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Theoretical Studies of Photodynamic Therapy Properties of Azopyridine δ-$OsCl_2(Azpy)_2$ Complex as a Photosensitizer by a TDDFT Method

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Abstract

Photochemical reactions have an important place in photodynamic treatments. A good use of this therapeutic method requires a good mastery of the mechanisms of the reactions involved. Therefore, we have explored in this work the photosensitization mechanism of an organometallic complex of azopyridine δ-$OsCl_2(Azpy)_2$ through a calculation with the method of Time Dependent Density Functional Theory TDDFT. First, we evaluated the effect of polar and non-polar solvents on the triplet and singlet excited states of this complex. Then secondly, we highlighted the photosensitization mechanism to understand how the complex acts over the diseased cells. These investigations have shown that the δ-$OsCl_2(Azpy)_2$ complex is likely to develop photodynamic activity according to two mechanisms: on one hand, it can generate damage to DNA bases or target tissues indirectly through the production of singlet oxygen in water and in DMSO. On the second hand, through the production of the anionic superoxide radical $O_2^{\bullet -}$ in water can act directly or indirectly on these substrates. In addition, polar solvents are assumed to better carry out the photochemical reactions of this azopyridine complex of osmium.

Keywords

Time Dependent-Density Functional Theory, Azopyridine, Excited States, Photosensitization, Photodynamic Therapy, Osmium

1. Introduction

Organometallic complexes of arylazopyridine type represent a class of compounds with interesting biological properties, in particular their anticancer properties [1]. Group 8 metals, iron, ruthenium and osmium, are of great interest for the development of metal-based anti-cancer drugs [2]. Hotze *et al.* in their study of this type of complex, have demonstrated, on the one hand, their antiproliferative properties *in vitro* of cancer cells and, on the other hand, their antitumor activity *in vivo* [3]. Moreover, ANG has shown that the anticancer properties of these complexes depend strongly on their molecular structures [1]. Besides, few Arylazopyridine ruthenium complexes are assumed to act on several tumor cell lines [3]. Moreover, these complexes are discovered as photosensitizers thereby allowing them to emit electrons under the light effect. Thus, they have a wide absorption band in the visible range. Therefore, their photophysical properties are exploited in photovoltaic cells [4].

In the treatment of cancers, traditional techniques such as surgery, chemotherapy and radiotherapy are subject to a number of disadvantages and risks that are often reported [2]. Thus, approaches to the development of a new treatment that is safer, more powerful and less expensive are needed. Photodynamic therapy (PDT) is a therapeutic strategy based on the activation of photosensitive molecules that have already a chemotherapy property. It is a recent therapeutic strategy in the treatment of cancer. It is intensely invested with great interest by the scientific community. Photoactivatable molecules or photosensitizers (PS) induce photochemical reactions that lead to the destruction of neoplastic cells by necrosis or apoptosis. These photochemical reactions are preceded by the excitation of the photosensitizer. This excitation is generally based on radiation from the UV or visible range. Indeed, the photosensitizer absorbs a photon which makes it pass from the fundamental singlet state (S_0) to an excited singlet state of higher energy. The PS excited can return to the first excited singlet state (S_1^*) by internal conversions. Internal conversions are only allowed between electronic states of the same multiplicity. The return to the fundamental state of the excited photosensitizer from the S_1 state is done either by fluorescence or by inter-system conversion [5]. Here, fluorescence is a radiative phenomenon that takes place with conservation of the photosensitizer's spin. It has an application in the photodiagnosis of tumors. On the other hand, inter-system conversion is non-radiative and implies a change in the multiplicity of the photosensitizer. It takes place from the excited singlet state S_1 to an excited triplet state Tn of lower energy. And T_1 represents the lowest excited triplet state of the photosensitizer. Following an inter-system conversion, the photosensitizer in a triplet state Tn can return to the ground state S_0. Also, triplet states are assumed to have a much longer lifetime than singlet states. Thus, this is very useful for the generation of photo-active species such as radicals and reactive oxygen species ROS. These photo-active species are responsible for the cytotoxicity of photosensitizers. Furthermore, there are two types of mechanisms for the photo-active species pro-

duction based on photo-oxidation reactions. The type I mechanism involves a transfer of electrons or protons between the photosensitizer in the excited state and biological substrates to form radicals and radical ions. These radicals or radical ions can lead to the formation of reactive oxygen species (ROS). In the type II mechanism, singlet oxygen ($^1O_2$) is produced via a transfer of the excitation energy from the triplet photosensitizer to the triplet basic oxygen [6]. **Figure 1** schematically summarizes the two types of mechanism.

Photodynamic therapy (PDT) requires the action of the photosensitizer, the light and oxygen molecule. The photosensitizer plays a very important role in this original therapeutic technique. It must therefore comply with a certain number of biological and photophysical criteria. In the latter case for example, its absorption range must contain the therapeutic window for its efficient exploitation [8]. In a recent study, Ouattara *et al.* [9] determined the absorption characteristics of arylazopyridine complexes of the three transition metals Fe, Ru and Os. Among these complexes, ε-Fe, δ-Ru and δ-Os showed absorption bands that display the therapeutic window. It is a spectral domain where only the photosensitizer can be excited. It is assumed to be comprised between 600 and 1000 nm. With this wavelength, it is also possible to produce oxygen singlet and to reach the deep cells. In this study, the δ-Os complex will be of interest because it has shown the best cytotoxicity characteristics [9]. Moreover, the presence of heavy atoms within these molecular structures is an important asset for intersystem conversion (ISC) [10] [11]. These complexes, known for their various anticancer properties, are therefore interesting for pharmacological studies. In the present study, quantum chemistry methods are used to characterize the photophysico-chemical properties of δ-$OsCl_2(Azpy)_2$ in order to elucidate its anticancer mechanisms [1] [8].

