Structural Basis of the Biomolecular Action of Paddlewheel- and N-Heterocyclic-Carbene-Based Antitumor Metallodrugs: A Computational Perspective

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Abstract. Metallodrugs are an essential component of the contemporary medicinal chemistry since they represent a crucial inventory of therapeutic agents against a myriad of cancers as well as viral, bacterial, and parasitic infections. Their unique features based on the presence of a metal center capable of transforming the electronic and steric features of its ligands incorporate the (possible) activation mechanisms, capability to multitarget, and the specific way of attacking a target via the ligand substitution mechanism. This minireview is dedicated to a short overview of the computational studies of paddlewheel- and N-heterocyclic-carbene-based antitumor metallodrugs with biomolecular targets, performed in our group. We particularly focus our attention on the structural features of the investigated systems, which present excellent examples highlighting the significance of incorporation of steric effects originating from metallodrug's ligands as well as the impact of the surrounding milieu.

1 Introduction

Development of transition-metal-based metallodrugs is a fast developing field nowadays [1, 2]. The reason of it is the wide range of properties of metal centers, the rational employment of which permits the design of the metal scaffolds with a set of desired qualities [3]. The ability to reciprocally change their electronic structure along with the structure of their ligands is the source of the transition metal center propensity to form the coordinative bonds with both electrostatic and covalent nature. This phenomenon affects greatly the flexibility of these metal centers during the ligand substitution reactions in metallodrugs [4].

Since the serendipitous finding of cisplatins's antitumor properties, metallodrugs became an essential component of a medicinal toolkit not only in the sphere of anticancer agents, but also in other domains, due to their antiviral, antibacterial, and antiparasitic qualities [5, 6]. Nevertheless, metallodrugs display severe toxic side effects, in particular nephro- and neurotoxicity, caused by the low selectivity of metal centers in targeting

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various metabolic pathways simultaneously. The control of side effects motivates the ongoing efforts to fine-tune the properties of metallodrug scaffolds.

Nowadays the computational chemistry is an essential instrument in the toolkit of inorganic and bioinorganic medicinal chemistry, by providing an atomistic insight on the behavior of metal ions in physiological milieu [7, 8] as well as a support to the rational design of metallodrugs and to the exploration of their modes of action [9–11]. The central difference in the computational investigation of purely organic versus metal-based drugs is the non-applicability to the latters of the quantitative structure-activity relationships (QSAR) techniques [12, 13]. While these methods are the major workhorse in the field of prediction of biological effect of organic compounds due to the capacity to formulate connections between chemical properties and biomolecular effects, this approach is intrinsically inapt for the metal complexes due to several reasons [3]. Primarily, many metallodrugs should undergo activation before becoming capable of attacking their targets. Furthermore, the attack happens via the ligand exchange mechanism, which assumes the presence of a detachable, labile ligands at the metal center versus the carrier ligands which are strongly bound and are not expected to sustain cleavage. Finally, metallodrugs are able to coordinate to not a single but multiple biomolecular targets [14].

We describe in this minireview various computational studies performed in our group, which were focused on the reactivity of paddlewheel- and N-heterocyclic-carbene-based antitumor metallodrugs with their biological targets. These investigations shed light onto the mechanistic description of the metalation process which is the culmination of their biomolecular action.

2 Paddlewheel-Based Antitumour Metallodrugs

There is a renewed interest in the scientific community focusing on the synthesis of novel anticancer drugs in the diRh- and diRu-based paddlewheel tetraacetate complexes characterized by the formula $[M_2(O_2CR)_4L_2]^{n+}$, (M = Rh(II), Ru(II/III); R = CH_3^-, L = solvent molecule or anionic ligand) (Fig. 1) [15, 16].

The medicinal properties of diRh(II)-based complex have a broad spectrum. It is a potent agent against various types of tumours: leukemias P388 [17] and L1210 [18], sarcomas 180 [17], and the Ehrlich-Lettre ascites carcinoma [19, 20]. A plethora of various intracellular targets is suspected from amino acids [21, 22] and peptides [23, 24] to proteins [25, 26] and DNA [17]. Such an unselective behavior may explain well its heavy toxicity. However, apart from several studies on the protein and peptide metalation by these complexes, which have elucidated slightly the binding preferences of this diRh(II) complex (Asn, Asp, C-terminal, His, Lys) [25, 26], there is no consensus on its intracellular mode of action. On the contrary, the studies on the therapeutic employment of the structurally similar complex $[Ru_2(\mu\text{-}O_2CCH_3)_4Cl]$ are much more limited to date and are oriented on the usage of the Ru(II)Ru(III) core primary as a prodrug scaffold for the transport of the medicinally active ligands toward the intended target, for example, ibuprofenate, naproxenate, indomethacinate, ketoprofenate, -the deprotonated species of non-steroidal anti inflammatory drugs-, or the anti glioblastoma indolylglyoxylyl agents [27–29]. The experimental and computational analyses of the biomolecular binding preferences of the diRu(II/III) drug are very scarce [30–32].

