

Research Article

Insights into the Intramolecular Properties of η6-Arene-Ru-Based Anticancer Complexes Using Quantum Calculations

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Received 21 May 2013; Revised 23 July 2013; Accepted 23 July 2013

Academic Editor: James W. Gauld

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The factors that determine the stability and the effects of noncovalent interaction on the η 6-arene ruthenium anticancer complexes are determined using DFT method. The intramolecular and intra-atomic properties were computed for two models of these half-sandwich ruthenium anticancer complexes and their respective hydrated forms. The results showed that the stability of these complexes depends largely on the network of hydrogen bonds (HB), strong nature of charge transfer, polarizability, and electrostatic energies that exist within the complexes. The hydrogen bonds strength was found to be related to the reported anticancer activities and the activation of the complexes by hydration. The metal–ligand bonds were found to be closed shell systems that are characterised by high positive Laplacian values of electron density. Two of the complexes are found to be predominantly characterised by LMCT while the other two are predominately characterised by MLCT.

1. Introduction

There have been several research efforts to synthesize Rubased anticancer complexes as alternative to *cis*-platin in cancer therapy [1–3]. Among the most studied compounds are the half-sandwich complexes of ruthenium due to their unique properties [4–6]. Among the most studied complexes are the half-sandwich complexes of ruthenium. Several of these half-sandwich ruthenium complexes have found numerous applications as catalysts for organic transformations, in the supramolecular field and in medicinal chemistry [7]. The applications of these complexes as anticancer agent have been reported [3, 8–12].

Some of the properties of interest are the existing noncovalent interactions and the effect of hydration on the interatomic interactions in the complexes. The noncovalent interactions such as hydrogen bonding, anion- π , cation- π , and π - π interactions and other weak forces are important in chemical reactions, molecular recognition, and regulation of biochemical processes [13, 14]. Deep understanding of these interactions has been pointed out to be of great importance in rationalizing their effects [14]. Using Bader's quantum theory of atoms in molecules (QTAIM) [15], the atomic properties such as electronic population, energies, and (de)localization are evaluated over the atomic basins. Computer simulation is known to be helpful in giving detailed atomic structural properties and in interpreting experimental data at atomic level of interaction to show the mechanisms of biomolecular function [16]. Also, the quantum calculation plays significant roles in determination of force fields [17, 18] necessary for the in silico drug designs which is known to be pivotal in discovering new drugs and designing more efficient ones [19, 20].

In this research work, we have selected two of the models compounds (Figure 1) which are [Ru(η 6-p-benzene) Cl₂(pta)] (RAPTA-H named as complexes 1 and 2) and [Ru(η 6-p-cymene)Cl₂(pta)] (RAPTA-C named as complexes 3 and 4) reported by Chatterjee et al. as anticancer agents [21]. The hydrated form of these complexes which are [Ru(η 6-p-benzene)Cl(H₂O)(pta)] named complex 2 and [Ru(η 6-p-cymene)Cl(H₂O)(pta)] named complex 4 (Figure 1) is considered since activation of Ru complexes is known to



FIGURE 1: The schematic structures of complexes 1, 2, 3, and 4.

occur through hydration [10, 22-24]. Complexes with PTA ligand have in recent years received attention because of their water solubility and applications as catalyst [25]. The only difference between complexes 1 and 3 is the use of cymene as arene unit in 3 while benzene is used in complex 1. This little change in ligand has been reported to enhance the anticancer activities of complex 3 compare to 1 [21]. The choice of ligand is important because a too strongly bound ligand could render the drug inactive, while a labile ligand could be easily hydrolysed or replaced [26]. Many of these ruthenium-arene complexes are known to have complicated and unstable ligand exchange [2]. In order to improve their anticancer activities and obtain a better lead compounds, their stability must be improved [2]. In this study, we have used the quantum theory of atoms in molecules (QTAIM) to understand the effects of noncovalent interactions on the stability and hydration of these complexes.

2. Computational Method

In this work, the geometries of the complexes were first optimized with PBE0 [27] functional and mixed basis sets SBKJC VDZ with effective core potential (ESP) [28] for Ru, P, and Cl while basis set 6-31G* was applied on other atoms in each of the complexes (this will subsequently be referred to as ECP (Ru,P,Cl)|6-31G^{*}). In the second optimization, the SBKJC VDZ is limited to only the ruthenium atom while the scaled-up basis set 6-31+G(d,p) was applied on other atoms in the complexes which shall subsequently be referred to as ECP(Ru)|6-31+G(d,p). The external basis sets were obtained from EMSL basis set library [29, 30] and were incorporated into the input files in a format that each FIREFLY and Gaussian 09 (G09) can read. SBKJC VDZ ECP basis set with PBE0 functional has been shown to be effective in treating complexes with large number of electrons and has been applied in computing properties of many metal clusters [31, 32]. Other properties of the complexes are computed at B3LYP hybrid functional level of theories [33] using basis set DGDVZP applied on Ru atom while others are treated with 6-31+G(d,p) which will be referred to as DGDVZP(Ru)|6-31+G(d,p) subsequently. Also lower basis set 3-21G [34] was applied on all atoms of the complexes in order to compare its values with DGDVZP(Ru)|6-31+G(d,p) systems. The Bader quantum theory of atoms in molecules (QTAIM) analysis was done mainly using the wavefunction obtained from both DGDVZP(Ru)|6-31+G(d,p) and 3-21G basis sets treated systems. A topological analysis was performed in order to calculate the charge density (ρ) and its second Laplacian derivative of charge density ($\nabla^2 \rho$) for the bond critical points (BCP).

The major computation tools used are **FIREFLY** 7.1.G [35] which is partially based on the GAMESS (US) [36] source code, Gaussian 09 [37], and AIMAll 12.06.03 [38]. NBO 5.0G program [39] as implemented in FIREFLY 7.1.G was used for the natural bond orbital (NBO) analysis [40] and natural energy decomposition analysis (NEDA) [41].

3. Result and Discussion

Stable stationary geometries were obtained for the four complexes which are characterized with zero imaginary number from the thermodynamic calculation. When the geometries of the complexes were further optimized from PBE0/ECP(Ru,P,Cl)| $6-31G^*$ to PBE0/ECP(Ru)|6-31+G(d,p), the highest contraction of bond lengths up to 0.05 Å was observed for Ru-Cl bonds (Table 1). There is also a slight change in bond orders up to 0.1 when comparing the two steps of optimization. Applying uniform basis set 3-21G on all atoms of the complexes, there is no significant change in the total energies from the first optimization (-6307.84, -5925.61, -6464.66, and -6082.04 A.U., resp.) to the second optimization (-6307.84, -5925.61, -6464.26, and -6082.04 A.U.). The bond orders of the Ru-Cl bonds increase in the hydrated complexes 2 and 4 which suggest that the possibility of displacing the second Cl atom with aqua ligand will be difficult [42]. But on the other hand, the Ru-P bond order decreases upon hydration of the complexes. The properties computed using combination of higher basis sets DGDVZP(Ru)|6-31+G(d,p) and those computed using lower basis sets 3-21G follow the same trend which is an indication that lower basis sets can give insight into the trend though it either underestimates or overestimates the computed properties.

