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Theoretical Investigation of Ru(II) Complexes as Photosensitizer for Photodynamic Therapy

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Abstract

This work was undertaken to see how Ru II complexes can be suitable for photodynamic therapy through theoretical prediction. For that, four Ru II complexes, α-$RuCl_2(Azpy)_2$, Fac-$Ru(Azpy)_3^{2+}$, Mer-$Ru(Azpy)_3^{2+}$ and $Ru(Bipy)_3^{2+}$ were used in unrestricted state by providing with no more energy than 2.68 eV. The unrestricted state allows the complex molecule to display each of its electrons in one orbital. All the calculations such as optimization, frequency and TD-DFT calculations were performed at WB97XD/Lanl2dz level. It resulted from this investigation that Ru II complexes are active for both mechanisms suitable for photodynamic therapy in presence or absence of $^3O_2$. Moreover, this reaction was assumed to take place only with Guanine DNA base as demonstrated in literature. Therefore, Guanine is admitted as the base most reacting with ruthenium complexes for photodynamic therapy. This work confirms our prediction regarding metallic complexes that are assumed to be photosensitized in condition that an electron must be isolated to favor the excitation. Nevertheless, Ru II complexes are found suitable for superficial therapy while Ru III must be active for deep therapy.

Keywords

TD-DFT, Ru(II), Photo-Dynamic Therapy (PDT), (Un)restricted Model

1. Introduction

Since discovered as cytotoxic agents, Ru complexes are of great interest [1] [2] [3]. Even if they differ from the nature of the ligand, most of them remain competitive comparatively to other metallic complexes like cisplatin and its derivative molecules [4]. Then, in our previous article, we made a comparison regard-

ing activity of Ru(II) and Ru(III) complexes irrespective of their ligands [5]. We found that both group of complexes are cytotoxic. In addition, we could not make any distinction between the charges of the central metal Ruthenium. However, concerning the photodynamic therapy (PDT) properties, they were obtained assuredly by Ru(III) complexes. We found out furthermore that the inactivity of Ru(II) complexes was certainly due to the couple paired of valence electrons. Therefore, they had failed to display a triplet state. Besides, within the present work that is a continuity of the previous one, we have selected four ruthenium II complexes that we will excite first in a triplet state to permit the separation of pair electrons and find out their cytotoxic effect as photodynamic therapeutic agent. It means that all calculations will be performed in unrestricted model. These complexes are α-$RuCl_2(Azpy)_2$, Fac-$Ru(Azpy)_3^{2+}$, Mer-$Ru(Azpy)_3^{2+}$ and $Ru(Bipy)_3^{2+}$ indicated by **Figure 1**. All of them are active cytotoxically except for Fac-$Ru(Azpy)_3^{2+}$.

The diagram of Jablonski highlights the principle of photodynamic therapy [6]. It states that the molecule responsible for the therapy must be irradiated first. Thus, this molecule is known as a photo-sensitizer (PS). Actually, the irradiation triggers a transition in the PS from the state of singlet (S1) to triplet state (T1) through intersystem crossing. Here, the triplet state is essentially responsible for the therapy as long as it allows the formation of species reactive oxygen [7].

2. Methods

DFT and TD-DFT calculations were performed at WB97XD/Lanl2dz level thanks to Gaussian 09 packages [8]. WB97XD is one of the widespread hybrid functional used for DFT calculations. Its advantage is that it is more accurate and displays better the symmetry of complex molecules [9] [10]. It means that the optimizations and the frequency calculations were performed with symmetry constraints. That process produces an accurate result close to reality. Lanl2dz is the pseudo basis set suitable for heavy elements and it minimizes the relativity effect [11] [12]. TD-DFT was calculated both at ground state and at first excited state to investigate the absorption properties of the Ru II complexes. The energy of the molecules was determined both in restricted and in unrestricted states.

3. Results and Discussion

3.1. Energy of Restricted and Unrestricted States

Both the restricted and unrestricted states can belong to fundamental state. The difference between them stems from the spin of the complex. In the restricted state known as close shell model, we have absolutely an even numbers of electrons. The electrons are coupled with opposite spin thereby giving the complex a singlet spin. In addition, every coupled electrons are in the same orbital. Whereas the unrestricted state, it regards the open shell model. In this case, electrons are unpaired, they are divided in spin up and spin down, and each electron is in a separate orbital. The lowest spin in this case for the molecule is triplet. The