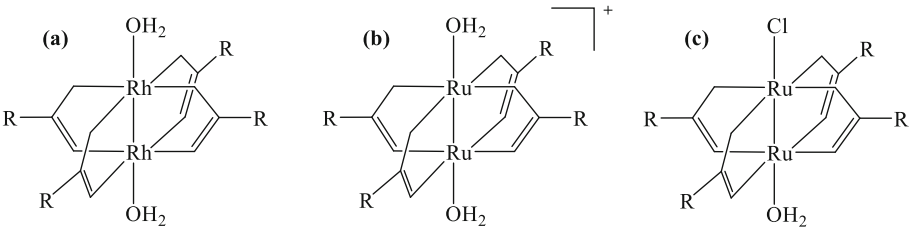

Fig. 1. Investigated dirhodium and diruthenium paddlewheel complexes: (a) $[Rh_2(\mu\text{-}O_2CCH_3)_4(H_2O)_2]$, (b) $[Ru_2(\mu\text{-}O_2CCH_3)_4(H_2O)_2]^+$, (c) $[Ru_2(\mu\text{-}O_2CCH_3)_4(H_2O)Cl]$.

Despite of the similar structure, the Rh- and Ru-based complexes have different metallic cores Rh(II)Rh(II) and Ru(II)Ru(III), respectively. Their valences and charges dictate their structural preferences, in particular the choice of the axial ligands, as well as the metal-metal bond stability. The +4 charge of the Rh-based core is completely compensated by four anionic bridging acetates, thus, the axial ligands are weakly coordinated and are neutral. On the other hand, the Ru-based core possesses the +5 charge which after summing up with the −4 charge of four acetates, yields the uncompensated positive charge which favors the coordination of anionic ligands (such as Cl^-) into the axial position. Additionally, it is noteworthy to mention that the Ru-based complex has the polymeric arrangement in a solid state with a unit $[ClRu_2(\mu\text{-}O_2CCH_3)_4Cl]$ and transforms into its conventional form $[Ru_2(\mu\text{-}O_2CCH_3)_4Cl]$, only via the loss of a Cl in solution due to the replacement by a neutral solvent molecule [31].

In order to shed light onto the reactivity of both complexes, the thermodynamics of the ligand exchange reactions taking place at the axial positions of $[Rh_2(\mu\text{-}O_2CCH_3)_4(H_2O)_2]$ and $[Ru_2(\mu\text{-}O_2CCH_3)_4(H_2O)Cl]$ during their reactions with the protein side chains and termini was computed by means of DFT approaches (Fig. 2) [30]. A large set of possible targets was considered which included most common nucleophiles such as Arg, Asn, Asp, Asp^-,Cys, Cys^-, His, Lys, Met, Sec, Sec^-, as well as termini C-term, C-$term^-$, N-term, thus allowing to infer the selectivity of the studied paddlewheel complexes at different values of pH. We have found out that the reactivity patterns of both diRh and diRu complexes differ significantly. The diRh complex demonstrated a low selectivity by interacting effectively with all considered targets. Nevertheless, taking into consideration the additional parameters such as the typical pH of appearance or the usual proximity to the solvent accessible surface, the deprotonated C-$term^-$ as well as the protein side chains Asp^-, His, and Sec^- were indicated as the most likely targets, although the latter is usually less sterically approachable. The complex $[Ru_2(\mu\text{-}O_2CCH_3)_4(H_2O)Cl]$ may undergo to the substitution of either water or chloride by the biomolecular nucleophiles. If the water is substituted, then the target selectivity of the diRu complex is the same as diRh complex. Nevertheless, the chloride exchange is more important at a higher pH, when the water at the axial position of diRu as well as the basic side chains are deprotonated. In these conditions, the diRu complex becomes more selective toward Arg and His via the exchange reaction with chloride. Interestingly, the reactions of both diRh and diRu complexes are highly exergonic with deprotonated Sec^- and Cys^-. This evidence suggests the capability of these metallic scaffolds to be developed into efficacious TrxR-inhibiting anticancer agents.