3.1. The Natural Bond Orbitals (NBO) Analysis. The total electron densities are characterised mostly as Lewis electrons which are higher than 97% in all the complexes indicating

	Complex 1			Complex 2		(Complex 3		(Complex 4	
Bond	Length	Order	Bond	Length	Order	Bond	Length	Order	Bond	Length	Order
				Р	BE0/ECP(I	Ru,P,Cl) 6-310) * I				
Ru-C2	2.206	0.451	Ru-C6	2.224	0.427	Ru-C6	2.231	0.416	Ru-C6	2.211	0.445
Ru-C3	2.249	0.375	Ru-C9	2.223	0.467	Ru-C17	2.205	0.441	Ru-C19	2.217	0.468
Ru-C4	2.210	0.444	Ru-C7	2.196	0.482	Ru-C9	2.198	0.446	Ru-C10	2.228	0.440
Ru-C6	2.250	0.374	Ru-C18	2.277	0.391	Ru-C14	2.205	0.452	Ru-C21	2.304	0.366
Ru-C7	2.210	0.444	Ru-C14	2.183	0.492	Ru-C10	2.236	0.392	Ru-Cl1	2.176	0.483
Ru-C9	2.206	0.451	Ru-C17	2.265	0.359	Ru-C16	2.295	0.332	Ru-C18	2.252	0.373
Ru-P11	2.406	0.727	Ru-P11	2.433	0.706	Ru-P13	2.420	0.725	Ru-P12	2.437	0.712
Ru-Cl5	2.490	0.967	Ru-O8	2.244	0.503	Ru-Cl19	2.500	0.966	Ru-O16	2.253	0.509
Ru-Cl17	2.490	0.967	Ru-Cl19	2.480	1.024	Ru-Cl20	2.496	0.947	Ru-Cl23	2.486	1.028
				P	BE0/ECP(R	au) 6-31+G(d,	p)				
Ru-C2	2.215	0.415	Ru-C6	2.244	0.378	Ru-C6	2.251	0.387	Ru-C6	2.222	0.393
Ru-C3	2.28	0.295	Ru-C9	2.201	0.435	Ru-C17	2.325	0.27	Ru-C19	2.182	0.449
Ru-C4	2.221	0.405	Ru-C7	2.229	0.442	Ru-C9	2.215	0.404	Ru-C10	2.239	0.419
Ru-C6	2.28	0.295	Ru-C18	2.282	0.309	Ru-C14	2.216	0.413	Ru-C21	2.28	0.308
Ru-C7	2.221	0.405	Ru-C14	2.309	0.305	Ru-C10	2.208	0.408	Ru-C11	2.235	0.418
Ru-C9	2.215	0.415	Ru-C17	2.187	0.478	Ru-C16	2.268	0.31	Ru-C18	2.326	0.307
Ru-P11	2.332	0.854	Ru-P11	2.362	0.799	Ru-P13	2.341	0.853	Ru-P12	2.368	0.789
Ru-Cl5	2.443	0.853	Ru-O8	2.254	0.413	Ru-Cl19	2.451	0.837	Ru-O16	2.259	0.408
Ru-Cl17	2.443	0.853	Ru-Cl19	2.423	0.934	Ru-Cl20	2.447	0.836	Ru-Cl23	2.437	0.912

that they are stable. Also, the negligible nature of extravalence orbitals (i.e., Rydberg) which is a slight departure from a localized Lewis structure model (0.14% in all the complexes) suggests the stability of the complexes. However, the relatively high electron delocalization which is the non-Lewis orbitals (little above 2.00%) indicates that they play significant roles in the stability of the complexes. The 4dorbitals of the ruthenium atom are lower in energy than 5s-orbital and are used preferentially in bonding with other atoms in the complexes.

The polarization features of some visible Ru-L bonding orbitals are shown in Table 2, while Table 3 shows the nature of the electron delocalization orbitals with their secondorder perturbation energy $(E^{(2)})$. The number of the electron transfer into each of the acceptor orbitals in Table 3 are shown in Table 4 with the values of their energy level. The bonding polarizations of the Ru-L are directed towards the ligand atoms (Table 2). The reverse is the case in all the antibonding orbitals interactions as a result of backbonding of electrons into the antibonding lone pair of ruthenium atoms. The features of the charge transfer are clearly seen from the delocalized orbitals that have notable interaction with the Ru atom or bonds and have significant stabilization energy $(E^{(2)})$ equal or greater than 10 kcal/mol as presented in Table 3. There are many bond to bond, atom to bond, and atom to atom delocalization orbitals of electrons in the complexes. The most significant feature is the presence of metal to ligand charge transfer (MLCT) from the lone pair of Ru to the antibonding lone pair of arene C atoms in all the complexes. There is also an observed MLCT from the lone

TABLE 2: The polarization of the bonding interaction of Ru(II) with ligand atoms.

Bonds	(NBO%) Polarization of pair atoms
Complex 1	
Ru-P11	$(37.49\%) 0.6123 * Ru \rightarrow (62.51\%) 0.7906 * P11$
Complex 2	
Ru-P11	$(35.61\%)\ 0.5967*{\rm Ru}\ \rightarrow\ (64.39\%)\ 0.8024*{\rm P11}$
Ru-Cl19	$(24.42\%) \ 0.4941 * \mathrm{Ru} \ \rightarrow \ (75.58\%) \ 0.8694 * \mathrm{Cll9}$
Complex 3	
Ru-P13	$(30.40\%) \ 0.5514* \mathrm{Ru} \ \rightarrow \ (69.60\%) \ 0.8343* \mathrm{P13}$
Ru-Cl19	$(22.81\%) \ 0.4776* \mathrm{Ru} \ \rightarrow \ (77.19\%) \ 0.8786* \mathrm{Cll}9$
Ru-Cl20	(22.72%) 0.4767 *Ru \rightarrow (77.28%) 0.8791 *Cl20
Complex 4	
Ru-P12	$(36.46\%) 0.6038 * \text{Ru} \rightarrow (63.54\%) 0.7971 * \text{P12}$

