Computational Studies Unveiling the Mechanism of Action of Selected Pt-, Te-, Au-, Rh-, Ru-Based Drugs

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Abstract. Modern medicinal chemistry is unimaginable without the employment of metallodrugs, which form a crucial source of novel anticancer, antiviral, antibacterial, and antiparasitic agents. The wide variety of molecular geometries, availability of several oxidation states, redox properties are ascribable to the presence of a metal center that can be exploited in the design of bioactive metal scaffolds with various modes of action, different selectivities, and activation mechanisms. This minireview focuses on an abridged account of the computational studies of the mechanism of action of selected Pt-, Te-, Au-, Rh-, Ru-based drugs, carried out in our group. This account is specifically focused on how the molecular geometry and the reactivity with the biological milieu may influence the modus operandi of these metal scaffolds.

1 Introduction

The unique characteristics for metallodrugs, such as wide range of coordination geometries and numbers, and attainability of various redox states, make them essential components of the toolbox of modern medicine [1, 2]. Furthermore, it is possible to synthesize novel derivative complexes on the basis of existing metal scaffolds via modification of ligands, thus finely regulating the electronic, steric, and electrostatic properties of the metallodrug [3].

After the cytotoxicity of cisplatin has been discovered, a plethora of metallodrugs based on other transition metals have been synthesized and studied [4]. The synthesis of novel scaffolds is guided by the necessity to circumvent the heavy toxic effects, which are, unfortunately, the intrinsic drawbacks of the medications based on metals due to the widespread reactivity of these complexes with biomolecular targets the inherent promiscuity of these complexes. The development of complexes with improved therapeutic profiles is gained by fine-tuning the reactivity of the metal-based pharmacophore via modulating its carrier ligands, i.e. those which stay bound to the metal center after its activation, or its labile ligands, the cleavage of which occurs during the activation.

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O. Gervasi et al. (Eds.): ICCSA 2023, LNCS 13956, pp. 67–81, 2023.
https://doi.org/10.1007/978-3-031-36805-9_5

Another valuable strategy is assembling active ligands and metal scaffolds, thus developing dual-acting drugs. This method allows to program the release of the therapeutically active ligands after the metallodrug coordinates to its biomolecular target, thus providing the effective scheme of delivery of medicinal agents. The above mentioned characterictics depict the reasons behind the success of metallodrugs in the fields of anticancer, antiparasitic, antibacterial, and antiviral agents [5–7].

The role of computational chemistry in the bioinorganic drug design is constantly expanding, driven by the growing hardware and software capabilities [8]. Calculations can be now addressed to accurately describe the mode of action of metallodrugs, thus being essential for their rational development. Density functional theory (DFT) provides for an accurate and robust computational paradigm for investigation of metallodrugs. DFT allows the accurate description of the major features describing the pharmaceutical profile of a metal scaffold: (1) its activation, which is essential before the biomolecular target is reached, (2) the undertaken ligand exchange scheme yielding its binding to a biomolecular target, and (3) the ability of metallodrugs to attack multiple targets [9].

This minireview features multiple computational investigations carried out in our group, unveiling the *modus operandi* of Pt-, Te-, Au-, Rh-, Ru-based drugs. The computational studies on the Pt-based arsenoplatin as well as diRh- and diRu-based paddlewheel metallodrugs shed light on the interaction of these metallodrugs with their biomolecular targets, by spotlighting the most likely protein binding sites. The investigation on the Te-based AS101 exemplified the importance of hydrolytic activation and, more specifically, how this feature may impact the biological activity of this species. The study of the Au-based auranofin and its acetylcysteine-based derivative evidenced how the strength of metal-ligand bonds may be pivotal in the mechanism of action of metallodrugs, and provided corroboration to the experimental data demonstrating the different mode of action of these two Au-based complexes.