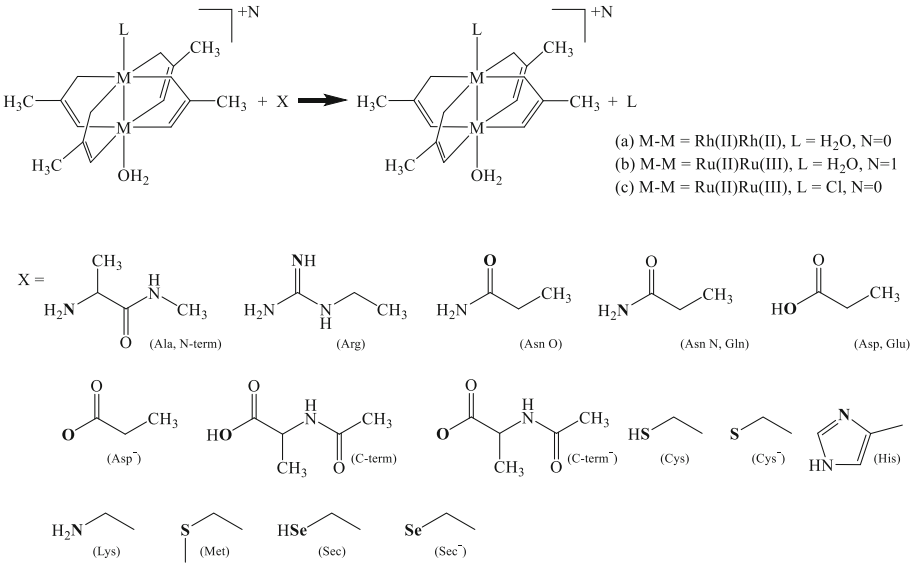

Fig. 2. The substitution reactions between the studied complexes $[Rh_2(\mu\text{-}O_2CCH_3)_4(H_2O)_2]$ (a), $[Ru_2(\mu\text{-}O_2CCH_3)_4(H_2O)_2]^+$ (b), $[Ru_2(\mu\text{-}O_2CCH_3)_4(H_2O)Cl]$ (c) and models of targeted protein side chains (X). The atoms bound to the metal centers in the resulting reactions are represented in bold.

In principle, the dimetallic paddlewheel complexes seem to be an ideal scaffold for the development of prodrugs, as many medicinally active molecules may be utilized as the bridging ligand in place of acetate. Recently, the anti glioblastoma indolylglyoxylyl-Leu-Phe (EB106) and indolylglyoxylyl-Phe-Leu (EB776) dipeptides were used as the substitutes of acetates for the diruthenium core with the intention of developing an antitumor agent (Fig. 3) [28, 29]. Nevertheless, depending on dipeptide sequence, the medicinal properties differed greatly. The computational analysis of the most favourable geometrical configurations, provided a plausible explanation to this different activity in the location of phenyl side chain. In case of the indolylglyoxylyl-Leu-Phe dipeptide EB106, the phenyl ring is situated in alpha position to the carboxylate, thus sterically hindering the metal-bound oxygens from possible hydrolytic or nucleophilic attacks. Moreover, EB106 was shown to be lacking the hydrophilic areas close to the carboxylate oxygens. On the other hand, the indolylglyoxylyl-Phe-Leu dipeptide, EB776, is characterized by the presence of several equally favorable configurations with unshielded carboxylate oxygens and the availability of hydrophilic pockets close to them. This is an excellent example of the way how the steric effects of the ligand may modulate the stability of a metallodrug and its mode of action.