Polarization coefficient c_A is the values with starred superscript, and the square of it is percentage of the NBO (c_A squared) on each hybrid orbital (in parentheses).

pair of ruthenium to the bonding lone pair of the same arene C atoms in complexes 2 and 3. In all the complexes there is also ligand to metal charge transfer from the arene C atoms into the antibonding lone pair of ruthenium atoms or antibonding orbitals of the ruthenium-ligand (σ RuL) bonds. All the backbonding of electronic charges is responsible for the significant effect of the non-Lewis backbonding contribution to the stability of the complexes. From the NEDA analysis, if the total charge transfer from ligand to the lone pair of

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	Complex 1		č	omplex 2			Complex 3		Ŭ	omplex 4	
Donor	Acceptor	$E^{(2)}$	Donor	Acceptor	$E^{(2)}$	Donor	Acceptor	$E^{(2)}$	Donor	Acceptor	$E^{(2)}$
90. LP (2)Ru	378. BD*(2) C3-C6	22.42	87. LP (2)Ru	90. LP (1) C6	14.91	1. BD (1)Ru-P13	460. BD*(1)Ru-Cl19	11.88	102. LP (2)Ru	494. BD*(2) C11-C19	10.06
91. LP (3)Ru	375. BD*(2) C2-C4	25.07	87. LP (2)Ru	100. LP*(1) C7	11.99	1. BD (1)Ru-P13	461. BD*(1)Ru-Cl20	11.88	102. LP (2)Ru	509. BD*(2) C18-C21	18.79
91. LP (3)Ru	385. BD*(2) C7–C9	25.08	87. LP (2)Ru	101. LP*(1) C9	23	107. LP (2)Ru	111. LP (1) C10	18.88	103. LP (3)Ru	480. BD*(2) C6-C10	22.1
4. BD (2) C2-C4	103. LP*(4)Ru	67.13	87. LP (2)Ru	409. BD*(2) C14-C18	19.88	107. LP (2)Ru	119. LP*(1) C6	29.14	103. LP (3)Ru	494. BD*(2) C11-C19	21.2
4. BD (2) C2-C4	104. LP*(5)Ru	20.9	88. LP (3)Ru	90. LP (1) C6	10.98	107. LP (2)Ru	498. BD*(2) C16-C17	19.25	15. BD (2) C6-C10	115. LP*(4)Ru	64.38
4. BD (2) C2-C4	372. BD*(1)Ru-P11	10.22	88. LP (3)Ru	95. LP (1) C17	46.13	108. LP (3)Ru	111. LP (1) C10	38	15. BD (2) C6-C10	116. LP*(5)Ru	16.97
6. BD (1) C3-C6	372. BD*(1)Ru-P11	10.83	88. LP (3)Ru	100. LP*(1) C7	49.06	108. LP (3)Ru	119. LP*(1) C6	16.16	15. BD (2) C6-C10	466. BD*(1)Ru-P12	14.65
7. BD (2) C3–C6	372. BD*(1)Ru-P11	39.87	88. LP (3)Ru	101. LP*(1) C9	41.74	108. LP (3)Ru	483. BD*(2) C9-C14	31.27	16. BD (1) C6-C11	116. LP*(5)Ru	10.69
14. BD (2) C7–C9	103. LP*(4)Ru	67.15	15. BD (1) C6-C7	378. BD*(1)Ru- Cl19	13.76	17. BD (1) C6-C10	461. BD*(1)Ru-Cl20	15.15	29. BD (2) C11-C19	115. LP*(4)Ru	69.89
14. BD (2) C7–C9	104. LP*(5)Ru	20.9	22. BD (1) C9-C17	99. LP*(4)Ru	14.48	24. BD (1) C9-C14	460. BD*(1)Ru-Cl19	16.07	29. BD (2) C11-C19	116. LP*(5)Ru	23.38
14. BD (2) C7–C9	372. BD*(1)Ru-P11	10.21	33. BD (2) C14-C18	377. BD*(1)Ru-P11	35.44	25. BD (2) C9-Cl4	460. BD*(1)Ru-Cl19	52.3	44. BD (2) C18-C21	466. BD*(1)Ru-P12	38.6
92. LP (1) Cl5	103. LP*(4)Ru	10.93	95. LP (1) C17	99. LP*(4)Ru	45.96	39. BD (1) C16-C17	459. BD*(1)Ru-P13	11.35	108. LP (2) O16	115. LP*(4)Ru	22.23
92. LP (1) Cl5	104. LP*(5)Ru	13.01	95. LP (1) C17	378. BD*(1)Ru- Cl19	13.17	40. BD (2) C16-C17	459. BD*(1)Ru-P13	31.97	108. LP (2) O16	116. LP*(5)Ru	33.01
95. LP (4) Cl5	103. LP*(4)Ru	105.18	92. LP (2) O8	99. LP*(4)Ru	51.52	111. LP (1) C10	461. BD*(1)Ru-Cl20	41.72	111. LP (1) Cl23	115. LP*(4)Ru	12.65
95. LP (4) Cl5 95. LP (4) Cl5 98. LP (1) Cl17	104. LP*(5)Ru 372. BD*(1)Ru-P11 103. LP*(4)Ru	54.32 13.89 10.93							111. LP (1) Cl23 114. LP (4) Cl23 114. LP (4) Cl23	116. LP*(5)Ru 115. LP*(4)Ru 116. LP*(5)Ru	11.17 104.34 44.64
98. LP (1) Cl17	104. LP * (5)Ru	13.01							114. LP (4) Cl23	466. RD*(1)R11-P12	12.83
101. LP (4) Cl17 101. LP (4) Cl17 101. LP (4) Cl17	103. LP*(4)Ru 104. LP*(5)Ru 372. BD*(1)Ru-P11	105.16 54.31 13.89									

TABLE 3: The delocalization orbitals with their second perturbation energies $(E^{(2)})$.

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The orbital analyses in the table are defined in terms of the second perturbation energy or stability energy $(E^{(2)})$ in kcal/mol).

