein binding.

Discussion

Exchange-inert Rh^{III} complexes as scaffolds for protein inhibitors

The most studied and successful use of rhodium complexes for biological applications is likely for medicinal chemistry. Meggers was the first to identify that the octahedral structure of rhodium(III) complexes provides a geometric space largely inaccessible to traditional small molecules (Fig. 1).[11] As part of a broader program developing closed-shell transition-metal-complex protein inhibitors with a variety of metals and ligands,[12] a rhodium complex containing a staurosporine-like phenanthroline-derivative was found to bind and inhibit the protein Src tyrosine kinase. A structure-guided ligand optimization resulted in a 1.8-nM inhibitor that is also significantly more synthetically accessible, due decreasing stereoisomerism resulting from a symmetrical tridentate ligand. The unique octahedral structure with the staurosporine-based ligand fits well with a model of the Src

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binding pocket (Fig. 1b). The robust stability and rigid shape of octahedral staurosporine-like complexes has enabled structural analysis of protein–metal co-crystals for analogous complexes with other metals,[14] although a crystal of a rhodium inhibitor has not yet been reported. Unlike the Rh^{II} complexes discussed below, the staurosporine-like complexes are indefinitely stable in the presence of biologically-relevant thiol concentrations.[11] A similar structural approach has also been successfully applied to the development of rhodium-based inhibitors of NEDD8-activating enzyme (Fig. 1b), which demonstrated in vivo activity in a mouse model of inflammation.[13]

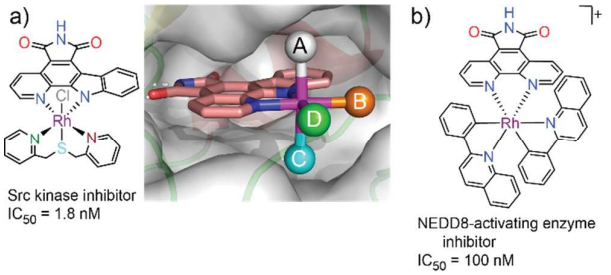

Fig. 1 Rhodium(III)-based protein inhibitors. a) (left) An inhibitor with a pyridocarbazole-based ligand. A schematic image of the complex bound to a protein adapted from a previous report.[11] Copyright 2015 Elsevier. (b) An inhibitor of NEDD8-activating enzyme.

In situ formation of octahedral Rh^{III}-arene complexes

The thermodynamic and kinetic stability of octahedral Rh^{III} complexes is also a useful product structure for building metalated proteins and peptides.

Although attaching metal complexes to proteins and peptides has a long history,[15–17] recent years have seen several important discoveries in the construction of stable Rh^{III} complexes a direct, intimate connection between the metal center and an individual aromatic side chain. Work with rhodium in this arena took a significant step with the observation that a rhodium *tris*-aquo salt, $[Cp^*Rh^{III}(H_2O)_3](OTf)_3$ ($Cp^* = \eta^5\text{-}C_5Me_5$) forms an η^6-arene complex with the phenolic side chain of tyrosine residues (Fig. 2, left).[18] This chemistry was demonstrated with fairly large, complex peptides, and the stability of this organometallic sandwich complex in biological environments is noteworthy. Furthermore, competitive binding experiments of the peptide to a somatostatin receptor in AR42J cells confirmed conservation of the binding capability after the rhodium core attachment (Fig. 2, left).

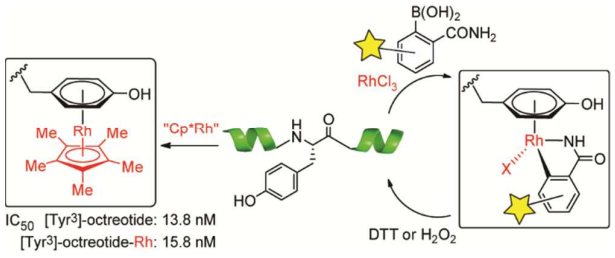

Fig. 2 Direct rhodium(III)-arene complex formation reaction on a tyrosine residue of peptides or proteins. Left: Attachment of Cp*Rh moiety to a tyrosine-containing peptide. Cp*: pentamethylcyclopentadienyl. Right: Three-component arene complex formation of a tyrosine by rhodium (III) chloride and *o*-amido-phenylboronic acid.