2 Pt-Based Antitumour Metallodrug: Arsenoplatin

Arsenoplatin-1(AP-1) is a metallodrug that features both the square-planar Pt(II) and the arsenic trioxide bound to it (Fig. 1) [10]. This complex has demonstrated elevated antitumor effects against a multitude of cancers [10, 11]. Nevertheless, the biomolecular basis for the action of this drug is not disclosed yet [12, 13]. A recent study has shown that this metallodrug is able to form the adducts with the DNA of MDA-MB-231 cancer cell line [10]. It was reported that the coordination of DNA via its Pt center induces the collapse of the arsenic center and concomitant release of the cytotoxic $As(OH)_2$ portion. The major target of arsenoplatin is expected to be the guanine nucleobase, which makes this Pt-based scaffold different from other Pt-based complexes which target adenine [14]. At variance from cisplatin, AP-1 attacks DNA nucleobases in its non-aquated form due to the high activation energy of aquation. Therefore, it was shown recently that in bovine pancreatic ribonuclease (RNase A) and hen egg white lysozyme (HEWL) AP-1 may bind at histidine residues, through the the Pt center coordination [10]. This is strikingly different from the protein binding profiles of cisplatin and carboplatin, which were found to preferentially target the Met side chains in RNase A [15]. This distinction is attributed to the As-Pt bond and to the trans effect of As on the reactivity of Pt center. In order to

get a clearer picture of the selectivity of AP-1, our group has studied its reactions with the side chains of histidine, methionine, cysteine, and selenocysteine residues by means of DFT [16]. These protein side chains were modelled with their nucleophilic groups, (imidazole, CH_3S^-, HS^-, and HSe^- for His, Met, Cys, and Sec residues) attached to ethyl (Fig. 1). The computational investigation of thermodynamics revealed that the exchange reactions of AP-1 with only neutral histidine and anionic cysteine and selenocysteine are favourable. Indeed, the reaction energy values for Cys^- and Sec^- are −16.2 and −15.5 kcal/mol, whereas only slight exergonicity is observed for His, the reaction energy being -0.8 kcal/mol. On the other hand, the barriers within the range 15–19 kcal/mol are consistent with fast reactions.

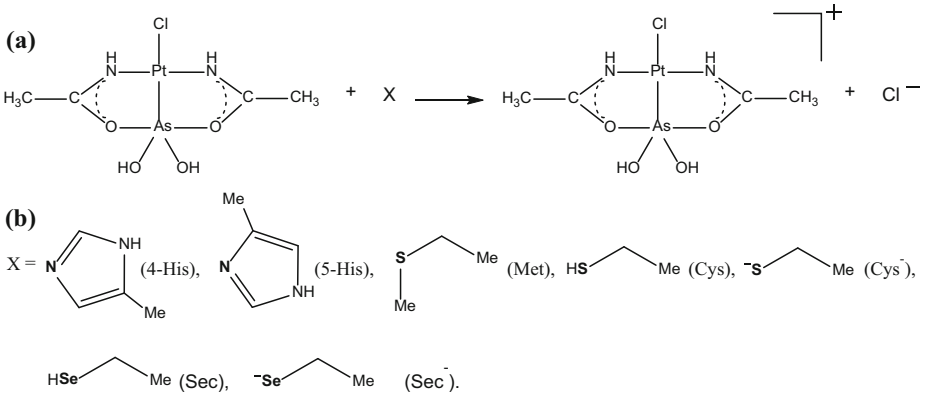

Fig. 1. Studied reaction of AP-1 (a) with the protein residue side chains (b).

3 Te-Based Antitumour Metallodrug: AS101

Not only transition metals but also most metalloids – chemical elements the properties of which include both features of metals and nonmetals – are xenobiotics that can be employed in the synthesis of complexes with extraordinary therapeutic activity [17]. Ammonium trichloro dioxoethylene-O,O′ tellurate (AS101, Fig. 2) is the first Te-based complex that has entered the clinical phase of development, which demonstrates immunomodulatory activity and is used against a plethora of diseases, including chemotherapy-induced thrombocytopenia, acute myeloid leukemia, HIV, psoriasis, and dermatitis [18, 19]. AS101 targets thiol-containing biomolecules, for example, cysteine proteases [20]. This scaffold has also found an application in the development of organotelluranes via the substitution of its chloride ligands with various halides [21].

There is a general consensus that AS101 needs to be activated via the aquation in order to yield the species $TeOCl_3^-$ which in turn attacks the thiols [22]. This mechanism suggests the crucial role of the aquation in the mode of action of this metalloid-based drug. In order to study the effect of various ligands on the aquation of AS101, its bromido- and iodido-based derivatives were synthesized, and their reactivity was studied via a joint

experimental-theoretical approach [23]. It was demonstrated that the aquation of AS101 became more likely with moving down in the halogens' group.