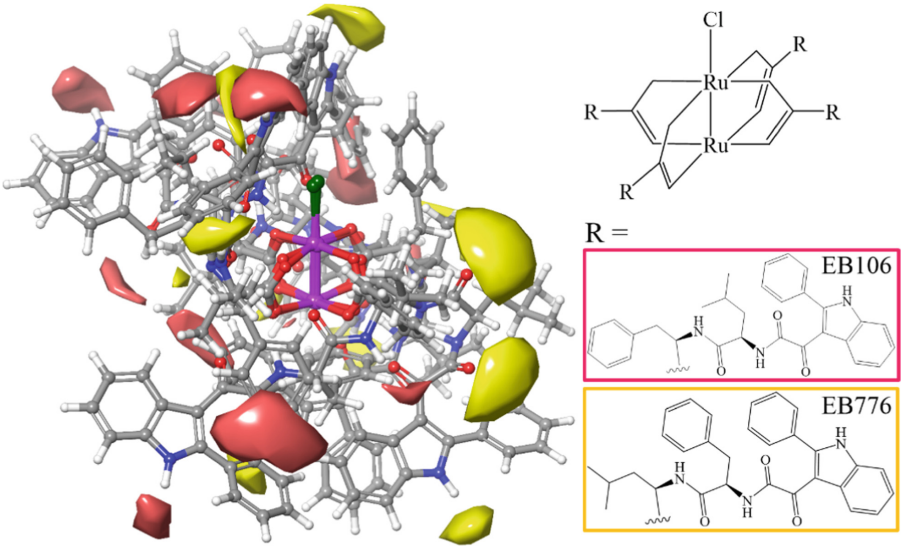

Fig. 3. (Left) Superposition of the most representative conformers of complexes $[Ru_2(EB106)_4Cl]$ and $[Ru_2(EB776)_4Cl]$ and their hydrophilic fragments in pink and in yellow, respectively. Color scheme: Ru (violet), Cl (dark green), O (red), C (gray), H (white). (Right top) Structure of paddle-wheel Ru_2(II,III) complex. (Right bottom) Its bridging ligands are either indolylglyoxylyl EB106 or EB776. Hydrophilic surface in yellow (EB776) is substantially closer to carboxylate oxygens bound to metals than the hydrophilic surface in pink (EB106). (Color figure online)

3 N-Heterocyclic-Carbene-Based Antitumor Metallodrugs

A vast exploitation of the N-heterocyclic carbenes (NHCs) in the design of antitumour metallodrugs [33, 34] can be well explained by two important features. Primarily, the increased robustness of the metal-carbene bond based on σ-donation and π-back-donation prevents its facile cleavage via the ligand substitution reactions. Secondly, it is possible to add various decorations to carbene's nitrogens, thus alternating the sterical and electronic properties of the whole complex. Various transition-metal-based scaffolds have been proposed as novel anticancer agents [35, 36]. The coinage metals Au(I) and Ag(I) demonstrated peculiar cytotoxic features in vitro and in vivo [37, 38]. Although numerous modes of the apoptosis induction were proposed, including targeting of topoisomerase, DNA, and mitochondrial thioredoxin reductase (TrxR) [39, 40], the latter pathway has been shown to be of an utmost importance in NHC-based Au, Ag, Ru, Rh complexes [41–43]. These metal complexes possess a certain degree of promiscuity and are capable to multitarget various cellular biomolecules, yet they all display a special chemoselectivity toward thiols and selenols. This capability makes them excellent scaffolds for targeting the Sec-containing TrxR proteins overexpressed in several cancer types [44, 45].

The bicoordinated Au(I) complexes can be divided in two distinct groups: the neutral ones combining one monocarbene and one halide ligands, with a halide being

facilely exchanged in physiological conditions, and the cationic Au(I) complexes with two attached carbenes [46].

In a recent computational study, the reactivity of the complex Au(I)(NHC)Cl (Fig. 4, complex a) with water, N-terminus, and various protein side chains was analyzed [47]. All the reactions were found to be strongly exergonic. It was clearly shown that although the aquation of the complex is characterized by a barrier of 23.0 kcal/mol, the barriers for reactions with other nucleophiles boast even lower values of less than 19 kcal/mol, thus suggesting that the complex Au(I)(NHC)Cl attacks its intracellular biomolecular targets in its administered, unhydrolyzed form. Au(I) being a soft center was found to majorly bind at Cys and Sec side chains, in their anionic thiolate and selenolate forms, with the activation energies of 17.4 and 12.8 kcal/mol, respectively, whereas neutral Cys, Sec, Arg, Lys, and N-terminus are easily targeted as well with the activation energies within the range 16.2–20.6 kcal/mol. The lack of major distinction between S^-, Se^-, and N-based binding sites implies that the accessibility of these protein targets may play a predominant role, i.e., if Cys and Sec are buried in the inner protein structure, then other nucleophile sites are attacked, nevertheless, if they are facilely approachable, they turn to represent the major targets of metallation.