Recently, the scope of this chemistry was expanded significantly in a discovery of a one-pot, three-component tyrosine metalation reaction. Treatment of a peptide or protein with $RhCl_3$ and an arylboronic acid leads to unique organometallic rhodium aryl species with a tyrosine η^6-arene ligand (Fig. 2, right).[19] The stability of simple rhodium-arenyl organometallics in aqueous media is striking, and the nature of the three-component-coupling approach with a simple rhodium salt allowed a broad range of functional group handles to be incorporated by this reaction. The tyrosine metalation was used to directly incorporate fluorescent labels or affinity handles onto a polypeptide. It was also demonstrated that large proteins are also amenable to this bioconjugation approach, and that the tyrosine-rhodium linkage is susceptible to cleavage with redox mediators, including dithiothreitol (DTT) and hydrogen peroxide, which offers the potential for spatio-temporal release of an attached functionality.

Jun Ohata received his B.S. and M.S. degrees from Osaka Prefecture University (Japan) studying reactive carbon species (e.g. methylidyne and carbide) on diruthenium complexes under the guidance of Hiroyuki Matsuzaka. He moved to Rice University to study transition-metal-mediated protein modification in Zachary Ball's group and received his Ph.D. degree in 2018. He is currently a JSPS postdoctoral fellow in the Chang group at the University of California–Berkeley.

Rh^{II} complexes that target DNA

Apart from octahedral Rh^{III} complexes, the other major medicinal chemistry effort with rhodium complexes has been targeting DNA with dimetallic Rh^{II} complexes. Containing a classic "paddlewheel" structure (Fig. 3),[20] these complexes typically contain two "axial" sites which bind aquo or other ligands only weakly.[3,21] In contrast to octahedral Rh^{III} complexes, the anti-tumor activity of Rh^{II} is fundamentally

dependent on the availability of axial binding sites and the ligand-exchange processes that axial sites make possible; complexes with blocked axial sites as not efficacious.[22] Studies over many years established that Rh^{II} complexes bind directly to Lewis bases on DNA (Fig. 3)[10,23] via initial axial coordination and eventual displacement of equatorial ligands, such as acetate, to form bridging DNA complexes (Fig. 3a),[24] and ligands with extended π conjugation, such as 1,10-phenanthroline derivaties, exhibit generally enhanced DNA affinity and cell-killing activity (Fig. 3b).[25] The importance of photoirradiation on anti-tumor activity have also been realized in more recent efforts. In some cases, $^1O_2$ (singlet oxygen) production by rhodium is responsible for photoactivated cell killing.[26] However, photoirradiation also facilitates ligand exchange processes that lead to DNA binding.[27,28] An oxopyridine-bridged complex (Fig. 3c) has short (<1 ns) excited-state lifetimes that prevent $^1O_2$ generation, and exhibits oxygen-independent cell killing—presumably via photoinducted ligand exchange—that is important for targeting hypoxic tumors.[29]

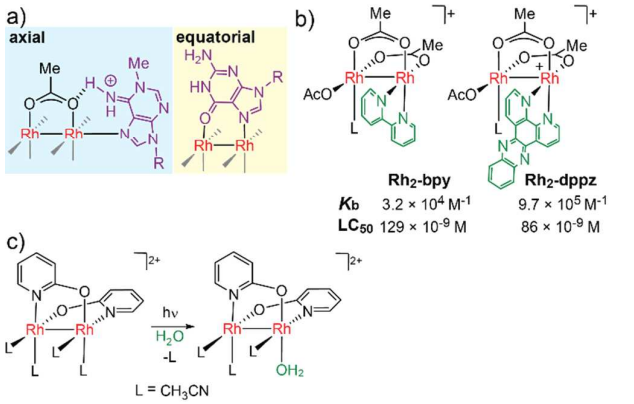

Fig. 3 Exchange-labile rhodium(II) complexes as a DNA binders. a) Depiction of the axial and equatorial DNA-binding modes. b) Structure of the DNA-binding rhodhium(II) complexes (**Rh_2-bpy** and **Rh_2-dppz**). Their binding constant (K_b)/median lethal dose (LC_{50}) are shown on the bottom. (c) Rhodium complexes with efficient photo-induced equatorial ligand exchange.