Hydrolysis of AS101 and its bromide and iodide derivatives includes two attacks of the water molecules which result in the glycol detachment and formation of $TeX_3(OH)_2$, with X = Cl, Br, or I (Fig. 2), followed by dehydration which yields the product TeX_3O^-. The DFT study has shown that the reaction free energies of the aquation were quite high, i.e., 13.0, 9.9, 9.4 kcal/mol for Cl, Br, and I, respectively. Nevertheless, the reaction rate determining barriers were 23.8, 21.9, and 20.5 kcal/mol for Cl, Br, and I, thus consistent with kinetically viable reactions. Taking into account the 20-fold excess of water in experimental conditions and assuming the second-order reaction ($v = k[\text{reactant}][H_2O]$), the activation barrier estimates were further refined by –1.7 kcal/mol, thus yielding the activation free energies 20.5, 19.7, and 17.0 kcal/mol for the Cl-, Br-, and I-based complexes, respectively.

These DFT results discloses a tight correlation between the basicity of oxygens of the chelating glycol and the nature of halide ligands on the Te center. With the diminishing of electronegativity of halides, the enhancement of oxygen basicity is observed, thus the reaction barriers trend is I < Br < Cl. As a result, the hydrolysis of the Cl-based AS101 is the least favorable, whereas the I-based compound features the highest rate.

This investigation exemplifies the way in which a small alteration of the chemical scaffold of AS101 results in disparity in the activation barrier and conceivably distinctive biological behaviour. Indeed, the study demonstrates a perfect agreement between the computational and experimental results, which show the increase of cytotoxicity moving down the group of halogens, i.e., from AS101 to its iodide-based derivative.

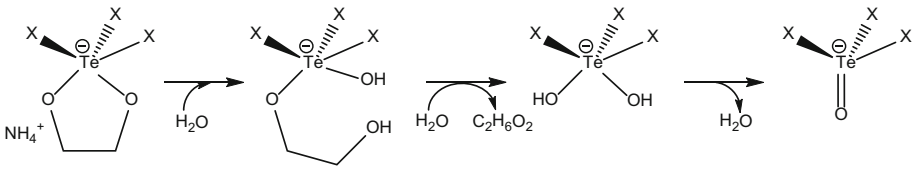

Fig. 2. Hydrolysis of AS101 (X = Cl) and its halide derivatives (X = Br, I).

4 Au-Based Metallodrug: Auranofin

Gold-based complexes have been employed in medicine for many centuries due to their unique antirheumatic, anticancer and anti-infective properties [24–26]. Recently, gold complexes have drawn the attention of medicinal chemists as perspective agents against bacterial infections in the framework of drug repurposing strategy [27]. Auranofin (1-thio-β-D-glucopyranosatotriethylphosphine gold-2,3,4,6-tetraacetate, AF, Fig. 3) is the most known Au(I)-based compound [28]. Its repurposing as an antibacterial drug eventuated exceptionally auspicious [29].

AF has been found out to be efficacious against Gram-positive strains, yet demonstrating inferior activity against Gram-negative bacteria [30, 31]. Nevertheless, the accurate understanding of its *modus operandi* on a biomolecular level is largely missing.

There is a general consensus that its gold center targets thiol- and selenol-containing proteins, thus impeding their crucial cellular functions [32]. Indeed, gold-based complexes were proven to proficiently inhibiting the thiol-redox balance via hampering the activity of thioredoxin reductase. Other presumed pharmacological targets of AF were DNA, procariotic cell wall, and bacterial protein biosynthesis machinery [32]. In 2009, on the basis of an investigation of AF activity against the oral bacterium *Treponema denticola,* it was proposed that AF inhibits the selenium metabolism, thus impeding the production of selenoproteins due to the subtracted accessibility of Se indispensable for the production of essential bacterial proteins [33]. Indeed, multiple computational studies also demonstrated the selectivity of AF toward selenocysteine [32]. On the other hand, the marginal inhibition of Gram-negative bacteria is probably caused by the impermeability of the outer membrane [34].

The general consensus is that the $[Au(PEt_3)]^+$ cation forming after the activation of auranofin, i.e. the detachment of thiosugar in the aqueous/biological milieu, is the true pharmacophore [35]. Taking into account this activation mechanism, the substitution of thiosugar, which is non-crucial from the pharmacological point of view, with other ligands is a viable approach to the synthesis of novel auranofin analogues.

