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## RESEARCH ARTICLE

# COMPARISON OF DONOR PROPERTIES OF N-HETEROCYCLIC RINGS IN RUTHENIUM COMPLEXES BY QUANTUM MECHANICAL CALCULATIONS

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**ABSTRACT**

The Ru complexes are synthesized and electron transfer process has been analyzed by theoretical studies. The electron donating ability from the donor sites for the ligand towards Ru can be understood from the reduction of charge density of these atomic sites. Formation of stable complexes is expected from the extent of charge transfer from ligand to Ru. Moreover coordinating ability of donor sites is closely related to the stability of the complex leading to the variation of redox potential. The computed values of oxidation (OX) and reduction (RD) for these complexes vary significantly which are related to frontier energy gap.



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## INTRODUCTION

Ruthenium complexes are considered as potential anticancer agent. Electronic mobility of ligands present in ruthenium complexes fairly influence the oxidation ability of Ru metal. As such DNA and protein binding ability by these complexes is generally considered as one of the essential factor for being anticancer agent (Wilson *et al*., 2014; Muhammad *et al*., 2014; Medici *et al*., 2015; Trudu *et al*., 2015). There may be various types of substituents in a Ruthenium complex i.e acidic group, basic and aromatic group. Choosing the right substituent in the synthesis of Ru complexes is very essential for enhancing binding with biomolecules. The acidic or basic nature of the substituents as well as oxidation ability of Ru is relevant to anticancer activity (Trudu *et al*., 2015; Ramu *et al*., 2015; Bergamo, 2015; Motswainyana, 2015). Moreover, consideration should be made on the hydrophobicity and steric factors of any aromatic ligands and large substituents present in the complexes. These parameters should be considered in explaining the properties of various oxidation states i.e Ru(II), Ru (III) and Ru(IV) complexes (Bergamo, 2015; Motswainyana, 2015; Blunden *et al*., 2014; Bergamo, 2015; Trondl *et al*., 2014; Dömötör *et al*., 2013).

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In some cases small ligand contribute important role in DNA binding. Also coordination of Ru with the N7 of guanine in DNA is found to be the main factor for DNA binding. The electronic effect of substituents may produce certain change on the electronic mobility in Ru complexes which in turn very useful for the stabilization of a complex within DNA (Valente, 2014; Sundararajan *et al*., 2011; Jaque *et al*., 2007; Baik, 2002; Cossi *et al*., 2003; Uudsemaa, 2003 Hughes *et al*., 2012; Cramer, 2009; Becke, 1988). In this study, the electronic properties i.e redox potential have been used to understand the electron donating and electron accepting ability of some synthesised complexes. Quantum mechanical methods have been found useful in understanding the electronic behavior of molecules, so the substituent effect on the variation of redox potential may be studied with this method (Cossi *et al*., 2003; Uudsemaa, 2003 Hughes *et al*., 2012; Cramer, 2009; Becke, 1988; Becke, 1993; Lee, 1988; Castro, 2013; Roy *et al*., 2009; Zhao *et al*., 2007; Cramer *et al*., 2009). The importance of electron transfer behavior in biological system is highlighted in drug discovery. Better understanding of electron transfer mechanism of these ruthenium complexes may be useful to locate the active centre for binding with biomolecules. So the redox potential usually represents the electron mobility in the complexes either from Ru to ligand or vice versa. It may provide some information of the complexes for binding with biomolecules (Motswainyana, 2015; Blunden *et al*., 2014;

Bergamo, 2015; Trondl *et al*., 2014; Dömötör *et al*., 2013; Valente, 2014). There are remarkable electrochemical studies for metal complexes, and also some theoretical studies for predicting redox potential are also found (Wilson *et al*., 2014; Muhammad *et al*., 2014; Medici *et al*., 2015; Trudu *et al*., 2015; Ramu *et al*., 2015; Bergamo, 2015; Motswainyana, 2015; Blunden *et al*., 2014; Bergamo *et al*., 2015; Trondl *et al*., 2014; Dömötör *et al*., 2013; Valente, 2014; Sundararajan, 2011). In this study we explain the theoretically predicted redox potential and the nature of charge distribution of a few Ruthenium complexes. The synthesized complexes Ruthenium 2 acetamidothiazole (Ru-AT) and trichloro (bis 2-acetamido-5-nitropyridine) dimethylsulphoxideruthenium (III) (Ru-ANP), trichloro(bis2-acetamidothiazole) dimethylsul phoxideruthe nium(III) (Ru-ATDM) and transtetrachloro(dimethyl sulphoxide)ruthenium(III) (Ru-VIMD) complexes are taken in this study (Medhi, 2013).