Exchange-labile Rh^{II} complexes as hybrid organic–inorganic inhibitors

While targeting DNA with Rh^{II} complexes is thought to require access to equatorial coordination, explicit axial-only interactions between Rh^{II} and a specific Lewis-basic side chain form the key to protein inhibitors with improved potency and selectivity (Fig. 4).[30] A concept of hybrid organic-inorganic inhibition was used to build conjugates of known inhibitors with a Rh^{II} complex (Fig. 4a). A structure-guided inhibitor design positions the rhodium core near a Lewis basic amino acid—principally histidine or methionine—flanking the protein-inhibitor interface.[31] Importantly, this approach provides a way to build highly selective protein-binders targeting a specific member of a large, homologous protein family, for which promiscuous binding is common with traditional small-molecule inhibitors. Identifying specific histidine residues unique to a protein of interest led to selective binders for a PDZ domain,[31] or for the SH3 domain of the Lyn tyrosine kinase.[32] In the case of Lyn, two proximal histidine residues, each binding to one of the two Rh atoms, resulted in a remarkably potent SH3-binder (Fig. 4c, 6-nM affinity, >400-fold stronger than the parent peptide inhibitor). Mutagenesis studies established that both histidine residues are necessary for full affinity gains (Fig. 4c). Consistent with the trans effect weakening the binding energy of a second axial ligand,[33,34] the majority of the binding energy gains derive from the first histidine binding.

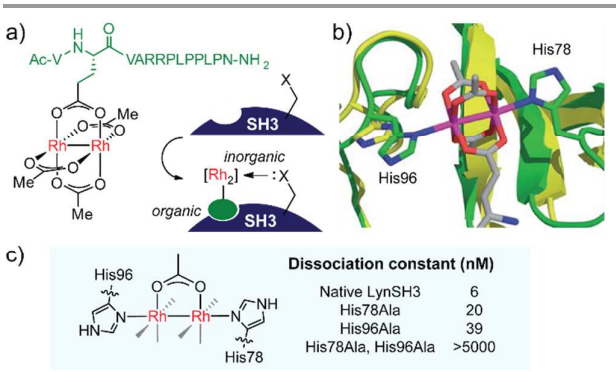

Fig. 4 Exchange-labile rhodium(II) complexes as a protein binder. a) Left: structure of dirhodium(II)–metallopeptide complex targeting SH3 domain of tyrosine kinase. Right: Schematic description of hybrid organic–inorganic interactions upon binding of the metallopeptide. X: Lewis-basic side chain (i.e. imidazole or thioether). b) A computational model metallopeptides–Lyn binding shows specific coordination with two histidine residues. The image is adapted from a previous report.[32] Copyright 2015 Royal Society of Chemistry. c) The binding constant of the depicted metallopeptide to LynSH3 variants.

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Current research interests include transition metal complexes for catalysis and other interesting function in biological environments.

On intracellular stability of exchange-labile Rh^{II} complexes

Despite the utility of the transition-metal complexes in biological contexts, understanding their intracellular fate has long hindered their development as useful tools in chemistry biology and in therapeutic development. The absorption, distribution, metabolism, and excretion (ADME) properties of coordination complexes are essential to understand their activity in cells, but very limited analytical tools exist to answer these important questions.[35] Measurements such as ICP-MS quantitation of total metal ion concentration are often used,

but these methods cannot measure intact metal complexes or address subtle ligand exchange processes that are essential for function.