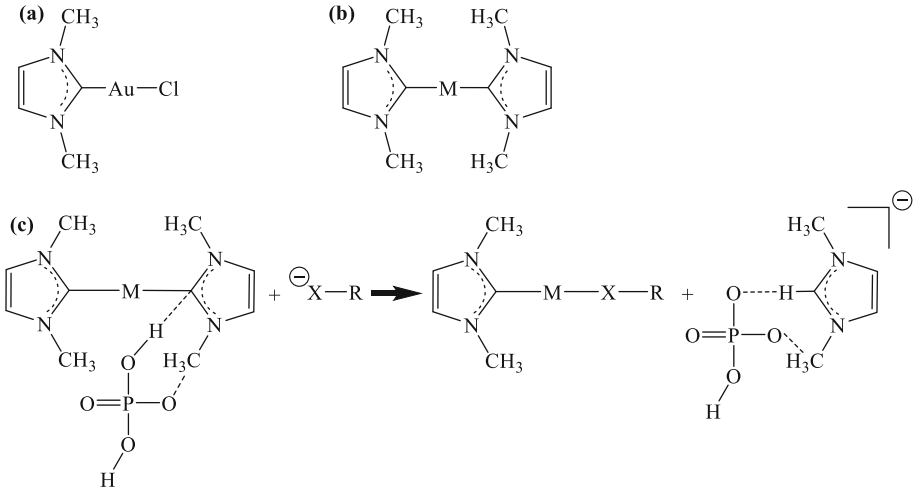

Fig. 4. Coinage metal NHC-based antitumour complexes: (a) [Au(I)(NHC)Cl^-], (b) $[(Me_2Im)_2M]^+$ (M = Au, Ag, Cu), (c) Crucial reaction route incorporating aid of an outside proton donor, in which the hydrogen atom is delivered from the acidic constituent of exterior buffer to the liberated carbene (M = Cu, Ag, Au; X = S, Se; X-R = capped Cys, Sec).

Contrarily to Au(I)(NHC)Cl, which reacts with the nucleophiles via the halide substitution, biscarbene complexes of the type $[Au(I)(NHC)_2]^+$ with NHC = Me_2Im, react with cysteine by releasing stepwisely both NHC moieties, and yielding the complex $[Au(Cys)_2]$ [48]. Nevertheless, the mechanism of this substitution reaction has been yet not fully elucidated. Moreover, a similar mechanism is expected to be enrolled by the analogous $[M(Me_2Im)_2]^+$ complexes with M = Ag(I) and Cu(I), indeed, both

Ag- and Cu-based biscarbene complexes were found to disclose recently a cytotoxic activity [33, 49]. Similarly, the complex bis(1-(anthracen-9-ylmethyl)-3-ethylimidazol-2-ylidene) (EIA) silver chloride, $[Ag(I)(EIA)_2]Cl$, and anthracene functionalized silver carbenes demonstrated robust cytotoxic effects incorporating TrxR inhibition [50]. Although the modus operandi of Cu(I) NHC complexes is less comprehended –likely incorporates the generation of reactive oxygen species (ROS) impairing the cytoplasm, mitochondria, and DNA [51, 52] –, the structural resemblance with the corresponding Au(I) and Ag(I) complexes advocates the targeting of TrxR as an alternative mechanism for the anticancer activity of Cu(I) NHC complexes. The metal-carbene bonds formed by gold, silver, and copper are characterized by a particular high strength and their cleavage turns to be a highly endothermic process.

Recently, computational investigations analyzed various pathways of metal-carbene dissociation through the attack of either neutral or deprotonated Cys and Sec residues and by modelling the concomitant protonation of the leaving carbene (Fig. 4) [53]. An important conclusion was made about the necessity of a simultaneous protonation of the leaving carbene that basically compensates the high energy cost for the metal-carbene dissociation, thus the availability of a proton source was demonstrated to be indispensable. Hence, the presence of a buffer in a physiological solution is crucial, and reflects the significance of the biological milieu in the thermodynamical control of these reactions. All these considerations allowed the calculation of the NHC substitution barriers of 19.8, 12.7, and 13.6 kcal/mol for Au(I), Ag(I), and Cu(I) complexes, respectively, with deprotonated Sec, which indicated Sec-containing proteins to be the designated targets of NHC coinage metal complexes, as also experimentally demonstrated [54].