## MATERIALS AND METHODS

The density functional theory method has been used to examine the redox potentials of Ruthenium complexes (16-21). The one electron transfer mechanism was used to describe the change in redox energies. The one-electron electrochemical potentials were calculated using the B3LYP/SDD theoretical method. The structures of the complexes were completely optimized before calculating the redox potentials. With the developed *JoinMolecule* programme packages and Gaussview the geometries of the complexes were constructed before performing computation with Gaussian programme code (28(a-b)). Theoretical redox potentials were obtained from the following equation. The results of oxidation(OX) Ru III to Ru IV and reduction potential(RD) Ru III to Ru II were computed from the following equation..

$$\Delta E = E - E^{0}$$

$E^{0}$ = Energy of ground state structure of complex. $E$ = Energy of one-electron oxidized or reduced complex. Natural population analysis (NPA) were performed for all these complexes. We have also analyzed frontier orbital diagram and HOMO-LUMO gap of these complexes.

## RESULTS AND DISCUSSION

The optimized structures of the Ru complexes were used to calculate oxidation (OX) and reduction (RD) potentials(Figures 1-2). In Ru-AT complexes the values of OX (Ru III/IV) and RD Ru III/II) are significantly different (Table 1). For such complexes one electron reduction may be easier than oxidation. The variation of OX and RD values for other complexes Ru-ATDM, Ru-ANP and Ru-VIMD are similar (Table 1). The one electron reduction mechanism is more feasible than oxidation. The ligands used in the synthesis and the complexes are shown in Figures 2(a)-(d). It is also possible that reduction potential may offer another mechanism of electron transfer between complex and biomolecule. Such change in electrochemical behavior is possible because some of the biomolecule like DNA are negatively charged, consequently electron transfer may takes place from biomolecule to the complex. Hence complexes of ligands, AT, ATDM, ANP and VIM may undergo such electron transfer mechanism. The synthesised complexes ruthenium 2 acetamidothiazole (Ru-AT) and trichloro(bis 2-acetamido-5-nitropyridine) dimethylsulphoxideruthenium(III)(Ru-ANP), trichloro (bis2-acetamidothiazole) dimethyl sulphoxideruthenium (III) (Ru-ATDM) and transtetrachloro (dimethyl sulphoxide) ruthenium(III) (Ru-VIMD) complexes are taken in this study (27). The coordination site of ligand to Ru metal is very important to understand how effectively ligand- metal bonds are formed. The nitrogen and oxygen atomic sites of ligands are usually found coordinated to Ru metal. There are possibilities of charge transfer from Ru or ligands .It depends on the shifting of electron density after coordination of Ru with electron donating sites nitrogen and oxygen of ligands. Tables 1 and 3 show the OX and RD potentials of Ru-AT complex and NPA charges on bonding atoms of ligands. It is essential to analyse the NPA charges on the coordinating atoms of ligand with Ru. We have also examined the electron transfer ability of AT ligand from the one electron ligand oxidation and net charges (NPA) on the donor atoms particularly are shown in Table 3. Such observation in fact indirectly explains the extent of ligand coordination in Ru-AT complex. Table 3 shows the NPA connecting atoms of Ru-AT and AT. It is a common feature that shifting of electron density consequently produces decrease or increase of electron density of certain sites. So the changes in the OX and RD potentials must be related to the variation of electron densities of certain atomic sites and Ru metal.

