An comprehensive analysis of the biological aspects of Ruthenium(II) mixed halide complexes

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ABSTRACT

The versatility of Ruthenium in its ability to adopt multiple oxidation states is a key feature driving its diverse applications. Ruthenium readily forms coordination complexes, contributing to its utility across various fields. Its expanding chemistry finds relevance in tasks ranging from determining calcitonin levels in blood to estimating folate deficiency in RBCs through assays like Eleecysfolate RBC assay. Additionally, Ruthenium complexes serve as immunosuppressants, antimicrobial agents, and inhibitors of nitric oxide overproduction in biological cells. Moreover, they exhibit potential as metallopharmaceuticals for treating diseases including cancer and AIDS, with radio sensitizers aiding in radiation therapy and anti-metastasis drugs. The prospect of leveraging Ru complexes in photochemistry and agrochemicals is also anticipated. The synthesis of novel ligands capable of complexing with Ruthenium in various oxidation states holds promise for material development. Presently, interdisciplinary research at the nexus of biology, chemistry, and physics is shifting focus from mere drug synthesis to informed drug design, facilitated by computational chemistry and sophisticated software. This study aims to delve into the electronic structure of ruthenium(II) mixed halides, offering insights into their properties and potentially enabling the creation of new complexes or fine-tuning existing ones.

I. INTRODUCTION:

Ruthenium's capacity to assume multiple oxidation states is a crucial aspect enhancing its utility across various applications. It readily forms coordination complexes, which find widespread use in diverse fields. The expanding realm of ruthenium chemistry stems from its direct or indirect involvement in numerous applications, including determining calcitonin levels in blood, estimating folate deficiency in RBCs through assays like Eleecysfolate RBC assay, serving as immunosuppressants and antimicrobial agents, acting as inhibitors of nitric oxide overproduction in biological cells, and functioning as metallopharmaceuticals for treating diseases such as cancer and AIDS. Ruthenium complexes are also utilized as radio sensitizers in radiation therapy and as anti-metastasis drugs. Notably, Dragutan et al., in an editorial special issue review, anticipate the future valorization of Ru complexes in photochemistry and agrochemicals. The literature underscores the potential for developing new materials through the design of ligands capable of complexing with ruthenium in various oxidation states. Presently, the focal point of interdisciplinary research spanning biology, chemistry, and physics has shifted from the mere synthesis of drugs to informed drug design. The advent of computational chemistry, coupled with physics and diverse software tools, has imbued drug development with a quantitative nature, elucidating the relationship between drugs and their properties, thus expanding their potential applications. This study aims to delve into the electronic structure of ruthenium(II) mixed halides, with the precise goal of explicating their properties and facilitating the development of new ruthenium(II) complexes or refining the properties of existing ones.

Complexes of ruthenium(II) mixed halides refer to coordination compounds containing ruthenium atoms bonded to a mixture of halogen atoms, typically chlorine, bromine, or iodine. These complexes are of interest due to their diverse applications in fields such as catalysis, medicine, and materials science. The biology of ruthenium(II) mixed halide complexes encompasses their interactions with biological systems, mechanisms of action, metabolic fate, and potential applications in cancer therapy and other biomedical fields. Continued research in this area is critical for harnessing the full therapeutic potential of these fascinating coordination compounds.

Ruthenium readily form coordinate complexes and these complexes have their applications in diverse fields, as shown in scheme 1.Ru forms compounds in -2, 0, +2, +3, +4, +6 and +8 oxidation states. -2 and 0 oxidation states are unusual oxidation states, scheme 2. The ability of Ru to exist in many oxidation states is an important property of this element, which plays an important role in its applications [1]. Day-to-day expanding in the chemistry of ruthenium and its complexes is due to their applications directly or indirectly pre-requisite for many of today's problems related to anticancer drugs, polymers, materials science and nanoscience. This is due to its versatile electron-transfer pathways. Survey of literature shows that ruthenium and its compounds

now used: in solar cells, as catalyst, as determination of calcitonin level in blood, in Eleecysfolate RBC assay to estimate folate deficiency in RBC, as immunosuppressant, as antimicrobial agents, as antibiotic agents, as inhibitors to inhibit over production of nitric oxide in biological cell, as metallopharmaceuticals in treatment of various diseases including cancer, radio sensltizers complexes with ruthenium are used in radiation therapy, as anti-metastasis drugs [1-7]. Dragutan et al. in editorial special issue review wrote "Valorization of Ru complexes in photochemistry and agrochemicals will undoubtedly be forthcoming" [3].Poursharifi et al. have their focus on encapsulating ruthenium-based carriers of nanosized structures or adduct with various macro biomolecules to generate efficacious anti-cancer therapies [8]. Ruthenium based complex compound have also been used as drugs to activate or help to generate redox reactions[9-11].