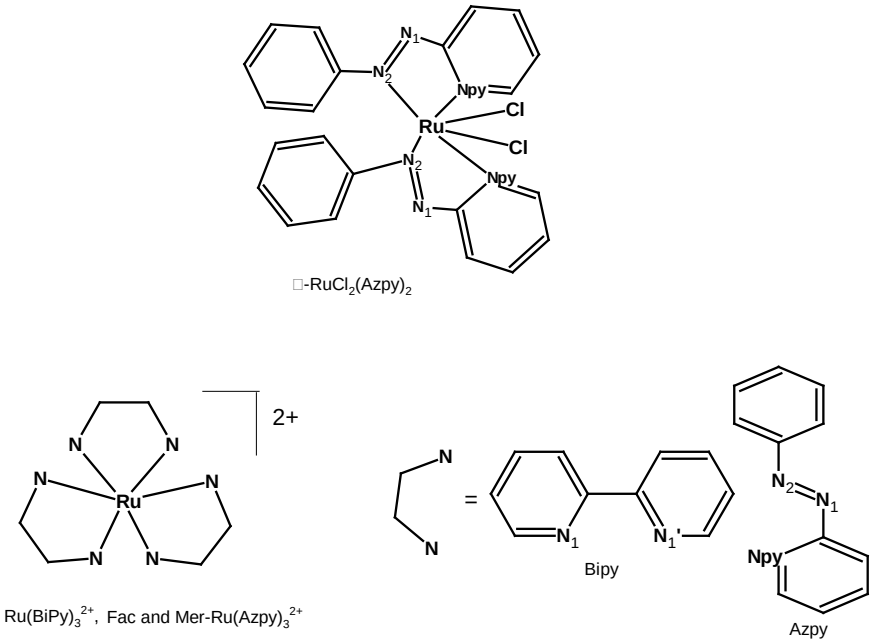

Figure 1. Structure of Ru (II) complexes, a-RuCl2(Azpy)$_2$, $\mathrm{Ru}\left(\mathrm{Bipy}\right)_3^{2+}$, Fac and Mer-$\mathrm{Ru}\left(\mathrm{Azpy}\right)_3^{2+}$.

unrestricted model can naturally be encountered especially when the molecule has odd numbers of electrons in fundamental state and in the excited state [13]. Thus, it can be imposed for the even numbers electrons. **Figure 2** displays both models regarding an even electron numbers.

When we look **Figure 2**, we figure out that from close shell to the open shell, energy of the molecule must increase and the molecule becomes unsteady. Therefore, **Table 1** shows the energy recorded from restricted and unrestricted states of the four Ru II complexes.

Table 1 presents the difference of energy between close shell molecules and open shell molecules. We can see that the difference of energy $\Delta E_{\mathrm{S}\to\mathrm{T}}$ between both states is positive. This means that the open shell molecule is more unstable and more reactive than the close shell molecule. Moreover, $\mathrm{Ru}\left(\mathrm{Bipy}\right)_3^{2+}$ requires the highest energy with 2.68 eV to dissociate electrons and create two high occupied molecular orbitals (HOMO) with different energy. Besides, α-$\mathrm{RuCl_2(Azpy)_2}$ requires the least energy to unpair electrons with 1.21 eV. Always in **Table 1**, we present the difference energy between the highest HOMO and its corresponding LUMO. In this case, the gap energy $\Delta E_{\mathrm{H}\to\mathrm{L}}$ (in eV) is the lowest in the isomers Fac-$\mathrm{Ru}\left(\mathrm{Azpy}\right)_3^{2+}$ and Mer-$\mathrm{Ru}\left(\mathrm{Azpy}\right)_3^{2+}$ with respectively 4.64 eV and 4.81 eV thereby making them the most reactive complexes. Furthermore, the total energy required for a molecule with close shell electrons to be excited is the sum of both $\Delta E_{\mathrm{S}\to\mathrm{T}}$ and $\Delta E_{\mathrm{H}\to\mathrm{L}}$. This energy shows that both isomers Fac-$\mathrm{Ru}\left(\mathrm{Azpy}\right)_3^{2+}$ and Mer-$\mathrm{Ru}\left(\mathrm{Azpy}\right)_3^{2+}$ are the most active with respectively 6.60 and 6.72 eV. $\mathrm{Ru}\left(\mathrm{Bipy}\right)_3^{2+}$ presents the highest energy with 8.14

eV. Henceforth, since the low value noticed between close shell and open shell statute, all calculations will take place at unrestricted state. Figure 3 displays the structure of the four Ru II complexes calculated at unrestricted state after optimization.

3.2. Photophysical Properties of Complexes at Unrestricted State

Table 2 and Table 3 display the 20 first singlets and triplets excited states with the unrestricted model at wb97xd/b3lyp level.

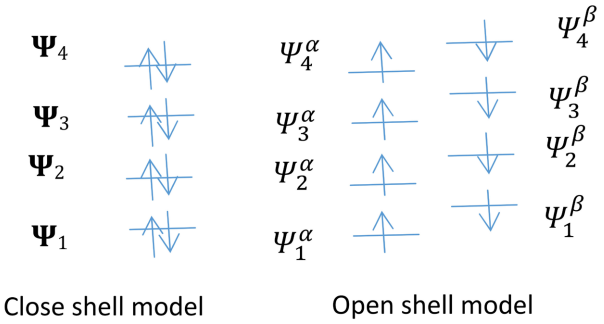

Figure 2. Close shell and open shell models known respectively as restricted and unrestricted states.

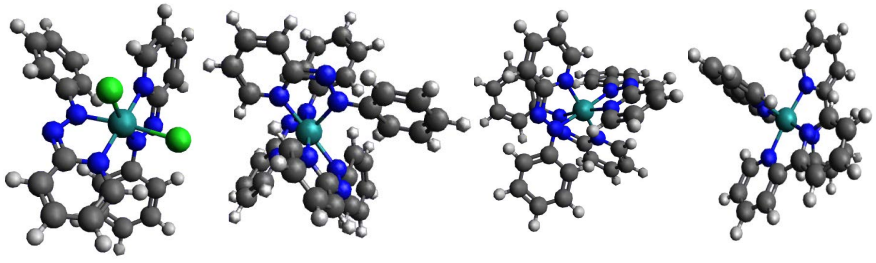

Figure 3. Structures from left to right of α-$RuCl_2(Azpy)_2$, FAC-$Ru(Azpy)_3^{2+}$, MER-$Ru(Azpy)_3^{2+}$ and $Ru(Bipy)_3^{2+}$ calculated at unrestricted state at wb97xd/Lanl2dz level.

Table 1. Energy of close and open shells models and energy of frontiers orbitals of unrestricted state of the Ru(II) complexes calculated at WB97XD/Lanl2dz level.