Rhodium(II) tetracarboxylates strongly quench nearby fluorophores, and this observation allowed direct assessment of the uptake and stability of rhodium coordination complexes in a complicated cellular environment. Rhodium–fluorophore conjugates are initially in a "dark" state, with up to 124-fold weaker fluorescence than free fluorophore (Fig. 5a).[36] Ligand loss or breakdown of the rhodium core structure releases a free, strongly emissive fluorophore. As a result, cell permeability could be assessed, and differences in intracellular stability could be directly measured under various conditions.

The fluorescence quenching properties of Rh^{II} complexes are quite sensitive to structure. By intelligent choice of structure and fluorophore, a bipyridine-linked BODIPY-rhodium(II) scaffold was separately found to have sufficient brightness to allow imaging of subcellular localization of the rhodium complex (Fig. 5b).[37] In this case, the authors were able to develop a rhodium conjugate with only modest (4-fold) quenching of fluorescence quantum yield. As a result, lysosome and mitochondria localization of the rhodium complex could be visualized. Taken together, these studies indicate that judicious choice of structure could permit imaging and analysis of many different aspects of inorganic therapeutics, including cellular uptake, intracellular trafficking, active efflux from cells, and chemical and/or enzymatic degradation.

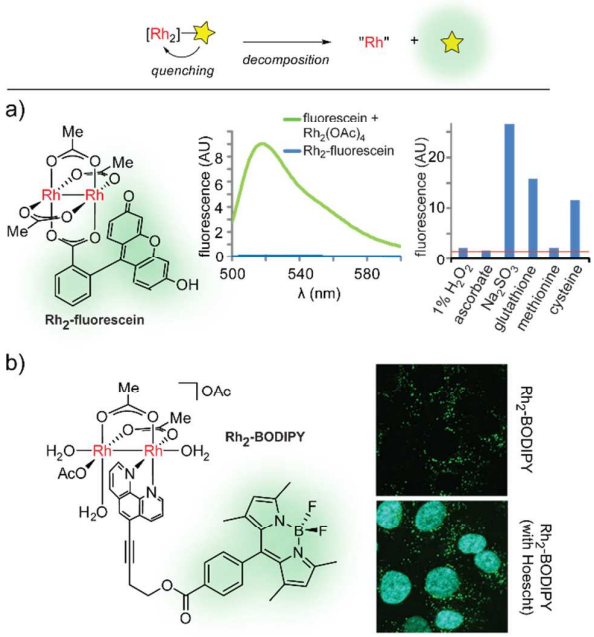

Fig. 5 Fluorescence turn-on by decomposition of fluorophore–dirhodium complex. a) Structure of dirhodium (II)–fluorescein complex. A plot in the middle showing fluorescence curve of complexed and uncomplexed fluorescein. A bar graph on the left showing stability of the complex assessed by the fluorescence turn-on phenomenon. Figures are adapted from the original report.[36] Copyright 2016 Royal Society of Chemistry. b) Structure of cationic dirhodium(II)-BODIPY complex and its lysosome/mitochondria staining image. Cell images are adapted from the original report.[37] Copyright 2014 American Chemical Society.

Catalysis with Rh^{II} complexes: protein affinity labelling

Beyond medicinal chemistry, the catalytic activity of Rh^{II} complexes has elucidated a new binding sites on the surface of the oncoprotein STAT3. Rh^{II} complexes catalyze reactions of diazo compounds in water,[39] via a metallocarbene intermediate.[38] Peptide– or small molecule–rhodium conjugates catalyze modification of specific side chains flanking a protein binding interface. This rhodium catalysis has very wide amino-acid scope; the amino acids successfully modified through a designed proximity-driven approach include Trp, Tyr, Phe, Cys, His, Lys, Asp, Glu, Asn, and Ser.[40] The chemistry succeeded even for a rhodium conjugate catalyst of weakly binding ligands (>10 μM), making it suitable for analysis of initial hit compounds. In order to identify an unknown binding site for a STAT3 inhibitor, Ball and co-workers synthesized inhibitor conjugate C188-9-Rh_2 (Fig. 6a).[41] With the dirhodium–inhibitor conjugate as a catalyst, the proximity-driven modification with an alkyne-diazo reagent (Fig 6b) successfully identified the region around Phe174 as the binding site, overturning previous assumptions of SH2 domain binding (Fig. 6c).