Recent investigations of half-sandwich Ru-, Os-, Rh-, and Ir-based metal complexes allowed to regard them as robust leads for synthesizing new anticancer drugs [43, 55, 56]. Their hallmark is the presence of a π-bound arene, cyclopentadienyl (Cp), or its derivative, for example, η^5-pentamethylcyclopentadienyl (Cp*). Broadly employed σ-ligands are RAPTA (η^1-1,3,5-triaza-7-phosphaadamantane PTA) [57] and RAED (η^2-1,2-diaminoethane) [58] complexes. Indeed, there are many investigations focused on the cytotoxicity of Ru(II)-, Os(II)-, Rh(III)-, and Ir(III)-based half-sandwich complexes bearing a NHC ligand [43, 59, 60]. Recent studies of the cytotoxic activity against four human cancer lines involved several isostructural NHC complexes: Ru^{II}-, and Os^{II}-based complexes $[M^{II}(cym)(NHC)Cl_2]$, Rh^{III}- and Ir^{III}-based compounds $[M^{III}(Cp^*)(NHC)Cl_2]$, NHC being either dmb = 1,3-dimethylbenzimidazol-2-ylidene or dbb = 1,3-dibenzylbenzimidazol-2-ylidene (Fig. 5, complexes 1–4) [43, 61]. Although all four complexes demonstrated an excellent cytotoxicity with the IC50 values in the low micromolar range, the complex $[Rh(Cp^*)(dbb)Cl_2]$ featured the most robust activity. Interestingly, several evidences indicate that all studied complexes targeted TrxR [43].

With the aim to disentangle the reaction pathways of these complexes with the selenoprotein TrxR, their reactivity toward water, Cys, Cys^-, Sec, and Sec^- was analyzed via the usage of the DFT calculations of the thermodynamics and kinetics of the possibly occurring ligand exchange reactions (Fig. 5) [62].

Since the hydrolytic activation of these complexes was demonstrated to be unfavorable, it was assumed that the metal complex attack is operated via the substitution

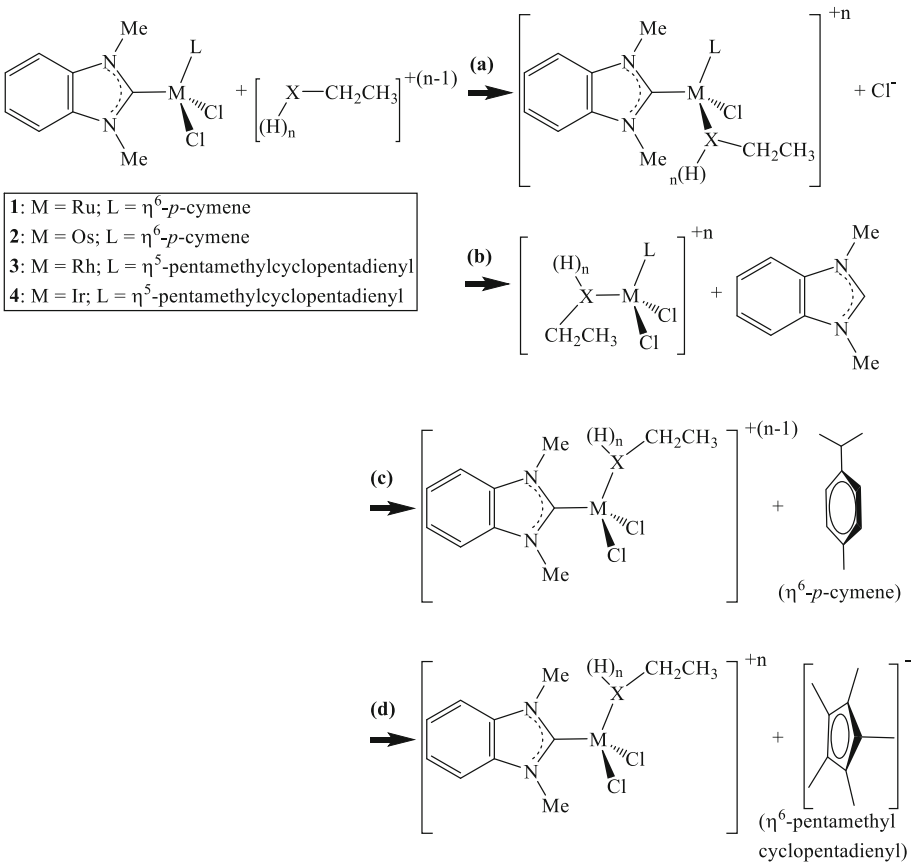

Fig. 5. Investigated NHC-complexes: (1) Ru-, (2) Os-, (3) Rh-, (4) Ir-based (top left). Studied ligand substitution reactions: (a) chloro, (b) dmb, (c) cym only for Ru- and Os-based complexes (1, 2) and (d) Cp* only for Rh- and Ir-based complexes (3, 4). X stands for S or Se in the models of side chains Cys or Sec, respectively.