2. Calculation Methodology

The study of photochemical and photochemical processes involves the fundamental and excited states of the photosensitive system. Elaborated theories exist

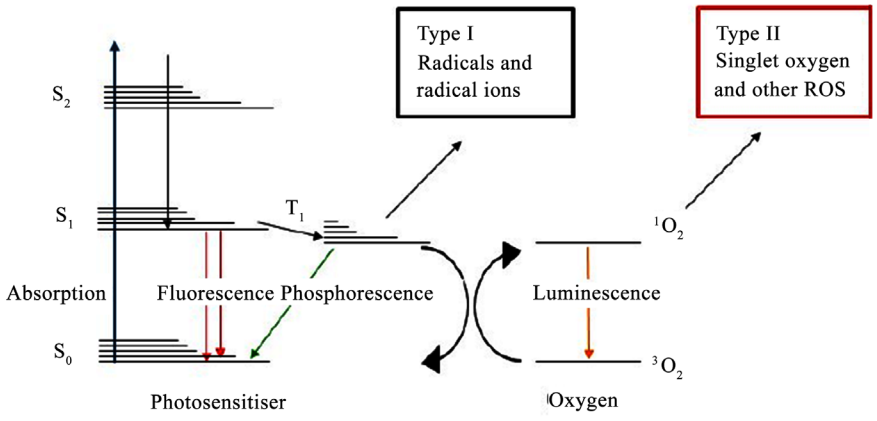

Figure 1. Representative diagrams of type I and II photochemical reactions after irradiation [7].

and allow to have in the whole essential parameters for the prediction and understanding of the properties related to excited electronic states and photochemical reactions. All the photo-physicochemical parameters can only be determined on the fundamental state of the chemical species concerned. To obtain this state, all geometrical optimization calculations are always followed by frequency calculations. In this work, all calculations of electronic structures are performed from the Gaussian 09 software using the DFT method with its B3LYP functional and the pseudo-potential Lanl2dz basis set [12].

2.1. Photophysical Characteristics

Absorption spectra of the complex were obtained with the TDDFT method by calculating the first 20 singlets and triplets' roots in the gas and solvent phase. The TDDFT calculations in the gas phase are currently known to be accurate at about 0.2 eV (5 kcal/mol) [13]. These calculations have been performed on the optimized gas-phase and solvent-phase geometries of the complex. The B3LYP function was chosen for the TDDFT calculations for its ability to quantitatively reproduce the experimental results [13]. The solvent effect has been included through the polarized continuum model (PCM) of Tomasi and colleagues at B3LYP/Lanl2dz level [14]. The energy calculations were performed in single point. Four different solvents were used in this work. They are water ($\varepsilon = 78.39$), DMSO with $\varepsilon = 46.83$, ether with $\varepsilon = 4.34$ and Benzene with $\varepsilon = 2.27$. These four types of solvents are samples reflecting on the one hand the protic or aprotic character of a solvent and on the other hand the polar or non-polar character of a solvent. Moreover, the choice of these solvents is also due not only to the fact that some of these solvents are widely used in the medical field but also by the fact that during the synthesis of these complexes, the purification is done in water and diethylether [15].

2.2. Photochemical Characteristics

The various parameters determined make it possible to characterize the photochemical reactivity as well as the possibility of reaction of the complexes with the bases of the DNA. They make it possible to rationalize the possible movements of transfer and/or acquisition of electrons by the δ-$OsCl_2(Azpy)_2$ complex. The ability of different molecular species to capture electrons is defined by the vertical electron affinity (VEA). It corresponds to the difference in energy between the neutral molecule and the corresponding anion according to the following relation:

$$VEA_{SO} = Ea - Ep \quad (1)$$

Thus, the electron sensor character increases with the VEA. Also, from a thermodynamic point of view, the VEA can be interpreted as the enthalpy variation that accompanies the formation of the anion. Besides, the Vertical Ionization Potential (VIP) measures the tendency of a chemical system to give up its electron. It is determined by calculating the difference in energy between the

neutral molecule and the corresponding cation according to the relationship:

$$VIP_{SO} = Ec - Ep \quad (2)$$

It is an energetic greatness that is always positive. The energies of the anions and cations are determined from a single point calculation performed by keeping the same optimized geometry of the corresponding neutral systems by a charge assignment with −1 or +1 respectively. These single point calculations have been performed at the B3LYP/Lanl2dz theory level.

All the photophysical and photochemical properties are determined both in the gaseous medium and in the solvents. The different solvents selected, water, DMSO, diethylether and benzene allow to cover the different state of organic solvents which can be polar, protic, aprotic and apolar. Solvent effects were taken into account by performing single point calculations including the polarizable continuum model (CPCM) developed by Tomasi *et al.* at the B3LYP/Lanl2dz level [14] at the same level of calculation.

3. Results and Discussion

The frequency calculation that followed the geometrical optimization of the complex and each base of the DNA or RNA showed the absence of imaginary frequencies in all Hessian matrices. This confirms the fundamental state of the structure at the B3LYP/Lanl2dz level. **Figure 2** shows the optimized structure of the azopyridine complex δ-$OsCl_2(Azpy)_2$. This structure of the complex was discovered and named according to the nomenclature proposed by Velders et al [16].

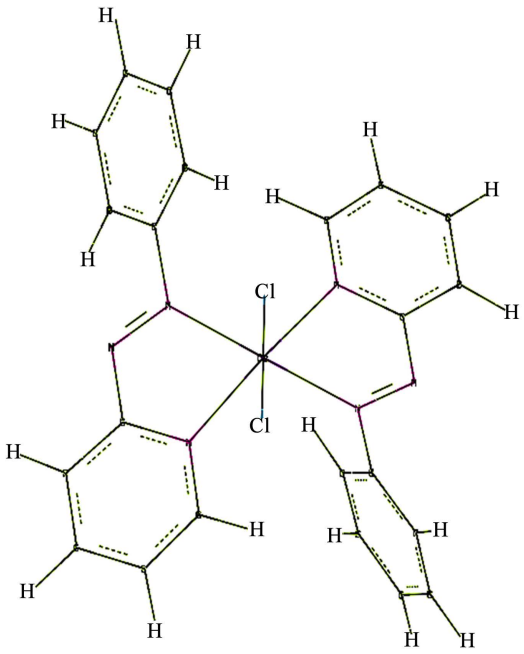

Figure 2. Optimized structure of the azopyridine complex δ-$OsCl_2(Azpy)_2$ performed at the B3LYP/Lanl2dz level. It is an isomer where both ligands Azpy and Cl atoms are in *trans* position.

3.1. Photo-Physicochemical Properties of the δ-$OsCl_2(Azpy)_2$ Complex and the DNA or RNA Bases

DNA and NRA are composed of a series of six bases that are Adenine, Cytosine, Guanine, Thymine and Uracil. There are the molecules through which the drug is reported to bind for the apoptosis of the tumor cell. Since the photochemical reactions of the δ-$OsCl_2(Azpy)_2$ complex and the DNA or the RNA bases are related to the properties of the excited states of these molecules, then we evaluated the lowest energy excited states of this molecule with both the excited states singlet and triplet either in vacuum or in the presence of solvent at the B3LYP/Lanl2dz level.

3.1.1. Photo-Physicochemical Properties of DNA or RNA Bases

The excited states Singlets and triplets of DNA or RNA bases were performed in vacuum. Table 1 displays the excitation energies and the probability coefficients of the six lowest excited singlet and triplet states of DNA or RNA bases calculated in vacuum at the B3LYP/Lanl2DZ level.