Similarly, ANP ligand is found coordinated to Ru through Nitrogen and Oxygen of ligand (Figure 1 b). The net charges involve in coordination with Ru in the complex and that of free ligand are shown in Table 4. The computed OX and RD values are given in Table 1. One electron ionization ability of ANP ligand is shown in Table 2. We observed significant change in the net charges of connecting atoms after coordination with Ru in Ru-ANP complex .Fair change in the values of one electron OX potentials is observed but still RD values for Ru(III) to Ru(II) are different from OX value for Ru(III) to Ru(IV) for both Ru-AT and Ru-ANP complexes. This observation may be due to OX or RD potential response of ligand types and coordination ability of ligands for the stabilization of Ru (III) oxidation state. Likewise the structures, bonding and redox potentials of Ru-VIMD and Ru-ATDM have been studied. The redox potentials of these complexes depend on the ligand type that can efficient transfer electron density towards Ru. Hence OX value of Ru-VIMD is larger than that of Ru-ATDM (Table 1). From the coordination distances of the bonding atoms with Ru, Ru-VIMD is expected to be light ligand binding complex compared to Ru-VIMD, since the coordination distances are less than that of Ru-VIMD (Table 3,4).

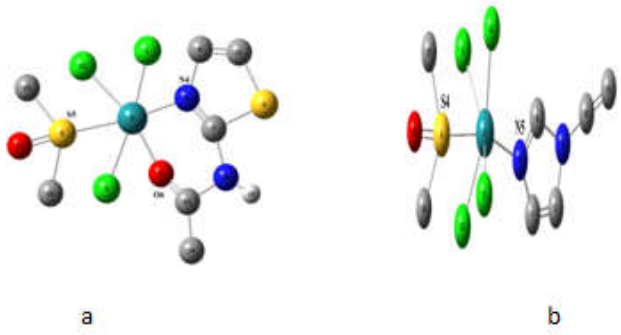
Hence the extent of Ligand coordination to Ru is clearly shown for these complexes which are closely related to redox potential. Such characteristics are very important to understand the binding ability of ruthenium complexes with certain biological molecules. Ligand exchange is an important determinant of biological activity, as very few metal drugs reach the biological target. Many Ru(II) and Ru(III) complexes have been evaluated for the treatment of cancer, due to having similar ligand exchange kinetics similar to those of Pt(II) complexes. The redox potential of a complex can be evaluated by changing the ligand type. The redox potential of ruthenium compounds can be exploited to understand indirectly the effectiveness of drug binding in the clinic study. Accordingly, we have analysed the Ru-ligand coordination lengths and redox potentials, and the values are significantly different for these complexes.

**Table 1. Redox energies of different ruthenium complexes**

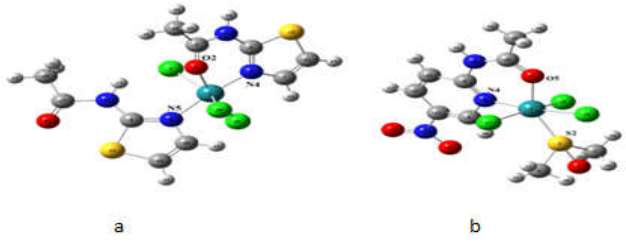
| Complexes | Redox States | Energy values (a.u) | Redox Energies ($kcalmol^{-1}$) |
|---|---|---|---|
| Ru-AT | Ru(III)-AT | -3027.6672 | |
| | Ru(IV)-AT | -3026.9745 | 434.23 |
| | Ru(II)-AT | -3028.1912 | -328.81 |
| Ru-ATDM | Ru(III)-ATDM | -2796.1118 | |
| | Ru(IV)-ATDM | -2795.3246 | 493.968 |
| | Ru(II)-ATDM | -2796.6420 | -332.7005 |
| Ru-ANP | Ru(III)-ANP | -2687.5289 | |
| | Ru(IV)-ANP | -2686.8461 | 428.457 |
| | Ru(II)-ANP | -2688.1258 | -374.555 |
| Ru-VIM D | Ru(III)-VIMD | -2782.3864 | |
| | Ru(IV)-VIMD | -2781.5545 | 522.017 |
| | Ru(II)-VIMD | -2782.9490 | -353.031 |