of chloride, with the exception of the Ru-based complex for which the exchange of cym was shown to be feasible as well. The investigated complexes revealed a contrasting behavior in which the Ru and Os complexes displayed a higher preference toward Cys and Sec, albeit with a lesser thermodynamic favorability, whereas the Rh and Ir compounds exhibited a greater reactivity (low activation barriers), and resulted more selective to Cys^- and Sec^-. By decomposing the activation free energy values into the sum of electronic, solvation, and thermal terms, it was shown that the higher selectivity of Ru and Os-compounds toward Cys and Sec can be explained by a solvation energy contribution more beneficial in case of these neutral moieties in comparison with their anionic forms, hence enabling these metal complexes to effectively bind to Cys and Sec in a low pH milieu. The Rh and Ir complexes majorly target the anionic forms Cys^- and Sec^- because of the favorable solvation contributions as well. On the basis of these findings, it was demonstrated that Cp*-bound Rh and Ir complexes are more effective

binders of selenoenzymes, for instance, TrxR, because the Sec is predominantly present in its deprotonated, anionic form at physiological pH.

4 Computational Perspective

Computational investigations of the biomolecular action of antitumor metallodrugs are predominantly focused on the mechanistic comprehension of the process of metalation of the targeted biological moiety, which includes the structural optimizations for all moieties present in the reaction profile as well as the accurate computations of the reaction energy describing well the process thermodynamics and the barrier energies detailing the kinetics. This is done ubiquitously by means of DFT, a tool widely employed for the description of chemical processes in organometallic and bioinorganic chemistry [63–65].

Despite the choice of a computational program does not affect accuracy, computational cost, or memory requirements for any given computation, the selection of the appropriate density functional is crucial. While the omnipresent B3LYP describes quite accurately main-group elements' systems, the structure and reactivity of transition metal complexes are better described by the range-corrected density functional ωB97X, routinely employed in our group [3]. Indeed, the inclusion of empirical dispersion corrections accounting for dispersive interactions, i.e., the attractive part of the van der Waals interaction potential between atoms and molecules, results to be indispensable in large biomolecular systems. The choice of suitable basis set schemes is also crucial: typically, the geometry optimization is performed with a medium-sized basis set whereas the energy calculations usually incorporate a larger and thus more flexible basis set. It is a common practice to describe the core electrons of a metal atom as well as their relativistic effects via the usage of effective core potential, usually with double-zeta and triple-zeta quality for optimization and single point energy calculations [3].

The solvent (water) plays an important role in the mechanism of action of most metallodrugs which tend to undergo the hydrolytic activation prior to attacking their biomolecular targets. Based on the good accuracy/computational efficiency balance, the implicit solvation is more commonly used to predict free energies of solvation of both neutral and ionic solutes, and to model the reaction kinetics and thermodynamics in solution, as well as other bulk properties such as pKa of ionizable groups [3].

The usual biomolecular targets are DNA nucleobases or the protein side chains, among which Sec is the major target due to its overexpression in the tumor cells [44, 45]. Nevertheless, a recent discovery of the targeting of Cys in AQP3 by Aubipy resulted in a plethora of synthesized Au(III)-based drugs with the similar modes of action [46, 66].

The studies presented in this short minireview indicate that ligand decoration of active metal centers may play a pivotal role in the control of activation, approach, and final reaction with biomolecular targets. In many presented instances, the reactivity of the metal center with the intended biomolecular targets is dominated by the steric effects exerted by the metallodrug's ligands and their impact in the interaction with bulk and with the target environment [28, 29, 53]. It is worth noticing that a full elucidation of these structural aspects can be often gained only computationally by the use of multilayered approaches [3, 67].