The singlet states of these bases have absorption bands that range from 190 nm to 300 nm. In addition, the UV-visible spectrum of these bases in vacuum indicates that they absorb between 130 nm and 300 nm in vacuum (Figure 3). Thus, these nitrogenous bases of DNA absorb all in the UV. Therefore, the use of any wavelength within the therapeutic window will not cause any alteration on these bases [17].

As for the triplet states, we note that these states have low oscillation forces except for a few states whose forces are significant. Actually, the states with very low values of oscillation forces are less likely to occur. Therefore, they will not be considered in our analyses. Only states with oscillation forces greater than or equal to 0.001 will be considered. Based on this principle, we have a diversification of the number of significant states from one base to another. For the adenine base, we have three significant states, the first of which is at 1306 nm; for the cytosine base, we have three significant states, the first of which is at 1644 nm. The guanine displays four significant states and the first one occurs at 1227 nm. For the thymine, four significant states are also observed, the first of which

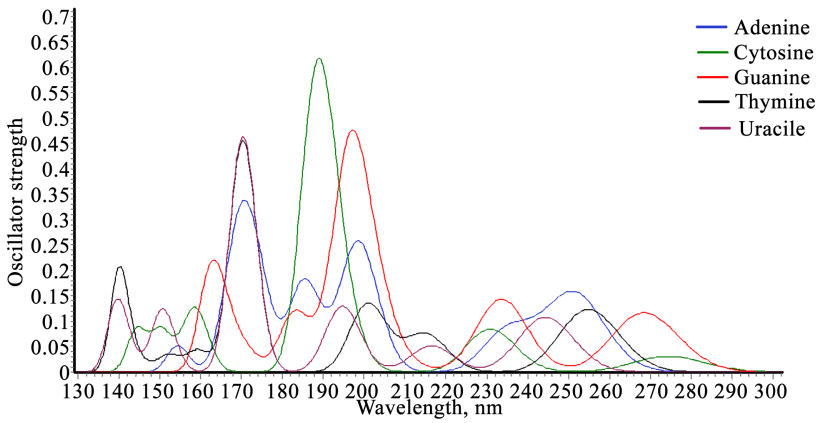

Figure 3. Absorption spectrum of DNA or RNA bases in vacuum.

Table 1. Six smallest excitation energies (E, eV), oscillation forces (f) and wavelengths (nm) of the excited singlet and triplet states of the DNA or RNA bases in vacuum.

			S1	S2	S3	S4	S5	S6
Etats Singlets	Adénine	E	4.545	4.929	5.184	5.263	5.4896	6.166
		λ	272.810	251.530	239.150	235.580	225.890	201.070
		f	0.000	0.154	0.001	0.085	0.003	0.049
		S^2	0.000	0.000	0.000	0.000	0.000	0.000
	Cytosine	E	4.461	4.516	4.794	5.334	5.369	5.831
		λ	277.950	274.540	258.620	232.450	230.910	212.620
		f	0.000	0.031	0.001	0.0001	0.085	0.000
		S^2	0.000	0.000	0.000	0.000	0.000	0.000
	Guanine	E	4.616	4.714	5.307	5.519	5.748	6.082
		λ	268.610	263.040	233.640	224.640	215.680	203.840
		f	0.116	0.001	0.143	0.002	0.004	0.105
		S^2	0.000	0.000	0.000	0.000	0.000	0.000
	Thymine	E	4.445	4.907	5.551	5.848	5.867	6.184
		λ	278.500	252.680	223.340	212.000	211.320	200.480
		f	0.000	0.115	0.000	0.091	0.000	0.130
		S^2	0.000	0.000	0.000	0.000	0.000	0.000
	Uracil	E	4.378	5.074	5.471	5.726	5.834	6.279
		λ	283.190	244.370	226.620	216.520	212.520	197.450
		f	0.000	0.109	0.000	0.052	0.000	0.000
		S^2	0.000	0.000	0.000	0.000	0.000	0.000
			T1	T2	T3	T4	T5	T6
Etats Triplets	Adénine	E	0.676	0.949	1.361	1.710	1.812	2.476
		λ	1835.100	1306.240	910.860	725.180	684.310	501.940
		f	0.0003	0.002	0.002	0.000	0.024	0.000
		S^2	2.043	2.029	2.015	2.050	2.040	2.050
	Cytosine	E	0.754	0.853	1.125	1.366	3.046	3.799
		λ	1644.200	1452.700	1102.400	907.670	407.010	326.320
		f	0.007	0.0001	0.004	0.000	0.061	0.001
		S^2	2.010	2.028	2.021	2.066	2.032	2.025
	Guanine	E	0.961	1.011	1.355	1.530	2.012	2.458
		λ	1290.500	1226.880	915.070	810.230	616.300	504.350
		f	0.0002	0.001	0.015	0.006	0.0002	0.037
		S^2	2.033	2.019	2.022	2.018	2.039	2.036
	Thymine	E	0.930	1.345	1.945	2.233	3.485	3.765
		λ	1333.600	921.440	637.500	555.240	355.720	329.330
		f	0.000	0.002	0.018	0.000	0.069	0.001
		S^2	2.031	2.014	2.036	2.049	2.042	2.019
	Uracil	E	0.665	1.241	2.001	2.067	3.563	3.854
		λ	1863.400	999.410	619.52	599.740	347.980	321.680
		f	0.000	0.005	0.018	0.000	0.057	0.001
		S^2	2.031	2.014	2.025	2.040	2.032	2.045

is at 921 nm, and for the uracil base, three significant states are observed with the first at 999 nm. These triplet states have S^2 values very close to 2, which attests that these states are free of any contamination [18].

3.1.2. Photophysical and Chemical Properties of the δ-$OsCl_2(Azpy)_2$ Complex

In this section, we first focused on the singlet states of these complexes. The singlet states provide information on the absorption bands of the molecules. We evaluated the six lowest-energy singlet states of the δ-$OsCl_2(Azpy)_2$ complex with a view to highlight the absorption bands that lie within the therapeutic window [17]. Secondly, we were interested in the triplet states. In fact, photosensitive reactions generally occur in the triplet excited state because of the much longer lifetime of this state compared to the singlet excited state. This very long lifetime of the triplet state considerably increases the probability of collision and thus of interaction and/or reaction with other molecules [19]. Therefore, photosensitized reactions will almost always involve the triplet state of a molecule. Besides, we have determined the excitation energies (ET1) of the six lowest energy triplet states of photosensitizers that are crucial in understanding the photosensitization mechanisms. The values of the energies of these singlet S and triplet T states of the photosensitizers were calculated by the TD-DFT method in vacuum and solvent. The different results are reported in **Table 2**. Only states with an oscillation force greater than or equal to 0.001 will be taken into account in the analysis of these results. **Figure 4** shows the absorption spectrum of the δ-$OsCl_2(Azpy)_2$ complex in vacuum and solvent.