1.1. Ruthenium-based Anti-cancer Drugs: As most of the ruthenium complexes are less toxic than their platinum counter parts, this offers development of ruthenium-based anticancer drugs. (imidazole-H)[*trans*-RuCl$_4$(dmso-S)(imidazole)] has entered onto phase-I clinical trial showed anti-canceractivity against solid tumor metastasis [12]. Some bidentate N-donor or arene ligands,when complexed with Ru(II) have also been found to show significant anti-cancer activities [6,13-15]. Ruthenium(II) complex, "[Ru(*t*Bu$_2$byp)$_2$-(2-appt)](PF$_6$)$_2$" has been shown to exhibit moderate cytotoxicities towards several established various human cancer cells. [16-19]. Sun et al. [20] examined nucleotide binding properties and cytotoxicity of several ruthenium(II) complexes with quinonediimine as auxiary ligand. Ruthenium(II) complexed with ligand 9,10-phenanthroquinonediimine has highest DNA binding contstant attributed due to its flat and large surface area, which provide a geometry that permits sizeable overlap with DNA base pairs. It has mild cytotoxicity with 5o% inhibitory concentration of ~200μM against carcinoma cell lines. The cell growth inhibition activity of complex [Cl(terpy)(tmephen)Ru]$^+$is due its binding affinity towards purines sites of nucleptide of DNA, and this depends upon chloride ligand.Binding of the *trans*-[Cl$_4$(Im)$_2$Ru]$^-$ toapotransferrin for its anti-tumor activitytakes several hours, but its Ind-derivatives, *trans*-[Cl$_4$(Ind)$_2$Ru]$^-$showed very fast action pn few minutes. To kill the undesired cells in the body using N-heterocyclic ligands complexed with Ru(II) has also been reported in literatures. This photodynamic therapy (PDT) activity of agents depends on their ability to associate with biopolymers or cell membranes or DNA[21-27]. The radiophysical properties of ^{97}Ru are nearly ideal for some type of radiodiagnosticimagaing [28].

1.2. Ruthenium-based Anti-HIV Drugs: Ruthenium-oxooxalato cluster Na$_7$[Ru$_4$(μ-O)$_4$(C$_2$O$_4$)$_6$] exhibited promising anti-HIV-1 activity over 98% inhibition [29]. The IC$_{50}$ of this compound to reduce the catalytic activity of reverse transcriptase enzyme of human immunodeficiency virus-1 in nanomolar is 1.9 as reported by Sun et al. This activity of this compound is ten times more than the most used drug 3'-azido-3'-deoxythmidine-5'-triphosphate (AZT-TP)whose,IC$_{50}$innanomolar is 68.Further, this compound was able to show only antiviral activity instead of killing the host cells [7].

1.3. Ruthenium-based anti-microbialAgents: Anti-microbial activities in both bacterial and fungal cells of "octahedral polypyridylruthenium(III) complexes" were also reported by Yang et al. It is worthwhile mentioned that "octahedral ruthenium(II) complexes" have remarkable applications in Bio-medical sciences [29-31].
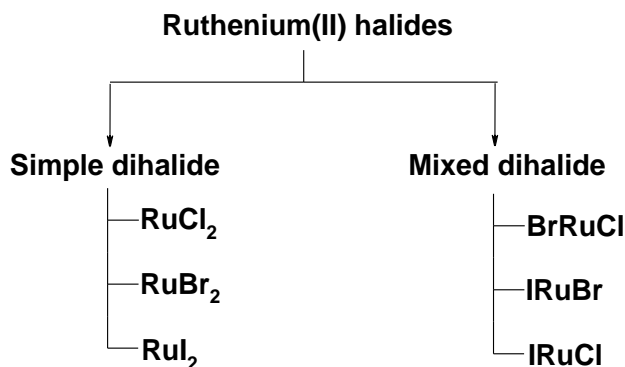
1.4. Ruthenium-based catalysis: Early metathesis catalysis formed in situ from transition-metal halides has their limitation due to their high compassion and lower easiness. Ruthenium based catalysts have remarkably high compassion and lower easiness.In 1960s first catalytic activity of Ru based complex has been reported in literature and this was due to the RuCl$_3$(H$_2$O)$_n$ metathesis. The catalysis of "areneruthenium(II) complexes" ranges from hydrogen transfer to ring-closing.García-Peňa et al., have made solventless synthesis of Ru nanoparticles along with the use of polyphosphorhydrazonedendrons as coatings leads to Ru nanoparticles in zero oxidation state which are air stable, and proved to be very good nanomaterials for hydrogenation catalysis [22-31].

