The Beauty of Gold: Knowledge of Mechanisms Leads to Different Applications of Organogold Compounds in Medicine and Catalysis

Angela Casini*[1] and Sophie R. Thomas[1,2]

[1]Chair of Medicinal and Bioinorganic Chemistry, Department of Chemistry, Technical University of Munich, Lichtenbergstr. 4, 85748 Garching, Germany [2]School of Chemistry, Cardiff University,
Main Building, Park Place, CF10 3AT Cardiff, United Kingdom

E-mail: angela.casini@tum.de

Sophie Thomas graduated with a Master of Chemistry at Cardiff University (UK) in 2017 before gaining a place on the EPSRC Centre for Doctoral Training in Catalysis programme. In 2018, Sophie obtained a Master of Research in Catalysis and then began her PhD under the supervision of Prof. Angela Casini at Cardiff University. Her research interests include the use of gold complexes as therapeutic agents, with a focus on achieving catalysis in living cells.

Professor Angela Casini completed her PhD in Chemistry at the University of Florence (Italy) in 2004. Between 2011-2015 she was assistant professor at the University of Groningen (The Netherlands), holding a Rosalind Franklin Fellowship. Between 2015-2019, she was also Chair and Director of Postgraduate Taught Masters at Cardiff University (UK), before taking up her current position as Chair of Medicinal and Bioinorganic chemistry at the Technical University of Munich (Germany). The study of the mechanisms of action of metal-based drugs are active topics of her research program, as well as the development of new supramolecular materials for biomedical applications.

Abstract

This review is aimed at providing a concise overview of the results obtained by our group in the field of organometallic chemistry of gold. Therefore, a selection of examples amongst the most extensively explored families of bioactive gold complexes ® Au(I) N-heterocyclic carbenes and cyclometalated Au(III) compounds ® is presented. Insights into the bio-inorganic mechanisms of reactivity of organogold compounds obtained by an integrated investigational approach, and knowl-edge of structure-activity relationships are discussed also in relation to novel applications of gold-based catalysts and metal-mediated transformations in aqueous environment.

Keywords: Organometallic complexes | Gold | Mechanism of action

1. Introduction

Aurum, Gold, Oro, Or, Złoto are names in various languages for a metal which has captured the imagination of humanity for years until today, due to its golden shine and chemical inertness, leading to its unparalleled use in jewelry, currency, decorations, electronics, and even medicine. In recent years, due to the availability of soluble gold compounds and the observation that gold nanoparticles are catalytically active in a number of reactions, interest has increased in the chemistry of Au(I) and Au(III) complexes. The position of Au in the Periodic Table of the Elements is unique, and the metal is endowed with large relativistic effects, increased ionization energies, and high redox potential. In detail, the relativistic effects lead to con-traction of the s- and p-orbitals, which affects the expansion of the outer d- and f-orbitals, and contributes to the Lewis acidity of the gold center. Particularly in the case of Au(I) complexes, relativistic effects strongly influence their geometric features (linear geometry), electronic structure and reactivity ('soft' Lewis acid). Thus, Au(I) complexes bind preferentially to 'soft' electron donor atoms like P and S. Steric factors allowing, Au(I) compounds have also a marked tendency to interact with neighboring Au(I) centers or with other heavy metals to give "aurophilic" or, more generally, "metallophilic" interactions.[1]

On the other hand, Au(III) is a 'hard' Lewis acid favoring 4-coordinated complexes with square planar geometry, and bind-ing to the lone pairs of heteroatoms, such as O, N and S. In line with the reduced influence of relativistic effects, in Au(III) complexes aurophilic interactions are essentially absent.[2]

When comparing ionization energies of group 11 transition metals, Au has a significantly higher ionization energy than Cu or Ag. In catalysis such higher ionization energies potentially limit key putative steps, including oxidative addition in the gold redox cycle. Moreover, the symmetry and steric changes that result from oxidative addition to linear Au(I) complexes kinetically disfavor the process. Similarly, the high electron affinity of Au presents the challenge of rapid reduction of the metal complex prior to its catalytic function. The latter feature also affects the biological applications of gold compounds, since uncontrolled metal speciation, i.e. fast ligand exchange reac-tions, eventually leading to reduction to Au(0), is highly favored in aqueous environment.