	Energy	-0.34383	0.04602	-0.20332	-0.14052	-0.13302	-0.12782
x 4	e_	0.7717 -	0.25086 -	0.41636 -	0.38112 -	0.39198 -	0.31948 -
Comple	Acceptor	115. LP*(4)Ru	116. LP*(5)Ru	466. BD*(1)Ru-P12	480. BD*(2) C6-C10	494. BD*(2) C11-C19	509. BD*(2) C18-C21
	Energy	0.0264	-0.0177	-0.01498	-0.1717	-0.01059	0.00534
ex 3	е -	0.28052	0.31342	0.31388	0.97701	0.3977	0.31534
Compl	Acceptor	459. BD*(1)Ru-P13	460. BD*(1)Ru-Cl19	461. BD*(1)Ru-Cl20	119. LP*(1) C6	483. BD*(2) C9-C14	498. BD*(2) C16-C17
	Energy	-0.12373	-0.18575	-0.20458	-0.319	-0.31816	-0.14131
lex 2	е_	0.34162	0.36076	0.3616	0.95425	0.94513	0.2906
Comp	Acceptor	99. LP*(4)Ru	377. BD*(1)Ru-P11	378. BD*(1)Ru-Cl19	100. LP*(1) C7	101. LP*(1) C9	409. BD*(2) C14-C18
	Energy	-0.23304	0.09026	-0.08239	-0.0176	-0.00519	-0.0176
olex 1	е	0.86632	0.29265	0.4201	0.3873	0.30743	0.38731
Com	Acceptor	103. LP*(4)Ru	104. LP*(5)Ru	372. BD*(1)Ru-P11	375. BD*(2) C2-C4	378. BD*(2) C3-C6	385. BD*(2) C7-C9



FIGURE 2: The HOMO (a) and the LUMO (b) of complexes 1, 2, 3, and 4 in an ascending order.

ruthenium metals (LMCT) is subtracted from that of metal to ligand (MLCT), the overall features show that complexes 1 and 4 are predominantly characterised with LMCT with respective total charges of -0.56209 and -0.47667 transfer to the lone pair of ruthenium atoms from ligand atoms while complexes 2 and 3 are predominately characterised with MLCT of total charges of 0.37489 and 0.45986 transfer from the Ru lone pair to the ligand atoms on bonds. These features are typical nature of π ligand metal complexes with intense intramolecular CT between metal and ligand (MLCT or LMCT) transitions and associated with π backbonding [43, 44].

The features of the electronic orbitals in Figure 2 give an insight into observed MLCT and LMCT in the complexes. The ruthenium atom is characterised as part of both HOMO

and LUMO as a result of bonding electron contribution of metal and the backbonding contribution of the ligands. The PTA ligand dominates the HOMO orbitals of the hydrated complexes **2** and **4** compared to the Ru and Cl atoms which characterise the HOMO of the unhydrated complexes **1** and **3**. The arene ligand is predominantly the LUMO which confirms the existence of MLCT between the Ru atom and the π orbital of the arene moiety of the ligand. The HOMO nature of the Ru and the Cl atom in complexes **1** and **3**, significantly reduced upon being hydrolysed to complexes **2** and **4**, respectively.

3.2. Natural Energy Decomposition Analysis. Results obtained from the NEDA analysis are shown in Table 5. The complexes **1**, **2**, **3**, and **4** are fragmented into four, three, two, and six units, respectively. The respective fragmentations

TABLE 5: The NEDA analysis of the complexes showing the contribution of different factors to the total interaction energies (i.e., stability energies).

	Complex 1	Complex 2	Complex 3	Complex 4
ES	-613.65	-232.72	-195.41	-1180.24
POL	-1005.45	-755.32	-631.22	-1056.91
XC	-865.43	-200.66	-178.08	-923.35
DEF	2694.41	1567.78	1317.34	3295.35
SE	488.65	373.76	312.37	454.75
Electrical (ES + POL + SE)	-1130.45	-614.27	-514.26	-1782.4
Charge transfer (CT)	-661.56	-472.22	-351.67	-1441.76
Core (XC + DEF – SE)	1340.33	993.36	826.89	1917.24
Total interaction (<i>E</i>)	-451.67	-93.14	-39.04	-1306.93

of complexes 1, 2, 3, and 4 are shown in Table 6 except the last two fragments of complex 4 which are the two hydrogen atoms of the aqua ligand that have negligible zero contribution. The number of the fragmentations in the complexes significantly correlates with their total interaction energy (Table 5). The strength of the interaction energy does not correlate with the number of hydrogen bond in the complexes. There are two, one, four, and five hydrogen bonds in complexes 1, 2, 3, and 4, respectively, as shown in Figure 3. The result shows that either polarization (POL) (complexes 1, 2, and 3) or charge transfer (CT) (complex 4) has the greatest contribution to the stability of the complexes. The significant values of the POL and ES result in the electrical energy having the highest contribution to the stability of the complexes (Table 5). The hydrated complex 4 has the highest interaction energy as a result of its significant high CT, ES, and POL. On the contrary, the hydrated complex 2 has lower interaction energy compared to its unhydrated complex 1. The high stability of interaction energy of RAPTA-C (i.e., hydrated complex 4) should significantly contribute to its experimentally reported higher anticancer activity than the other RAPTA complexes [21]. In all the complexes, the high negative values of CT, ES, and POL balance up the strong core repulsion energy that is made up of the sum of exchange interaction (XC) and deformation energy (DEF).

The first fragment in each of the complexes comprises the Ru and the PTA atoms while the second fragment is made up of their respective arene ligands. The arene fragment stability is greatly enhanced in the presence of other fragments in the complexes resulting in high induced energy (Table 6). The significant high induced dipole moment of the remaining chloride atom of complex 4 will definitely enhance the second hydration by exposing better to electrophilic attack. The high induced dipole moment and energy of the fragments in each complex are an indication that the fragments are synergistic. The improvement in the stability energy of one unit on the other is due to the synergistic effect of the ligands that are

		Fragment 1	Fragment 2	Fragment 3	Fragment 4
1	E (ind)	-1.292	-1.506	-0.748	-0.748
1	Dipole (ind)	24.135	0.854	1.163	1.163
2	E (ind)	-0.652	-1.388	-0.458	
2	Dipole (ind)	6.816	0.927	0.544	
3	E (ind)	-0.576	-1.524		
5	Dipole (ind)	0.655	1.133		
4	E (ind)	-1.411	-1.420	-1.695	-0.726
-	Dipole (ind)	28.107	1.755	14.771	1.135

coordinated to the metal centre which is a unique property of metal complexes that is suggested to be responsible for the observed cytotoxic effect of many ligands [45]. The significant values of the induced dipoles in the complex especially from the acceptor unit imply that there is no strict orthogonality required from wavefunctions of the fragments which is responsible for the significant polarization, thereby exposing them as better acceptor and donor to nucleophilic and electrophilic attacks.