**Table 2. One electron oxidation energies of different ligands**

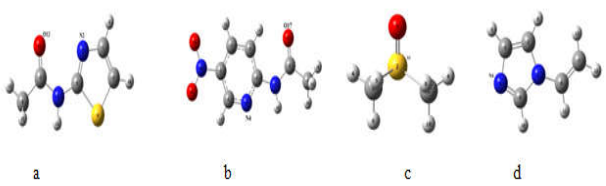
| Ligands | One electron oxidation energies of ligand ($kcalmol^{-1}$) |
|---|---|
| 2- AcetamidoThiazole (AT) | 197.665 |
| 2- Acetamido- 5 nitro pyridine (ANP) | 216.491 |
| Vinyl Imidazole (VIM) | 203.313 |
| Dimethyl sulphoxide (DMSO) | 195.156 |




**Figures 1. Structures of (a) trichlorobis (2acetamidothiazole)dimethylsulfoxideruthenium(III) (Ru-ATDM) complex.(b) Structure of trans-tetrachloro (dimethylsulfoxide) vinylimidazoleruthenium (III) (Ru-VIMD) complex**



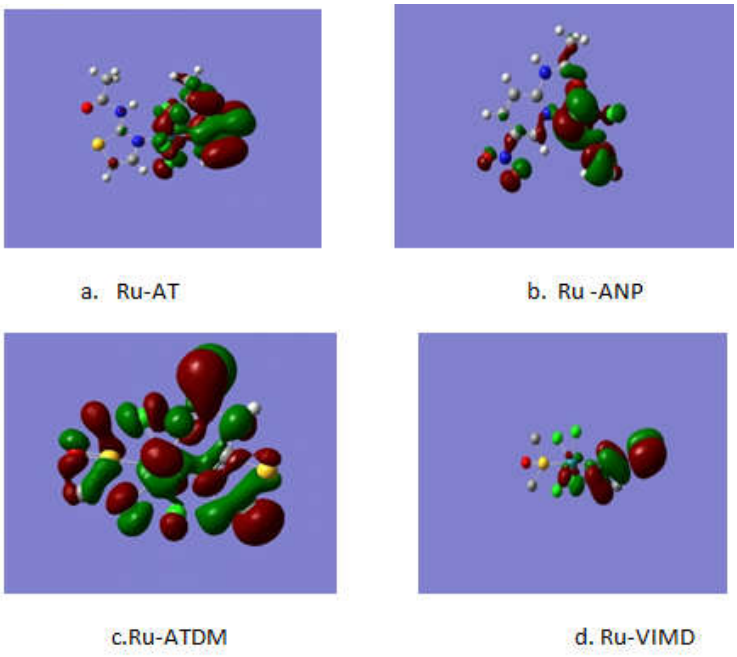

**Figures 2. Structures of (a) trichlorobis(2 acetamidothiazole) ruthenium(III) (Ru-AT) complex (b) trichlorobis (2acetamido-5-nitro pyridine) dimethylsulfoxideruthenium (III) (Ru-ANP) complex**




**Figures 3. Structures of (a)2-acetamido thiazole (AT) (b) 2-acetamido-5-nitro pyridine (ANP), (c)Dimethyl sulphoxide(DMSO) (d) Vinyl Imidazole(VIM) ligand.**

Better coordination is expected for the complexes with smaller bond lengths and formation of comparatively stable complex is expected. For such complex electronic mobility may be less resulting large values of OX potential (Table 1). So the behavior of Ru-ANP ligand is not of similar to that of Ru-AT, the value of OX value for Ru-ANP is comparatively larger than that of Ru-AT. It might be due to the coordination ability of ligand towards Ru of this complex resulting formation of stable complex (Figure 1b). In most of the complexes the atomic sites involved in coordination are electron donor atoms like O and N. In this situation the ligand to Ru charge transfer is the main process in the coordination bond formation. The OX value may arise from Ru in the case of tight bonded ligands. As we know that Ru exhibit in various oxidation states +II, +III and +IV, etc. Some complexes follow RD mechanism in the process of binding with biomolecules. For such complexes OX and RD values may be largely different. The behavior of RD potential may be hysteresis for certain complexes. It on the other hand indicates less mobility of electron which usually results large OX values and hysteresis in RD is expected. The NPA of the complex only for the Ru bonded atoms are shown in Tables (3-6). The variation of NPA values at different sites including Ru clearly indicates the extent of electron density migration from ligand to Ru. Hence prominent increase of electron density at Ru has been observed. The electronically sensitive sites are very important for interaction with biomolecules. Such analysis may be useful if Ru binding with biomolecule is dominated in the overall binding. We have also analysed frontier orbital diagrams of these complexes. Figures 4a-d show the positions of HOMO-LUMO in these complexes and the energy gaps are given in Table 7.