In an attempt to circumvent the outlined problems and to set the stage for practically relevant Au catalysts and/or bioactive compounds, several strategies have been developed, mostly relying on the fine-tuning of the ligand framework of gold compounds. Concerning Au(I) complexes, the most common ligands are phosphines, N-heterocyclic carbenes (NHCs), N-acyclic(diamino)-carbenes (ADCs), or cyclic(amino)(alkyl)-carbenes (CAACs), with modulable electronic or steric proper-ties.[3,4] Ligands featuring chelating bi- and tridentate scaffolds are instead able to efficiently stabilize Au(III) ions modifying their redox potential, thus, providing stability against reduction. Therefore, chelating N^N ligands, dithiocarbamates and cyclo-metalated C^N/C^P ligands, as well as pincer ligands have been widely explored.[3,5-7]

1.1 Therapeutic Gold-based Compounds. Concern-ing biological applications of gold complexes, a plethora of studies describe their therapeutic effects in the treatment of a variety of diseases. Interest in antimicrobial gold complexes originated at the end of the 19th century from the work of Robert Koch, who showed that potassium dicyanidoaurate(I), $K[Au(CN)_2]$, possesses activity against Mycobacterium tuber-culosis.[8] By the early 1930s, gold therapy (chrysotherapy) was discontinued as a treatment of tuberculosis based on its ineffectiveness.[9] However, it is still widely used for the management of rheumatoid arthritis; for example in the form of auranofin ([triethylphosphine(2,3,4,6-tetra-O-acetyl-ϕ-1-D-(thiopyranosato-S)Au(I)]) (Ridaura·, Figure 1).[10] Early studies on the anticancer activity of auranofin revealed activity levels similar to cisplatin in vitro, which led to a large number of Au(I) complexes being evaluated for their antiproliferative effects.[11] In this context, Au(III) compounds, either coordination or organo-metallics, were amongst the first to be tested for antitumor potential owing to their square planar coordination geometry as in cisplatin, although endowed with higher oxidative character

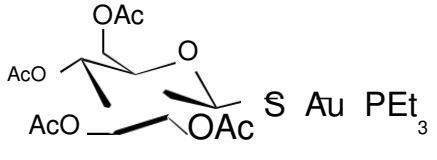

Figure 1. Structure of the Au(I) complex auranofin.

with respect to Pt(II) complexes.[12] Both cytotoxic Au(I) and Au(III) complexes exert their antiproliferative effects via multi-modal modes of action, often involving direct binding to protein targets relevant to cancer.[13-16] Concerning biodistribution, metabolism and excretion, several factors affect such properties, particularly the nature of the ligands bound to gold. Therefore, it is impossible to draw a generalized description for the various families of cytotoxic gold compounds. However, concerning toxicity, it should be noted that so far there are no detailed cases of long-term severe or permanent renal damage caused by gold compounds, as established in the case of cisplatin. Instead, some adverse effects can be related to immune-stimulating reactions.[11]

Recently, some examples have appeared concerning the use of gold compounds for selective modifications of biomolecules via C-C or C-X (X = heteroatom) bond formation for different applications in biological systems.[17] In detail, the use of gold-mediated cross-coupling reactions for covalent modification of proteins or to activate unsaturated bonds in a chemoselective manner in vitro and in vivo, has been successfully explored for Au(III) C^N type compounds.[18-21] Noteworthy, this research area combines the challenges of gold compounds' design for catalytic and therapeutic applications. In fact, in both cases the main issue is the control of the gold complex's reactivity (e.g. ligand exchange and redox reactions) and binding selectivity in aqueous environment.

In this review, we will provide a selection of examples from our group of the above-mentioned families of organometallic Au(I)/Au(III) complexes, including compounds designed as anticancer drugs and antiprotozoal agents, as well as chemical probes to study protein functions in living systems. Specifically, we will focus on organogold complexes featuring NHCs and/or cyclometalated ligands and summarize the relevant structure-activity-relationships obtained so far. Moreover, insights into our most investigated biological targets and mechanistic hypotheses for anticancer gold compounds will be provided. We refer the reader to more extensive, complementary reviews for deeper insights into this field.[22,23]

2. Bioactive Au(I) N-Heterocyclic Carbenes Acting via Non-covalent Interactions

Carbenes are neutral, electron deficient molecules contain-ing a neutral carbon atom with a valence of two and two unshared valence electrons. The best known class of carbenes demonstrating particular stability are the N-heterocyclic car-benes (NHCs).[24] In fact, the σ-electron-withdrawing and π-electron-donating nitrogen atoms flanking the carbene carbon stabilize the NHC by lowering the energy of the occupied σ-orbital and concomitantly increasing the electron density in the empty p-orbital. Furthermore, the cyclic NHC structure confers additional stabilization to the singlet sp^2 hybridized carbene state.[25] Currently, NHCs are privileged ligands for a wide range of transition metals, main group elements and f-block species.[26-28] Due to their high structural versatility and ease of derivatization, N-heterocyclic carbenes perfectly fit prerequisites for an efficient drug design and tuning of the metal compound's reactivity and physicochemical properties.[22,29] Thus, numerous cytotoxic metal NHC complexes, including of Au(I), have been synthesized and characterized for their mechanisms of biological action.[29,30]