In a recent study, an AF derivative was synthesized with the acetylcysteine ligand linearly attached to the gold(I) center (AF-AcCys, Fig. 3) and its antibacterial effects were investigated [36]. Biological experiments comparing the antibacterial activity of AF-AcCys and AF included the inhibition of *S. aureus*, in which both drugs demonstrated the same efficacy, and the application against *S. epidermidis*, in which AF-AcCys showed an abrupt activity drop. With the aim of elucidating the impact of the ligand replacement, we performed the DFT calculations of the energies required for the breaking of the bond between Au and its ligands in AF and AF-AcCys. It was shown that the Au-S bond in AF-AcCys (bond dissociation enthalpy of 51.8 kcal/mol) is slightly more stable in comparison with the Au-thiosugar bond in AF (49.8 kcal/mol). The Mulliken charges analysis corroborated that the stronger Au-S bond in Au-AcCys emerges from the greater electrostatic character of the bond as compared to the same bond in AF. Hence, calculations showed that the activation profiles of AF-thiosugar and AF-AcCys are similar, yielding comparable amounts of released active species $[AuP(Et)_3]^+$. Thus, the lower lipophilicity of AF-AcCys, rather than the slight difference in Au–S bond enthalpies, may better account for the diverse antimicrobic activity of this AF analogue, i.e., active on *S. aureus* and much less active on *S. epidermidis* [34].

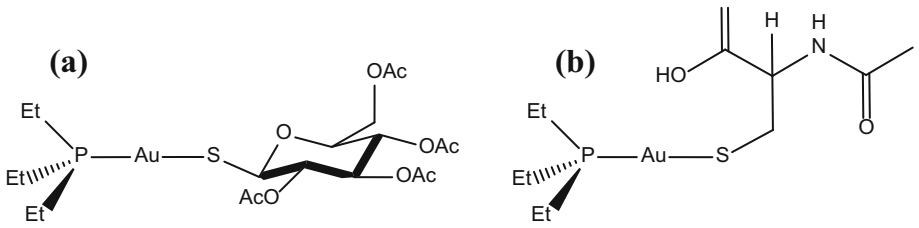

Fig. 3. Structures of auranofin (a) and its acetylcysteine analogue (b).

5 DiRh- and diRu-Based Paddlewheel Metallodrugs

Dirhodium and diruthenium complexes with the general formula $[M_2(O_2CR)_4]L_2$ (M = Rh, Ru; R = CH_3^-, $CH_3CH_2^-$, etc., L = solvent molecule or anionic ligand) have been long known in the field of metal-complex-mediated catalysis, nevertheless, their appreciable cytotoxicity drew the attention of the medicinal chemists [37, 38]. Despite similar structure incorporating four carboxylate bridging ligands positioned in a lentern-like fashion around the axial dimetallic center, the paddlewheel complexes based on Rh and Ru atoms demonstrate different patterns of reactivity.

The dirhodium paddlewheel complex is efficient versus various cancer lines, namely, Ehrlich-Lettre ascites carcinoma [38], L1210 tumors [39], sarcoma 180 [37], and P388 leukemia [37]. However, the basis of its biomolecular action remains largely undisclosed. It is assumed that it attacks amino acids [40, 41], peptides [42, 43], proteins [44, 45], single- and double-stranded DNA [37]. Rh compounds form adducts with proteins by means of direct coordination of metal center [46, 47] or non-covalent interaction between Rh ligands and protein residues, i.e., dative anchoring [45]. Experiments reveal that the $[Rh_2(\mu\text{-}O_2CCH_3)_4]$ complex binds selectively to side chains of protein residues Asn, Asp, His, Lys, as well as the C-terminal carboxylate [45, 48].

Ru-based complex $[Ru_2(\mu\text{-}O_2CCH_3)_4Cl]$ possesses a (II,III) mixed valence type defined by the availability of three uncoupled electrons [49]. While this compound exists in the form of polymer incorporating bimetallic members bridged by chlorides in solid state, the monomeric structure emerges in solution, yielding either $[Ru_2(\mu\text{-}O_2CCH_3)_4(H_2O)Cl]$ or $[Ru_2(\mu\text{-}O_2CCH_3)_4(H_2O)_2]^+$ complexes [50]. Experimental evidence on selectivity of these complexes in biological milieu is largely non-existent, except for its interactions with proteins [44, 45, 48]. The crystallographic data demonstrated the formation of adducts of these Ru-based complexes and aspartate side chains [51].