The determination of the six lowest energy singlet and triplet states was performed by the TDDFT method in vacuum and at the B3LYP/LANL2DZ level. As the photochemical reactions of this complex are carried out in biological milieu, it seems justified to evaluate the impact of the solvent on these triplet states. At this level, it should be noted that the solvents can be grouped into four categories which are: polar protic solvents, dipolar aprotic solvents, low-polar aprotic solvents and apolar aprotic solvents. In the coming work, we will use a sample of each of the above solvent types. The first of these solvents is water. It is a polar

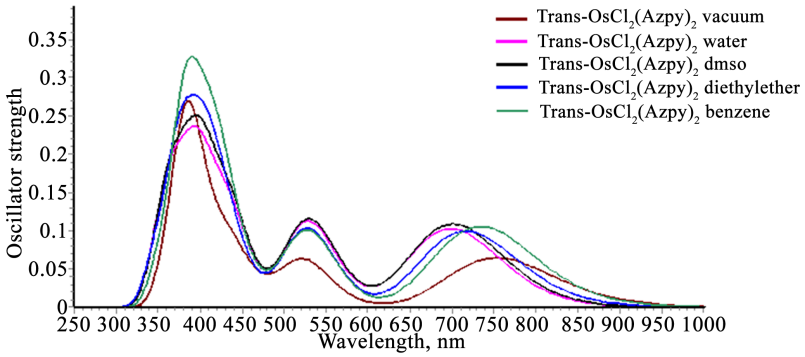

Figure 4. Absorption spectrum of the $OsCl_2(Azpy)_2$ complex in vacuum, water, Dmso, diethylether and benzene.

Table 2. Six smallest excitation energies (E, eV), oscillation forces (f) and wavelengths (nm) of the excited singlet and triplet states of the δ-$OsCl_2(Azpy)_2$ complex in Vacuum, Water, DMSO, Diethylether and Benzene.

			S1	S2	S3	S4	S5	S6
Etats Singlets δ-Os	Vide	E	0.650	1.358	1.646	1.787	2.369	2.568
		λ	1907.230	912.730	753.350	693.700	523.320	422.740
		f	0.000	0.000	0.014	0.000	0.060	0.003
		S^2	0.000	0.000	0.000	0.000	0.000	0.000
	Eau	E	0.777	1.499	1.726	1.775	2.345	2.759
		λ	1596.200	826.990	718.430	698.430	528.690	449.440
		f	0.000	0.000	0.000	0.102	0.112	0.000
		S^2	0.000	0.000	0.000	0.000	0.000	0.000
	DMSO	E	0.775	1.497	1.726	1.769	2.342	2.755
		λ	1600.720	827.920	718.440	700.980	529.440	449.950
		f	0.000	0.000	0.000	0.109	0.115	0.000
		S^2	0.000	0.000	0.000	0.000	0.000	0.000
	Diethylether	E	0.740	1.457	1.731	1.748	2.351	2.703
		λ	1675.450	850.790	716.390	709.250	527.430	458.740
		f	0.000	0.000	0.992	0.000	0.103	0.000
		S^2	0.000	0.000	0.000	0.000	0.000	0.000
	Benzene	E	0.709	1.427	1.689	1.759	2.350	2.659
		λ	1748.00	868.950	733.930	704.800	527.690	466.210
		f	0.000	0.000	0.105	0.000	0.100	0.000
		S^2	0.000	0.000	0.000	0.000	0.000	0.000
			T1	T2	T3	T4	T5	T6
Etats Triplets δ-Os	Vide	E	0.726	0.763	0.769	1.763	2.055	2.181
		λ	1708.150	1625.300	1611.200	703.120	603.430	568.510
		f	0.056	0.000	0.016	0.018	0.000	0.005
		S^2	1.997	2.022	2.010	2.057	2.839	2.546
	Eau	E	0.734	0.749	0.777	1.700	2.075	2.233
		λ	1689.800	1654.800	1595.200	729.480	597.450	555.180
		f	0.012	0.000	0.062	0.002	0.000	0.000
		S^2	2.012	2.022	1.995	2.053	2.834	2.057
	DMSO	E	0.733	0.749	0.772	1.703	2.075	2.207
		λ	1690.760	1654.370	1606.150	728.040	597.580	561.860
		f	0.017	0.000	0.060	0.002	0.000	0.003
		S^2	2.011	2.022	1.997	2.053	2.838	2.057
	Diethylether	E	0.747	0.752	0.783	1.774	2.051	2.182
		λ	1659.200	1648.800	1583.200	698.940	604.540	568.190
		f	0.045	0.000	0.027	0.001	0.000	0.000
		S^2	2.001	2.022	2.007	2.056	2.893	2.476
	Benzene	E	0.740	0.755	0.798	1.834	2.030	2.151
		λ	1674.680	1642.620	1554.070	676.110	610.760	576.450
		f	0.067	0.000	0.008	0.002	0.000	0.000
		S^2	1.993	2.022	2.014	2.060	2.909	2.522

protic solvent. It can form hydrogen bonds, it has a strong ionizing power and a high separating power. The second of these solvents is dimethyl sulfoxide (DMSO). It is a dipolar aprotic solvent. It cannot form hydrogen bonds, but its molecules act as dipoles. It is observed that opposite charges appear by mesomerism. It has a strong dipole moment and a high dielectric constant. The third of these solvents is diethylether. It is an aprotic solvent with a low polarity. It has a low dipole moment. It cannot form hydrogen bonds. The fourth solvent is benzene. It does not influence, or influences very little the reaction.

The results reported in **Table 2** indicate that δ-$OsCl_2(Azpy)_2$ complex has its absorption bands beyond 400 nm. A portion of the absorption bands of these complexes is composed mainly of transitions $t_{2g} \rightarrow \pi^*$ that are located in the therapeutic window [17]. In vacuum, the most significant state that belong to the therapeutic window is the excited state 3, which is located at 753.35 nm. In solvents, we observe a hypsochromic effect with respect to vacuum, which increases with the polarity of the solvent in the singlet states. This effect is accompanied by an increase in the energies of the singlet states of the complex.