An excellent example proving the effects of the bulky ligands on the metal center action is the sharp contrast between the reactivity of the diRu paddlewheel metallodrugs decorated with indolylglyoxylyl dipeptides, described in Sect. 2 [28, 29]. Indeed, a stark discrepancy between the stability of a scaffold with EB106 or EB776 bridging ligands means for this drug a switch between a completely uncytotoxic complex in the first case and the metallodrug with the exceptional antiprolific properties in the second case. A position of a mere phenyl ring fully determines the complex's mode of action. The conformational exploration of both EB106 and EB776 scaffolds, followed by the characterization of the corresponding solvent-accessible surfaces, resulted to be indispensable to the elucidation of their different activity, thus corroborating the importance of computational insights in the metallodrugs' molecular design.

A demonstration of the effects of the chemical environment onto the metallodrug reactivity is represented by the protonation of leaving NHC ligands upon their substitution and release into the bulk [53]. Indeed, the complexation of active metal centers like Au(I) or other coinage metals with NHC ligands has been exploited in force of the high stability of the M–C bond that, in principle, should enhance the chemoselectivity of these metal scaffolds. Indeed, without a proton transfer, the utter unfavorability of the M–C dissociation thermodynamics makes the substitution of a NHC ligand from a metal center unviable, thus evidencing the utmost importance of proton transfer processes in the metallodrugs' pharmacodynamics and pharmacokinetics. In this frame, accurate quantum chemistry methods, in particular those based on the density functional theory, are the most suitable to correctly assess the partecipation of either the bulk or the protein environment in proton transfer processes concomitant and/or assisting the exchange of NHC ligands.

A possible use of the ligand decoration is represented by the control of the solubilty or, more generally, the solvation properties of a metallodrug; such an approach is often employed to enhance the bioavaialbility of the administered metal complex [3, 67]. We envision at least two ways to control the metal complex solvation via ligand decoration: i) using ligands with highly hydrophilic pendants, or ii) using either charged or uncharged ligands to induce a non zero total charge to the metal complex. Notably, the latter approach not only enhances the metal complex solvation, but inevitably affects the reactivity of the metal center in terms of ligand exchange. As shown above, the half-sandwich metal complexes of Ru, Os, Rh, and Ir bearing either the neutral cymene or the anionic Cp* ligand show significantly different reactivity with Cys and Sec [62]. In particular, the $[M(\eta^6\text{-cym})]^{2+}$ scaffolds with M = Ru(II), Os(II) are more reactive with the neutral side chains of Cys and Sec, whereas the $[M(\eta^5\text{-Cp*})]^{3+}$ scaffolds with M = Rh(III), Ir(III) were found to be more reactive with the anionic forms of Cys and Sec. The computational analysis of the activation barriers for the binding of either $[M(\eta^6\text{-cym})]^{2+}$ or $[M(\eta^5\text{-Cp*})]^{3+}$ scaffold at nucleophilic protein sites unveiled that the above highlighted selectivity is mostly determined by solvation. Again, quantum chemistry methods can easily assess the impact of solvation on ligand exchange processes, in terms of both thermodynamics and kinetics, and thus represent indispensable components in the rational design of metallodrugs.

5 Conclusions

Modern medicinal chemistry is unimaginable without metallodrugs which form an essential supply to the treatment of a plethora of cancers, bacterial, viral, and parasitic infections.

The most advantageous feature of metallodrugs is the capacity to develop the complex scaffolds on the basis of the metal center versatile geometry. It allows to design the metallodrugs rationally via the modulation of electronic and steric features. The employment of bigger or charged ligands may modulate the membrane permeability and the ease with which the metallodrugs attack their targets. The accurate selection of ligands may allow to fine-tune their properties by alternating the bond strengths between metal centers and the ligands. Finally, the phenomenal ability of metallodrugs to bind at diverse biomolecular sites is another feature characterizing them as a source of specialized pharmaceutical agents.

In this minireview, the computational studies of reactivity paddlewheel- and N-heterocyclic-carbene-based antitumor metallodrugs with biomolecular targets, carried out in our group, were presented. A particular accent was made on the structural features of the studied systems, which form the basis of such mechanistic studies. Two main points inferred from the presented studies are noteworthy: (i) the importance of inclusion of steric effects produced by metallodrug's ligands if a complex is richly decorated and (ii) impact of the surrounding milieu.

Another important conclusion is that the computational modelling of metallodrug reactivity should be an essential step both on the stage of the metallic scaffold rational design as well as *in vitro* and *in vivo* examinations. A careful apprehension of the mechanistic processes underlying the activation of metallodrug as well as its target selectivity are essential for its structural development, whereas the computational analysis of the metal center promiscuity can be used to predict the possible toxic side effects and improve our understanding of the drug's targeted delivery.

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