Several recent computational studies performed by our group investigated the selectivity of paddlewheel bimetallic complexes $[Rh_2(\mu\text{-}O_2CCH_3)_4(H_2O)_2]$, $[Ru_2(\mu\text{-}O_2CCH_3)_4(H_2O)Cl]$, and its hydroxo form $[Ru_2(\mu\text{-}O_2CCH_3)_4(OH)Cl]^-$ for binding to various protein residue side chains and protein terminals: Arg, Asn, Asp, Asp^-, C-term, $C\text{-term}^-$, Cys, Cys^-, His, Lys, Met, N-term, Sec, Sec^- (paddlewheel complexes at Fig. 4, models of side chains Figs. 1 and 4) [52, 53]. DFT calculations were employed for studies of thermodynamics and kinetics of the ligand exchange reactions at axial sites of the paddlewheel scaffolds. In particular, the pseudo-molecular model was adopted to model the approach of the protein site to the diRu and diRh paddlewheel complexes and to allow the optimization of reactant and product adducts (RA and PA, respectively) and the connecting transition state structures (TS) at the PCM/ωB97X/def2SVP level of theory. The energy of the optimized pseudo-molecular models was then recalculated at the ωB97X/def2TZVP level of theory to provide for more accurate estimate of thermodynamics and kinetics of protein sites binding of diRu and diRh complexes.

The study of the thermodynamics for the reactions of the axial ligand exchange indicated that the dirhodium complex showed a little selectivity, reacting favorably with all the studied protein side chains. It was concluded that the main targets of this scaffold in physiological conditions are Asp^-, $C\text{-term}^-$, His, and Sec^-, based on the calculated Gibbs free energies and the experimental factors such as their most probable protonation states

and likely degree of their solvent-accessibility. The same selectivity is demonstrated by the diruthenium complex in case when the axial water is substituted. Nevertheless, the exchange of Cl plays a major role at higher pH, when the basic side chains (Arg, Lys, His) are deprotonated, thus becoming the likely targets of the Ru(II)Ru(III) scaffold upon the chloride cleavage.

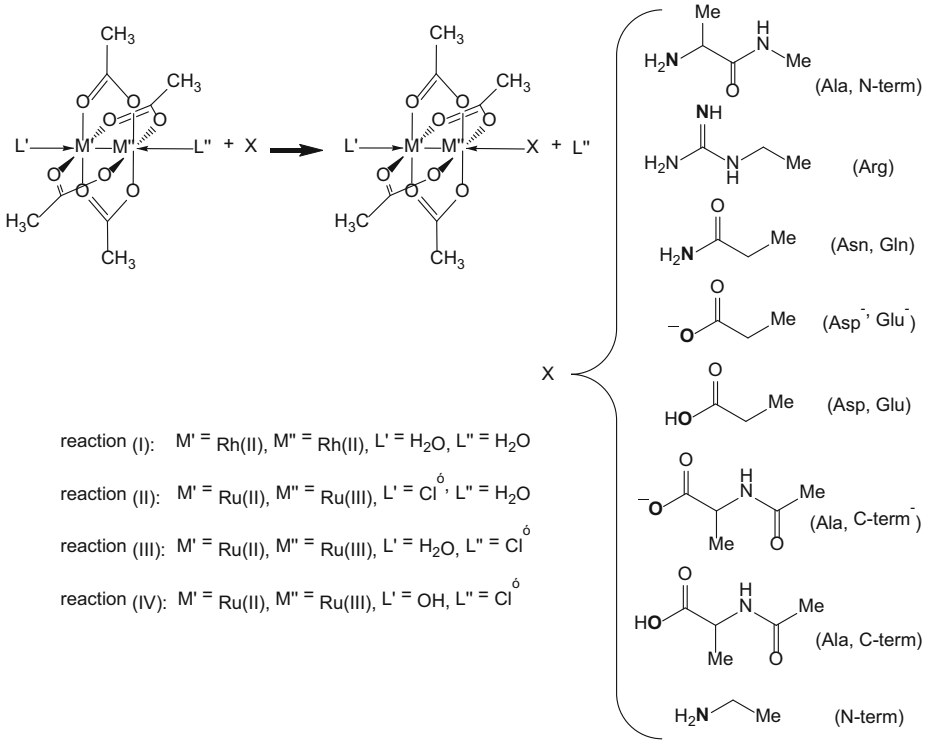

Fig. 4. The substitution reactions I-IV between the studied complexes $[Rh_2(\mu\text{-}O_2CCH_3)_4(H_2O)_2]$ (reaction I), $[Ru_2(\mu\text{-}O_2CCH_3)_4(H_2O)Cl]$ (II, III), $[Ru_2(\mu\text{-}O_2CCH_3)_4(OH)Cl]^-$ (IV), and selected protein side chains (X).

