Computational studies of the electronic, conductivities, and spectroscopic properties of hydrolysed Ru(II) anticancer complexes

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HIGHLIGHTS

- We computed the spectroscopic and conductivity properties of Ru(II) anticancer complexes.
- Complexes geometries were optimised with PBE0 hybrid DFT.
- QTAIM was used to analyse the spectroscopic properties and thermodynamic changes.
- Mechanism of hydrolysis and anticancer properties were compared.

GRAPHICAL ABSTRACT
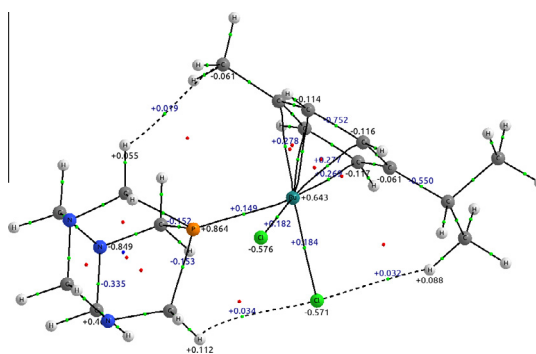
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ABSTRACT

The mechanism of activation of metal-based anticancer agents was reported to be through hydrolysis. In this study, computational method was used to gain insight to the correlation between the chemistry of the hydrolysis and the anticancer activities of selected Ru(II)-based complexes. Interestingly, we observed that the mechanism of activation by hydrolysis and their consequential anticancer activities is associated with favourable thermodynamic changes, higher hyperpolarizability (β), lower band-gap and higher first-order net current. The Fermi contact (FC) and spin dipole (SD) are found to be the two most significant Ramsey terms that determine the spin–spin couplings (J(HZ)) of most of the existing bonds in the complexes. Many of the computed properties give insights into the change in the chemistry of the complexes due to hydrolysis. Besides strong correlations of the computed properties to the anticancer activities of the complexes, using the quantum theory of atoms in a molecule (QTAIM) to analyse the spectroscopic properties shows a stronger correlation between the spectroscopic properties of Ru atom to the reported anticancer activities than the sum over of the spectroscopic properties of all atoms in the complexes.

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Introduction

In search for novel anticancer complexes, many Ru(II)-based complexes have been synthesised especially the half-sandwich where Ru atom is coordinated with the η6-arene unit [1–4]. Ruthenium is an element with rich redox properties but the presence of an arene ligand greatly stabilizes Ru(II) compared with Ru(III) [5]. Activation of ruthenium compounds occurs through hydrolysis [3,5–7] but the hydrolysed complexes are most often difficult to characterise and their pharmacokinetics difficult to study thus limiting their pharmaceutical applications [8]. The complexes that hydrolyse either rapidly have been shown to be active over cancer cells while the complexes that do not aquate were found inactive [5]. Also, another ligand considered important is the PTA used in RAPTA complexes which is known to make the complexes hydrophilic [9]. This is of critical importance for it could facilitate the administration, transportation of the drugs and

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exhibit the pH-dependent DNA damage [9,10]. One of the limitations of RAPTA complexes is that they are prone to hydrolysis and would have to be administered in saline to suppress the cleavage of the chloride ligands [9]. Also, some of these ruthenium-arene complexes are reported to be unstable and have complicated ligand exchange chemistry [9]. Therefore, increasing their stability might provide better drug candidates.

The goal of synthesising many of these Ru-based complexes is to find an alternative to *cis*-platin suitable for application as anticancer drug [1,9]. There have been some controversies about similarities and differences in the anticancer chemistry of *cis*-platin and Ru(II) complexes with some suggesting that Ru(II) complexes probably function in a different manner from *cis*-platin while other stated they mimic *cis*-platin [11]. However, the organometallic Ru(II) anticancer complexes are reported to be more similar to cis-platin than to inorganic Ru(II) compounds [11].

In this work, computational method is applied to compute the properties of four different forms of organometallic Ru(II) anticancer complexes known as RAPTA-H (complex **1**), RAPTA-C (complex **3**), RAPTA-T (complex **5**) [3] and RAPTA-CF3 (complex **7**) [6] with their respective hydrated complexes **2**, **4**, **6** and **8** to understand the properties that enhance their activation by hydrolysis. There have been reported kinetic study of the hydrolysis of the Ru–Cl bond of the prodrug to generate an active complexes of the form $[(\eta 6\text{-arene})Ru(en)(H_2O)]^{2+}$ [11]. The kinetic studies showed that the Ru–Cl bond hydrolysis can be strongly influenced by the nature of the coligands as well as the nature of the metal ion.

What is of interest to us is the possible changes in the properties of these complexes upon hydrolysis that is responsible for their activation using the electronic and the quantum theory of atoms in a molecule (QTAIM). Based on the knowledge that these type of the complexes should be characterised with an intense intramolecular charge transfer transitions which will definitely lead to a very large value for hyperpolarizability (β) [12] as consequence of the π back-donation in the complexes [12,13], the non-linear optical (NLO) properties were also computed to understand their correlation to the anticancer activities and the possibility of using the complexes alternatively as NLO materials. To the best of our knowledge, these types of correlation studies of the electronic and spectroscopic properties of these complexes with their anticancer activities have not been considered in the literatures.