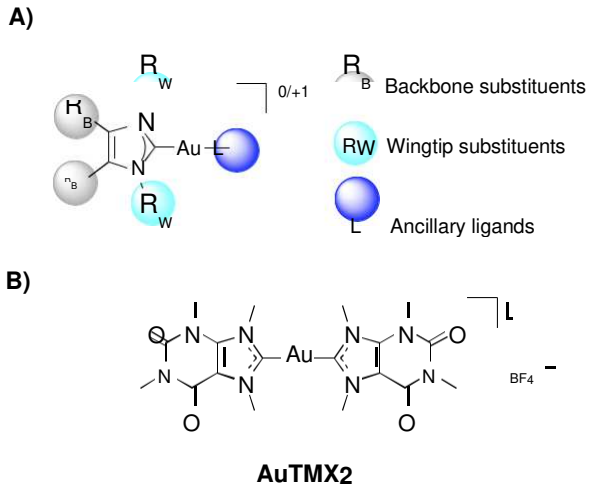

Figure 2. (A) General structure of Au(I) NHC complexes and possible modifications; (B) Structure of the cationic bis-NHC Au(I) complex $[Au(9\text{-methylcaffeine-8-ylidene})_2]^+$ ($AuTMX_2$) as selective G4 stabilizer.

Overall, various studies showed the great influence of the NHC scaffold on the anticancer activity of the resulting metal compounds ® with e.g. imidazol-2-ylidene carbenes being generally more active than benzimidazol-2-ylidene ones ® as well as the role of the derivatization of the NHC backbone, of the wingtip substituents and of the ancillary ligands (Figure 2A) on the resulting Au(I) complex bioactivity.

In general, the aforementioned (benz)imidazolylidene Au(I) complexes target only indirectly DNA, and exert their mecha-nism of activity mainly via interactions with proteins/enzymes following ligand exchange reactions.[22] The positively charged Au(I) NHCs endowed with high lipophilic character were also observed to selectively target mitochondria in cancer cells, inducing calcium-sensitive mitochondrial membrane permeabi-lization (MMP) accompanied by mitochondrial swelling, as well as by inhibition of mitochondrial enzymes.[13]

However, in 2014, in collaboration with the group of Pierre Le Gendre and Michel Picquet in Dijon, we reported on the synthesis and antiproliferative properties of xanthine-derived Au(I) NHC complexes as anticancer agents.[31] The compounds were hypothesized to exert their cytotoxic effects mainly via non-covalent adduct formation with biomolecules, specifically G-quadruplex (G4) DNA.[32] The cationic caffeine-based bis-NHC Au(I) complex $[Au(9\text{-methylcaffeine-8-ylidene})_2]^+$ ($AuTMX_2$, Figure 2B) emerged as the most efficient G4 stabilizer, also endowed with selectivity for G4 structures over duplex DNA, at variance with the benzimidazolylidene Au(I) analogue.[31] The selectivity of $AuTMX_2$ could be rationalized by the ability of the caffeine-ylidene scaffold to mimic the guanines of the G4s.

Of note, the presence of two NHC ligands is essential to achieve the highest possible stabilization of the G4 structure. Indeed, X-ray studies of the adduct formed by $AuTMX_2$ with a model of telomeric G4 (hTel23) showed that the compound binds non-covalently between neighboring quadruplexes in the crystal lattice.[33] Further structural characterization of the binding modes of $AuTMX_2$ with different G4 structures was achieved

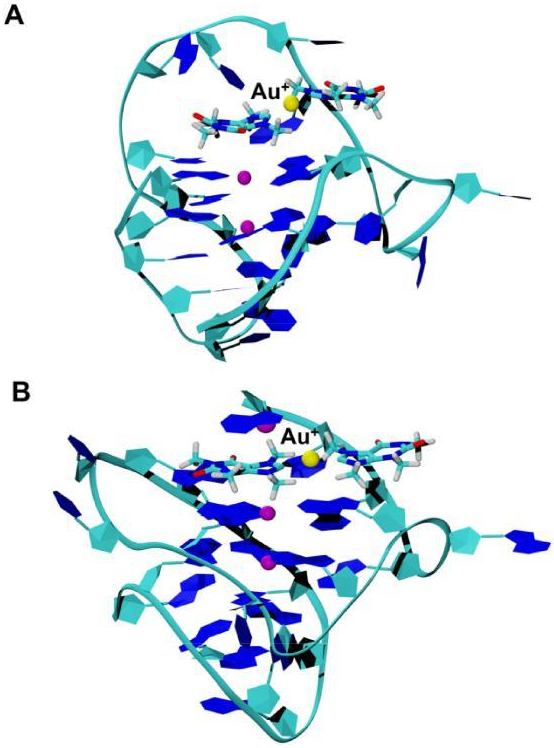

Figure 3. Adducts of the cationic bis-NHC Au(I) complex $AuTMX_2$ with (A) telomeric G4 structure (hTelo) and (B) promoter G4 structure (cKIT) calculated by multiple collective variable (CV) metadynamics.[34] G4s color scheme: sugar back-bone = turquoise, DNA bases = blue, potassium ions = purple spheres. Compound $AuTMX_2$ in stick representation, color scheme: carbon = turquoise, nitrogen = blue, oxygen = red, hydrogen = white, Au(I) = yellow sphere. Figure generated with VMD software.[42]