Furthermore, the results unequivocally indicate that occupation of the axial position by soft ligand, e.g. Sec^- and His, is able to weaken the metal-metal bonds in either Rh- or Ru-based complexes with bare or negligible destabilization of the bridging acetates' coordination. Taking into account that the principal impact was observed in Ru-based paddlewheel complexes, it was observed that these scaffolds are more likely to yield two monometallic parts, therefore disrupting the μ-coordination of carboxylate ligands. Furthermore, the availability of several neighbour nucleophiles in the protein may produce a synergetic effect via the multiple binding to the metals – a sort of chelate-effect; such a concerted effort would weaken the stability greatly. Hence, there exists a robust thermodynamic stimulus to the bimetallic complex disruption if several coordination sites are situated in the same region of the biomolecular target, i.e. in proximity one from another,

indicating that the preferred targets of these complexes are the tiled regions, whereas the effects of other parameters, such as the pH, the solvent's nature, the composition of the bulk, may be less significant.

Computational investigation of the reaction kinetics showed that the acidic milieu assists the reactions including the substitution of water at the axial position (reactions I and II), providing the thermodynamic control for these reactions, thus shifting the selectivity in favor of Arg, Cys^-, and Sec^- (Fig. 4). On the contrary, at the elevated pH the availability of the hydroxo over the aquo form in the paddlewheel complexes is favoured. Thus, the water bound at the axial site deprotonates to a hydroxide, inducing the chloride exchange feasible (reaction IV). The analysis of the geometrical structures of transition states disclosed that the early or late nature of transition state affects the sterical hinderance of the paddlewheel scaffolds onto the selectivity for targeted protein residues. For example, when the transition state is early, the attacked ligand is far from the bimetallic axis of the paddlewheel scaffold. This results in its bridging ligands being at a substantial distance from the approaching nucleophile, which guarantees a marginal steric effect (reactions I and II). On the other hand, when the transition state has an intermediate or late nature, the steric clash between the bulky bridging and the incoming ligands is more probable (reactions III and IV).

Reactions I-IV with His are characterized by TS geometries of notable earliness/lateness of the axial ligand (water or chloride) substitution. Figure 5 presents both the Ru–N and Ru–O/Cl distances, i.e. the metal center-incoming/leaving ligand distances. We also indicate the distances between the methyl of proximal bridging acetate of the metal scaffold and the 4-methyl group of imidazole, this parameter representing the possible steric contact for the attack of the metal complex onto the protein residue. Figure 5 shows that the transitions states for reactions I and II are early, being characterized by the elongated distances between metal and the approaching ligand (augmented by 90–98% with respect to their lengths in corresponding minima). Conversely, these bonds are enhanced slightly (1–7%) in the case of reactions III and IV which exemplify customary late transition states. Moreover, the late nature of the transition states in reactions III and IV also necessitates a more immediate contact of the metal complex and the nucleophilic site of the protein residue. For instance, the smallest distance between the methyl of the closest bridging carboxylate in the metal scaffold and the 4-methyl group of imidazole diminishes by 1.7–2.0 Å with respect to corresponding structures in reactions I and II. This indicates the crucial influence of the steric impediment originating from the metal complex onto the chloride substitution. As shown recently [54], bulky ligands decoring the paddlewheel scaffolds can be exploited to fine-tune their reactivity towards biomolecular targets and as a new design strategy in the development of paddlewheel metallodrugs.

It is demonstrated that the reaction IV featuring the presence of hydroxo complex should be considered as the most advantageous. Indeed, the complex $[Ru_2(\mu\text{-}O_2CR)_4(OH)Cl]^-$ reveals a substantial selectivity toward Lys, Cys^-, and Sec^- and an intrinsic susceptibility to produce early TS structures in the reaction with the protein residue side chains caused by the steric obstruction originating from availability of bulky bridging ligands.