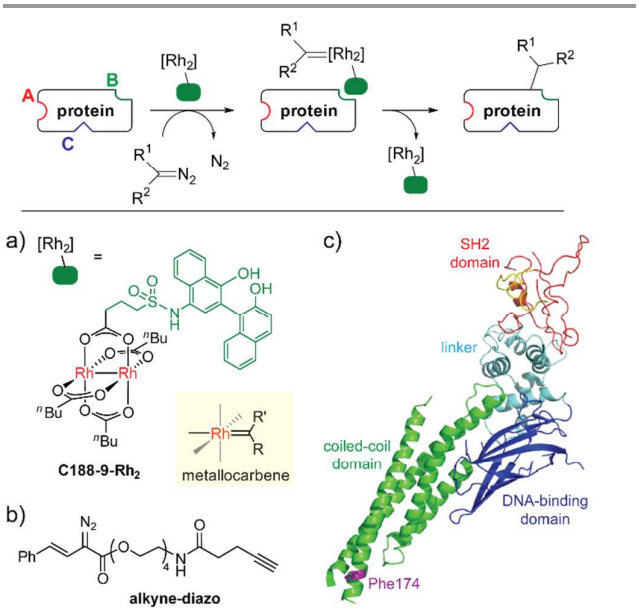

Fig. 6 Identification of binding site of a small–molecule inhibitor by dirhodium (II) complex-mediated diazo decomposition reaction. The inhibitor–rhodium complex (**C188-9-Rh_2**) binds to only the target site (depicted as "B" in green) and labels an amino acid nearby the binding site through proximity-driven reactivity. a) Structure of dirhodium–inhibitor complex (**C188-9-Rh_2**). b) Structure of alkyne-functionalized diazo reagent used for the study. c) Crystal structure of STAT3 (PDB ID: 3CWG). SH2 domain, DNA-binding domain, linker, coiled coil domain, and the modification site (Phe174) are shown in red, blue, cyan, green, and purple, respectively.

Catalysis with Rh^{II} complexes: preparation of protein–drug conjugates

The proximity-driven catalytic modification, outlined above, is also useful for building molecularly-defined antibody-drug conjugates (Fig. 7).[42] Site-specific modification of natural antibodies represents a formidable challenge, given their large size (~150 kDa), multi-chain structure, and complex glycosylation. Unlike alternative approaches that rely on engineered amino acid sequences, rhodium metallopeptides are uniquely able to deliver site-specific modification for a broad range of natural antibodies.

Starting from a known helical peptide with known affinity for the constant region of an antibody,[43] it was discovered that multiple metal centers, acting in concert, deliver superior catalytic reactivity toward site-selective modification of antibodies at asparagine-79 of the Fc fragment. Metallopeptides with a single dirhodium core displayed decreased catalytic efficiency (Fig. 7d). Although the exact roles of the individual metal centers have not been fully elucidated, this result represents a rare example of cooperative, multimetallic catalysis on a biopolymer (Fig. 7a).

