

# Computational Evaluation of Ruthenium Complexes as Potential Chemotherapeutic Agents

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## Introduction

Currently, many different treatments are used in the fight against cancer. Most available treatments, however, display very limited selectivity for tumorous cells *in vivo*. Radiation and current chemotherapeutic techniques are effective in killing not only cancer cells, but healthy tissue cells as well. Future treatments must be able to maintain a lethal nature, while also selectively choosing cancerous cells as their targets. Thus, this increase in selectivity will also inadvertently decrease the unwanted side effects that are experienced with modern cancer treatments.

Photodynamic therapy (PDT) is a treatment for cancer that uses light to activate a photo-sensitizer *in vivo*.<sup>1</sup> This photo-sensitizer is administered to the patient in an inactive form, but is then altered via light of a certain wavelength to create an active species.<sup>2</sup> The active species then creates damage within the tumor cell and eventually leads to photo necrosis. Ruthenium nitrosyl complexes, which are photochemically activated to selectively release nitric oxide (NO), rely upon the high toxicity of NO in an *in vivo* environment for their PDT effect.<sup>2</sup> Many concerns arise from the use of PDT. First, is the administration of light of high energy to an *in vivo* system. High-energy photons have the ability to damage healthy tissue and possibly create a mutation, which can become cancerous. Therefore, it is necessary for photo-sensitizing agents to be photochemically activated by relatively low energy wavelengths (visible region). Most ruthenium nitrosyl complexes, however, photochemically irradiate the nitrosyl ligand in the high energy ultra-violet region.<sup>1,3-4</sup> The photochemical properties of ruthenium nitrosyl complexes can be examined based upon the coordination of various ligands to the metal center. It is postulated that various equatorial plane ligands will create varying  $\lambda_{\max}$  values, which proves to be true. Also, it is necessary to examine the bonding characteristics of the nitrosyl ligand. The nitrogen to oxygen bond of the nitrosyl ligand is shown by the molecular orbital theory to have a bond order of 2.5. This implies that the bond can have the characteristics of a double bond, a triple bond, or a combination of the two. This bonding property will influence the photochemical behavior of the complex and is examined through molecular modeling.

Chemotherapy is the treatment of cancer cells utilizing specific chemical agents to destroy malignant cells and tissue. Chemotherapy destroys malignant cells by interrupting and inhibiting the growth and reproduction of cancer cells. Additionally, cancer cells are constantly reproducing and constantly dividing cells, which cause the cell to become extremely permeable. This permeable nature allows foreign materials inside the cell.<sup>5-8</sup> Consequently, chemotherapeutic agents will have an increased ability to flow into the cancer cell to cause apoptosis (programmed cell death). Although chemotherapy is used to treat cancer, it also destroys healthy non-malignant cells. Therefore, it is

necessary to create complexes, which will destroy malignant cells, without destroying healthy cells in the process. The characteristics of several different ruthenium complexes can be examined through molecular modeling to determine their stability and rate of formation. This is done to determine whether or not the molecule would be favorable as a chemotherapeutic agent.

## **Objective**

Although computational chemistry provides an effective method for the examination of new chemotherapeutic agents, the data obtain from such a method should not be immediately considered fact. It was deemed necessary to examine the applicability of the Spartan Molecular Modeling program to ruthenium chemotherapeutic agents, specifically ruthenium nitrosyl complexes. Once a specific calculation type and parameter set can be determined as a “best-fit” model for ruthenium complexes, then new chemotherapeutic agents can be examined using this method. Additionally, several pre-existing chemotherapeutic agents will be evaluated to determine if a relationship exists between cyto-toxicity and stability. Finally, the effect of the charge on a ruthenium complex, in terms of the solubility of the complex was examined through the addition of water molecules to the calculation of the overall stability of the complex.

## **Results**

Comparing bond angles and bond distances to previously characterized complexes determined the applicability of the Spartan Molecular Modeling Program towards ruthenium coordinated chemotherapeutic agents. Specifically, the x-ray diffraction data of crystal structures was used in the comparison to the data calculated by the Spartan program. The data calculated can be viewed in Tables 1 – 4.