Recently, the experimental and theoretical studies of Ru complexes have been increased extensively. The cyclic voltammetry (CV) is widely applied in the studies of redox potential. So lots of studies are carried on the electron-transfer property metal complexes, it is important to understand redox potential of still essential particularly for new complexes. Therefore, we select these Ru complexes to investigate the electron-transfer properties by employing theoretical methods. The one electron transfer properties of various oxidized and reduced chemical species have been studied DFT calculations (B3LYP/SDD). The calculated OX values for Ru-AT Ru-ANP, Ru-ATDM, and Ru-VIM are very different, which indirectly predicts the ability of electron transfer depending on the ligand type. Then, we found significant changes in NPA charges of atoms at coordination atoms. As shown in Table 1, the N-Ru bond lengths are 2.170 Å for Ru-AT whereas the values for Ru-ANP complex is 2.007 Å. Moreover the coordination distances of N and O from Ru are 2.170 Å and 2.065 Å, for Ru-AT whereas for Ru-ANP, the coordination distances are 2.007 Å and 1.982 Å respectively. The two N atoms are close Ru in Ru-ANP complex compared to the corresponding distances of Ru-AT complex. It indirectly shows the formation of stable complexes of Ru with various ligand types. The calculated results show that the OX values complement to the change in NPA charges. The calculated one electron ionization value for ANP ligand is are more than that of AT ligand (Table 6) which indicates that the coordination of ANP ligand with Ru may be stronger than that of AT ligand with the directional migration of electron density towards Ru. Therefore, we expect ligand to Ru charge transfer process in forming coordination bond formation in these, which on the other hand results variation of OX and RD potentials.




**Figures 4. Frontier orbital diagrams of (a) Ru-AT(b)Ru- ANP (c)Ru- ATDM (d)Ru-VIMD.**

**Table 3. Computed NPA charges on the atoms co-ordinated to Ruthenium(Ru) in Ru-AT complex along with the free ligand (AT) and the bond length between Ru-coordinated atom.**

| Bond length between Ru and coordinated atom | NPA charges on atoms co-ordinated with Ru | | NPA charges on atoms of free 2-Acetamido Thiazole (AT) ligand. | |
|---|---|---|---|---|
| | Co-ordinated atom | Charges | Co-ordinated atom | Charges |
| Ru-$N_4$ = 2.170 | $N_4$ | -0.250 | $N_2$ | -0.324 |
| Ru-$N_5$ = 2.324 | $N_5$ | -0.301 | | |
| Ru-$O_2$ = 2.065 | $O_2$ | -0.225 | | -0.408 |
| Ru-$Cl_3$ = 2.391 | | | $O_{12}$ | |
| Ru-$Cl_{20}$ = 2.392 | | | | |
| Ru-$Cl_{21}$ = 2.311 | | | | |

**Table 4. Computed NPA charges on the atoms co-ordinated to Ruthenium(Ru) in Ru-ANP complex along with the free ligand (ANP) and (DMSO) and the bond length between Ru-coordinated atom.**

| Bond length between Ru and coordinated atom | NPA charges on atoms coordinated with Ru | | NPA charges on atoms of free 2-Acetamido-5-nitro pyridine (ANP) ligand | | NPA charges on atoms of free Dimethyl sulfoxide (DMSO) ligand | |
|---|---|---|---|---|---|---|
| | Co-ordinated atom | Charges | Co-ordinated atom | Charges | Co-ordinated atom | Charges |
| Ru-$N_4$ = 2.007 | $N_4$ | -0.481 | $N_4$ | -0.519 | | |
| Ru-$O_5$ = 1.982 | $O_5$ | -0.577 | $O_{17}$ | | $S_2$ | 1.142 |
| Ru- $S_2$ = 2.205 | $S_2$ | 1.082 | | -0.614 | | |
| Ru-$Cl_{17}$ = 2.329 | | | | | | |
| Ru-$Cl_{18}$ = 2.320 | | | | | | |
| Ru-$Cl_{19}$ = 2.321 | | | | | | |