by advanced atomistic simulations, namely by metadynamics (Figure 3), evidencing the importance of π-π stacking and possibly electrostatic interactions in stabilizing the gold com-plex/G4 adducts.[34]

Regarding structure activity relationships, xanthine-derived Au(I) NHC complexes with different substituents at the N-7 position of the ligand scaffold had markedly reduced affinity towards G4 stabilization compared to $AuTMX_2$.[31] Similarly, substitution of the N-1 position as well as replacement of one of the two NHC ligands with alkynyl moieties, to achieve neutral complexes, resulted in loss of affinity to G4s.[35] Based on the available structural information, it is likely that steric effects in the substituted $AuTMX_2$ analogues may play a role in interfering with the non-covalent adduct formation and relative stability.

Recently, to shed light into the molecular reactivity of $AuTMX_2$, shotgun proteomics was applied in human A2780 ovarian cancer cells treated with the metallodrug.[36] Specifically, following global protein expression changes of treated cancer cells enabled the elucidation of a multi-modal mode of action of $AuTMX_2$ involving alterations in the nucleolus, telomeres, actin stress-fibers and activation of stress-responses; these results were further corroborated by pharmacological assays, fluorescence microscopy and cellular Au accumulation experiments.[36] More-over, electrospray ionization mass spectrometry studies (ESI-

MS) showed that the compound is unreactive with model amino acids and proteins.[36]

Considering that, beside humans, putative G4-forming sequences have been found in other mammalian genomes, yeasts, protozoa,[37,38] bacteria and viruses,[39] this type of organo-gold complexes, active via non-covalent interactions and targeting secondary nucleic acids structures, could certainly be of value in other research disease areas. Following this reasoning, we recently reported on the comparative investigation of a series of mononuclear coordination and organometallic Au(I)/Au(III) complexes as antileishmanial agents. Thus, $AuTMX_2$ and derivatives were tested against promastigotes and amastigotes, the clinically relevant parasite form, of L. amazonensis and L. braziliensis in vitro.[40] In this compounds' series, the cationic $[Au(1\text{-benzyl-}3,7,9\text{-trimethylxanthin-}8\text{-ylidene})_2]BF_4$ complex displayed low EC_{50} values (ca. 4 $^{-}$M) in promastigotes cells and no toxicity in host macrophages, the selectivity index being higher than those previously reported for other Au(I) NHCs, and of the approved first-line drug amphotericin B.[41] It was hypothesized that an ideal balance of hydrophilic/lipophilic character and reduced metallodrug speciation may be responsible for the overall observed effects of the compound in the parasite. Initial mechanistic studies showed the disruptive effects of the Au(I) NHC complex on L. amazonensis' plasma membrane integrity.[40] In general, the remarkable effect observed in parasite infections in vitro, combined with its activity against axenic amastigotes cultured in acidic medium, suggest that the leishma-nicidal effect of the gold complex is preserved in the vacuolar environment; representing a relevant pharmacological feature for the development of novel gold-based leishmanicidal candidates.

3. Bioactive Cyclometalated Au(III) Complexes Mediating Cross-coupling Reactions

Over the years, in collaboration with the group of Maria Agostina Cinellu at the University of Sassari, we started working on cyclometalated Au(III) complexes of different families as possible novel anticancer metallodrugs. Within this framework, our group focused on Au(III) C^N complexes, including the compound $[Au(py^b)PTACl]^+$ (py^b = 2-benzylpyridine, PTA = 1,3,4-triaza-7-phosphaadamantane) and its derivatives (Figure 4).[43,44] The antiproliferative screening carried out on different human cancerous cell lines showed that $[Au(py^b)PTACl]^+$ was more potent that its dichlorido precursor, most likely due to its positive charge that, together with the PTA moiety, increases the compound's water solubility.[43] Furthermore, this series of compounds was also shown to potently target and inhibit the zinc