3.3. The Bond Critical Points Analysis. The bonds properties from both the B3LYP/DGDVZP(Ru)|6-31+G(d,p) treated systems (Table 7) and B3LYP/3-21G (see Supplementary Table S1 available online at http://dx.doi.org/10.1155/2013/ 892052) methods of computation were obtained from the quantum theory of atoms in molecules (QTAIM) analysis of their respective electron density wavefunctions. The features of the interatomic interaction were explained in terms of the critical points density (ρ) to obtain information about the existence of bonds and the Laplacian of the electron density $(\nabla^2 \rho)$ at that point which gives the kind of interactions and their strength based on the sign and magnitude, respectively. The $\rho(r)$ and $\nabla^2 \rho(r)$ of all the Ru–L bonds are shown in Table 7 and S1. All the Ru-L bonds of the complexes are characterized with positive but higher $\nabla^2 \rho$ (Table 7 and S1 and Figure 3) than hydrogen bonds confirming that they are closed shell interactions like dative, hydrogen, ionic, and van der Waals bonds [46, 47]. The features of the bonds are shown using the contour plot of the $\nabla^2 \rho$ along the plane of the P, Ru, and Cl or O atoms where the hydrated complexes are considered (Figure 3). Many of the atoms of the complexes are found to be on the chosen plane and all the ligandligand bonds are characterised with negative $\nabla^2 \rho$ (solid lines) while the metal-ligand bonds are characterised with positive $\nabla^2 \rho$ (dash lines). All the covalent bonds in the complexes are characterised with high negative values of $\rho(r)$, lower ε , and higher values of the Laplacian of the electron-nuclear attractive contribution to virial field (∇^2 Ven). All the strong noncovalent bonds like Ru-L in the complexes are also characterised with the same properties of the covalent bond



FIGURE 3: Laplacian of the electron density in a plane containing P, Ru, and Cl or O nuclei (positive contours as dash and negative contours as solid lines are drawn from 0 to ±800) and bonds (strong bonds in solid and HB in dash lines).

except that their values are lower and the $\nabla^2 \rho(r)$ has positive values.

Complexes 1, 2, 3, and 4 have two, one, four, and five hydrogen bonds, respectively (Figure 3). In the literature there have been reports of unusual alkyl and halogen Hbonds [48–54] which are also observed in these complexes. There are unusual H-bonds between the alkyl C atoms of the cymene unit of complexes 3 and 4 and also H bonds between the chloride atoms and H atom of aqua, PTA, and arene ligands which contribute significantly to the H bond networks of complexes 1, 3, and 4. Hydrogen bonding is known to be a stabilizing interaction that influences the structure, function, and dynamics of many chemical and biological systems in the gaseous, liquid and solid states [49, 50]. Hydrogen bonds are significantly important in defining the crystal packing of many organic and organometallic molecules and the 3D structure of biological macromolecules as well as modulating the reactivity of different groups within a molecule [49]. Peculiar to complexes 3 and 4, one chloride atom forms two hydrogen bonds with the nearby hydrogen atoms from PTA, aqua, and arene ligands. The introduction of cymene as source of π bond in the arene moiety of complexes 3 and 4 other than the benzene of complexes 1 and 2 brings about significant differences in their HB network. This network of HB further gives insight into the nature

of electron communication that results in the synergistic effects of the coordinated ligands. The higher HB network in complexes 3 and 4 indicates that many of the atoms in these complexes will be sensitive to macromolecular interactions and should be responsible for their experimental reports of high cytotoxic activities than complexes 1 and 2 [21]. The hydrated forms (complexes 2 and 4) are characterised with extra and stronger HB suggesting that the activation mechanism of these complexes by hydration [10, 22-24] can possibly be the result of increase in the sensitivity of the atoms as a result of increased networks of HB and electronic interactions. There is a unique HB that exists between Cl and H atoms of the water molecules in the hydrated forms that is stronger than any other existing HB based on a higher value of $\nabla^2 \rho(r)$ and $\rho(r)$ (Figure 3). The values of the ratio of the magnitude of potential energy (P.E) and the kinetic energy (K.E) of the electrons (|V|/G) in Table 7 and S1 are relatively low indicating a balance between stronger bond interactions and high density in the regions [15]. A high value of |V|/Gcorresponds to higher density and stronger bonds except where the $\nabla^2 \rho(r)$ is small (Table 7 and S1 and correlation in Table S2). The unique HB in the hydrated complexes that are also recognised in the bond order analysis is characterised with higher values of |V|/G which is closed to that of the metal-ligand bonds than other HB. The very low average

TABLE 7: The QTAIM properties of selected bonds in complexes 1, 2, 3, and 4 that are associated with metal using DGDZVP.

	$\rho(r)$	$\nabla^2 \rho(r)$	ε	K	BPL-GBL_I	V	G	L	GBL_I	∇^2 Ven	V/G
	1.	, , ,			Comple	ex 1					. , .
Ru1-P11	0.096	0.147	0.156	0.030	0.005	-0.097	0.067	-0.037	4.408	-7.633	1.450
Ru1-C2	0.077	0.247	0.585	0.014	0.014	-0.091	0.076	-0.062	4.186	-11.882	1.189
Ru1-C4	0.077	0.263	1.723	0.014	0.037	-0.093	0.079	-0.066	4.198	-12.781	1.170
Ru1-C9	0.077	0.247	0.584	0.014	0.014	-0.091	0.076	-0.062	4.186	-11.880	1.189
Ru1-C7	0.077	0.263	1.728	0.014	0.037	-0.093	0.079	-0.066	4.198	-12.783	1.170
Ru1-Cl5	0.064	0.208	0.194	0.007	0.003	-0.067	0.059	-0.052	4.616	-10.204	1.122
Ru1-Cl17	0.064	0.208	0.194	0.007	0.003	-0.067	0.059	-0.052	4.616	-10.205	1.122
					Comple	ex 2					
Ru1-P11	0.092	0.131	0.147	0.028	0.002	-0.089	0.061	-0.033	4.463	-6.546	1.463
Ru1-C7	0.076	0.227	0.394	0.015	0.015	-0.086	0.071	-0.057	4.212	-10.511	1.206
Rul-C9	0.081	0.249	0.744	0.016	0.014	-0.095	0.079	-0.062	4.160	-11.938	1.209
Rul-C17	0.081	0.250	0.496	0.017	0.017	-0.096	0.079	-0.063	4.133	-11.911	1.211
Ru1-O8	0.054	0.311	0.504	-0.004	0.005	-0.070	0.074	-0.078	4.260	-14.561	0.946
Ru1-Cl19	0.067	0.218	0.298	0.008	0.003	-0.071	0.063	-0.054	4.580	-10.442	1.133
					Comple	ex 3					
Ru1-P13	0.094	0.151	0.162	0.029	0.006	-0.095	0.067	-0.038	4.424	-8.327	1.433
Rul-C9	0.077	0.258	0.981	0.015	0.020	-0.094	0.079	-0.065	4.187	-13.648	1.184
Ru1-C10	0.078	0.248	0.476	0.015	0.016	-0.092	0.077	-0.062	4.173	-13.001	1.197
Ru1-C14	0.077	0.241	0.623	0.015	0.015	-0.090	0.075	-0.060	4.188	-12.683	1.199
Ru1-Cl19	0.063	0.206	0.219	0.007	0.004	-0.065	0.058	-0.052	4.632	-10.869	1.117
Ru1-Cl20	0.063	0.209	0.182	0.007	0.003	-0.066	0.059	-0.052	4.624	-11.039	1.118
					Comple	x 4					
Ru1-P12	0.090	0.138	0.154	0.027	0.003	-0.088	0.061	-0.034	4.475	-7.374	1.439
Ru1-C6	0.078	0.243	0.868	0.015	0.016	-0.091	0.076	-0.061	4.199	-12.578	1.198
Ru1-C11	0.074	0.262	3.945	0.012	0.029	-0.089	0.077	-0.065	4.223	-13.605	1.150
Ru1-C10	0.073	0.250	1.462	0.012	0.026	-0.087	0.075	-0.063	4.231	-12.862	1.161
Rul-C19	0.084	0.228	0.279	0.020	0.011	-0.096	0.077	-0.057	4.123	-11.721	1.257
Rul-O16	0.054	0.305	0.490	-0.004	0.006	-0.069	0.073	-0.076	4.268	-15.482	0.950
Ru1-Cl23	0.065	0.215	0.313	0.008	0.003	-0.069	0.061	-0.054	4.605	-11.089	1.124