Methods

The geometries of the complexes were optimised using PBE0 hybrid density functional [14] and two external basis set obtained from EMSL Basis Set Library [15,16] were incorporated in a way that both Firefly 7.1.G [17] and Gaussian 03 (G03) [18] can read. The first basis set is SBKJC VDZ [19] with effective core potential (ECP) which was used for the P, Cl and Ru atoms while the remaining atoms were represented using the basis set 6-31G∗ with polarization added to all atoms other than H. ECP methods have been pointed out as a viable method for accurate calculations of transition metal polarizabilities [20]. The PBE0 is obtained by casting the functional and correlation of Perdew, Burke and Ernzerhof in a hybrid HF/DFT scheme with a fixed 1/4 ratio [21]. This functional has been reported to improve the accuracy of excitation energies and charge transfer bands in metal complexes both in gas phase and in solution [22]. All other properties like hyperpolarizability (NLO), magnetizabilities and NMR shielding and spin–spin coupling constant are computed using DFT hybrid functional B3LYP [23] and all electron basis set 3-21g [24] on the optimised geometries at gas phase of 1 atm and default temperature of 273.15 K. The NMR isotropic shielding (σ) were calculated using

the gauge-including atomic orbitals (GIAO) [25] method and the one-bond NMR spin–spin coupling constants J(A,B) [26,27] associated with atoms A and B were also determined.

The accurate single values of first static hyperpolarizability (β) of the complexes were computed using Quasi-Pythagorean problem [28] on the 10 components of the $3 \times 3 \times 3$ matrix as β_{xxx}, β_{xxy}, β_{xyy}, β_{yyy}, β_{xxz}, β_{xyz}, β_{yyz}, β_{xzz}, β_{yzz}, β_{zzz} respectively from G03 output as:

$$\beta_{\text{tot}} = (\beta_x^2 + \beta_y^2 + \beta_z^2)^{1/2}$$

where $\beta_x = (\beta_{xxx} + \beta_{xyy} + \beta_{xzz})$, $\beta_y = (\beta_{yyy} + \beta_{yxx} + \beta_{yzz})$ and $\beta_z = (\beta_{zxx} + \beta_{zyy} + \beta_{zzz})$. Since these β values of G03 W are reported in atomic units (a.u.), the calculated β total values were converted into electrostatic units (esu) (1 a.u. = 8.6393 $\times 10^{-33}$ esu).

Further analysis of the spectroscopic properties of the complexes to understand the contribution of each atom in a complex was done using the quantum theory of atoms in a molecule as implemented in AIMAll version 12.06.03 [29]. The wavefunction derived from the computation with the b3lyp functional and 3-21g basis set was used to compute the magnetizabilities, current tensor and NMR shielding tensor of the complexes in AIMAll. All the correlation table of the result was constructed using the statistical package R [30].

Results and discussion

The geometrical and the infrared properties

The optimised geometries of the complexes (Fig. 1) were obtained using PBE0 hybrid functional and two mixed basis sets that comprises of SBKJC VDZ basis set with ECP that was applied on the Ru, Cl and P atoms and all electron basis set 6-31G∗ that was applied on the remaining atoms of the complexes. All the Ru–Cl bond distances through all the complexes are within the range of 4.67–4.73 (au), the Ru–O where the O atom from water molecule is within the range of 4.21–4.25. The bond angle Cl–Ru–Cl in complexes **1**, **3**, **5** and **7** are 90.42°, 89.64°, 90.75° and 89.73° respectively while the bond angle Cl–Ru–O of their respective hydrated complexes **2**, **4**, **6** and **8** are 79.99°, 76.65°, 76.99° and 77.02° respectively.

The features of the infrared (IR) (Fig. 2) shows that the complexes share many bands indicating that the overall structures of the complexes are not very different. Large spectra difference is observed only when each of the complexes hydrolysed to their respective complexes. A further difference is also observed when the methyl group on the arene units of complexes **5** and **6** are substituted with trifloromethyl group to form complexes **7** and **8**. From the knowledge of the reported experimental IR value for the Ru–O stretching frequency at 580 cm^{-1} [31], we can allocate the computed Ru–O strength in the hydrated complexes **2**, **4**, **6** and **8** to the observed absorption at 645, 636, 626 and 638 cm^{-1} respectively which is not obvious in the unhydrated complexes **1**, **3**, **5** and **7** (Fig. 2). In the hydrated complexes **2**, **4**, **6** and **8**, there is a peculiar vibration at 1622, 1617, 1617 and 1616 cm^{-1} respectively which can be assigned to the activities of the water molecules that donate at least one hydrogen bond to the complexes in line with a range of 1600–1700 cm^{-1} that have been experimentally proposed for such kind of water molecule activities [32]. While two other unique stretching vibrations of each hydrated complexes **2** (3635, 3309), **4** (3623, 3292), **6** (3636, 3304) and **7** (3640, 3308) can be assigned to O-H from water molecule having two different modes due to the formation of hydrogen bond. In another reported experimental IR information, Ru–P is assigned 280 cm^{-1}, (C–H) or δ(C–H) of the benzene ring 3057–3024 cm^{-1} or 1035–1000 cm^{-1}, the (C–H) of the CH$_3$ is assigned 2932–2874 cm^{-1} [33]. Therefore the Ru–P is assigned to be the