Ru(II) complexes	Close shell energy	Open shell energy	$\Delta E_{S\to T}$ (en eV)	Unrestricted state			Total energy required (eV)
	E_{S0} (en a.u.)	E_T (en a.u.)		E_{HOMO} (en a.u.)	E_{LUMO} (en a.u.)	$\Delta E_{H\to L}$ (en eV)	
α-$RuCl_2(Azpy)_2$	−1301.00	−1300.95	1.21	−0.31	−0.09	6.01	7.22
Fac-$Ru(Azpy)_3^{2+}$	−1859.08	−1859.01	1.96	−0.49	−0.32	4.64	6.60
Mer-$Ru(Azpy)_3^{2+}$	−1859.08	−1859.01	1.91	−0.49	−0.31	4.81	6.72
$Ru(Bipy)_3^{2+}$	−1579.03	−1578.93	2.68	−0.49	−0.29	5.46	8.14

Total energy required = $\Delta E_{S\to T} + \Delta E_{H\to L}$.

Table 2. The 20 lowest singlet excitation energies (eV), wavelength (nm) and oscillation strength (f) of Ru II complexes under unrestricted model calculated at WB97XD/Lanl2dz level.

Complexes		S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14	S15	S16	S17	S18	S19	S20
	E	1.126	1.182	1.622	1.647	1.703	1.884	1.959	1.978	2.125	2.505	2.512	2.679	2.879	2.935	2.943	3.051	3.139	3.203	3.217	3.269
α-$RuCl_2(Azpy)_2$	∠	1101.28	1048.99	764.4	752.72	727.9	657.91	633.01	626.7	583.5	494.85	493.54	462.73	430.59	422.47	421.23	406.34	393.98	387.04	385.44	379.25
	f	0	0	0	0	0.007	0	0	0	0.002	0	0	0	0	0	0	0	0	0	0	0
	E	1.798	1.798	1.801	2.528	2.55	2.550	2.587	2.587	2.637	2.637	2.639	2.655	2.694	2.694	2.738	2.933	2.9613	2.961	2.985	3.088
Fac-$Ru(Azpy)_3^{2+}$	∠	689.67	689.65	688.56	490.46	486.21	486.19	479.25	479.22	470.14	470.11	469.72	467.01	460.16	460.14	452.9	422.67	418.68	418.65	415.36	401.46
	f	0	0	0	0	0.008	0.008	0	0	0	0	0	0.0145	0	0	0	0	0	0	0.002	0.006
	E	1.722	1.822	1.923	2.345	2.410	2.429	2.472	2.511	2.592	2.597	2.628	2.639	2.660	2.751	2.777	2.907	2.9102	2.947	2.963	3.047
Mer-$Ru(Azpy)_3^{2+}$	∠	719.92	680.6	644.68	528.63	514.5	510.38	501.63	493.67	478.36	477.36	471.69	469.81	466.18	450.76	446.45	426.51	426.03	420.66	418.46	406.88
	f	0	0	0	0	0.006	0	0.003	0	0	0	0.008	0	0	0	0	0	0	0	0	0
	E	2.796	2.796	2.868	2.916	3.038	3.038	3.148	3.148	3.172	3.173	3.235	3.302	3.332	3.332	3.362	3.436	3.4362	3.458	3.459	3.461
$Ru(Bipy)_3^{2+}$	∠	443.43	443.4	432.32	425.14	408.11	408.09	393.88	393.84	390.82	390.69	383.3	375.46	372.1	372.07	360.83	360.83	360.81	358.42	358.42	358.24
	f	0	0	0	0	0	0	0	0	0	0	0.002	0	0	0	0	0.001	0.0012	0.146	0.146	0

Table 3. the 20 lowest triplet excitation energies (eV), wavelength (nm) and oscillation frequencies (f) of Ru II complexes under unrestricted models calculated at WB97XD/Lanl2dz level.

Complexes		T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	T20
	E	−0.257	0.2	0.409	1.694	1.753	2.085	2.193	2.216	2.266	2.300	2.412	2.507	2.520	2.657	2.716	2.733	2.7661	2.821	2.900	3.068
α-$RuCl_2(Azpy)_2$	∠	−4829.47	6328.88	3030.09	731.99	707.14	594.77	565.3	559.45	547.2	539.02	513.98	494.48	491.96	466.59	456.43	453.66	448.22	439.56	427.5	404.09
	f	−0.017	0.001	0	0.006	0	0.000	0.009	0.010	0.010	0.001	0.003	0.000	0.006	0.029	0.000	0.008	0.007	0.0001	0.006	0.001
	E	0.372	0.487	0.726	0.762	0.894	1.246	1.731	1.798	1.892	1.9	2.089	2.256	2.408	2.473	2.521	2.556	2.581	2.592	2.673	2.795
Fac-$Ru(Azpy)_3^{2+}$	∠	3335.95	2544.31	1708.43	1626.57	1386.32	994.78	716.43	689.52	655.36	652.54	608.1	549.61	514.91	501.33	491.88	485.06	480.46	478.32	463.79	443.52
	f	0.001	0	0	0.001	0.014	0.002	0.000	0.0003	0.003	0.001	0.002	0.002	0.005	0.005	0.019	0.005	0.000	0.003	0.000	0.002
	E	0.0332	0.446	0.549	0.725	1.148	1.480	1.679	1.767	1.853	1.916	2.129	2.247	2.416	2.431	2.517	2.570	2.610	2.655	2.830	2.872
Mer-$Ru(Azpy)_3^{2+}$	∠	3736.05	2778.51	2257.76	1709.81	1080.4	837.63	738.48	701.78	669.1	647.24	582.34	551.64	513.25	510.09	492.66	482.35	474.94	466.93	438.17	431.66
	f	0.000	0.000	0.002	0.000	0.008	0.003	0.000	0.005	0.001	0.000	0.000	0.003	0.027	0.001	0.003	0.000	0.000	0.001	0.000	0.002
	E	0.114	0.192	0.405	0.430	0.997	1.022	1.212	1.310	1.608	1.624	1.808	1.866	1.927	2.756	3.153	3.153	3.240	3.260	3.274	3.367
$Ru(Bipy)_3^{2+}$	∠	1083	6451.11	3060.16	2885.42	1243.84	1213.3	1022.63	946.08	771.07	763.53	685.75	664.45	643.25	449.79	393.25	393.16	382.68	380.26	378.68	368.22
	f	0.000	0.000	0.000	0.001	0.002	0.000	0.002	0.042	0.002	0.0005	0.011	0.001	0.002	0.117	0.000	0.000	0.024	0.004	0.001	0.000