Table 1: Bond Distances for Ruthenium Nitrosyls (Triple Bonded Nitrosyl)

Complex	Parameter	Atoms Frozen	Actual Value (Å)	MMFF (Å)	PM3 (Å)	reference
[(bpb)Ru(NO)(Cl)]	Ru-NO	Yes	1.7534	2.209	2.209	3
[(Me2bpb)Ru(NO)(Cl)]	Ru-NO	Yes	1.7425	2.193	2.193	3
[(Me2bpb)Ru(NO)(py)](BF4)	Ru-NO	Yes	1.7582	2.192	2.192	3
[(Me2bqb)Ru(NO)(Cl)]	Ru-NO	Yes	1.7389	2.193	2.193	3
[Ru(PaPy3)(NO)](BF4)2	Ru-NO	Yes	1.7792	2.213	2.213	4
Ru(Salen)(ONO)(NO)	Ru-NO	Yes	1.7466	2.211	2.211	1
[(bpb)Ru(NO)(Cl)]	Ru-NO	No	1.7534	2.209	1.896	3
[(Me2bpb)Ru(NO)(Cl)]	Ru-NO	No	1.7425	2.209	1.896	3
[(Me2bpb)Ru(NO)(py)](BF4)	Ru-NO	No	1.7582	2.221	1.933	3
[(Me2bqb)Ru(NO)(Cl)]	Ru-NO	No	1.7389	2.209	2.193	3
[Ru(PaPy3)(NO)](BF4)2	Ru-NO	No	1.7792	2.213	1.757	4
Ru(Salen)(ONO)(NO)	Ru-NO	No	1.7466	2.211	1.876	1
[(bpb)Ru(NO)(Cl)]	N-O	Yes	1.1444	1.083	1.135	3
[(Me2bpb)Ru(NO)(Cl)]	N-O	Yes	1.1544	1.083	1.137	3
[(Me2bpb)Ru(NO)(py)](BF4)	N-O	Yes	1.1473	1.083	1.135	3
[(Me2bqb)Ru(NO)(Cl)]	N-O	Yes	1.1463	1.083	1.138	3
[Ru(PaPy3)(NO)](BF4)2	N-O	Yes	1.1423	1.083	1.107	4
Ru(Salen)(ONO)(NO)	N-O	Yes	1.1386	1.083	1.141	1
[(bpb)Ru(NO)(Cl)]	N-O	No	1.1444	1.083	1.166	3
[(Me2bpb)Ru(NO)(Cl)]	N-O	No	1.1544	1.083	1.166	3
[(Me2bpb)Ru(NO)(py)](BF4)	N-O	No	1.1473	1.083	1.156	3
[(Me2bqb)Ru(NO)(Cl)]	N-O	No	1.1463	1.083	1.138	3
[Ru(PaPy3)(NO)](BF4)2	N-O	No	1.1423	1.083	1.159	4
Ru(Salen)(ONO)(NO)	N-O	No	1.1386	1.083	1.169	1

Table 2: Bond Distances for Ruthenium Nitrosyls (Double Bonded Nitrosyl)

Complex	Parameter	Atoms Frozen	Actual Value		reference	
			(Å)	MMFF (Å)		
[(bpb)Ru(NO)(Cl)]	Ru-NO	Yes	1.7534	2.221	2.221	3
[(Me2bpb)Ru(NO)(Cl)]	Ru-NO	Yes	1.7425	2.221	2.221	3
[(Me2bpb)Ru(NO)(py)](BF4)	Ru-NO	Yes	1.7582	2.251	2.251	3
[(Me2bqb)Ru(NO)(Cl)]	Ru-NO	Yes	1.7389	2.226	2.226	3
[Ru(PaPy3)(NO)](BF4)2	Ru-NO	Yes	1.7792	2.219	2.219	4
Ru(Salen)(ONO)(NO)	Ru-NO	Yes	1.7466	2.227	2.227	1
[(bpb)Ru(NO)(Cl)]	Ru-NO	No	1.7534	2.221	2.219	3
[(Me2bpb)Ru(NO)(Cl)]	Ru-NO	No	1.7425	2.221	2.227	3
[(Me2bpb)Ru(NO)(py)](BF4)	Ru-NO	No	1.7582	2.251	2.219	3
[(Me2bqb)Ru(NO)(Cl)]	Ru-NO	No	1.7389	2.226	2.227	3
[Ru(PaPy3)(NO)](BF4)2	Ru-NO	No	1.7792	2.219	1.757	4
Ru(Salen)(ONO)(NO)	Ru-NO	No	1.7466	2.227	1.876	1
[(bpb)Ru(NO)(Cl)]	N-O	Yes	1.1444	1.235	1.134	3
[(Me2bpb)Ru(NO)(Cl)]	N-O	Yes	1.1544	1.235	1.136	3
[(Me2bpb)Ru(NO)(py)](BF4)	N-O	Yes	1.1473	1.236	1.133	3
[(Me2bqb)Ru(NO)(Cl)]	N-O	Yes	1.1463	1.236	1.135	3
[Ru(PaPy3)(NO)](BF4)2	N-O	Yes	1.1423	1.236	1.102	4
Ru(Salen)(ONO)(NO)	N-O	Yes	1.1386	1.236	1.139	1
[(bpb)Ru(NO)(Cl)]	N-O	No	1.1444	1.235	1.166	3
[(Me2bpb)Ru(NO)(Cl)]	N-O	No	1.1544	1.235	1.166	3
[(Me2bpb)Ru(NO)(py)](BF4)	N-O	No	1.1473	1.236	1.156	3
[(Me2bqb)Ru(NO)(Cl)]	N-O	No	1.1463	1.236	1.136	3
[Ru(PaPy3)(NO)](BF4)2	N-O	No	1.1423	1.236	1.159	4
Ru(Salen)(ONO)(NO)	N-O	No	1.1386	1.236	1.169	1