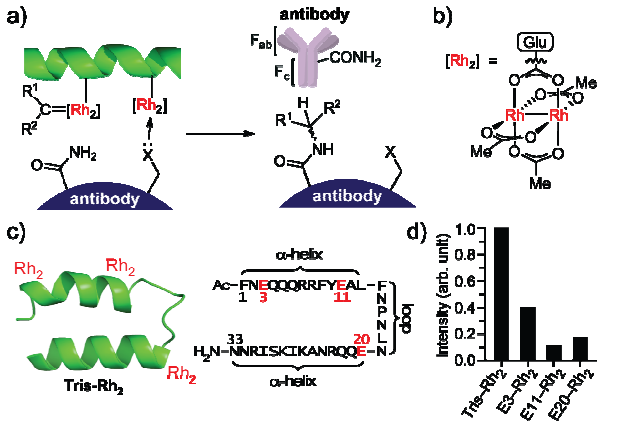

Fig. 7 Site-specific modification of antibodies through cooperative action of dirhodium cores. a) Depiction of site-specific modification of an asparagine residue on an antibody through proximity-driven metallocarbene chemistry enhanced by organic-inorganic interaction. b) Structure of dirhodium complex in the metallopeptide catalyst. c) Structure and amino acid sequence of metallopeptide catalyst (**Tris-Rh$_2$**). d) A bar graph representing the better modification efficiency of the triply-metallated peptide than singly-metalalted peptides, analyzed by detection of alkyne handle on blot membrane.[44] The graph is adapted from the original report.[42] Copyright 2017 American Chemical Society.

Conclusions

Rhodium-based methods for bioconjugation, medicinal chemistry, and bioloigcal probe development all rely on unique chemical properties of rhodium that made these discoveries possible. We see a bright future for rhodium in biological contexts, precisely because rhodium complexes have such unique structural and catalytic properties that are often difficult to replicate in complexes of other metals. At present, the uses of rhodium fall into two main fields. In the first major area, Rh^{III} complexes have robust stability and predictable structure that is important for building predictable and well-behaved therapeutics. But little is known about how reactivity or photochemical processes of these complexes might be harnessed in new ways. In the second major area, Rh^{II} complexes have unique reactivity unobtainable with other metal catalysts, and ligand-exchange reactions provide unique interactions unobtainable with organic molecules. However, this reactivity leads to limited half-lives in cells, and hampers robust characterization of metal-protein interactions with these species. Overall, many of the reports discussed here are proof-of-concept demonstrations. Further work is needed to ascertain the generality of many conclusions. To mention just one obvious case, extending biophysical characterizations to cellular or in vivo applications remains limited. DNA-targeting Rh^{II} complexes are well studied in cellular contexts, and the recent application[14] of a Rh^{III} complex to a mouse model of inflammation indicates whole-animal activity might well be feasible with well-designed complexes.

Acknowledgements

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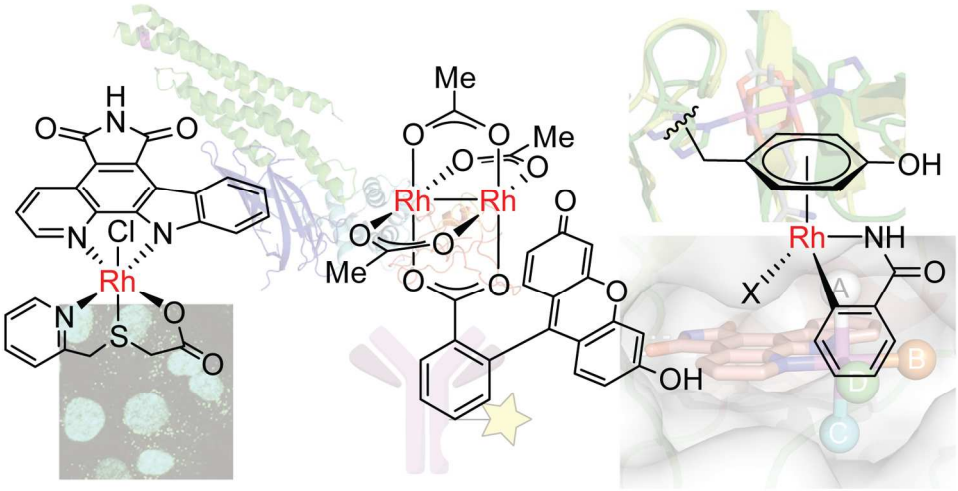
References