Regarding Table 2 that shows up the singlet states of the complexes, we can notice that α-$RuCl_2(Azpy)_2$ presents two bands at S5 and S9. The lowest energy here is 1.703 eV. This energy corresponds to the wavelength at 727.9 nm and to the transition $t_{2g} \rightarrow \pi^*$. The last band is observed for the excitation state S9. The energy required for that band is 2.12 eV, which is known suitable for deep phototherapies. Both isomers Fac-$Ru(Azpy)_3^{2+}$ and Mer-$Ru(Azpy)_3^{2+}$ present their first singlet band at respectively 2.55 eV and 2.41 eV. However, these energies correspond respectively to wavelengths 486.21 and 514.6 nm showing that the first isomer is qualified for deep therapy and the last one can be used for superficial tumors [14] [15]. These bands correspond to the fifth excited state of the molecules. Whereas $Ru(Bipy)_3^{2+}$, its first singlet excitation appears at S11 with 3.23 eV as energy required. The corresponding wavelength is 383.3 nm.

Nevertheless, we can see many other bands at high energy and low wavelength. Anyhow, this cation displays only transitions suitable for deep tumors [16] [17].

Table 3 records all information of the 20 first triplets states for each complex calculated at Wb97xd/lanl2dz level in the unrestricted model. We can see therefore that all the complexes show significant wavelengths corresponding to oscillation forces higher than 0.001. Thus, α-$RuCl_2(Azpy)_2$ displays fourteen important wavelengths where the first is 6328.88 nm and the energy corresponding is 0.20 eV. Regarding Fac-$Ru(Azpy)_3^{2+}$, its first triplet wavelength appears at 3335.95 nm and the energy necessary for this excitation is 0.37 eV. In the case of Mer-$Ru(Azpy)_3^{2+}$ we can see that its first excitation wavelength is set at 2257.76 nm. The energy required for this transition is 0.55 eV. For the last molecule $Ru(Bipy)_3^{2+}$, its first transition is shown at the wavelength 2885.42 nm and the energy necessary is 0.43 eV. Contrary to the close shell state, we can see that the molecules in unrestricted state display actually E_T energy [5]. This witness their abilities to be therapeutically active. By comparison of their first energy of the triplet state, we have: $E_{T1}(\alpha\text{-}RuCl_2(Azpy)_2) < E_{T1}(\text{Fac-}Ru(Azpy)_3^{2+}) < E_{T1}(Ru(Bipy)_3^{2+}) < E_{T1}(\text{Mer-}Ru(Azpy)_3^{2+})$. Besides, Figure 4 and Figure 5 show the spectra relative to previous tables regarding the wavelengths of the complexes respectively at singlet and triplet states.

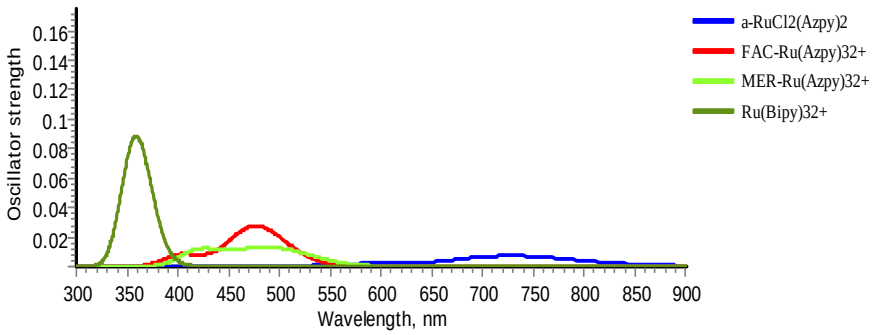

Figure 4. Electronic spectra of Ru II complexes calculated at wb97xd/lanl2dz level in unrestricted singlet state.

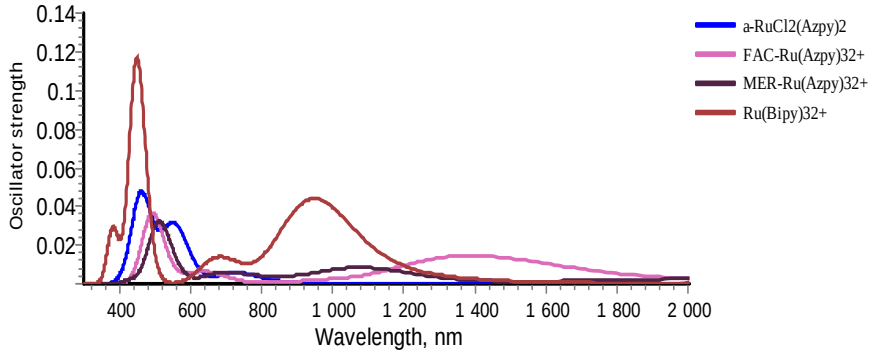

Figure 5. Electronic spectra of Ru II complexes calculated at wb97xd/lanl2dz in unrestricted triplet state.

