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Theoretical investigation of the reduction potential of ruthenium(III/II) complexes with potential antitumor activity and their interactions with biological targets

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Abstract: Complexes of Ruthenium (II and III) have attracted the interest of the scientific community as potential antitumor drugs, thanks to their low toxicity and ability to overcome drug resistance [1]. Although Ru metallodrugs exhibit antitumor activity in both oxidation states, the Ru (III) metal ion is likely to be reduced to Ru (II) in vivo. In this way, Ru (III) complexes would act as a prodrug, which is activated byreduction in vivo to bind more efficiently to the biological target . There are currently two antitumor compounds of ruthenium(III) in the clinical phase, thanks to their ample anti-neoplastic activity: *trans*-tetrachloro (dimethylsulfoxide) imidazole ruthenate(III) [Im]trans-[RuCl4(Im)(DMSO)] (NAMI-A) and *trans*-[tetrachlorobis (1H-indazole) ruthenate(III) [IndH]trans-[RuCl4(Ind)2] (KP1019). It is believed that in the mechanism associated with these Ru(III) complexes, activation by reduction and exchange of chloride ligands by water molecules of the solvent (hydrolysis or aquation) are two important steps for the antitumor function of such metallodrugs Based on experimental observations, three events are connected with the biological activity of NAMI-A and KP1019: i) Reduction of the Ru(III) center, (ii) chloride exchange reaction with water molecules of the solvent medium and (iii) interaction with the biological targets. The sequence of the events will depend, on the kinetics of these reactions and also on the reduction potential of the species, chloride concentration and thermodynamic stability of the complexes formed. In this work we employed the Density Functional Theory

(DFT), at the TPSSh/Def2-TZVP level, in combination with the SMD continuum solvation model, to investigate the electrochemistry of NAMI-A, KP1019 and their hydrolysis products as well as the thermodynamics of their interactions with S-donor (cystine (Cys), glutathione (GSH)) and N-donor (guanine at the coordination sites N3 and N7) biological molecules. Our results show that the compounds exhibit different electrochemical behavior upon hydrolysis. The reduction potential of NAMI-A is sensitive to the degree of hydrolysis, increasing with the number of chloride ligands replaced by water. On the other hand, the reduction potential of KP1019 does not vary with the hydrolysis and remains almost constant. The calculations showed that for both complexes the thermodynamics of the hydrolysis processes are extremely favorable and the Gibbs free energy calculations for the successive hydrolysis reactions revealed that all chloride ligands can be favorable replaced by water. Interestingly, the Gibbs free energy for the chloride exchange by water varies linearly with the number of water, that is, the ΔG for the second hydrolysis is twice the valor for the first hydrolysis and the free energy for the third hydrolysis is three times the value for the first hydrolysis. This trend is observed for both the NAMI-A and KP1019 complexes. Our results shows that thermodynamically, the NAMI-A and KP1019 complexes are reduced first and undergoes hydrolysis after, since the free energy involved in the reduction process of the complexes is more negative. Our results are shows that the NAMI-A complex have more affinity for the S-donor ligand glutathione (ΔGsol = -24.5 kcal/mol and ΔGsol = -30.8 kcal/mol for the circular and extend forms, respectively) than for the guanine base (ΔGsol = -0.4 kcal/mol for the interaction at the N7 site). On the other hand, for the KP1019 complex, the only favorable interaction in solution is with guanine at the N7 site, with ΔGsol = -4.8 kcal/mol. Interaction with the S-donor ligands are unlikely to happen, with for the interaction with cysteine and 11,01 and 18.6 kcal/mol for the interaction with glutathione extend and circular form, respectively.

Key-words: **NAMI-A, KP1019, electrochemical behavior, biological activity**
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