 ∇^2 Ven: Laplacian of the electron-nuclear attractive contribution to virial field, $\nabla^2 \rho(r)$: Laplacian of the electron density.

kinetic energy which is responsible for higher |V|/G has been pointed out through the uncertainty principle to be the nature of loosely bound density [15].

The strength of the two Ru-Cl bonds in terms of the $\nabla^2 \rho$ and ε is not equal in complex 3 compared to complex 1 (Table 7 and S1) which is also observed in their bond order (Table 1). The imbalance features of the two Ru-Cl in complex 3 can enhance the aqua substitution of the weaker Ru–Cl to form Ru-OH₂ which may also play significant role in the reported higher anticancer activity of RAPTA-C since easy hydration has direct correlation with the higher anticancer activity [24]. The $\nabla^2 \rho$ of Ru–P bond in all the complexes is found to be the lowest in all the existing metal-ligand bonds which would have suggested it as the most possible leaving unit except for its higher $\rho(r)$, lower ε , and relatively high ∇^2 Ven values (Table 7 and S1). The $\nabla^2 \rho(r)$ of Ru–P bond slightly reduces in value in the hydrated complexes 2 and 4 compared to complexes 1 and 3, respectively, while the $\nabla^2 \rho(r)$ of the σ RuCl bond of the retained Cl atom slightly increased just as it was observed for the bond order analysis.

The relationships between the computed factors of the bonds are constructed over all the existing bonds in the complexes (Supplementary Table S2). A very high negative value of $\nabla^2 \rho(r)$ is an indication of strong covalent bond while a high positive value corresponds to a strong noncovalent bond. The general relation is that high negative value of $\nabla^2 \rho(r)$ is directly proportional to high $\rho(r)$, high ∇^2 Ven, lower bond stretch (BPL-GBL_I), lower kinetic energy (K), high negative values of potential energy (V), lower ellipticity (ε), and relatively high value of |V|/G. The higher electronic kinetic energy (K) is an indication of lower values of $\nabla^2 \rho(r)$, ε , and potential energy (V) but a higher value of $\rho(r)$ (Supplementary Table S2). These observed correlations further confirmed the reported nature of very flat electron density region that is characterised with a very low average values for $\rho(r)$, $\nabla^2 \rho(r)$ which is usually found to have a relatively high ε [55].

The QTAIM analysis using the wavefunction file obtained from the mixed basis set where the ECP is applied on Ru, P, and Cl atoms (PBE0/ECP(Ru,P,Cl)|6-31G^{*} treated systems) gives spurious topological features of the complexes. We observed common nonnuclear attractor (NNA) critical points (CP), that is, (3, -3), between the Ru–P and Ru– Cl bonds which were completely absent when all electron

basis sets DGDVZP(Ru)|6-31+G(d,p) and 3-21G were used. The existence of NNA in only ECP models suggests it is just a computational artefact of ECP basis set. However, the existence of NNA has been reported to be not just an artefact of computational methods but a genuine feature of the electron density distribution of some complexes [56]. An instance of the first unambiguous experimental evidence of such a feature in a stable molecule was reported by Platts et al. [15]. Our observation shows that the pseudopotentials that are used to represent the core electrons cannot conveniently account for all the electrons distribution around these complexes and it is responsible for the introduced NNA. This agrees with report which shows that NNA originate from the shape of valence molecular orbitals that might occur in bonds of low polarity in which core contributions are negligible and the radial form of the valence orbitals dominates the total density [15, 57].

3.4. The Intra-Atomic Properties. The properties of some selected atoms in each of the four complexes are presented in Table 8 and supplementary Table S3. The integrated Lagrangian values L(A) of all the atomic basins are approximately equal to zero, which is an indication of satisfactory numerical integration [15]. The distribution of the atomic charges shows that the arene C atoms have gain charges confirming the existence of MLCT. For all the atoms in the complexes other than H atoms, the values of the percentage localization ($(\%\lambda(A))$) are higher than the percentage delocalization (% $\delta(A, A')$). The reverse nature of the % $\lambda(A)$ and $\%\delta(A, A')$ of the H atoms indicates that they can be easily perturbed by an external electric field [15]. The atomic volume (Vol(A)) of Ru and P atoms increases in the respective hydrated complexes 2 and 4 while that of the Cl atom decreases. The $\%\lambda(A)$ of the Ru and arene C atoms increases in the respective hydrated complexes 2 and 4 while that of the P and Cl atoms decreases which consequentially leads to a reverse trend in their $\delta(A, A')$. Both bonding $(|\mu_{bond}(A)|)$ and total dipole ($|\mu_{Total}(A)|$) moments of the Ru and Cl atoms are higher than the intra-atomic dipole moment $(|\mu_{\text{Intra}}(A)|)$ in all the complexes, but the reverse is the case of the P atom. The magnitude of the three dipole moments of the Ru atom decreases in the respective hydrated complexes 2 and **4**. The bonding dipole of the P atom increased appreciably in the hydrated complexes 2 and 4 but still lower than its intraatomic dipole moment. The contribution of Ru atom to electronic energy of molecule (Ee(A)) slightly decreases in the hydrated complexes and also decreases sequentially from complexes 1 to 4 while the values of the K_{Scaled} increases. The Ru atom of complex 4 has a significantly higher and different value of its out of plane magnetizability contribution (χ_{zz}) compared to its values in other complexes as a result of its higher intraatomic magnetizability than the bonding magnetizability. This further distinguishes hydrated RAPTA-C complex which is experimentally reported as having better anticancer activities than others. The N atoms from the PTA which have been reported to usually take part in HB interaction of the complexes with macromolecule [58] are observed to have virtually the same charges in all the

complexes and a very little reduction in the Vol(A) in the hydrated forms. The H atoms from the water molecule of the hydrated forms which are involved in HB are characterised with higher q(A), lower Vol(A), and lower K(A) compared to other H atoms from the PTA and arene units that are also involved in HB.