**Table 5. Computed NPA charges on the atoms co-ordinated to Ruthenium(Ru) in Ru-ATDM complex along with the free ligand (AT) and (DMSO) and the bond length between Ru-coordinated atom.**

| Bond length between Ru and coordinated atom | NPA charges on atoms coordinated with Ru | | NPA charges on atoms of free 2-Acetamido Thiazole (AT) ligand. | | NPA charges on atoms of free Dimethyl sulfoxide (DMSO) ligand | |
|---|---|---|---|---|---|---|
| | Co-ordinated atom | Charges | Co-ordinated atom | Charges | Co-ordinated atom | Charges |
| Ru-$N_4$ = 1.928 | $N_4$ | -0.309 | $N_2$ | -0.324 | | |
| Ru-$O_6$ = 1.927 | $O_6$ | -0.264 | $O_{12}$ | -0.408 | | |
| Ru- $S_5$ = 2.376 | $S_5$ | 0.237 | | | | 1.148 |
| Ru-$Cl_1$ = 2.127 | | | | | $S_2$ | |
| Ru-$Cl_3$ = 2.296 | | | | | | |
| Ru-$Cl_{13}$ = 2.317 | | | | | | |

**Table 6. Computed NPA charges on the atoms co-ordinated to Ruthenium (Ru) in Ru-VIM D complex along with the free ligand (VIM) and (DMSO) and the bond length between Ru-coordinated atom.**

| Bond length between Ru and coordinated atom | NPA charges on atoms coordinated with Ru | | NPA charges on atoms of free Vinyl Imidazole(VIM) ligand | | NPA charges on atoms of free Dimethyl sulfoxide (DMSO) ligand | |
|---|---|---|---|---|---|---|
| | Co-ordinated atom | Charges | Co-ordinated atom | Charges | Co-ordinated atom | Charges |
| Ru-$N_5$ = 2.024 | $N_5$ | -0.328 | $N_4$ | -0.505 | | |
| Ru-$S_4$ = 2.380 | $S_4$ | 0.168 | | | | |
| Ru- $Cl_1$ = 2.281 | | | | | $S_2$ | 1.142 |
| Ru-$Cl_3$ = 2.286 | | | | | | |
| Ru-$Cl_{11}$ = 2.280 | | | | | | |
| Ru-$Cl_{12}$ = 2.280 | | | | | | |

**Table 7. Differences of Frontier orbital energies of complexes**

| Complex | $\Delta E=E_{LUMO}-E_{HOMO}$ (a.u) |
|---|---|
| Ru-AT | 0.04092 |
| Ru-ATDM | 0.04292 |
| Ru-ANP | 0.01744 |
| Ru-VIM D | 0.06486 |

## Conclusion

The electron transfer property of Ru-AT is less feasible than Ru-ANP complex. The ANP ligand has more electron donation ability than AT ligand. The results indicate that the one electron transfer in electrochemical reaction is controlled by type of ligand and formation of stable complexes. By employing theoretical methods, the electron-transfer properties of Ru at different redox states can be calculated and the values are different depending on the type of ligand. Oxidation potential of Ru-AT is larger than Ru-ANP. Similarly redox potentials of Ru-VIMD is larger than that of Ru-ATDM. Our calculated results suggest that the one electron transfer redox mechanism for these complexes is significantly different depending on the ligand type. The variation of NPA charges of Ru for Ru-AT and Ru-ANP are clearly found for these complexes and significant decrease in NPA charges of bonding atoms is indicated after coordination.

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