We can see in Figure 4 that actually, only *α*-$RuCl_2(Azpy)_2$ presents a wavelength higher than 700 nm that comprises the therapeutic window. We notice the same fact for Mer-$Ru(Azpy)_3^{2+}$ which main wavelength is higher than 500 nm. This means that only these complexes can probably be active for deep cancers. Besides, the two other complexes such as Fac-$Ru(Azpy)_3^{2+}$ and $Ru(Bipy)_3^{2+}$ can be active for superficial tumors regarding their wavelength lower than 500 nm. In Figure 5, we can see that all complexes display electronic spectra meaning that they can be active for phototherapy dynamic.

3.3. Vertical Electron Affinity VEA and Vertical Ionization Potential VIP

The photosensitizing process depends in the attitude of the photosensitizer to give or to accept electrons. Therefore, VEA and VIP of the ruthenium complexes have been predicted at unrestricted state and recorded at both ground and excited states in Table 4 and Table 5.

At ground state S_0, we can see in Table 4 that the energies necessary for ruthenium to receive electrons (VEA_{S0}) is negative for all the ruthenium complexes. Besides, the most molecule able to accept electrons with the lowest energy are both isomers Fac and Mer-$Ru(Azpy)_3^{2+}$ and their energy is −0.350 eV. Whereas the vertical ionization potential VIP_{S0}, its lowest energy is displayed by *α*-$RuCl_2(Azpy)_2$ with 0.208 eV meaning that this complex is the most capable to liberate electron. Regarding the excited state in Table 5, we can notice that all the energy regarding VAE_{T1} is negative. Here, Mer-$Ru(Azpy)_3^{2+}$ presents the lowest energy necessary to accept electron. Whereas VIP_{T1}, its lowest energy is still presented by Mer-$Ru(Azpy)_3^{2+}$ with −0.086 eV.

Actually, photodynamic therapy can be performed only if PS can exchange electron with DNA bases of the cancer cells. These DNA bases are Adenine, Cytosine, Guanine, Thymine and Uracil. As explained in our previous article and in literature, they are assumed to give electron to the PS. Therefore, Table 6 displays the VEA and VIP of the DNA that react with the photosensitizer PS [5] [18] [19].

Table 4. Electronic energies of parent molecule (E_p, (in hartree)), anion radical (E_a, (in hartree)), cation radical (E_c, (in hartree)), vertical electronic affinity (VEA, eV) and vertical ionization potential (VIP, eV) of ruthenium complexes at unrestricted state calculated at Wb97xd/Lanl2dz level.

Complexes	E_p	E_a	E_c	[a]VEA_{S0}	[b]VIP_{S0}
α-$RuCl_2(Azpy)_2$	−1300.951	−1301.076	−1300.743	−0.125	0.208
Fac-$Ru(Azpy)_3^{2+}$	−1859.012	−1859.362	−1858.609	−0.350	0.403
Mer-$Ru(Azpy)_3^{2+}$	−1859.014	−1859.364	−1858.606	−0.350	0.408
$Ru(Bipy)_3^{2+}$	−1578.93	−1579.249	−1578.586	−0.319	0.344

[a]$VEA_{S0} = E_a - E_p$. [b]$VIP_{S0} = E_c - E_p$.

Table 5. Vertical electronic affinity (VEA eV), vertical ionization potential (VIP, eV) both at ground and excited states and the lowest energy at excited state E_{T1} (eV) of ruthenium complexes at unrestricted state at Wb97xd/Lanl2dz level.

Complexes	VEA_{S0}	VIP_{S0}	E_{T1}	VAE_{T1}	VIP_{T1}
α-$RuCl_2(Azpy)_2$	−0.125	0.208	0.200	−0.325	0.008
Fac-$Ru(Azpy)_3^{2+}$	−0.350	0.403	0.372	−0.722	0.031
Mer-$Ru(Azpy)_3^{2+}$	−0.350	0.408	0.549	−0.899	−0.141
$Ru(Bipy)_3^{2+}$	−0.319	0.344	0.430	−0.749	−0.086

[a]$VEA_{T1} = VEA_{S0} - E_{T1}$. [b]$VIP_{T1} = VIP_{S0} - E_{T1}$.

Through Table 6, we realize that the DNA base that most needs least ionization energy is Guanine with 0.297 eV. Besides, Uracyl is known to accept electron with the lowest energy through vertical electronic affinity.

Furthermore, it is admitted that photodynamic therapy takes place according to two possible steps as mechanisms.