1.5. Ruthenium-based Photoactive materials: Santoro et al. have developedtris(1,10-phenantroline)ruthenium(II)(Ru(phen)$_3$)$^{+2}$ as a thermometer of nanosized doped with nanosized silica, applicable to monitor the temperature of membrane surfaces in real membrane process [22]. These workers also developed nanoparticals that have application for high photochemical and strong phosphorence activity with respect to Ru(phen)$_3$$^{+2}$. Millett and Durham have developed a new method to study intracomplex electron transfer that utilizes a photoactive tris(bispyridine)ruthenium group [Ru(II)] which was covalently attached to a protein (cytochrome c).Application of ruthenium based sensitizers having thiocyanate and other ligands have been reviewed by Qin and Peng for dye-sensitized solar cells (DSSCs), among them several sensitizers have ten percentages more efficiency with respect to available sensitizers [23-24]. The aim of present study is "to study the atomic and sub-atomic i.e., electronic structure of ruthenium(II) halides by evaluating eigenvalues, eigenvector and overlap matrix of molecular orbitals".During the study, three objectives arose: (i) to draw the 3D structure of all the compounds and to optimize their geometry (ii) to evaluate the eigenvector, overlap matrix and eigenvalues of the compoundsand (iii) build up molecular orbital diagram of compounds that at a

glance provides clear cut electronic picture of the molecule, which more precisely can explain or help to explain the various properties of the molecule.

II.   MATERIAL AND METHOD:

Ruthenium dihalides can be classified in to two groups based on halogen atom bonded to Ru. These are simple dihalides and mixeddihalides. In simple dihalides, RuX_2, where X = halogen atom and are same but in mixeddihalides, these are different (X=halogen, $X_1 \neq X_2$) as shown below.

Ruthenium(II) halides

Simple dihalide
- $RuCl_2$
- $RuBr_2$
- RuI_2

Mixed dihalide
- $BrRuCl$
- $IRuBr$
- $IRuCl$

Three simple ruthenium dihalides exist. These are ruthenium(II) chloride, ruthenium(II) bromide and ruthenium(II) iodide, except ruthenium(II) fluoride which does not exist. Three ruthenium mixeddihalide are possible. These are Br−Ru−Cl, I−Ru−Br and I−Ru−Cl. A survey of literature shows that designing of new ligands that can complexed with ruthenium in different oxidation states can lead to develop new materials [5, 10, 11, 26]. For new materials of diverse applications there is and will be a continuous step-by-step study to discover new ligands and their new ruthenium complex. These complex compounds can formed either from their simple compounds or by substitution reactions from pre-synthesized complex compounds. The development of new Ru-based materials is and will be an ongoing need for various fields of science and technology, and thus for society. It is difficult to synthesize new molecule and test their various properties in laboratory, because, it involves huge expenditure and consumes enormous time. Now, chemistry together with physics and computer science has shifted from, how to make a molecule to what molecule to make, in other words molecule design. The emergence of computational chemistry and various software shave given a quantitative nature to the relationship between molecule, its property, its synthesis and thus its various applications [25-27]. The method adopted for various calculations are based on Mulliken population analysis (MPA) [30]. Mulliken defined MOs (ϕ_i), the contributions of electrons ($n_{r,i}$) in each occupied MO and overlap population ($n_{r-s,i}$) that defines bonding, antibonding and nonbonding nature of bond through which the constituting atoms combine to form polyatomic molecule, as below:

$$\phi_i = \sum_{rk} c_{irk} \chi_{rk} \quad \text{Eq.1;} \qquad n_{r,i} = n_i c_{ri}^2 \quad \text{Eq.2;} \qquad n_{r-s,i} = n_i (2 c_{ri} c_{si} S_{rs}) \quad \text{Eq.3}$$

here n_i is the number of electron in MO ϕ_i ($i = 1-17$), c_{ri} is the coefficient of atomic orbitals for one atom, c_{si} is the coefficient of AOs for other atom and S_{rs} is the overlap integral between the two AOs (one of an atom and one of other atom). The 3D modeling and geometry optimization of the ruthenium(II) halides have been done by CAChe software using molecular mechanics with EHT option [31-32]. Eigenvectors, overlap matrix and eigenvalues have been computed with the same software, using the same option.