As for the triplet states, δ-$OsCl_2(Azpy)_2$ indicates four significant states at 1708 nm, 1611 nm, 703 nm and 568 nm with energies of 0.7258 eV; 0.7695 eV; 1.7634 and 2.1808 eV respectively. These triplet states have S^2 values very close to 2, which attests that these states are devoid of any contamination [18]. In solvents, there is an increase of the energy in the triplet states. In water, the first triplet state is at 1689 nm with an energy of 0.7337 eV. A conservation of the number of significant states is noted, accompanied by a decrease in the oscillation forces. In DMSO, the first state is at 1690.76 nm. We also note an increase in the number of significant triplet states. For instance, the state of δ-Os goes from 3 significant triplets in water to 4 significant triplet states in DMSO. We believe that these changes are due to the dipole moment of the complex which interacts with those of the solvent molecules (DMSO). In diethylether, the δ-$OsCl_2(Azpy)_2$ complex admits its first significant triplet state at 1659 nm with an energy of 0.7473 eV. This complex retains the same number of significant triplet states as in DMSO. In benzene, δ-$OsCl_2(Azpy)_2$ provides with energies close to those obtained in diethylether. However, the values of these energies are higher than those obtained in water and DMSO. Besides, δ-$OsCl_2(Azpy)_2$ complex admits its first significant triplet state at 1674 nm with an energy of 0.7403 eV. It has three significant states in this solvent.

From the above, we can say that the polarity of the solvent influences the absorption and emission spectra. The transition from a polar medium such as water or DMSO to a less polar medium such as diethylether or apolar benzene is accompanied by a shift towards high energies. This shift is certainly due to the dipolar interactions between the complex and the solvent, also indicating the existence of a stabilized charge-transfer state CT in a polar medium. This result is in agreement with that found by the team of B. BENALI *et al.* who studied the effect of solvent polarity on the properties of excited electronic states of

l,l-binaphthyl by UV-visible spectroscopy [20]. The order of magnitude of the energies of the first significant triplet states for the complex δ-$OsCl_2(Azpy)_2$ is as follows:

ET1 (vacuum) < ET1 (DMSO) < ET1 (water) < ET1 (benzene) < ET1 (diethylether).

By comparing the evolution of the energies of the first significant triplet states of this complex in the different solvents, we can conclude that the energies of the triplet states of the organometallic complexes are a function of the polarity of the solvent.

3.1.3. Vertical Electron Affinity and Vertical Ionization Potential of DNA or RNA Bases

In order to determine the behavior of DNA or RNA bases following electronic exchanges, we determined the vertical electron affinity and vertical ionization potential of these bases. The results obtained are shown in **Table 3**.

Table 3. Total electronic energies of the parent molecule (Ep, Hartree), of the anionic radical (Ea, Hartree) and cation radical (Ec, Hartree) of the DNA bases in vacuum, in water, in DMSO, in Benzene and in diethylether.

		Ep	Ea	Ec	VEA_{s0}	VIP_{s0}
Adenine	Vacuum	−467.227	−467.202	−466.926	0.669	8.188
	Water	−467.244	−467.291	−467.007	−1.271	6.457
	Dmso	−467.246	−467.290	−467.007	−1.176	6.525
	Diethylether	−467.238	−467.266	−466.986	−0.761	6.860
	Benzene	−467.234	−467.246	−466.968	−0.311	7.257
Cytosine	Vacuum	−394.868	−394.852	−394.547	0.416	8.739
	Water	−394.895	−394.946	−394.648	−1.389	6.710
	Dmso	−394.895	−394.945	−394.625	−1.369	7.336
	Diethylether	−394.886	−394.919	−394.630	−0.889	6.970
	Benzene	−394.879	−394.895	−394.604	−0.435	7.495
Guanine	Vacuum	−542.445	−542.423	−542.155	0.613	7.905
	Water	−542.466	−542.513	−542.238	−1.287	6.214
	Dmso	−542.466	−542.512	−542.237	−1.267	6.230
	Diethylether	−542.459	−542.487	−542.216	−0.766	6.631
	Benzene	−542.454	−542.466	−542.197	−0.310	7.018
Thymine	Vacuum	−454.071	−454.067	−453.746	0.107	8.836
	Water	−454.090	−454.147	−453.839	−1.559	6.815
	Dmso	−454.090	−454.146	−453.838	−1.541	6.836
	Diethylether	−454.084	−454.124	−453.814	−1.092	7.339
	Benzene	−454.079	−454.104	−453.792	−0.661	7.805
Uracil	Vacuum	−414.757	−414.756	−414.415	0.005	9.304
	Water	−414.777	−414.839	−414.515	−1.684	7.117
	Dmso	−414.776	−414.838	−414.514	−1.665	7.139
	Diethylether	−414.770	−414.815	−414.488	−1.214	7.675
	Benzene	−414.766	−414.795	−414.465	−0.783	8.171

VEA_{so} = Ea − Ep, VIP_{so} = Ec − Ep.

The values of the vertical VIP ionization potentials of the DNA or RNA bases indicate that Guanine is the most easily ionizable base because of its lowest VIP values in vacuum as well as in solvents. In vacuum, the VIP_{so} value of guanine is 7.91. This value decreases in a solvent. The main decrease is recorded in water. The reactivity of DNA or RNA nucleobases during ionization decreases in the following order: Guanine > Adenine > Cytosine > Uracil > Thymine. In addition, it is found that VIP_{so} of each base increases in solvents as follows the rank: vacuum > Benzene > diethylether > DMSO > water. So VIP_{so} values evolve in the opposite direction of the solvent polarity. Therefore, we can assume that polar solvents are favorable to the ionization of the DNA or RNA bases.

As for the VEA_{so} vertical electron affinity values, the order of reactivity of the bases during electron capture is as follows: Adenine < Guanine < Cytosine < Thymine < Uracil. Thus, the Uracil is the DNA base that has the greatest ease of electron acceptance. The VEA_{so} values indicate the following ranking with respect to the polarity of the solvent: VEA_{so} (vacuum) > VEA_{so} (Benzene) > VEA_{so} (diethylether) > VEA_{so} (Dmso) > VEA_{so}(water). The electronic affinity VEA_{so} evolves in the same direction as the polarity of the solvent. In order to evaluate the behavior of these bases in their triplet state, we determined the parameters VEA_{T1} (vertical electronic affinity in the triplet state) and VIP_{T1} (vertical ionization potential in the triplet state). VEA_{T1} indicates the ability for the molecule to extract an electron in its immediate environment while VIP_{T1} indicates the ability to yield an electron [21]. The results of these parameters are reported in **Table 4**.

VEA_{T1} values indicate that the anion-forming reactions at the triplet state of DNA or RNA bases are thermodynamically favorable. In addition, the Thymine base is the most capable of receiving an electron in its immediate environment. Moreover, VEA_{T1} values show that the anions of these bases are better stabilized in polar solvents [6]. When looking at the VIP_{T1} values, Guanine is still the most easily ionizable base in each of the three media considered. These results agree with those obtained by the team of Liang Shen *et al.* [6].

3.1.4. Vertical Electron Affinity VEA and Vertical Ionization Potential of δ-$OsCl_2(Azpy)_2$ Complex

As in the case of DNA bases, these same parameters were evaluated at the level of the photosensitizer complex. The results obtained are shown in **Table 5** and **Table 6**.

