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Mechanism of aquation and nucleobase binding of ruthenium (II) and osmium (II) arene complexes: A systematic comparison DFT study

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ABSTRACT

A systematic mechanistic study is reported for the aquation and nucleobase binding process of a series of Ru^{II} and Os^{II} arene-based anticancer drug complexes using density functional theory and COSMO implicit solvent model. The structures of Ru^{II} and Os^{II} complexes are similar to each other because of lanthanide contraction of osmium. However, the aquation was substantially more facile for Ru^{II} complexes than Os^{II} complexes. As to nucleobase substitution, various possible paths were explored based on considering the initial conformation of ethylenediamine (en) and the orientation of guanine (G) and adenine (A). Both Ru and Os complexes exhibited much lower free energy barrier for G than A. This observed predominance toward G mainly originated from larger stabilization energy for the initially formed complex, compared with A, in combination with favored kinetics and thermodynamics. Moreover, the calculations indicated that pK_as of Os-bound water molecules were uniformly much lower than those of Ru-bound water molecules. Analysis of the natural bond orbital (NBO) charge reveals that Os^{II} has a higher net positive charge than Ru^{II}, leading to a stronger electrostatic attractive interaction between Os^{II} and chloride or water, resulted in higher activation barrier for their departure. These differences between Ru^{II} and Os^{II} en complexes discussed in our study may partly explain the inertness of the Os^{II} complexes in biological system.

1. Introduction

It is well-accepted that the most widely used anticancer compounds in chemotherapy, platinum-based drugs, bind to genomic DNA in the cell. Despite their success, these agents exhibit a number of dose-limiting side-effects, including fatigue, nausea, nephro- and neurotoxicity, and the issue of acquired resistance [1,2]. There is need for new metal-based drugs that offer better viability, which might help to overcome existing chemotherapeutic limitations.

Because of the diversity in coordination chemistry of ruthenium, much effort has been directed in the last decade towards Ru-centered anticancer drugs [3–5]. Based on the model of cisplatin, some ruthenium (III) complexes have demonstrated favorable antitumor properties toward a number of in vitro and in vivo tumor models while showing lower systemic toxicity than platinum(II) compounds [6–8]. Among them, NAMI-A and KP1019 have recently completed phase 1 clinical trials [7]. Another group of cytotoxic Ru compounds are Ru^{II} arene complexes, which have emerged as promising antitumor compounds [9–30]. The complexes are stable and water-soluble, and their frameworks provide considerable scope for optimizing the design, due to their large diversity of structure and binding modes. Ruthenium arene complexes of formula $[(\eta^6\text{-arene})Ru(en)(Cl)]^+$ (en = ethylenediamine) has been investigated extensively [20–29]. Similar to cisplatin, Ru arene complexes undergo aquation before reaching its intracellular target DNA, and show exceptional cytotoxicity toward cisplatin-resistant cells. Chemical and spectroscopic studies reveal the predominant preference for guanine (G) over other nucleobases, being even more pronounced than cisplatin [20–29]. This specificity for G is aided by strong H-bonding between an NH of en and C6 carbonyl of G, and by π–π stacking involving the extended arene and DNA bases [23–27]. Very recently, the chemical and biological activity of analogous half-sandwich osmium arene complexes is becoming an active area of research [17,31–42]. Osmium complexes show

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a notably different chemical activity and pharmacological profile despite being in the same group with ruthenium. Certain classes of organometallic Os^{II} arene complexes appear to have promising in vitro cancer cell activity and their aqueous reactivity appears to be tunable. Half-sandwich Os^{II} arene complexes of the type [(η^6-arene)Os(XY)Cl] where XY = N,O-chelating ligands such as picolinate showed promising activity toward human lung and ovarian cancer cells [35–39]. In addition, [(η^6-arene)Os(en)(Cl)]$^+$ exhibited much slower hydrolysis than their Ru^{II} analogs, and was found to be as cytotoxic to human A549 lung and A2780 ovarian cancer cells as the drug carboplatin, but only at ambient temperature in the dark [40,41].

Several theoretical papers have been published on the reactivity of Ru^{II} and Os^{II} arene anticancer complexes [29,42–48]. Recently, the aquation processes (substitution of X by H_2O) of Ru^{II} arene complexes were investigated using the DFT (PW91) method [29]. The binding energies between the metal (Ru and Os) centers and the surrounding ligands were investigated with DFT, and the results were in good agreement with data obtained using electrospray ionization mass spectrometry [42]. A study on structural and energetic properties of organometallic Ru^{II} diamine anticancer compounds and their interaction with nucleobases using the DFT (BP86) and MP2 calculations together with Car-Parrinello molecular dynamics has been reported by Rothlisberger and coworkers [43,44]. They also investigated the binding processes of two Ru^{II} arene complexes to double-stranded DNA and characterized the resulting structural perturbations using classical and QM/MM molecular dynamics simulations [45]. More recently, the structure, stability and reactivity of [(η^6-arene)Ru^{II}(en)Cl] were further characterized by Burda using several theoretical methods [46].