3.3.1. Mechanism I

The first mechanism is assumed to occur directly between the PS and the DNA base either by exchange of electron or energy without oxygen molecule. The following equations show up all possibilities for PS to oxidize the DNA bases.

$$[Ru-K](T_1)+B \rightarrow [Ru-K]^{-} + B^{+} \quad (1)$$

$$[Ru-K](T_1)+[Ru-K](S_0) \rightarrow [Ru-K]^{-} + [Ru-K]^{+} \quad (2)$$

$$[Ru-K](T_1)+[Ru-K](T_1) \rightarrow [Ru-K]^{-} + [Ru-K]^{+} \quad (3)$$

$$[Ru-K]^{+} + B \rightarrow [Ru-K](S_0)+B^{+} \quad (4)$$

Equation (1) shows that PS at an excited state T_1 can receive directly electron from the DNA base that is known to be at a ground state S_0. This reaction is characterized by the sum of VEA_{T1} and VIP_{S0} (base) so that their sum is negative. In fact, the negative sum is at the stake of reaction thermodynamically feasible [20]. Moreover, a cation PS can receive electron from the DNA base (Equation (4)). The cation PS is actually produced through auto-ionization by combination of two excited PS at T1 state (Equation (3)) or by reaction between the excited PS and the PS at a fundamental state (Equation (2)). These reactions are respectively expressed by the sum either VEA_{T1} + VIP_{S0} or VIP_{T1} + VEA_{S0} for Equation (2) and by the sum VEA_{T1} + VIP_{T1} (Equation (3)). Table 7 shows the results from these reactions.

Table 7 shows us that the reaction regarding Equation (1) of all the complexes is possible insofar that the sum of VEA_{T1}(C) and VIP(G) is negative meaning that the PS at excited and unrestricted state can actually receive electron from the DNA base. Moreover, the reaction related to the auto-ionization to produce radical cation of the PS is possible. In fact, all the sums are also negative. It means that in unrestricted state, the ruthenium II complexes are active and can

Table 6. Vertical electronic affinity (VEA, eV) and vertical ionization potential (VIP, eV) calculated on DNA and RNA bases at wb97xd/Lanl2dz level.

	E_p	E_c	E_a	VEA_{SO}	VIP_{SO}
Adénine	−467.069	−466.757	−467.030	0.039	0.312
Cytosine	−394.734	−394.414	−394.704	0.031	0.320
Guanine	−542.276	−541.979	−542.222	0.053	0.297
Uracile	−414.618	−414.265	−414.600	0.018	0.353
Thymine	−453.922	−453.586	−453.901	0.021	0.336

Table 7. Sum of the VEA_{T1} parameters of the complex and VIP parameters of the Guanine reflecting the interactions according to Equation (1), Sum VEA_{T1} + VIP_{S0} or VIP_{T1} + VEA_{S0} both reflecting the auto ionization reaction and VIP_{T1} + VEA_{T1}, all performed at B3lyp/wb97xd level over the unrestricted complexes.

Complexes	VEA_{S0}	VIP_{S0}	E_{T1}	VAE_{T1}	VIP_{T1}	VEA_{T1}(C) + VIP(G)	VIPT1 + VEA_{S0}	VEA_{T1} + VIP_{S0}	VIP_{T1} + VEA_{T1}
α-$RuCl_2(Azpy)_2$	−0.125	0.208	0.200	−0.325	0.008	−0.028	−0.117	−0.117	−0.317
Fac-$Ru(Azpy)_3^{2+}$	−0.350	0.403	0.372	−0.722	0.031	−0.425	−0.319	−0.319	−0.690
Mer-$Ru(Azpy)_3^{2+}$	−0.350	0.408	0.549	−0.899	−0.141	−0.602	−0.491	−0.491	−1.040
$Ru(Bipy)_3^{2+}$	−0.319	0.344	0.430	−0.749	−0.086	−0.452	−0.405	−0.405	−0.835

react with the Guanine weather directly or through auto-ionization for cation production. Therefore, we can conclude that Ru II complexes at unrestricted state are active as photosensitive molecules through mechanism I.

3.3.2. Mechanism II

Regarding the second mechanism, it is an indirect reaction between DNA and the PS molecule. It requires a presence of oxygen molecule in a third state $^3O_2$. It is characterized by the Equation (5).

$$[Ru-K](T_1)+{}^3O_2 \rightarrow [Ru-K](S_0)+{}^1O_2 \quad (5)$$

The oxygen molecule in the third state must be shifted in singlet that is assumed to be active as destructor of the tumor cell. To obtain the singlet oxygen molecule, the energy of triplet state of PS must be higher than the energy necessary to change the state. According to literature, this energy required is estimated to 1.06 eV [21] [22] [23]. Therefore, in **Table 3** that displays the first twenty triplet states, we can see that T1 is not suitable for this reaction in any complex. However, even though it is possible, only high transitions are admitted. For instance, with α-$RuCl_2(Azpy)_2$, T4 is suitable with 1.694 eV. With Fac-$Ru(Azpy)_3^{2+}$, T6 is the first transition necessary for 1.246 eV. Regarding Mer-$Ru(Azpy)_3^{2+}$, T6 is the transition acceptable for energy 1.148 eV. Whereas $Ru(Bipy)_3^{2+}$, the first transition necessary is T7 with the energy 1.212 eV. Anyway, Mer-$Ru(Azpy)_3^{2+}$ presents the lowest energy required to transform $^3O_2$ at the state ($^3\Sigma_g^-$) in to $^1O_2$ with the state ($^1\Delta_g$).

Table 8. Sum of VIP_{T1} of Ru complex and $AEA(O_2)$ of oxygen in eV calculated at Wb97xd/lanl2dz level.