Table 5 shows the VIP_{so} and VEA_{so} of δ-$OsCl_2(Azpy)_2$ in solvent and in vacuum. The lowest VIP_{so} values are found with polar solvents with values of 5.156 and 5.154 in water and DMSO respectively. Whereas the vertical electron affinity VEA_{so}, the best results are obtained in the aqueous phase with −3.907 hartree. These results also indicate that this complex reacts better in polar solvents.

Table 6 shows the VIP_{T1} and VEA_{T1} values of the δ-$OsCl_2(Azpy)_2$ complex in solvent and vacuum. The VEA_{T1} values indicate that the reactions of triplet anion formation of the complex are thermodynamically favorable. In addition,

Table 4. Excitation energies of the weakest triplets (ET1 in eV), vertical electron affinities (VEA in eV) and vertical ionization potentials (VIP in eV) of DNA bases in vacuum, water, diethylether, DMSO and Benzene.

		ET	VEA_{T1}	VEA_{s0}	VIP_{T1}	VIP_{S0}
Adenine	Vacuum	0.949	−0.280	0.669	7.238	8.188
	Water	0.875	−2.145	−1.271	5.582	6.457
	DMSO	0.876	−2.052	−1.176	5.649	6.525
	Diethylether	0.893	−1.659	−0.761	5.967	6.860
	Benzene	0.913	−1.223	−0.311	6.344	7.257
Cytosine	Vacuum	0.754	−0.339	0.415	7.985	8.739
	Water	0.727	−2.117	−1.389	5.983	6.710
	DMSO	0.727	−2.096	−1.369	6.609	7.336
	Diethylether	0.727	−1.616	−0.889	6.243	6.970
	Benzene	0.719	−1.154	−0.435	6.775	7.495
Guanine	Vacuum	1.011	−0.398	0.613	6.894	7.905
	Water	1.020	−2.307	−1.287	5.194	6.214
	DMSO	1.020	−2.286	−1.267	5.210	6.230
	Diethylether	1.015	−1.782	−0.766	5.615	6.631
	Benzene	1.012	−1.321	−0.310	6.006	7.018
Thymine	Vacuum	1.346	−1.239	0.107	7.490	8.836
	Water	1.897	−3.455	−1.559	4.919	6.815
	DMSO	1.897	−3.436	−1.540	4.939	6.836
	Diethylether	1.329	−2.421	−1.091	6.010	7.339
	Benzene	1.336	−10.162	−8.826	6.468	7.805
Uracil	Vacuum	1.241	−1.235	0.005	8.063	9.304
	Water	1.222	−2.906	−1.683	5.894	7.117
	DMSO	1.223	−2.888	−1.665	5.915	7.139
	Diethylether	1.230	−2.444	−1.214	6.445	7.675
	Benzene	1.232	−2.015	−0.783	6.939	8.171

Table 5. Total electron energies of δ-$OsCl_2(Azpy)_2$ in its fundamental state (Ep, Hartree), the anionic radical state (Ea, Hartree) and radical cation state (Ec, in Hartree) in vacuum, water, DMSO, Benzene and diethylether.

		Ep	Ea	Ec	VEA_{s0}	VIP_{s0}
δ-$OsCl_2(Azpy)_2$	Vacuum	−1298.545	−1298.636	−1298.324	−2.476	5.992
	Water	−1298.571	−1298.715	−1298.382	−3.907	5.156
	DMSO	−1298.571	−1298.714	−1298.381	−3.900	5.154
	Diethylether	−1298.564	−1298.690	−1298.366	−3.412	5.385
	Benzene	−1298.556	−1298.670	−1298.353	−3.096	5.526

$VEA_{so} = E_a - E_p$, $VIP_{so} = E_c - E_p$.

Table 6. Excitation energies of the lowest triplets (ET1 in eV), vertical electron affinities (VEA) in eV) and vertical ionization potentials (VIP in eV) of the δ-$OsCl_2(Azpy)_2$ complex in vacuum, water, DMSO, Benzene and diethylether.

		ET1	VEA_{T1}	VEA_{s0}	VIP_{T1}	VIP_{s0}
δ–$OsCl_2(Azpy)_2$	Vacuum	0.726	−3.202	−2.476	5.266	5.992
	Water	0.734	−4.641	−3.907	4.423	5.156
	DMSO	0.733	−4.632	−3.899	4.420	5.154
	Diethylether	0.747	−4.159	−3.412	4.637	5.385
	Benzene	0.740	−3.837	−3.096	4.786	5.526

$VEA_{T1} = VEA_{so} - E_{T1}$, $VIP_{T1} = VIP_{S0} - E_{T1}$.

δ-$OsCl_2(Azpy)_2$ has the highest affinity in the aqueous phase. It is therefore more capable of stripping electrons from its environment in water. As far as VIP_{T1} values are concerned, δ-$OsCl_2(Azpy)_2$ is still the most easily ionizable complex in water and in DMSO. The reactivity of this complex during an ionization according to the solvents considered is presented in the following order: DMSO > water > diethylether > benzene > vacuum.

From the abovementioned statement, we can say that the change in multiplicity increases the donor character of this molecule. This increase is certainly due to the rise in the number of unpaired electrons within the molecular edifice.

3.2. Elucidation of the Photosensitization Mechanisms of the δ-$OsCl_2(Azpy)_2$ Complex

Photosensitization in photodynamic therapy can be understood through two mechanisms: in the mechanism I, the photosensitizer reacts directly with the target substrates such as DNA, RNA, and proteins. Whereas the mechanism II, the photosensitizer is assumed to cause damage to the target substrates via reactive oxygen species (ROS) created by an electron or energy transfer between the photosensitizer and molecular oxygen.

3.2.1. Photosensitization Mechanism I of the δ-$OsCl_2(Azpy)_2$ Complex

Here, azopyridine complex associates with DNA or RNA by the intercalation mode [22] [23] [24]. Considering this mode of association and the photosensitivity of the complex, irradiation of the latter must lead to several reactions that are bond to occur.

Firstly, this complex can react in its T1 triplet state with the bases of DNA or RNA by stripping them of an electron leading to their ionization state. In this case, the donor is the DNA or RNA base and the acceptor is the azopyridine complex. This reaction can be translated by Equation (3):

$$\left[\delta\text{-}OsCl_2\left(Azpy\right)_2\right]\left(T_1\right) + B \rightarrow \left[\delta\text{-}OsCl_2\left(Azpy\right)_2\right]^{\bullet -} + B^+ \quad (3)$$

where B stands for DNA or RNA base.