Arene metal complexes exhibit a rich structural diversity and can be fine-tuned by changing the nature of the metal center (Ru^{II} or Os^{II}) or of the arene ligand, or by introducing a chelating ligand [9–42]. Here we have studied a series of Ru^{II} and Os^{II} arene complexes [(η^6-arene)M(en)Cl]$^+$ as shown in Scheme 1, in which **1**&**2**, **3**&**4** and **5**&**6** differ in their central metals and **1**&**3**&**5** and **2**&**4**&**6** differ in their arene ligand. In the first part of the present study, we explored the similarities and differences in the aquation for Ru and Os complexes. Subsequently, the nucleobase substitution of Ru and Os complexes was examined. Finally, we investigated the pK_a of the complexes to further understand the aqueous chemistry of this type of arene complexes. We have sought to correlate their differences in aqueous reactivity and nucleobases binding with cytotoxicity toward cancer cells from thermodynamic and kinetic point of view.

2. Computational details

The general structure of this class of complexes is drawn in Scheme 1, where a pseudo octahedral arrangement of the Os and Ru is assumed. The compounds of [(η^6-arene)M(en)Cl]$^+$, (η^6-arene = *p*-cymene (*p*-cym), benzene (benz), biphenyl (bip), M = Ru^{2+}, Os^{2+}) were examined using DFT methods with B3LYP hybrid functional [49,50], which was demonstrated to be an effective tool for the theoretical studies of metal complexes [46,51,52]. The 6–31G** basis sets were employed for H-, C-, N-, O- and Cl-atoms, and the LanL2DZ basis set was employed for Os and Ru [53–55], labeled as BS1. Geometry optimizations were then redone using the COSMO implicit solvent approach with dielectric constant $\varepsilon = 78.36$ [56,57]. Thermal energies were extracted from vibrational frequency calculations, which were used to verify the correct nature of the stationary points at 298.15 K and 1 atm. The frequency calculations also served for confirmation of the correct character of transition state (TS) structures as well as reactant and product (super) molecules. The natural bond orbital (NBO) analysis was performed at BS1 level [58,59], which was implemented in the Gaussian 03 program [60]. To obtain accurate energies for the reaction surfaces, single-point energies were further calculated based on the COSMO optimized structures using a higher basis set of LanL2DZ-(f) used for Ru and Os ($\zeta_f = 1.235$ for Ru and $\xi_f = 0.886$ for Os) [61] and 6–311++G** for all other atoms, labeled as BS2.

As Scheme 2 shows, the first reaction profile determined was the substitution of chloride by water, namely, aquation; the second reaction profile was the replacement of the aqua ligand with model nucleobases (G and adenine (A)), because they are the preferred nucleotide binding sites for many transition metal ions. Reaction rates were calculated for aquation and nucleobase substitution using transition state theory. The Eyring equation was employed to obtain the rate constant, *k*. The standard concentration ($c_0 = 1$ mol/L) was considered:

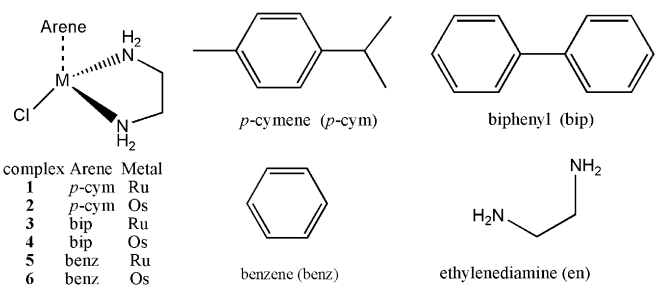
$$k = (k_B T/h)\exp(-\Delta G^{\neq}/RT) \quad (1)$$

where k_B is the Boltzmann constant, *T* is the absolute temperature, *h* is the Planck constant, and $\Delta G^{\neq}$ is the activation free energy [62].

Models were create with the aqua adducts deprotonated to form the inactive hydroxo species depending in the solution pH as shown in Scheme 2. The pK_a value of a compound indicates the relative concentrations of the protonated and deprotonated forms in a solution of given pH [63–65],

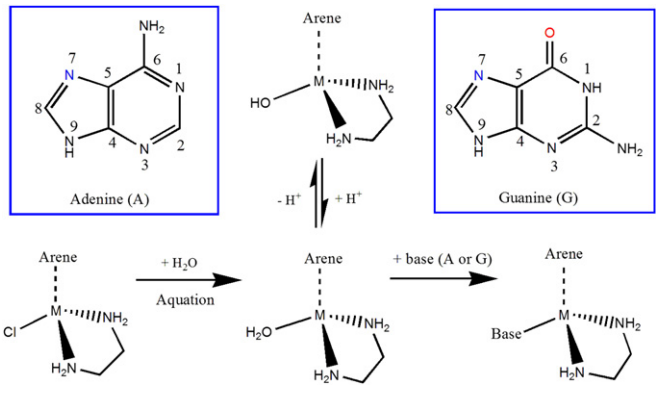
$$pK_a = \Delta G_{sol}/(2.303RT) \quad (2)$$

where ΔG_{sol} is the Gibbs free energy at 298 K for the deprotonation reaction, calculated as described in Scheme 3, *R* is the gas constant, and *T* is the temperature. Experimental values for $G(H^+_{gas}) = -6.28$ kcal/mol and $\Delta G_{sol}(H^+) = -264.61$ kcal/mol have been adopted in the calculation [63–65]. Except for NBO



complex	Arene	Metal
1	*p*-cym	Ru
2	*p*-cym	Os
3	bip	Ru
4	bip	Os
5	benz	Ru
6	benz	Os

Scheme 1. Chemical structures of [(η^6-arene)M(en)Cl]$^+$.



Scheme 2. Aqueous solution chemistry and nucleobase substitution of [(η^6-arene)M(en)Cl]$^+$.