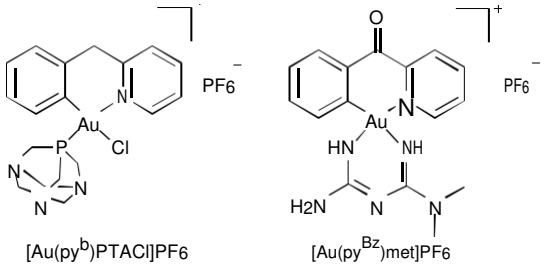

Figure 4. Bioactive cyclometalated Au(III) C^N complexes.

finger protein named poly(ADP-ribose)-polymerase 1 (PARP-1), one of the key DNA repair enzymes in the DNA damage response signaling pathways.[43] Of note, PARPs have become the pharmacological targets of novel anticancer drugs, particularly for ovarian and breast cancers with defective breast cancer susceptibility gene (BRCA).[45]

Further studies on the mechanisms of PARP-1 inhibition by Au(III) C^N complexes via interactions with its zinc finger (ZF) domain revealed that the compounds are able to form AuC^N-apo-ZF adducts, following Zn^{2+} displacement from the holo-peptide (Figure 5).[46] Using a hyphenated mass spectrometry approach, competition experiments were carried out, whereby each gold complex was exposed to a mixture of two different zinc fingers. Remarkably, some of the Au C^N complexes showed complete selectivity for binding to the ZF-PARP-1 domain with respect to the other ZF model.[46]

Most notably, further investigation of the binding mode of the neutral complex $[Au(py^b)Cl_2]$, with different ZF domains and model peptides, enabled the observation of a peculiar reactivity towards cysteine residues.[48] Specifically, following AuC^N-peptide adduct formation, the reaction could proceed to give cysteine arylation (Figure 6).[48] Combined mass spectrometry and density functional theory (DFT) calculations showed that formation of the C^N-peptide adduct is templated by the Au(III) center facilitating the C-S cross-coupling reaction via reductive elimination.[48,49] The chemoselectivity with respect to cysteine arylation was assessed by reacting the gold compounds

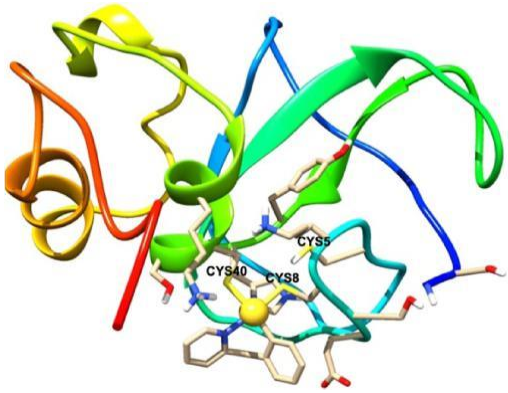

Figure 5. Gold finger formation. Representative adduct of Au(III) C^N complexes with the zinc finger domain of PARP-1, in which Zn^{2+} has been replaced by the Au(III) fragments, obtained by quantum mechanics/molecular mechanics (QM/MM).[46] The two chlorido ligands of the gold complex have been replaced by two cysteinato groups. Drawings produced by the UCSF Chimera package.[47]

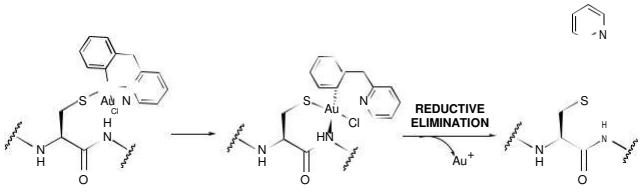

Figure 6. Proposed mechanism of cysteine arylation by Au(III) C^N complexes via reductive elimination.

with different model peptides, with and without cysteine residues, as well as with cysteine at the terminal sites of the peptidic chain.[49] Interestingly, the latter could not be arylated and only Au(C^N)-peptide adducts could be formed. Therefore, a general reaction mechanism for cysteine arylation was proposed whereby a cysteinate residue binds Au(III) trans to the N of the C^N ligand, while a second amino acid residue (A) coordinates to Au(III), favoring the bond breakage between the nitrogen and the metal to achieve [Au(C^N)(Cys)(A)Cl] species. Formation of the latter intermediate is crucial to promote the observed C-S cross-coupling.[48,49]

Of note, a just published study on $[Au(py^{Bz})met]^+$ (py^{Bz} = 2-benzoylpyridine) featuring metformin (met) as ancillary ligand (Figure 4), showed that the compound is 6000-fold more cytotoxic compared to uncoordinated metformin in vitro, and demonstrated synergistic action of metformin and Au(III) species in vivo.[50] It is likely that part of the observed anticancer effects are due to the covalent modifications of cysteine residues in target proteins.