This reaction is governed by the vertical electronic affinities in the VEA_{T1} triplet state of the complex and the VIP vertical ionization potentials of the DNA

bases. A negative sum of the two parameters indicates that this reaction is feasible [13]. Thus, we evaluated these parameters at the B3LYP/Lanl2DZ level in vacuum and in the presence of the solvents water, DMSO, diethylether and benzene. The results obtained are shown in Table 5 and Table 6. The various interactions following this reaction are recorded in Table 7.

Through Table 7, we can notice that the values are all positive. This indicates that no interaction following this reaction is thermodynamically favorable.

Second, the radical cation $[\delta\text{-OsCl}_2(\text{Azpy})_2]^{\circ+}$ of each photosensitizer complex can react with DNA or RNA bases by accepting an electron according to the Equation (4):

$$\left[\delta\text{-OsCl}_2\left(\text{Azpy}\right)_2\right]^{\bullet+} + \text{B} \rightarrow \left[\delta\text{-OsCl}_2\left(\text{Azpy}\right)_2\right]\left(\text{S}_0\right) + \text{B}^{\bullet+} \tag{4}$$

This radical cation $\left[\delta\text{-OsCl}_2\left(\text{Azpy}\right)_2\right]^{\bullet+}$ of the photosensitizer complex can be generated by self-ionization reactions between the states T_1 and S_0 (Equation (5)) or the two T_1 states (Equation (6)).

$$\begin{aligned}&\left[\delta\text{-OsCl}_2\left(\text{Azpy}\right)_2\right]\left(\text{T}_1\right) + \left[\delta\text{-OsCl}_2\left(\text{Azpy}\right)_2\right]\left(\text{S}_0\right)\\ &\rightarrow \left[\delta\text{-OsCl}_2\left(\text{Azpy}\right)_2\right]^{\bullet+} + \left[\delta\text{-OsCl}_2\left(\text{Azpy}\right)_2\right]^{\bullet-}\end{aligned} \tag{5}$$

$$\begin{aligned}&\left[\delta\text{-OsCl}_2\left(\text{Azpy}\right)_2\right]\left(\text{T}_1\right) + \left[\delta\text{-OsCl}_2\left(\text{Azpy}\right)_2\right]\left(\text{T}_1\right)\\ &\rightarrow \left[\delta\text{-OsCl}_2\left(\text{Azpy}\right)_2\right]^{\bullet+} + \left[\delta\text{-OsCl}_2\left(\text{Azpy}\right)_2\right]^{\bullet-}\end{aligned} \tag{6}$$

Reaction 3 is governed by the sum VEA_{T1} + VIP or VIP_{T1} + VEA of the photosensitizer complex. A negative value of one of these sums indicates a thermodynamically favorable reaction. We have evaluated the different sums and the results are recorded in Table 8.

Table 7. Sum of the VEA_{T1} parameters of the complex and VIP parameters of the DNA or RNA bases reflecting the interactions according to Equation (1).

		C-A	C-C	C-G	C-T	C-U
δ-$OsCl_2(Azpy)_2$	Vacuum	4.99	5.54	4.70	5.63	6.10
	Water	1.82	2.07	1.57	2.17	2.48
	DMSO	1.89	2.70	1.60	2.20	2.51
	Diethylether	2.70	2.81	2.47	3.18	3.51
	Benzene	3.42	3.66	3.18	3.97	4.33

C-A: VEA_{T1} (δ-$OsCl_2(Azpy)_2$) + VIP (Adenine); C-C: VEA_{T1} (δ-$OsCl_2(Azpy)_2$) + VIP (Cytosine); C-G: VEA_{T1} (δ-$OsCl_2(Azpy)_2$) + VIP (Guanine); C-T: VEA_{T1} (δ-$OsCl_2(Azpy)_2$) + VIP (Thymine); C-U: VEA_{T1} (δ-$OsCl_2(Azpy)_2$) + VIP (Uracil).

Table 8. Sum VEA_{T1} + VIP or VIP_{T1} + VEA reflecting the auto ionization reaction.

		VEA_{T1} + VIP	VIP_{T1} + VEA	VEA_{T1} + VIP_{T1}
δ-$OsCl_2(Azpy)_2$	Vacuum	2.790	2.790	2.064
	Water	0.515	0.515	−0.218
	DMSO	0.521	0.521	−0.212
	Diethylether	1.225	1.225	0.478
	Benzene	1.690	1.690	0.949

The values of the sums VEA_{T1} + VIP and VIP_{T1} + VEA are all positive, both in a vacuum and in a solvent. Therefore, reaction 3 is not thermodynamically favorable.

As for reaction 4, it is governed by the sum VEA_{T1} + VIP_{T1}. We have determined the different values of this sum. The results are shown in **Table 8**. All the values are positive except for two values. They are obtained with the polar solvents water and DMSO. They reflect the interaction between two molecules in the T1 triplet state of the δ-$OsCl_2(Azpy)_2$ complex. These sums are −0.218 and −0.212 in water and DMSO respectively. We can assume that reaction 4 is therefore allowed in these solvents because of the negative values. These results indicate that only δ-$OsCl_2(Azpy)_2$ is likely to form the radical cation $\left[\delta\text{-}OsCl_2\left(Azpy\right)_2\right]^{\bullet+}$. The formation of this cationic radical is also accompanied by the formation of an anionic radical $\left[\delta\text{-}OsCl_2\left(Azpy\right)_2\right]^{\bullet-}$ of this photosensitizer complex.

3.2.2. Photosensitization Mechanism II of the δ-$OsCl_2(Azpy)_2$ Complex

In photosensitization mechanism II, the photosensitizer must be in a triplet state. From this triplet T state, first the photosensitizer can react directly with oxygen by transferring its excess energy, which changes the oxygen $^3O_2$ to its singlet $^1O_2$ state. This singlet oxygen $^1O_2$ is a powerful oxidant that reacts with numerous cellular constituents such as saturated triacyl glycerols, membrane cholesterol, phospholipids, amino acids (histidine, tryptophan, methionine) and nucleic acids [25]. Due to its very short lifetime and high reactivity, $^1O_2$ reacts at its site of formation in the cell [25]. The interaction of the photosensitizer in the triplet state with oxygen in the triplet basic state ($^3O_2$) can be translated by the reaction translated by Equation (7).

$$\left[\delta\text{-}OsCl_2\left(Azpy\right)_2\right]\left(T_1\right)+{}^3O_2\rightarrow\left[\delta\text{-}OsCl_2\left(Azpy\right)_2\right]\left(S_0\right)+{}^1O_2 \qquad (7)$$

This reaction is highly dependent on the energy of the lowest triplet state of the photosensitizer. This is explained by the fact that a photosensitizer capable of producing singlet oxygen must have an energy gap between the fundamental singlet state and the lowest triplet state $\Delta E_{S\text{-}T}$ greater than the energy required to switch from the $^3O_2$ oxygen to its singlet $^1O_2$ state [19]. This energy is experimentally estimated at 0.98 eV [18]. Theoretically, this energy is sometimes estimated at 0.91 eV [18] or 1.06 eV [26]. The singlet oxygen $^1O_2$ is generated by a triplet-triplet energy transfer between the triplet ground state of the oxygen and the triplet excited state of the photosensitizer which is formed by inter-system conversion ISC [19]. This inter-system conversion can take place between two energy levels such as from S_1 to T_n or from T_1 to S_0 [19] [26] [27]. Therefore, we have evaluated the energies of the lowest triplet states of the azopydine complex in this work. The condition for the selection is the following: these energies of the triplet states T_n must be lower than those of their corresponding singlet states S_1. The energy gaps obtained after this selection are shown in the diagram in **Figure 5**.