III.   RESULT AND DISCUSSION:

At first we have to examined the extent of involvement of 4d, 5s and 5p AOs of Ru-1 in the formation of MOs in ruthenium(II) halides. For this, values of coefficient of each χ_{5s}, χ_{5px}, χ_{5py}, χ_{5pz}, $\chi_{4dx^2-y^2}$, χ_{4dxy}, χ_{4dxz} AO of Ru-1 in eleven MOs (ϕ_1-ϕ_{11}), has been added together with excluding the value of non-bonding orbitals χ_{4dz2} (χ_6) and χ_{4dyz} (χ_9), and the six vacant MOs (ϕ_{12}-ϕ_{17}).

ΣAO	Ru(II)Cl$_2$	Ru(II)Br$_2$	Ru(II)I$_2$	Ru(II)BrCl	Ru(II)IBr	Ru(II)ICl
Σ4dx2-y2	1.8387	1.9165	2.0004	2.4501	4.9002	9.8004
Σ4dxy	1.0407	1.1820	1.2399	2.1893	4.3786	8.7572
Σ4dxz	0.8364	0.9694	1.0145	2.1527	4.3054	8.2407
Σ5s	0.6598	0.6635	0.6742	1.1012	2.2024	4.4047
Σ5px	0.2471	0.2921	0.3385	0.7407	1.4814	2.8401
Σ5py	0.1477	0.1494	0.1498	0.6454	1.2908	2.5816
Σ5pz	0.1276	0.1254	0.1218	0.3866	0.7732	1.5464

The summation values of AOs in these eleven MOs clearly reflects maximum involvement is of 4d orbital (4dx^2-y^2> 4dxz > 4dxy). Next to this is 5s orbital. It is evident that major contribution is from 4d and 5s orbital. The 5p orbitals have negligible contribution. Landis has also forcefully deprived of the involvement of np orbital in hybridization in transition metals and supported sd^n hybridization (here n=1) [24]. He has also described the hybridization bond angle and idealized molecular shapes for sd^n-hybridization and plotted graph between energy and bond angle. Further, the summation values are highest in case of iodide and lowest in chloride. This is due to cloud expending of halides. For a given metal ion, the ability of ligands to induce this cloud expending increases according to nephelauxetic series: F$^-$< H2O < NH3 < en < ox < SCN <Cl$^-$<CN$^-$<Br$^-$ < I$^-$[35]. Thus, iodide produces greater cloud expending than bromide, which intern, produces higher than chloride in ruthenium diiodide, ruthenium dibromide and ruthenium dichloride, respectively. In orother words the effective positive charge on Ru(II) is reduced greater by iodide and lesser by chloride. The result is in good agreement with nephelauxetic series of ligands. In, Ru(II)ICl, iodine produces greater cloud expending effect due to its lowest electronegativity among halogen. In Ru(II)IBr, the difference in electronegativity ($\Delta\chi_{I-Br} = 0.3$) is not much lower as in case of Ru(II)ICl ($\Delta\chi_{I-Cl}= 0.5$), hence it produces less cloud-expending effect. Ru(II)BrCl having much low difference in electronegativity ($\Delta\chi_{Cl-Br} =0.2$) in turn produces lowest cloud-expending effect in ruthenium mixeddihalides. In order to get a precise description, the sum of overlap population for the eleven MOs of ruthenium dihalides and ruthenium mixeddihalides has also been worked out and results are presented in Table1 and 2, respectively. As can be seen from the Table 1, that among the eleven molecular orbital, nine are bonding (BMO) and two are nonbonding (NBO). The bonding molecular orbitals are ϕ_1–$\phi_5$and ϕ_8–ϕ_{11}. The nonbonding molecular orbital are ϕ_6 andϕ_7, which are purely two d atomic orbitals of ruthenium namely dxz and dz^2.

Table1. Nature of occupied molecular orbitals of ruthenium dihalides

MO No.	RuCl$_2$			RuBr$_2$			RuI$_2$		
	$\Sigma n_{r-s,i}$	sign	MOs	$\Sigma n_{r-s,i}$	sign	MOs	$\Sigma n_{r-s,i}$	sign	MOs
ϕ_1	0.1924	+	BMO	0.2091	+	BMO	0.3042	+	BMO
ϕ_2	0.1237	+	BMO	0.1371	+	BMO	0.1742	+	BMO
ϕ_3	0.4502	+	BMO	0.2487	+	BMO	0.0936	+	BMO
ϕ_4	0.2226	+	BMO	0.1395	+	BMO	0.0936	+	BMO
ϕ_5	0.2228	+	BMO	0.1395	+	BMO	0.1248	+	BMO
ϕ_6	0.0000	0	NBO	0.0000	0	NBO	0.0000	0	NBO
ϕ_7	0.0000	0	NBO	0.0000	0	NBO	0.0000	0	NBO
ϕ_8	0.2853	+	BMO	0.3256	+	BMO	0.3359	+	BMO
ϕ_9	0.1182	+	BMO	0.0941	+	BMO	0.1849	+	BMO
ϕ_{10}	0.1202	+	BMO	0.0940	+	BMO	0.0783	+	BMO
ϕ_{11}	0.0735	+	BMO	0.1433	+	BMO	0.0783	+	BMO