Complexes	VIP_{T1}	$AEA(O_2)$	$VIP_{T1} + AEA(O_2)$
α-$RuCl_2(Azpy)_2$	0.008	−0.59	−0.582
Fac-$Ru(Azpy)_3^{2+}$	0.031		−0.559
Mer-$Ru(Azpy)_3^{2+}$	−0.141		−0.731
$Ru(Bipy)_3^{2+}$	−0.086		−0.676

Furthermore, mechanism II can be also described by production of peroxide radical anion $O_2^{\cdot-}$ with the triplet oxygen molecule $^3O_2$. This reaction takes place between the triplet state of ruthenium complex and the triplet oxygen molecule. Equation 6 highlights this reaction.

$$[Ru-K](T_1) + {}^3O_2 \rightarrow [Ru-K]^{+} + O_2^{\cdot-} \quad (6)$$

Thermodynamically, this reaction means summation of VIP_{T1} for the ruthenium complex and the adiabatic electron affinity $AEA(O_2)$ of the oxygen. This latter energy is given in vacuum as −0.59 eV [14] [20]. **Table 8** shows the sum of both VIP_{T1} of PS and $AEA(O_2)$.

The result of the sum of VIP_{T1} and $AEA(O_2)$ is negative for each complex, it means the reaction is also thermodynamically possible. Therefore, we can retain that Ru II complexes can generate the superoxide anion $O_2^{\cdot-}$. Moreover, they are active as photosensitizer in photodynamic therapy through mechanism II provided they be in unrestricted state.

4. Conclusions

Ruthenium complexes at oxidation state II were investigated in this work as photodynamic therapy photosensitizers at unrestricted state. This is a state where electrons occupy lonely their orbitals. It required that the optimization and frequency calculations be performed in that abovementioned state. In our previous paper in which we compared state II and III of ruthenium complexes, we discovered that Ru complexes with the state II are naturally in restricted state. Therefore, it is very hard for them to liberate electron when they are excited to yield triplet state. Thus, they are not active for PDT.

Here, the use of Ru II begins by dissociating first the pair electrons for open shell model. Then excitation to a singlet and triplet is performed. The total energy required was comprised between 6.60 and 8.14 eV. These two extreme energies are respectively given by Fac-$Ru(Azpy)_3^{2+}$ and $Ru(Bipy)_3^{2+}$. TDDFT calculation in singlet state shows henceforth that α-$RuCl_2(Azpy)_2$ and Mer-$Ru(Azpy)_3^{2+}$ can be active for deep cancer as they display therapeutic windows. Whereas the two other complexes, they are assumed to neutralize superficial cancers. Besides, there are all discovered to bind with Guanine DNA base.

Regarding phototherapy dynamic, Ru II complexes at unrestricted state are

assumed to be active for both mechanisms either in presence or in absence of O_2. In addition, they do not require much energy to shift from restricted to open shell state. This tremendous result is showing that Ru II complexes can of course be used as Photosensitizer for photodynamic therapy providing that they be in unrestricted model. Therefore, our upcoming work will consist of synthetizing the Ru II complexes at unrestricted state and find out the difference with the restricted state complexes.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Velders, A.H., Kooijman, H., Spek, A.L., Haasnoot, J.G., De Vos, D. and Reedijk, J. (2000) Strong Differences in the Vitro Cytotoxicity of Three Isomeric Dichlorobis (2-Phenylazopyridine) Ruthenium (II) Complexes. *Inorganic Chemistry*, **39**, 2966. https://doi.org/10.1021/ic000167t

[2] Notaro, A. and Gasser, G. (2017) Monomeric and Dimeric Coordinatively Saturated and Substitutionally Inert Ru(II) Polypyridyl Complexes as Anticancer Drug Candidates. *Chemical Society Reviews*, **46**, 7317-7337. https://doi.org/10.1039/C7CS00356K

[3] Nobel, N.K., Bamba, K., Patrice, O.W. and Ziao, N. (2017) NBO Population Analysis and Electronic Calculation of Four Azopyridine Complexes by DFT Method. *Computational Chemistry*, **5**, 51-64. https://doi.org/10.4236/cc.2017.51005

[4] Sava, G., Bergamo, A., Zorzet, S., Gava, B., Casarsa, C., Cocchietto, M., Furlani, A., Scarcia, V., Serli, B., Iengo, E., Alessio, E. and Mestroni, G. (2002) Influence of Chemical Stability on the Activity of the Antimetastasis Ruthenium Compound NAMI-A. *European Journal of Cancer*, **38**, 427-435. https://doi.org/10.1016/S0959-8049(01)00389-6

[5] Bamba, K., Ouattara, W.P., Diarrassouba, F., Ouattara, L., Massapihanhoro, P.O., N'guessan, K.N., Ehouman, A.D. and Ziao, N. (2021) Theoretical Determination of Influence of the Metallic State of Oxidation toward Cytotoxic Activity: Case of Ruthenium Complexes. *Computational Chemistry*, **9**, 97-119. https://doi.org/10.4236/cc.2021.92006

[6] Harriman, A. (1995) CRC Handbook of Photochemistry and Photobiology. CRC Press, Boca Raton.

[7] Ouattara, W.P. (2021) Evaluation théorique de l'impact de la substitution des métaux de transition et des ligands sur les propriétés anticancéreuses, photodynamiques et de fluorescence des complexes azopyridines. Thèse de doctorat, Université Nangui Abrogoua, p. 98.