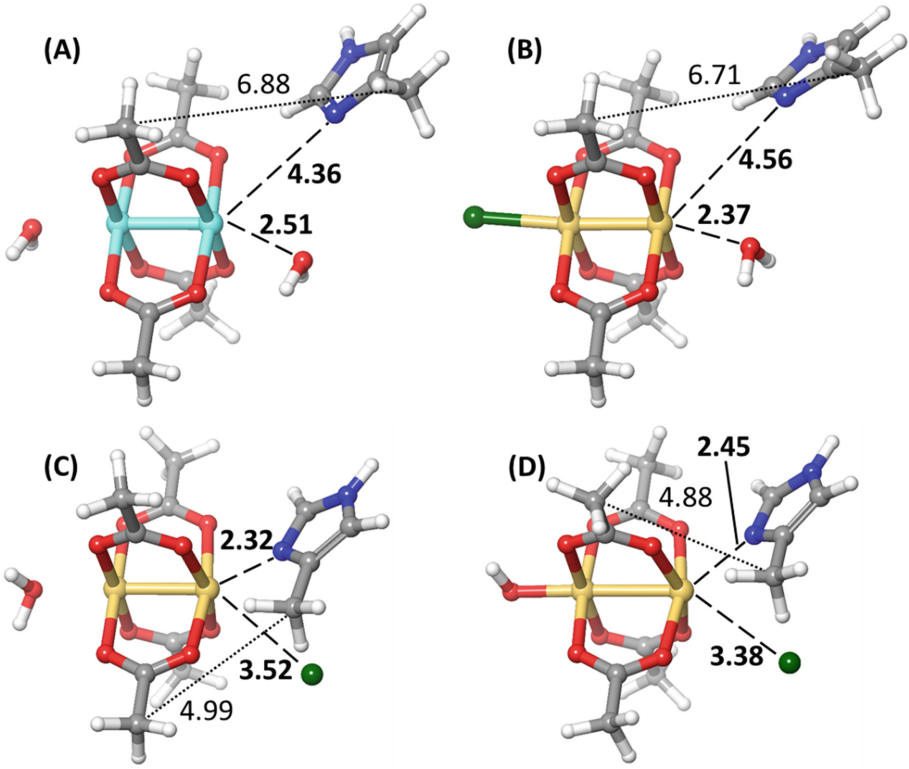

Fig. 5. Transition state geometries for the substitution reactions of the studied metal complexes with His: (A) $[Rh_2(\mu\text{-}O_2CCH_3)_4(H_2O)_2]$ (reaction I), (B, C) $[Ru_2(\mu\text{-}O_2CCH_3)_4(H_2O)Cl]$ (reactions II and III), (D) $[Ru_2(\mu\text{-}O_2CCH_3)_4(OH)Cl]^-$ (reaction IV). Dashed lines denote the distances between metals and approaching/leaving ligands, these values are **bold**. Dotted lines shows the distances between the 4-methyl group of imidazole and the closest C atom of the carboxylate methyl group. Colour scheme: Rh (cyan), Ru (faded orange), Cl (green), O (red), C (carbon), H (white). All distances in Å. (Color figure online)

The combination of these effects, i.e., (1) acidic pH, (2) accessibility of Lys, Cys^-, and Sec^- residues, and (3) the presence of steric constraints from the equatorial ligands, may result in the augmented selectivity of $[Ru_2(\mu\text{-}O_2CR)_4(OH)Cl]^-$ for thioredoxin reductase overexpressed in cancer cells.

6 Computational Perspective

DFT is broadly utilized in the domain of bioinorganic and organometallic chemistry [55–57]. Its employment permits the mechanistic description of the processes important for understanding the *modus operandi* of metallodrugs, such as metallodrug activation, its selectivity toward various biomolecular targets. This is done by means of optimizations of geometries of constituents of the investigated system, i.e., metallodrug and its targets,

as well as the calculations of reaction energy and activation energy which depict the thermodynamics and kinetics of the process.

There exist a plethora of computational chemistry software which provides the necessary capabilities for fast and efficient DFT calculations. Our group uses the Gaussian 16 modification of this ubiquitous program [58]. We usually use the memory 48 GB and 24 processors for the DFT calculations (%mem = 48 GB, %nprocshared = 24). The CPU time is 20–30 h for a standard job (geometry optimization) on a molecular system containing 60–70 atoms.

The most important parameters affecting the DFT computation results are the appropriate choice of density functional, basis set, and the methodology describing the solvation [59]. The long-range-corrected density functionals demonstrate an excellent accuracy in geometrical optimization and energy calculation, which originates in the long-range correction which significantly reduces the self-interaction error of the exchange integral kernel, which is the derivative of the exchange potential in terms of density [60]. Moreover, long-range correction also substantially augments the quality of description of van der Waals bonds. Our group uses the long-range-corrected functional ωB97X [61] for description of the chemistry behind the interactions of metal centers and biomolecules [62].