1 K. K.-W. Lo, Ed., *Inorganic and organometallic transition metal complexes with biological molecules and living cells*, Academic Press, an imprint of Elsevier, London, 2017.
2 Z. Wu and K. L. Hull, *Chem. Sci.*, 2016, **7**, 969–975.
3 J. Hansen and H. M. L. Davies, *Coord. Chem. Rev.*, 2008, **252**, 545–555.
4 S. Kim, S. Han, J. Park, S. Sharma, N. K. Mishra, H. Oh, J. H. Kwak and I. S. Kim, *Chem. Commun.*, 2017, **53**, 3006–3009.
5 W.-W. Chen and M.-H. Xu, *Org. Biomol. Chem.*, 2017, **15**, 1029–1050.
6 J. Liu, Y.-Z. Fan, X. Li, Z. Wei, Y.-W. Xu, L. Zhang and C.-Y. Su, *Appl. Catal. B Environ.*, 2018, **231**, 173–181.
7 V. Bernales, D. Yang, J. Yu, G. Gümüşlü, C. J. Cramer, B. C. Gates and L. Gagliardi, *ACS Appl. Mater. Interfaces*, 2017, **9**, 33511–33520.
8 F. Lieben, M. E. Sherief and F. Petuelli, *Biochem. Z.*, 1958, **330**, 576–578.
9 A. Erck, L. Rainen, J. Whileyman, I.-M. Chang, A. P. Kimball and J. Bear, *Proc. Soc. Exp. Biol. Med.*, 1974, **145**, 1278–1283.
10 R. A. Howard, E. Sherwood, A. Erck, A. P. Kimball and J. L. Bear, *J. Med. Chem.*, 1977, **20**, 943–946.
11 S. Mollin, R. Riedel, K. Harms and E. Meggers, *J. Inorg. Biochem.*, 2015, **148**, 11–21.
12 L. Feng, Y. Geisselbrecht, S. Blanck, A. Wilbuer, G. E. Atilla-Gokcumen, P. Filippakopoulos, K. Kräling, M. A. Celik, K. Harms, J. Maksimoska, R. Marmorstein,