Table 3: Bond Angles for Ruthenium Nitrosyls (Triple Bonded Nitrosyl)

Complex	Parameter	Atoms Frozen	Actual Value			reference
			(°)	MMFF	PM3	
[(bpb)Ru(NO)(Cl)]	Ru-N-O	Yes	172.37°	179.9°	174.77°	3
[(Me2bpb)Ru(NO)(Cl)]	Ru-N-O	Yes	173.90°	179.91°	170.27°	3
[(Me2bpb)Ru(NO)(py)](BF4)	Ru-N-O	Yes	170.02°	179.90°	169.65°	3
[(Me2bqb)Ru(NO)(Cl)]	Ru-N-O	Yes	177.77°	179.91°	168.52°	3
[Ru(PaPy3)(NO)](BF4)2	Ru-N-O	Yes	170.92°	179.84°	157.61°	4
Ru(Salen)(ONO)(NO)	Ru-N-O	Yes	176.46°	179.95°	158.80°	1
[(bpb)Ru(NO)(Cl)]	Ru-N-O	No	172.37°	179.91°	173.45°	3
[(Me2bpb)Ru(NO)(Cl)]	Ru-N-O	No	173.90°	179.91°	173.88°	3
[(Me2bpb)Ru(NO)(py)](BF4)	Ru-N-O	No	170.02°	179.88°	175.18°	3
[(Me2bqb)Ru(NO)(Cl)]	Ru-N-O	No	177.77°	179.91°	169.18°	3
[Ru(PaPy3)(NO)](BF4)2	Ru-N-O	No	170.92°	179.84°	178.60°	4
Ru(Salen)(ONO)(NO)	Ru-N-O	No	176.46°	179.95°	177.56°	1

Table 4: Bond Angles for Ruthenium Nitrosyls (Double Bonded Nitrosyl)

Complex	Parameter	Atoms Frozen	Actual Value	MMFF	PM3	reference
[(bpb)Ru(NO)(Cl)]	Ru-N-O	Yes	172.37°	110.66°	165.63°	3
[(Me2bpb)Ru(NO)(Cl)]	Ru-N-O	Yes	173.90°	110.67°	168.96°	3
[(Me2bpb)Ru(NO)(py)](BF4)	Ru-N-O	Yes	170.02°	110.48°	165.93°	3
[(Me2bqb)Ru(NO)(Cl)]	Ru-N-O	Yes	177.77°	110.57°	165.93°	3
[Ru(PaPy3)(NO)](BF4)2	Ru-N-O	Yes	170.92°	111.35°	173.65°	4
Ru(Salen)(ONO)(NO)	Ru-N-O	Yes	176.46°	110.51°	161.46°	1
[(bpb)Ru(NO)(Cl)]	Ru-N-O	No	172.37°	110.66°	173.68°	3
[(Me2bpb)Ru(NO)(Cl)]	Ru-N-O	No	173.90°	110.67°	173.77°	3
[(Me2bpb)Ru(NO)(py)](BF4)	Ru-N-O	No	170.02°	110.48°	175.77°	3
[(Me2bqb)Ru(NO)(Cl)]	Ru-N-O	No	177.77°	110.57°	166.34°	3
[Ru(PaPy3)(NO)](BF4)2	Ru-N-O	No	170.92°	111.35°	178.53°	4
Ru(Salen)(ONO)(NO)	Ru-N-O	No	176.46°	110.51°	177.46°	1

The results of the examination of chemotherapeutic agents, specifically the energy associated with these complexes, using PM3 calculations can be seen in Fig. 1. The computational data calculated for the determination of the effect of charge on the solubility of the complex is located in Fig. 2.