The features of the relation within the computed intramolecular properties can be seen from the constructed correlation in Table S4. Higher K(A) is found to be as a result of higher bonding dipole moment contribution of the atoms $(|\mu_{bond}(A)|)$, high number of electrons and relatively low Vol(A) that are poorly correlated. The high value of $|\mu_{bond}(A)|$ is an indication of low $\%\delta(A, A')$, high $\%\lambda(A)$, and high Vol(A) of atoms. The atoms that are characterised with bigger volume will be associated with higher negative values of the χ_{zz} . The atomic energy contribution (Ee(A)) to the virial energy of the system depends significantly on the number of the electrons and the number of localized electrons. The out of plane magnetizability (χ_{zz}) is proportional to the number of the atomic localized electrons and inversely proportional to the atomic delocalized number of electrons.

The total sum of the intraatomic properties computed over all existing atoms shows the changes in the computed atomic properties from one complex to another (Supplementary Table S5). The decrease in the values of the atomic energy contributions like Ee(A) and K_{Scaled} of the respective hydrated complexes shows the significant contribution of the Cl atom to the total energy of the systems. The average values of the percentage electron delocalization over all the atoms increase in the respective hydrated complexes while the average electron localization decreases which correspond with the theory of activation of this complexes by hydration. Also, the average electron delocalization and the three types of dipole moments in complexes **3** and **4** are higher than complexes **1** and **2** which further distinguishes RAPTA-C complex of reported better anticancer activities.

4. Conclusion

The quantum properties of complexes 1, 2, 3, and 4 were computed based on the NBO, NPA, NEDA, and QTAIM analyses using two mixed basis sets and single minimum basis set. Stable stationary geometries were obtained for the four complexes which are characterized with zero imaginary number. The bond orders, $\rho(r)$, and $\nabla^2 \rho(r)$ of the Ru–Cl bonds increase in the hydrated complexes 2 and 4 which suggests that the possibility of displacing the last Cl atom with aqua ligand will be difficult [42]. The results from the NBO and NEDA analyses with the features HOMO and LUMO show that complexes 1 and 4 are predominantly characterised with LMCT while complexes 2 and 3 are predominately characterised with MLCT. The result shows that either polarization (POL) (complexes 1, 2, and 3) or charge transfer (CT) (complex 4) has the greatest contribution to the stability of the complexes. The hydrated complex 4 has the highest interaction energy as a result of its significant high CT, ES, and POL which gives a possible distinguishing features that can contribute to the reported