Table2. Nature of occupied molecular orbitals of ruthenium mixeddihalides

MO No.	Ru(II)BrCl			Ru(II)IBr			Ru(II)ICl		
	$\Sigma n_{r-s,i}$	sign	MOs	$\Sigma n_{r-s,i}$	sign	MOs	$\Sigma n_{r-s,i}$	sign	MOs
ϕ_1	0.1604	+	BMO	0.1358	+	BMO	0.1585	+	BMO
ϕ_2	0.1719	+	BMO	0.2496	+	BMO	0.2527	+	BMO
ϕ_3	0.3051	+	BMO	0.2372	+	BMO	0.2523	+	BMO
ϕ_4	0.1949	+	BMO	0.1442	+	BMO	0.1848	+	BMO
ϕ_5	0.1949	+	BMO	0.1471	+	BMO	0.1848	+	BMO
ϕ_6	0.0000	0	NBO	0.0000	0	NBO	0.0000	0	NBO
ϕ_7	0.0000	0	NBO	0.0000	0	NBO	0.0000	0	NBO

ϕ^8	0.2422	+	BMO	0.1698	+	BMO	0.1824	+	BMO
ϕ^9	0.0504	+	BMO	0.0064	+	BMO	-0.0105	-	ABMO
ϕ^{10}	0.0495	+	BMO	0.0063	+	BMO	-0.0105	-	ABMO
ϕ^{11}	0.1626	+	BMO	0.2292	+	BMO	0.2270	+	BMO

As can also be seen from the Table 2, that in Ru(II)BrCl and Ru(II)IBr among the eleven molecular orbital, nine are bonding (BMO) and two are nonbonding (NBO). The bonding molecular orbitals are ϕ_1−ϕ_5 and ϕ_8−ϕ_{11}. The nonbonding molecular orbital are ϕ_6 and ϕ_7, which are purely two d atomic orbitals of ruthenium namely dxz and dz^2. But in Ru(II)ICl, among the eleven molecular orbital, seven are bonding (BMO), two are nonbonding (NBO) and two are antibonding (ABMO). The bonding molecular orbitals are ϕ_1−ϕ_5, ϕ_8 and ϕ_{11}. The nonbonding molecular orbital are ϕ_6 and ϕ_7, which are purely two d atomic orbitals of ruthenium namely dxz and dz^2. Remaining two ϕ_9 and ϕ_{10} are antibonding.

Sheme 3. Summary of topology of Ruthenium(II) halides and mixeddi halides

Molecule	$\sum\sum n_{r\text{-}s,i}$	Bond	Length (Å)	Bond	Length (Å)	Bond Angle(°)
Cl−Ru−Cl	1.8089	Cl−Ru	2.238	Ru−Cl	2.238	179.99°
Br−Ru−Br	1.5309	Br−Ru	2.389	Ru−Br	2.389	179.99°
I−Ru−I	1.4678	I−Ru	2.579	Ru−I	2.579	179.99°
Br−Ru−Cl	1.5319	Br−Ru	2.389	Ru−Cl	2.239	179.99°
I−Ru−Br	1.3256	I−Ru	2.579	Ru−Br	2.389	179.99°
I−Ru−Cl	1.4215	I−Ru	2.579	Ru−I	2.239	179.99°

From the scheme 3, it can be concluded that it is very difficult to replace Cl atom from Cl−Ru−Cl($\sum\sum n_{r\text{-}s,i}$ = 1.8089) to form Br−Ru−Cl. But, it can be easily prepared from Br−Ru−Br ($\sum\sum n_{r\text{-}s,i}$= 1.5309) by replacing one of its Br atoms by Cl atom through substitution reaction. Similarly, I−Ru−Br can be prepared easily by replacing one of the I−Ru−I ($\sum\sum n_{r\text{-}s,i}$= 1.4678) by Br atom. And, I−Ru−Cl can be prepared easily by replacing one of the I−Ru−I ($\sum\sum n_{r\text{-}s,i}$= 1.4678)by Cl atom than Br−Ru−Br. The study will helpful in designing of new ligands that can complexes with Ru in various oxidation states can lead to develop new materials.

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