Overall, gold compounds offer an opportunity to modulate bioprocesses through reactions that are complementary to enzymes, and emerge as new chemical tools for bio-orthogonal transformations. Ongoing studies in our laboratories explore the possibility to apply Au(III) C^N complexes in proteomic profiling of cysteine residues and of their oxidation states.[51,52] In the future, selective targeting of organogold complexes to cysteine residues of disease-relevant proteins may lead to new gold-based therapeutic agents.

4. From Bioinorganic Applications to Catalysis

The promising results obtained with Au(III) C^N complexes on C-S cross-coupling in aqueous environment prompted us to investigate them further as catalysts in different cross-coupling processes in mild reaction conditions. Thus, we recently reported on the Au(III)-mediated C_{aryl}-P bond formation occurring upon reaction of cyclometalated Au(III) complexes with phosphines. Specifically, the $[Au(C^N)Cl_2]$ complex featuring a bidentate 2-benzoylpyridine scaffold was found to react with PTA under mild conditions, including in water, to afford the corresponding phosphonium via C-P reductive elimination (Figure 7).[53] The proposed mechanism for the title reaction, based on in situ $^{31}P\{^1H\}$ NMR, X-ray diffraction and MS analyses combined with DFT calculations, points towards the formation of intermediate Au(III) species, whereby substitution reactions of the chlorido ligands with PTA, followed by decoordination of the N in the C^N ligand, are essential to enable the gold-templated cross-coupling.[53] The C-P coupling has been generalized to

Figure 7. C-P coupling upon reaction of the cyclometalated $[Au(C^N)Cl_2]$ complex (C^N = 2-benzoylpyridine) with PTA (1,3,5-triaza-7-phosphaadamantane) in water.

other cyclometalated Au(III) C^N complexes and other tertiary phosphines. Further studies are ongoing to elucidate the impact of the cyclometalated ligand and to determine the factors influencing C-P coupling at Au(III), including solvent and counter-anion effects, with the ultimate goal to exploit organo-gold complexes in catalytic transformations and bioconjugation reactions.

5. Conclusions and Perspectives

In conclusion, we have summarized here the results obtained by our group in the past decade on the use of gold compounds for biomedical applications and, more recently, in homogenous catalysis. In general, we have learnt that metal reactivity with biomolecules (either peptides or nucleic acids) cannot be simply predicted on the basis of the hard-soft acid-base (HSAB) theory and affinity of the metal for a certain nucleophilic site, but requires a deeper understanding of the mechanisms of reaction of the whole gold-ligand complex and knowledge of the influence of the chemical and structural complexity of the target biomolecule on the overall reactivity.

Such knowledge, together with the judicious choice of the organometallic ligands stabilizing the gold center, while enabling its bio-reactivity, will certainly make gold-templated reactions a significant addition to the toolbox of life compatible transformations. Alternatively, the ligand selection may produce physiologically stable compounds reacting with biomolecules mainly via non-covalent interactions. The latter have proven essential to define the chemoselectivity of metallodrugs towards a certain target.[54] In any case, the potential of organogold chemistry for biological and therapeutic applications still needs to be fully controlled and unraveled.

In this context, the mechanistic knowledge gained from a purely bioinorganic perspective may enable the development of other applications of gold chemistry, including in homogenous catalysis. In the latter, the majority of reactions discovered with gold complexes involve the electrophilic activation of carbon-carbon π-bonds and/or the generation of electrophilic gold carbene intermediates, whereby the formal oxidation state of gold remains unaltered throughout the stoichiometric reaction or catalytic cycle.[55-57] Instead, relatively few transformations have been proposed so far to access gold intermediates with different oxidation states (e.g. Au(I)/Au(II)/Au(III)).[58,59]

In general, reductive elimination plays a major role in transition-metal mediated reactions (cross-couplings in particular), and is the key product-releasing step of many transformations. Nevertheless, the determinants and mechanisms of this reactivity are still scarcely understood,[59] preventing its control. Our recent work on the Au(III)-mediated C_{aryl}-P bond formation has shed further light into the mechanisms of reductive elimination at gold.[53]

Finally, an observation should be made on the potential of gold chemistry in the oxidation state 0, powered by the use of N-heterocyclic carbene systems as Au nanoparticle (AuNP) stabilizers, for biomedical applications.[60] Within this framework, our group is actively involved in the design of NHC ligand shell functionality to stabilize AuNPs in aqueous environment, for targeted biocatalysts and theranostic agents. We hope to soon be able to add our contribution to this research area, still in its infancy, which holds great promise.

S.T. acknowledges EPSRC and CDT in Catalysis for funding under grant agreement n^{o} EP/L016443/1.