	q(A)	L(A)	K(A)	$K_{\rm contrad}(A)$	$E_{a}(A)$	$ \mathcal{M}_{\mathrm{rates}}(A) $	$ \mu_{\text{Bound}}(A) $	(A)	N(A)	$\lambda(A)$	$\%\lambda(A)$	$\delta(A,A')$	$\%\delta(A,A')$	Vol (A)	$\chi_{77}(A)$
		r					Complex 1			r.	r.				
Rul	0.77	0.00	4435.29	-4445.63	-4435.29	0.41	1.60	1.70	43.23	40.56	93.81	2.68	6.19	108.10	-6.80
33	-0.06	-1.94E - 04	37.84 37.83	-37.93 -3707	-37.84	0.11	0.13	0.07	6.06 6.04	3.96 3.96	65.42 65.52	2.10 2.08	34.58 34.48	71.99 74 58	-10.67
9 C 4	-0.07	-1.75E - 03	37.83	-37.92	-37.83	010	0.06	0.06	50.0 9	3.97	65.40	2.10	34.60	73.72	-10.43
C6	-0.04	8.70E - 05	37.83	-37.92	-37.83	0.13	0.12	0.07	6.04	3.96	65.52	2.08	34.48	74.49	-6.57
C7	-0.07	-1.43E - 04	37.83	-37.92	-37.83	0.10	0.06	0.06	6.07	3.97	65.40	2.10	34.60	73.67	-10.40
C9	-0.06	-2.27E - 04	37.84	-37.93	-37.84	0.11	0.13	0.07	6.06	3.96	65.42	2.10	34.58	72.00	-10.63
PII	1.51	-6.77E - 04	340.02	-340.81	-340.02	1.40	0.34	1.07	13.49	11.56	85.67	1.93	14.33	79.09	-10.43
Cl5	-0.58	1.05E - 04	459.41	-460.48	-459.41	0.13	1.27	1.36	17.58	16.96	96.47	0.62	3.53	239.75	-26.11
Cl17	-0.58	1.03E - 04	459.41	-460.48	-459.41	0.13	1.27	1.36	17.58	16.96	96.47	0.62	3.53	239.75	-26.11
							Complex 2								
Rul	0.77	-3.17E - 04	4435.24	-4445.98	-4435.24	0.38	0.92	1.06	43.23	40.65	94.04	2.58	5.96	112.07	-5.80
C6	-0.05	-1.00E - 05	37.83	-37.92	-37.83	0.13	0.08	0.09	6.05	3.96	65.52	2.09	34.48	74.04	-8.04
C7	-0.07	-2.46E - 04	37.84	-37.93	-37.84	0.11	0.06	0.06	6.07	3.97	65.51	2.09	34.49	72.85	-12.96
60	-0.06	-1.09E - 04	37.84	-37.93	-37.84	0.09	0.09	0.11	6.06	3.96	65.41	2.09	34.59	70.53	-11.30
C14	-0.05	4.20E - 05	37.83	-37.92	-37.83	0.13	0.08	0.06	6.05	3.97	65.65	2.08	34.35	76.53	-7.23
C17	-0.06	-3.69E - 04	37.85	-37.94	-37.85	0.12	0.11	0.08	6.06	3.97	65.50	2.09	34.50	71.93	-11.11
C18	-0.02	1.22E - 04	37.83	-37.92	-37.83	0.13	0.13	0.06	6.02	3.95	65.56	2.07	34.44	72.70	-6.69
P11	1.31	-3.08E - 04	340.13	-340.96	-340.13	132	0.97	0.37	13.69	11.70	85.45	1.99	14.55	88.25	-11.43
80	-117	4 40E - 05	75 21	-75 39	-75.21	0 31	0.6.0	0.61	9.17	8 24	89.89	0.93	10 11	120.85	-12 65
CI19	-0.54	6.20E - 05	459.43	-460.54	-459.43	0.06	1.23	1.20	17.54	16.88	96.21	0.67	3.79	228.21	-26.04
							Complex 3								
Rul	0.75	5.80E - 05	4435.21	-4446.21	-4435.21	0.42	1.61	1.66	43.25	40.58	93.85	2.66	6.15	108.97	-1.02
60	-0.08	2.05E - 04	37.85	-37.95	-37.85	0.09	0.02	0.07	6.08	3.97	65.37	2.11	34.63	72.50	-10.29
C10	-0.07	-2.39E - 04	37.86	-37.95	-37.86	0.09	0.07	0.03	6.07	3.97	65.35	2.10	34.65	70.76	-12.64
C14	-0.07	-9.64E - 04	37.86	-37.95	-37.86	0.09	0.10	0.05	6.07	3.97	65.35	2.10	34.65	70.15	-10.85
C16	-0.06	-1.10E - 05	37.86	-37.95	-37.86	0.10	0.08	0.06	6.06	3.97	65.40	2.10	34.60	71.55	-7.97
C17	-0.04	1.58E - 04	37.86	-37.95	-37.86	0.11	0.16	0.06	6.04	3.91	64.64	2.14	35.36	59.63	-6.69
P13	1.49	-6.44E - 04	340.01	-340.86	-340.01	1.42	0.21	1.21	13.51	11.58	85.72	1.93	14.28	80.37	-10.30
Cl19	-0.59	1.22E - 04	459.40	-460.54	-459.40	0.13	1.42	1.52	17.59	16.97	96.45	0.62	3.55	238.43	-23.78
C120	-0.59	1.12E - 04	459.41	-460.55	-459.41	0.12	1.06	1.14	17.59	16.94	96.32	0.65	3.68	233.70	-28.24
							Complex 4								
Rul	0.76	-6.20E - 05	4435.17	-4446.59	-4435.17	0.38	0.77	0.82	43.24	40.67	94.06	2.57	5.94	112.67	11.03
C6	-0.06	-1.85E - 04	37.85	-37.95	-37.85	0.09	0.08	0.11	6.06	3.96	65.37	2.10	34.63	70.51	-9.00
C10	-0.08	1.71E - 04	37.86	-37.95	-37.86	0.11	0.10	0.12	6.08	3.98	65.49	2.10	34.51	73.04	-10.70
CII	-0.05	1.09E - 04	37.85	-37.95	-37.85	0.11	0.09	0.04	6.05	3.91	64.58	2.14	35.42	60.21	-9.43
C18	-0.05	1.24E - 04	37.87	-37.97	-37.87	0.11	0.01	0.12	6.05	3.91	64.67	2.14	35.33	58.48	-6.52
C19	-0.06	-3.64E - 04	37.87	-37.96	-37.87	0.09	0.13	0.12	6.06	3.96	65.38	2.10	34.62	68.72	-12.22
C21	-0.06	2.07E - 04	37.85	-37.95	-37.85	0.12	0.12	0.12	6.06	3.97	65.50	2.09	34.50	73.24	-8.31
P12	1.31	1.50E - 05	340.12	-341.00	-340.12	1.36	0.77	0.59	13.69	11.71	85.54	1.98	14.46	89.10	-10.46
016	-1.17	1.17E - 04	75.21	-75.41	-75.21	0.31	0.90	0.62	9.17	8.23	89.78	0.94	10.22	119.64	-13.16
Cl23	-0.55	7.40E - 05	459.43	-460.61	-459.43	0.06	1.21	1.19	17.55	16.89	96.23	0.66	3.77	228.20	-23.81
q(A) is	net charge	of atom A, $L(A)$ is	Lagrangian o	f atom A, $N(A)$	is average num	ber of electrons	in atom A, $K(A)$	is electron	ic kinetic e	nergy of atc	om A (Hami	ltonian form)	$\%\lambda(A)$ is perce	ntage of avera	ige number
of elect	rons locall	zed in atom A, $\%0$	(A, A) is the	percentage of ele	ectron delocaliz	ation index of a	itom A, K _{Scaled} (- ∀ ^) is the volum	A) is appro مالماسم من	kimation to	virial-baso کا virial-baso	ed total ener معاصلين	gy of atom A,	µ _{Intra} (A) IS m	agnitude of 11 ¹ hw interation	itra-atomic
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higher anticancer activities of RAPTA-C [21]. In all the complexes, the high negative values of CT, ES and POL balance up the strong core repulsion energy that is made up of the sum of exchange interaction (XC) and deformation energy (DEF). The strength of the charge transfer within the complexes depends mostly on the fragmentation of each complex. The NEDA analysis of complexes shows that the coordinated ligands have high synergistic effects which may be responsible for their impacted anticancer activities. The differences in HB networks suggest a difference in sensitivity of the atoms in each complex and are found to correlate with the reported anticancer activities of these complexes. The networks of charge transfer and HB significantly contribute to the observed synergistic effects of the coordinated ligands confirming the possibility of these effects resulting in the high cytotoxicity as reported experimentally [45]. Several bond properties and intra-atomic properties have been used to explain the chemistry of these complexes, and the correlation of the computed properties was considered. The QTAIM analysis shows that all the metal-ligand bonds are closed shell interactions characterised with dative bonds. The HB interactions in the complexes increased when the benzene is substituted with cymene as the arene moiety of the ligand, and the hydrated forms are characterised with stronger HB interactions indicating that HB may have significantly affected their experimentally reported activation by hydration. The intra-atomic properties show that only the H atoms are characterised with high $\%\delta(A, A')$ and low $\%\lambda(A)$ indicating that they can be easily perturbed than any other atoms in the complexes. There is a little increase in Vol(*A*) of Ru and P atoms in the hydrated forms.

Acknowledgments

The authors gratefully acknowledge the financial support of Govan Mbeki Research and Development Centre, University of Fort Hare, South Africa. The CHPC and CSIR, Department of Science and Technology, South Africa, is gratefully acknowledged for providing the computing facilities and some of the software that is used for the computation.

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