The selection of a basis set adequate to the investigated system is another major factor for the successful characterization of the system. The metal ions are usually described via the application of the conventional basis set functions to define the valence electrons and effective core potentials, which depict the effects of the core-electrons and account for the relativistic effects [63, 64]. The standard choice is the employment of double- and triple-zeta quality basis sets for the optimization and energy computation for the valence electrons. Indeed, bond distances and angles are generally reputed to be adequately described via the use of double-zeta basis sets. Therefore, the use of smaller basis sets in geometry optimization runs also improves the localization of minimum and saddle points of the potential energy surface, e.g. by easing the employment of optimization algorithms based on the analytical Hessian. On the other hand, the electronic energies of the optimized structures can be significantly improved by the use of larger basis sets allowing a more accurate description of the electron density distribution within the molecular system.

The studies performed in our group and presented in the present minireview allow us to draw important conclusions on the effects of various parameters for the computation. The investigations of the reactivity of arsenoplatin as well as the diRh- and diRu-paddlewheel complexes with the protein residue side chains underline the importance of adoption of the smaller models for the biomolecular systems. Without such a facilitation, it is impossible to portray the biomolecular system usually consisting of bulky constituents. The simplified models of the protein side chains that we use are limited by size, yet they are an optimum choice for including the electronic and steric effects originating from the nucleophilic part of the protein side chains.

The investigation of the hydrolysis of the Te-based scaffold AS101 demonstrates the importance of the detailed mechanistic understanding of the very first reaction many metallodrugs may undergo in the physiological milieu, i.e., the hydrolytic activation. This study has shown that alteration of Cl ligands in the native AS101 scaffold to the

halides Br and I substantially modifies the behaviours of the drug by augmenting its activation rate. This is an excellent example of how the theoretical approach can interpret the impact of metal ligands changes to the speed of its transformation in the active form, thus affecting its pharmacochemical profile.

The DFT analysis of the strengths of the metal ligand bonds in auranofin and its acetylcysteine-based derivative has shown that the particular selection of the softer ligands for Au, a transition metal center of an intermediate yet slightly soft nature, permits to stabilize the bond to the point that it changes biological activity of the metal scaffold.

These theoretical data may be particularly useful in the design of AF analogues that need to be promptly activated in the site of administration.

The DFT-optimized geometrical structures of transition states in the diRh- and diRu-paddlewheel complexes demonstrated the effects of the bulky equatorial ligands in these lantern-shaped complexes on their selectivity. It was shown that the presence of the late transition state results into the steric clash between the bridging ligands and the entering nucleophile, thus increasing the barrier for this type of reactions, resulting into unfavourable kinetics. Moreover, it was shown that the acidic pH leads to the deprotonation of the axially bound water in the Ru-based complex, thus substantially strengthening its bond to the bimetallic unit and making the cleavage of Cl more favourable. It yields a better selectivity toward the thiols and selenols, typical targets for anticancer drugs.

7 Conclusions

Metallodrugs constitute an invaluable reserve of novel therapeutical agents against cancer, parasitic, viral, and bacterial infections. Their capability to produce various geometries originates in the unique features of transition metals, i.e., ability to assume a wide range of oxidation states and various electronic configurations. Moreover, the addition of electron-donating/withdrawing ligands allows to modulate the electrophilicity of metal centers, whereas the incorporation of bulky or electrically charged ligands allows the fine-tuning of their steric features and the strength of the metal-ligand bonds. These modifications permit to calibrate the selectivity of metal centers which tend to exhibit a substantial promiscuity versus various biological nucleophiles.

This minireview showcases several computational studies on the reactivity of Pt-, Te-, Au-, Rh-, Ru-based metallodrugs in the biological milieu, performed by our group. This short account emphasizes particularly the effects of the structure of these metal complexes and their environment. Indeed, all of the described investigations serve as the valuable examples of the consequences of the particular geometrical structure and specific choice of the ligands onto the selectivity of metal scaffold. On the other hand, the studies on the hydrolytic activation of AS101 and the reactivity of the paddlewheel complexes in the acidic pH corroborate the crucial effects of the milieu in which the metallodrug is administered onto its reactivity.

It is shown that the DFT computations permit to accurately characterize the behavior of metallodrug in physiological conditions. The computational description of the *modus operandi* of a metal complex is a valuable tool *per se* or as a part of a joint experimental-theoretical approach. It allows to carefully define its activation mechanism, its selectivity

toward various biomolecular targets, and the possible effects of modification of its structure on its behavior. That is why the *in silico* studies are an essential tool in the apparatus of modern bioinorganic chemistry.

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