References and Notes

1 H. Schmidbaur, A. Schier, Chem. Soc. Rev. 2008, 37, 1931.
2 L. Rocchigiani, M. Bochmann, Chem. Rev. 2020, doi: 10.1021/acs.chemrev.0c00552.
3 R. P. Herrera, M. C. Gimeno, Chem. Rev. 2021, doi:10.1021/ acs.chemrev.0c00930.
4 M. Soleilhavoup, G. Bertrand, Acc. Chem. Res. 2015, 48, 256.
5 W. Henderson, in Advances in Organometallic Chemistry, ed. by R. West, A. F. Hill, Elsevier 2006, Vol. 54, pp. 207- 265.
6 R. Kumar, C. Nevado, Angew. Chem., Int. Ed. 2017, 56, 1994.
7 C. Nardon, N. Pettenuzzo, D. Fregona, Curr. Med. Chem. 2016, 23, 3374.
8 R. Koch, Dtsch. Med. Wochenschr. 1890, 16, 756.
9 G. J. Higby, Gold Bull. 1982, 15, 130.
10 R. Eisler, Inflamm. Res. 2003, 52, 487.
11 S. Nobili, E. Mini, I. Landini, C. Gabbiani, A. Casini, L. Messori, Med. Res. Rev. 2010, 30, 550.
12 A. Casini, L. Messori, Curr. Top. Med. Chem. 2011, 11, 2647.
13 A. Bindoli, M. P. Rigobello, G. Scutari, C. Gabbiani, A. Casini, L. Messori, Coord. Chem. Rev. 2009, 253, 1692.
14 B. Aikman, A. de Almeida, S. M. Meier-Menches, A. Casini, Metallomics 2018, 10, 696.
15 A. de Almeida, B. L. Oliveira, J. D. G. Correia, G. Soveral, A. Casini, Coord. Chem. Rev. 2013, 257, 2689.
16 A. Casini, A. Guerri, C. Gabbiani, L. Messori, J. Inorg. Biochem. 2008, 102, 995.
17 S. R. Thomas, A. Casini, Curr. Opin. Chem. Biol. 2020, 55, 103.
18 K. K.-Y. Kung, H.-M. Ko, J.-F. Cui, H.-C. Chong, Y.-C. Leung, M.-K. Wong, Chem. Commun. 2014, 50, 11899.
19 K. Tsubokura, K. K. H. Vong, A. R. Pradipta, A. Ogura, S. Urano, T. Tahara, S. Nozaki, H. Onoe, Y. Nakao, R. Sibgatullina, A. Kurbangalieva, Y. Watanabe, K. Tanaka, Angew. Chem., Int. Ed. 2017, 56, 3579.
20 Y. Lin, K. Vong, K. Matsuoka, K. Tanaka, Chem.®Eur. J. 2018, 24, 10595.
21 K. Vong, T. Yamamoto, T. Chang, K. Tanaka, Chem. Sci. 2020, 11, 10928.
22 B. Bertrand, A. Casini, Dalton Trans. 2014, 43, 4209.
23 T. Zou, C. T. Lum, C.-N. Lok, J. J. Zhang, C. M. Che, Chem. Soc. Rev. 2015, 44, 8786.
24 P. de Frémont, N. Marion, S. P. Nolan, Coord. Chem. Rev. 2009, 253, 862.
25 D. J. Nelson, S. P. Nolan, Chem. Soc. Rev. 2013, 42, 6723.
26 M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, Nature 2014, 510, 485.
27 T. Scattolin, S. P. Nolan, Trends Chem. 2020, 2, 721.
28 A. Doddi, M. Peters, M. Tamm, Chem. Rev. 2019, 119, 6994.
29 W. Liu, R. Gust, Coord. Chem. Rev. 2016, 329, 191.
30 I. Ott, Coord. Chem. Rev. 2009, 253, 1670.
31 B. Bertrand, L. Stefan, M. Pirrotta, D. Monchaud, E. Bodio, P. Richard, P. Le Gendre, E. Warmerdam, M. H. de Jager, G. M. M. Groothuis, M. Picquet, A. Casini, Inorg. Chem. 2014, 53, 2296.
32 Ö. Karaca, S. M. Meier-Menches, A. Casini, F. E. Kühn, Chem. Commun. 2017, 53, 8249.
33 C. Bazzicalupi, M. Ferraroni, F. Papi, L. Massai, B. Bertrand, L. Messori, P. Gratteri, A. Casini, Angew. Chem., Int. Ed. 2016, 128, 4328.
34 D. Wragg, A. de Almeida, R. Bonsignore, F. E. Kühn, S. Leoni, A. Casini, Angew. Chem., Int. Ed. 2018, 57, 14524.
35 S. M. Meier-Menches, B. Aikman, D. Döllerer, W. T. Klooster, S. J. Coles, N. Santi, L. Luk, A. Casini, R. Bonsignore, J. Inorg. Biochem. 2020, 202, 110844.