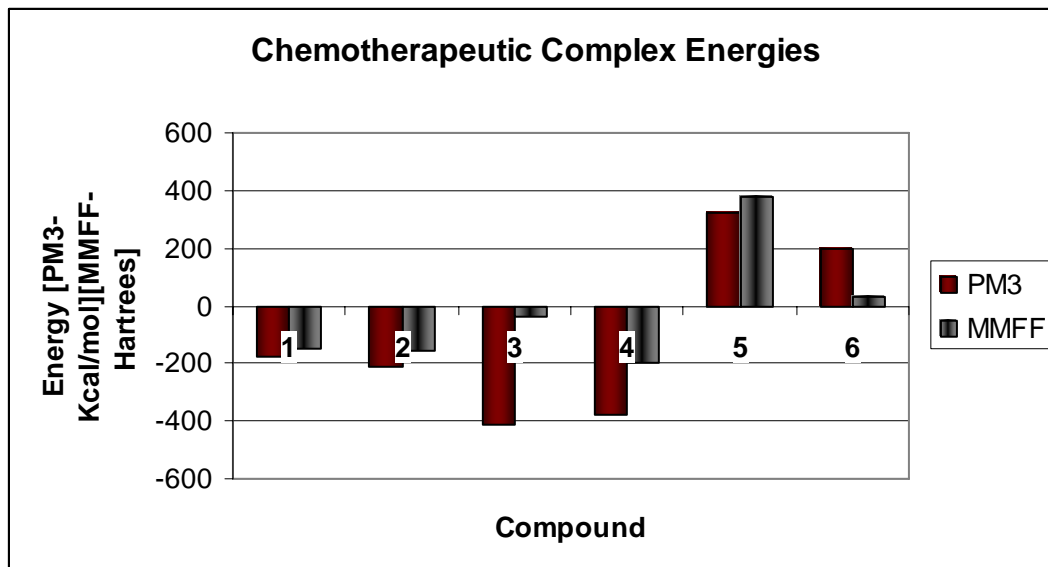


Fig. 1. Figure represents the calculated energies for the following complexes: 1-KP1019, 2-Ru(Im)<sub>2</sub>, 3-Ru(rap), 4-Ru(EDTA), 5- Ru(tpen), 6- cis-[Cl<sub>2</sub>(azpy)Ru]

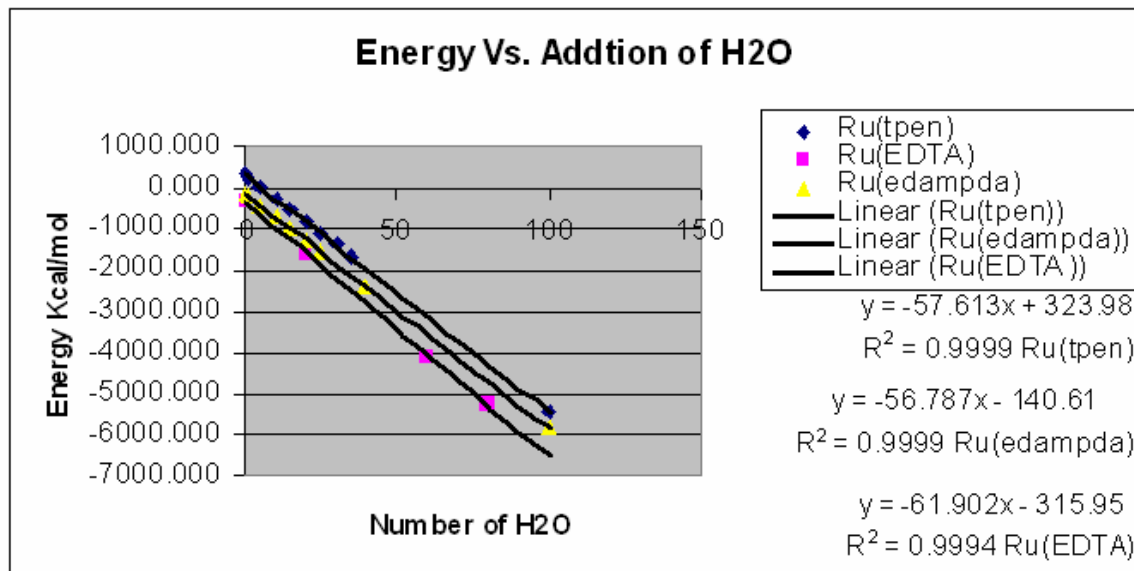


Fig.2. Represents the PM3 energy of Ru (tpen)<sup>+2</sup>, Ru (edta)<sup>-2</sup>, and Ru (edampda) with the addition of water.