[8] Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., Scalmani, G., Barone, V., Mennucci, B., Petersson, G.A., Nakatsuji, H., Caricato, M., Li, X., Hratchian, H.P., Izmaylov, A.F., Bloino, J., Zheng, G., Sonnenberg, J.L., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Montgomery Jr., J.A., Peralta, J.E., Ogliaro, F., Bearpark, M., Heyd, J.J., Brothers, E., Kudin, K.N., Staroverov, V.N., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A., Burant, J.C., Iyengar, S.S., Tomasi, J., Cossi, M., Rega, N., Millam, J.M., Klene, M., Knox, J.E., Cross,

J.B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R.E., Yazyev, O., Austin, A.J., Cammi, R., Pomelli, C., Ochterski, J.W., Martin, R.L., Morokuma, K., Zakrzewski, V.G., Voth, G.A., Salvador, P., Dannenberg, J.J., Dapprich, S., Daniels, A.D., Farkas, O., Foresman, J.B., Ortiz, J.V., Cioslowski, J. and Fox, D.J. (2009) Gaussian 09, Revision A.02. Gaussian, Inc., Wallingford CT, USA.

[9] Mazzone, G., Alberta, M.E., De Simone, B.C., Marino, T. and Russo, N. (2016) Can Expanded Bacterioclorins Act as Photosensitizers in Photodynamic Therapy? Good News from Density Functional Theory Computations. *Molecules*, **21**, 288. https://doi.org/10.3390/molecules21030288

[10] Erikson, E.S.E. and Erikson, L.A. (2011) Predictive Power of Long-Range Corrected Functionals on the Spectroscopic Properties of Tetrapyrrole Derivatives for Photodynamic Therapy. *Physical Chemistry Chemical Physics*, **13**, 7207-7217. https://doi.org/10.1039/c0cp02792h

[11] Bamba, K., Ouattara, W.P., N'Guessan, K.N. and Ziao, N. (2016) SARs Investigation of α-, β-, γ-, δ-, ε -$RuCl_2(Azpy)_2$ Complexes as Antitumor Drugs. *Computational Chemistry*, **4**, 1-10. https://doi.org/10.4236/cc.2016.41001

[12] N'guessan, K.N., Guy-Richard Koné, M., Bamba, K., Ouattara, W.P. and Ziao, N. (2017) Quantitative Structure Anti-Cancer Activity Relationship (QSAR) of a Series of Ruthenium Complex Azopyridine by the Density Functional Theory (DFT) Method. *Computational Molecular Bioscience*, **7**, 19-31. https://doi.org/10.4236/cmb.2017.72002

[13] Foresman, J.B. and Frisch, A. (1996) Exploiting Chemistry with Electronic Structure Methods. In: *Thermochemistry*, 2nd Edition, Gaussian, Inc., Pittsburgh, PA, p. 53.

[14] Liu, J., Zhao, Y.W., Zhao, J., Q., Xia A. D., Jiang L. J., Wu, S., Ma L. Dong Y. Q. Gu Y. H., (2002) Two Photon Excitation Studies of Hypocrellins for Photodynamic Therapy. *The Journal of Photochemistry and Photobiology B*: *Biology*, **68**, 156. https://doi.org/10.1016/S1011-1344(02)00379-2

[15] Zhao, X., Zheng, Z.B., Feng, S., Shi, Z.Q. and Chen, D.Z. (2009) A TD-DFT Study on the Photo-Physicochemical Properties of Chrisophanol from Rheum. *International Journal of Molecular Sciences*, **10**, 3186-3193. https://doi.org/10.3390/ijms10073186

[16] Gould, J.W., Mercurio, M.G. and Elmets, C.A. (1995) Cutaneous Photosensitivity Diseases Induced by Exogenous Agents. *Journal of the American Academy of Dermatology*, **33**, 551-573. https://doi.org/10.1016/0190-9622(95)91271-1

[17] Wu, W.T., Shao, X.D., Zhao, J.Z. and Wu, M.B. (2017) Controllable Photodynamic Therapy Implemented by Regulating Singlet Oxygen Efficiency. *Advanced Science*, **4**, Article ID: 1700113. https://doi.org/10.1002/advs.201700113

[18] Allardyce, C.S. and Dyson, P.J. (2001) Ruthenium in Medicine: Current Clinical Uses and Future Prospects. *Platinum Metals Review*, **45**, 62-69.

[19] Ouattara, W.P., Bamba, K., Thomas, A.S., Diarrassouba, F., Ouattara, L., Massapihanhoro, P.O., N'guessan, K.N., Guy Richard, K.M., Kodjo, C.G. and Ziao, N. (2021) Theoretical Studies of Photodynamic Therapy Properties of Azopyridine δ-$OsCl_2(Azpy)_2$ Complex as a Photosensitizer by a TDDFT Method. *Computational Chemistry*, **9**, 64-84. https://doi.org/10.4236/cc.2021.91004

[20] Rita, C.G. and Leif, A.E. (2005) Theoretical Study of Hypericin. *Journal of Photochemistry and Photobiology A*: *Chemistry*, **172**, 293-299. https://doi.org/10.1016/j.jphotochem.2004.12.025

[21] Llano, J., Raber, J. and Eriksson, L.A. (2003) Theoretical Study of Phototoxic Reactions of Psoralens. *Journal of Photochemistry and Photobiology A*: *Chemistry*, **154**,

235-243. https://doi.org/10.1016/S1010-6030(02)00351-9

[22] Sousa, F.F.R., Quartarolo, A.D., Sicilia, E. and Russo, N. (2012) A Time-Dependent Density Functional Study of a Non-Aromatic [1.1.1.1.1]-Pentaphyrin and Its Lutetium Complex. *The Journal of Physical Chemistry B*, **116**, 10816-10823. https://doi.org/10.1021/jp3068359

[23] Musa, K.A.K., Matxain, J.M. and Eriksson, L.A. (2007) Mechanism of Photoinduced Decomposition of Ketoprofen. *Journal of Medicinal Chemistry*, **50**, 1735-1743. https://doi.org/10.1021/jm060697k