36 S. M. Meier-Menches, B. Neuditschko, K. Zappe, M. Schaier, M. C. Gerner, K. G. Schmetterer, G. Del Favero, R. Bonsignore, M. Cichna-Markl, G. Koellensperger, A. Casini, C. Gerner, Chem.®Eur. J. 2020, 26, 15528.
37 N. Smargiasso, V. Gabelica, C. Damblon, F. Rosu, E. De Pauw, M.-P. Teulade-Fichou, J. A. Rowe, A. Claessens, BMC Genomics 2009, 10, 362.
38 H. M. Craven, R. Bonsignore, V. Lenis, N. Santi, D. Berrar, M. Swain, H. Whiteland, A. Casini, K. F. Hoffmann, PLoS Negl. Trop. Dis. 2021, 15, e0008770.
39 N. Saranathan, P. Vivekanandan, Trends Microbiol. 2019, 27, 148.
40 K. Minori, L. B. Rosa, R. Bonsignore, A. Casini, D. C. Miguel, ChemMedChem 2020, 15, 2146.
41 L. Paloque, C. Hemmert, A. Valentin, H. Gornitzka, Eur. J. Med. Chem. 2015, 94, 22.
42 W. Humphrey, A. Dalke, K. Schulten, J. Mol. Graphics 1996, 14, 33.
43 B. Bertrand, S. Spreckelmeyer, E. Bodio, F. Cocco, M. Picquet, P. Richard, P. Le Gendre, C. Orvig, M. A. Cinellu, A. Casini, Dalton Trans. 2015, 44, 11911.
44 S. Spreckelmeyer, M. van der Zee, B. Bertrand, E. Bodio, S. Stürup, A. Casini, Front Chem. 2018, 6, 377.
45 E. Nicolas, F. Bertucci, R. Sabatier, A. Gonçalves, Cancers (Basel) 2018, 10, 506.
46 M. N. Wenzel, S. M. Meier-Menches, T. L. Williams, E. Rämisch, G. Barone, A. Casini, Chem. Commun. 2018, 54, 611.
47 E. F. Pettersen, T. D. Goddard, C. C. Huang, G. S. Couch, D. M. Greenblatt, E. C. Meng, T. E. Ferrin, J. Comput. Chem. 2004, 25, 1605.
48 M. N. Wenzel, R. Bonsignore, S. R. Thomas, D. Bourissou, G. Barone, A. Casini, Chem.®Eur. J. 2019, 25, 7628.
49 S. R. Thomas, R. Bonsignore, J. S. Escudero, S. M. Meier-Menches, C. M. Brown, M. O. Wolf, G. Barone, L. Y. P. Luk, A. Casini, ChemBioChem 2020, 21, 3071.
50 M. V. Babak, K. R. Chong, P. Rapta, M. Zannikou, H. M. Tang, L. Reichert, M. R. Chang, V. Kushnarev, P. Heffeter, S.M. Meier-Menches, Z. C. Lim, J. Y. Yap, A. Casini, I. V. Balyasnikova, W. H. Ang, Angew. Chem., Int. Ed. 2021, doi:10.1002/anie.202102266.
51 K. M. Backus, B. E. Correia, K. M. Lum, S. Forli, B. D. Horning, G. E. González-Páez, S. Chatterjee, B. R. Lanning, J.R. Teijaro, A. J. Olson, D. W. Wolan, B. F. Cravatt, Nature 2016, 534, 570.
52 J. van der Reest, S. Lilla, L. Zheng, S. Zanivan, E. Gottlieb, Nat. Commun. 2018, 9, 1581.
53 R. Bonsignore, S. R. Thomas, W. T. Klooster, S. J. Coles, R. L. Jenkins, D. Bourissou, G. Barone, A. Casini, Chem.®

Eur. J. 2020, 26, 4226.
54 M. N. Wenzel, A. F. Mósca, V. Graziani, B. Aikman, S. R. Thomas, A. de Almeida, J. A. Platts, N. Re, C. Coletti, A. Marrone, G. Soveral, A. Casini, Inorg. Chem. 2019, 58, 2140.
55 A. S. K. Hashmi, Chem. Rev. 2007, 107, 3180.
56 R. Dorel, A. M. Echavarren, Chem. Rev. 2015, 115, 9028.
57 A. Nijamudheen, A. Datta, Chem.®Eur. J. 2020, 26, 1442.
58 B. Huang, M. Hu, F. D. Toste, Trends Chem. 2020, 2, 707.
59 M. Joost, A. Amgoune, D. Bourissou, Angew. Chem., Int. Ed. 2015, 54, 15022.
60 S. R. Thomas, A. Casini, J. Organomet. Chem. 2021, 938, 121743.