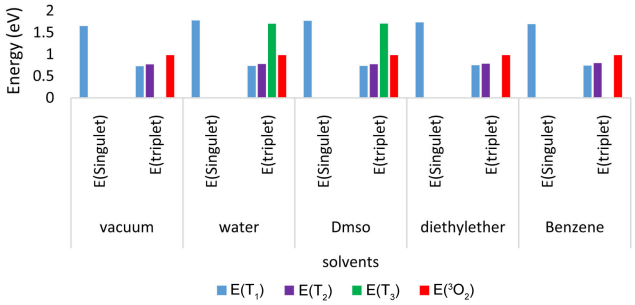

Figure 5. Energy maps of the singlet and triplet states of δ-$OsCl_2(Azpy)_2$ determined at the B3LYP/Lanl2DZ level. The blue color represents the S_1 singlet states and the first T_1 triplet states. The violet color represents the T_2 triplet states. The green color represents the energies of the triplet states T_3. The orange color represents the activation energy of the singlet oxygen 0.98 eV.

The diagram shows a large energy gap between the singlet and triplet states. All singlet states have energies above 1.5 eV. As for the δ-$OsCl_2(Azpy)_2$ complex, it has three triplet states T_1, T_2 and T_3 whose energies are lower than that of the singlet state S_1. The highest values of the energies of the T_1 triplet states of δ-$OsCl_2(Azpy)_2$ complex are 0.747 eV in diethylether and 0.740 in benzene, respectively. As for the other T_2 and T_3 states, the highest energies are obtained in polar solvents. In water, the highest value is 1.699 eV and in DMSO it is 1.703 eV. So, we can conclude that δ-$OsCl_2(Azpy)_2$ is able to produce singlet oxygen in these two polar solvents by energy transfer. The photocytotoxic activity will depend on the combination of the quantum yields of formation of the singlet state S_1, the conversion of S_1 to T_n, the efficiency of energy transfer from T_n to oxygen and the abundant presence of O_2.

Secondly, the complex in the T_1 state can react with $^3O_2$ by electron transfer to generate the anionic superoxide radical ($O_2^{\bullet -}$). This reaction can be translated by Equation (8).

$$\left[\delta\text{-}OsCl_2\left(Azpy\right)_2\right]\left(T_1\right)+{}^3O_2 \rightarrow \left[\delta\text{-}OsCl_2\left(Azpy\right)_2\right]^{\bullet +}+O_2^{\bullet -} \quad (8)$$

The condition for the realization of this reaction is that the sum of the ionization potential in the VIP_{T1} triplet state of the complex and the adiabatic electron affinity of oxygen $^3O_2$ must be negative. Furthermore, the adiabatic electron affinity of $^3O_2$ oxygen is −0.59 eV in vacuum, −3.91 eV in water; −3.65 eV in DMSO; −3.14 eV in ether and −2.33 eV in benzene [6] [13] [28]. The results of the evaluation of this sum are shown in **Table 9**.

Table 9 shows that Equation (6) which translates the electron transfer between the photosensitizer and oxygen in the triplet state is not possible with the solvents considered. However, there is another possibility of production of the anionic superoxide radical $O_2^{\bullet -}$. This is the electron transfer reaction between the anionic radical resulting from auto-ionization and oxygen in the triplet state. This reaction can be represented by Equation (9):

$$\left[\delta\text{-}OsCl_2\left(Azpy\right)_2\right]^{\bullet +}+{}^3O_2 \rightarrow \left[\delta\text{-}OsCl_2\left(Azpy\right)_2\right]\left(S_0\right)+O_2^{\bullet -} \quad (9)$$

Table 9. The sum of the ionization potential in the VIP_{T1} triplet state of the complex and the adiabatic electron affinity of oxygen $^3O_2$ and the difference between the adiabatic electron affinity of oxygen $^3O_2$ and the vertical electron affinity in the singlet state of the photosensitizer.

		$AEA(^3O_2) - VEA_{so}$	$VIP_{T1} + AEA(^3O_2)$
δ-$OsCl_2(Azpy)_2$	Vacuum	1.886	4.676
	Water	−0.003	0.513
	DMSO	0.249	0.770
	Diethylether	0.272	1.498
	Benzene	0.766	2.456

This reaction is possible if the difference between the adiabatic electron affinity of oxygen $^3O_2$ and the vertical singlet state electron affinity of the photosensitizer is negative. Table 9 indicates one possible reaction. This is the reaction between the δ-$OsCl_2(Azpy)_2$ and oxygen in water. Hence, δ-$OsCl_2(Azpy)_2$ will be able to generate the anionic superoxide radical $O_2^{\bullet -}$ in water. The superoxide radical anion $O_2^{\bullet -}$ thus formed can react directly with different substrates or act as a precursor of other ROS following the Fenton reaction [13] [29] or by the Haber-Weiss reaction [13] [30] which will effectively amplify the photosensitizing activity of these azopyridine complexes. The different ROS formed during these last photochemical reactions (H_2O_2, $O_2^{\bullet -}$, OH^-) represent powerful oxidants for a wide variety of biomolecules such as cholesterol or the side chains of certain amino acids (tryptophan, histidine and methionine) [31].

4. Conclusion

Photophysical and photochemical properties such as absorption spectrum, energies of the lowest triplet states, vertical electron affinities and vertical ionization potentials, of the azopyridine complex δ-$OsCl_2(Azpy)_2$ in polar and non-polar solvents were examined by the TDDFT method. The mechanisms of photosensitivity of this complex in photodynamic therapy were elucidated through these parameters. As a result of these analyses, the δ-$OsCl_2(Azpy)_2$ complex was found to develop photodynamic activity according to two mechanisms: firstly, it can generate damage to DNA bases or target tissues indirectly through the production of singlet oxygen in water and secondly, through the production of the superoxide anionic radical $O_2^{\bullet -}$ in water which can act directly or indirectly on these substrates.

Conflicts of Interest

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

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