G. Frenking, S. Knapp, L.-O. Essen and E. Meggers, *J. Am. Chem. Soc.*, 2011, **133**, 5976–5986.
13 P. Xie, D. S. Williams, G. E. Atilla-Gokcumen, L. Milk, M. Xiao, K. S. M. Smalley, M. Herlyn, E. Meggers and R. Marmorstein, *ACS Chem. Biol.*, 2008, **3**, 305–316.
14 H.-J. Zhong, W. Wang, T.-S. Kang, H. Yan, Y. Yang, L. Xu, Y. Wang, D.-L. Ma and C.-H. Leung, *J. Med. Chem.*, 2017, **60**, 497–503.
15 A. Monney and M. Albrecht, *Coord. Chem. Rev.*, 2013, **257**, 2420–2433.
16 M. Salmain and G. Jaouen, *Comptes Rendus Chim.*, 2003, **6**, 249–258.
17 F. Schwizer, Y. Okamoto, T. Heinisch, Y. Gu, M. M. Pellizzoni, V. Lebrun, R. Reuter, V. Köhler, J. C. Lewis and T. R. Ward, *Chem. Rev.*, 2018, **118**, 142–231.
18 H. B. Albada, F. Wieberneit, I. Dijkgraaf, J. H. Harvey, J. L. Whistler, R. Stoll, N. Metzler-Nolte and R. H. Fish, *J. Am. Chem. Soc.*, 2012, **134**, 10321–10324.
19 J. Ohata, M. K. Miller, C. M. Mountain, F. Vohidov and Z. T. Ball, *Angew. Chem. Int. Ed.*, 2018, **57**, 2827–2830.
20 J. F. Berry and C. C. Lu, *Inorg. Chem.*, 2017, **56**, 7577–7581.
21 H. T. Chifotides and K. R. Dunbar, *Acc. Chem. Res.*, 2005, **38**, 146–156.
22 J. D. Aguirre, D. A. Lutterman, A. M. Angeles-Boza, K. R. Dunbar and C. Turro, *Inorg. Chem.*, 2007, **46**, 7494–7502.
23 J. R. Rubin, T. P. Haromy and M. Sundaralingam, *Acta Crystallogr. C*, 1991, **47**, 1712–1714.
24 K. R. Dunbar, J. H. Matonic, V. P. Saharan, C. A. Crawford and G. Christou, *J. Am. Chem. Soc.*, 1994, **116**, 2201–2202.
25 J. D. Aguirre, A. M. Angeles-Boza, A. Chouai, J.-P. Pellois, C. Turro and K. R. Dunbar, *J. Am. Chem. Soc.*, 2009, **131**, 11353–11360.
26 L. E. Joyce, J. D. Aguirre, A. M. Angeles-Boza, A. Chouai, P. K.-L. Fu, K. R. Dunbar and C. Turro, *Inorg. Chem.*, 2010, **49**, 5371–5376.
27 H. T. Chifotides, D. A. Lutterman, K. R. Dunbar and C. Turro, *Inorg. Chem.*, 2011, **50**, 12099–12107.
28 D. A. Lutterman, P. K.-L. Fu and C. Turro, *J. Am. Chem. Soc.*, 2006, **128**, 738–739.
29 Z. Li, A. David, B. A. Albani, J.-P. Pellois, C. Turro and K. R. Dunbar, *J. Am. Chem. Soc.*, 2014, **136**, 17058–17070.
30 Z. T. Ball, *Curr. Opin. Chem. Biol.*, 2015, **25**, 98–102.
31 R. Kundu, P. R. Cushing, B. V. Popp, Y. Zhao, D. R. Madden and Z. T. Ball, *Angew. Chem. Int. Ed.*, 2012, **51**, 7217–7220.
32 F. Vohidov, S. E. Knudsen, P. G. Leonard, J. Ohata, M. J. Wheadon, B. V. Popp, J. E. Ladbury and Z. T. Ball, *Chem. Sci.*, 2015, **6**, 4778–4783.
33 J. L. Bear, R. A. Howard and J. E. Korn, *Inorganica Chim. Acta*, 1979, **32**, 123–126.
34 M. A. S. Aquino and D. H. Macartney, *Inorg. Chem.*, 1987, **26**, 2696–2699.
35 S. Dhar, N. Kolishetti, S. J. Lippard and O. C. Farokhzad, *Proc. Natl. Acad. Sci.*, 2011, **108**, 1850–1855.
36 M. B. Minus, M. K. Kang, S. E. Knudsen, W. Liu, M. J. Krueger, M. L. Smith, M. S. Redell and Z. T. Ball, *Chem. Commun.*, 2016, **52**, 11685–11688.
37 B. Peña, R. Barhoumi, R. C. Burghardt, C. Turro and K. R. Dunbar, *J. Am. Chem. Soc.*, 2014, **136**, 7861–7864.
38 J. M. Antos and M. B. Francis, *J. Am. Chem. Soc.*, 2004, **126**, 10256–10257.
39 K. P. Kornecki, J. F. Briones, V. Boyarskikh, F. Fullilove, J. Autschbach, K. E. Schrote, K. M. Lancaster, H. M. L. Davies and J. F. Berry, *Science*, 2013, **342**, 351–354.
40 B. V. Popp and Z. T. Ball, *Chem. Sci.*, 2011, **2**, 690–695.
41 M. B. Minus, W. Liu, F. Vohidov, M. M. Kasembeli, X. Long, M. Krueger, A. Stevens, M. I. Kolosov, D. J. Tweardy, M. S. Redell and Z. T. Ball, *Angew. Chem. Int. Ed.*, 2015, **54**, 13085–13089.
42 J. Ohata and Z. T. Ball, *J. Am. Chem. Soc.*, 2017, **139**, 12617–12622.
43 A. C. Braisted and J. A. Wells, *Proc. Natl. Acad. Sci.*, 1996, **93**, 5688–5692.
44 J. Ohata, F. Vohidov and Z. T. Ball, *Mol. Biosyst.*, 2015, **11**, 2846–2849.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