## Discussion

The relevance of each computational methodology can be determined based upon the mean difference of the calculated values and the experimentally determined values for each of the designated parameters, which is represented by equation 1. The mean difference equation was derived from similar equations used in the field of computational chemistry, which serve to examine the applicability of a specific computational method in terms of its ability to evaluate a specific system.<sup>9,10</sup>

$$MeanDifference = \frac{\sum (Calculated - Experimental)}{N}$$

Equation 1. Equation used to calculate the mean differences for all parameters.

Table 5 contains that mean differences for the Ru-NO bond length, Table 6 contains the data for the N-O bond lengths, and Table 7 contains the mean differences that were calculated for the Ru-N-O bond angles.

Table 5: Mean Difference From Actual Ru-NO Bond Length

Computation Method	Nitrosyl Bonding Type	Atoms Frozen	Mean Difference (Å)
MMFF	Triple Bond	Yes	0.4456
PM3	Triple Bond	Yes	0.4487
MMFF	Triple Bond	No	0.4589
PM3	Triple Bond	No	0.1720
MMFF	Double Bond	Yes	0.4744
PM3	Double Bond	Yes	0.4744
MMFF	Double Bond	No	0.4744
PM3	Double Bond	No	0.3754

Table 6: Mean Difference From Actual N-O Bond Length

Computation Method	Nitrosyl Bonding Type	Atoms Frozen	Mean Difference (Å)
MMFF	Triple Bond	Yes	-0.06255
PM3	Triple Bond	Yes	-0.01338
MMFF	Triple Bond	No	-0.06255
PM3	Triple Bond	No	0.01345
MMFF	Double Bond	Yes	0.09012
PM3	Double Bond	Yes	-0.01572
MMFF	Double Bond	No	0.09012
PM3	Double Bond	No	0.01312

Table 10: Mean Difference From Actual Ru-N-O Bond Angle

Computation Method	Nitrosyl Bonding Type	Atoms Frozen	Mean Difference
MMFF	Triple Bond	Yes	6.0880°
PM3	Triple Bond	Yes	-8.8440°
MMFF	Triple Bond	No	6.3267°
PM3	Triple Bond	No	1.0683°
MMFF	Double Bond	Yes	-62.867°
PM3	Double Bond	Yes	-6.6467°
MMFF	Double Bond	No	-62.867°
PM3	Double Bond	No	0.68500°

In terms of examining the stability of the chemotherapeutic complex and its potential relationship to cyto-toxicity, no direct correlation was evident. It was originally thought that the higher stability complexes would display a lessened degree of cyto-toxicity based upon the fact that they would be less likely to interact with bio-molecules within the cell. This, however, proved not to be the case, as the cyto-toxicity of the

ruthenium based chemotherapeutic agents proved to be completely independent of the stability of the molecule.

Additionally, since chemotherapeutic agents must act within a physiological environment, their aqueous solubility was of the utmost importance to evaluate. The data, when plotted as energy of the complex vs. the number of water molecules involved in the calculated, produced a linear fit for all of the complexes examined. Additionally, all of the best-fit lines generated displayed a very similar slope (-57.613, -56.787, and -61.902). Since all of the complexes examined displayed different charges it was possible to conclude that the solubility of the ruthenium coordinated chemotherapeutic complex was independent of the charge on the complex. This data will prove very useful in the design of potential new chemotherapeutic complexes because little to no attention needs to be paid to the charge associated with the overall complex.

## Conclusions

From the data calculated it can be concluded that the PM3 type calculation best describes the physical properties and geometry displayed by ruthenium chemotherapeutic agents. Also, it can be observed that the charge on the ruthenium complex does not play a role in the overall solubility of the complex. Finally, it was concluded that no relationship exists between the overall stability of the chemotherapeutic complex and the cyto-toxicity of the chemotherapeutic complex.

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