



Structural, spectral, biological and antioxidant analyses of baicalin and its vanadium complexes: a dft study

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Abstract

Molecular simulation analyses of baicalin and its vanadium complexes were done at B3LYP/6-31+G(d) and B3LYP/ANL2DZ levels, respectively. The conformer analyses were performed for baicalin and the most stable one is determined at OPLS3e method by using Maestro 11.9 program. Structural and spectral analyses of the baicalin – vanadium complex is performed in gas phase and water. Potential energy distribution (PED) analyses were done to evaluate the infrared (IR) spectra. ¹H- and ¹³C-NMR spectra of V (IV) complex are analyzed. Finally, biological reactivity of related compounds is compared with that of cisplatin by using quantum chemical descriptors (QCD). Antioxidant properties of related structures are compared with each other by using same QCDs. According to QCD rankings, antioxidant activity of baicalin is increased with the complexing of studied ligand.

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1. Introduction

Flavonoids are a broad class of low molecular weight secondary plant phenolics characterized by the flavan nucleus. Flavonoids are mainly found in leaf, seed, shell and plant flowers. Additionally, these compounds provide protection of plants against harmful items such as UV rays and etc. [1]. Additionally, flavonoids are also important in daily food intake [2-9]. In recent years, the use of natural products and medicinal plants has become increasingly widespread in order to protect the general health status of individuals and prevent and treat diseases. The fact that plant products are easily accessible and inexpensive increases their conscious or unconscious use in various diseases. Nowadays, many herbal substances which are claimed to have antimicrobial, antidiabetic, anti-inflammatory and antioxidant properties are used in the treatment of various diseases and even some herbal-derived substances are claimed to be used against cancer by providing tumor inhibition in experimental animals [10]. Most of the studies are focused on synthetic and plant-derived antioxidant compounds used against various diseases caused by free radicals. It is stated that most of the beneficial effects of herbal products on health are due to their antioxidant and phenolic compounds. Baicalin (baic) is the member of the flavonoid and has antiallergic, anti-inflammatory and

antioxidant activity [11]. Fruit and vegetable intakes are related to a reduction of cancer and cardiovascular disease risk. These effects are firstly attributable to beta-carotene and ascorbate while phenolic molecules may play a significant role. Baicalin and its vanadium (IV) complex have been investigated by Williams and co-workers in 2017 [12].

The aim of this study, the experimental results are supported with computational results and the investigation of how biological and antioxidant activities are changed by the complexing of baicalin. Because this issue is investigated neither experimentally and computational.

Baicalin is optimized at B3LYP/6-31+G(d) level in gas phase and the most stable structures are determined by using Maestro 11.9 program. The related metal complex is optimized at B3LYP/6-31+G(d)(LANL2DZ) level in gas phase and water. Structural, spectral, biological and antioxidant properties are investigated at the same level of theory. Some quantum chemical descriptors are used in this study. These descriptors can give foreknowledge about biological reactivity of chemicals. Therefore, they play important role in computational analyses. Considered quantum chemical descriptors are HOMO energy (EHOMO), LUMO energy (ELUMO), energy of ionization (I), electron affinity (A), energy gap

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(EGAP), hardness (η), global softness (S) softness (σ), electrophilicity index (ω), nucleophilicity index (N), electronegativity (χ), chemical potential (CP), and additional electronic charges (ΔN_{Max}). Additionally, molecular orbital energy diagram (MOED), contour plots of frontier molecular orbital, molecular electrostatic potential (MEP) map and density of state (DOS) spectrum are examined to propose the electronic properties of studied compounds. The calculated results are compared with cis-platin's results due to the fact that cisplatin is a reference material in the anticancer studies. Therefore, electronic properties of cisplatin are calculated to determine the anticancer properties of studied ligand and complex.

2. Method

Numerical calculations are performed by using ChemDraw 15.1, Gaussian 6.0.16, Gaussian 16 IA32W-G16RevB.01, Gaussian 09 AS64L-G09RevD.01, Maestro 11.9 and VEDA 4XX programs [13-18]. Firstly, baicalin was optimized at universal force field (UFF) method, one of the molecular mechanic methods. Then, conformer analyses were performed at OPLS3e method by using Maestro 11.9 at neutral conditions. The most stable structure of the baicalin was determined and re-optimized at B3LYP/6-31+G(d) level. The vanadium(IV) complex were optimized at B3LYP/6-31+G(d)(LANL2DZ) level in gas phase and water. For calculation in water, C-PCM model was taken into consideration in solute/solvent interactions. IR spectra in gas phase of baicalin-V(IV) complex was analyzed with potential energy distribution (PED) analysis by using VEDA 4XX program. Tetramethylsilane (TMS) was optimized at B3LYP/6-31+G(d) level and used as reference substance in the calculation of chemical shift values of hydrogen and carbon atoms. Related QCDs were calculated by using Eq. (1) – (11) [19-23].

$$I = -E_{HOMO} \quad (1)$$

$$A = -E_{LUMO} \quad (2)$$

$$E_{GAP} = E_{LUMO} - E_{HOMO} \quad (3)$$

$$\eta = \frac{I - A}{2} = \frac{E_{LUMO} - E_{HOMO}}{2} \quad (4)$$

$$\sigma = \frac{1}{\eta} \quad (5)$$

$$\chi = \frac{|I + A|}{2} = \frac{|-E_{HOMO} - E_{LUMO}|}{2} \quad (6)$$

$$CP = -\chi \quad (7)$$

$$\Delta N_{Max} = -\frac{CP}{\eta} \quad (8)$$

$$\omega = \frac{CP^2}{2\eta} \quad (9)$$

$$N = \frac{1}{\omega} \quad (10)$$

$$S = \frac{1}{2\eta} \quad (11)$$

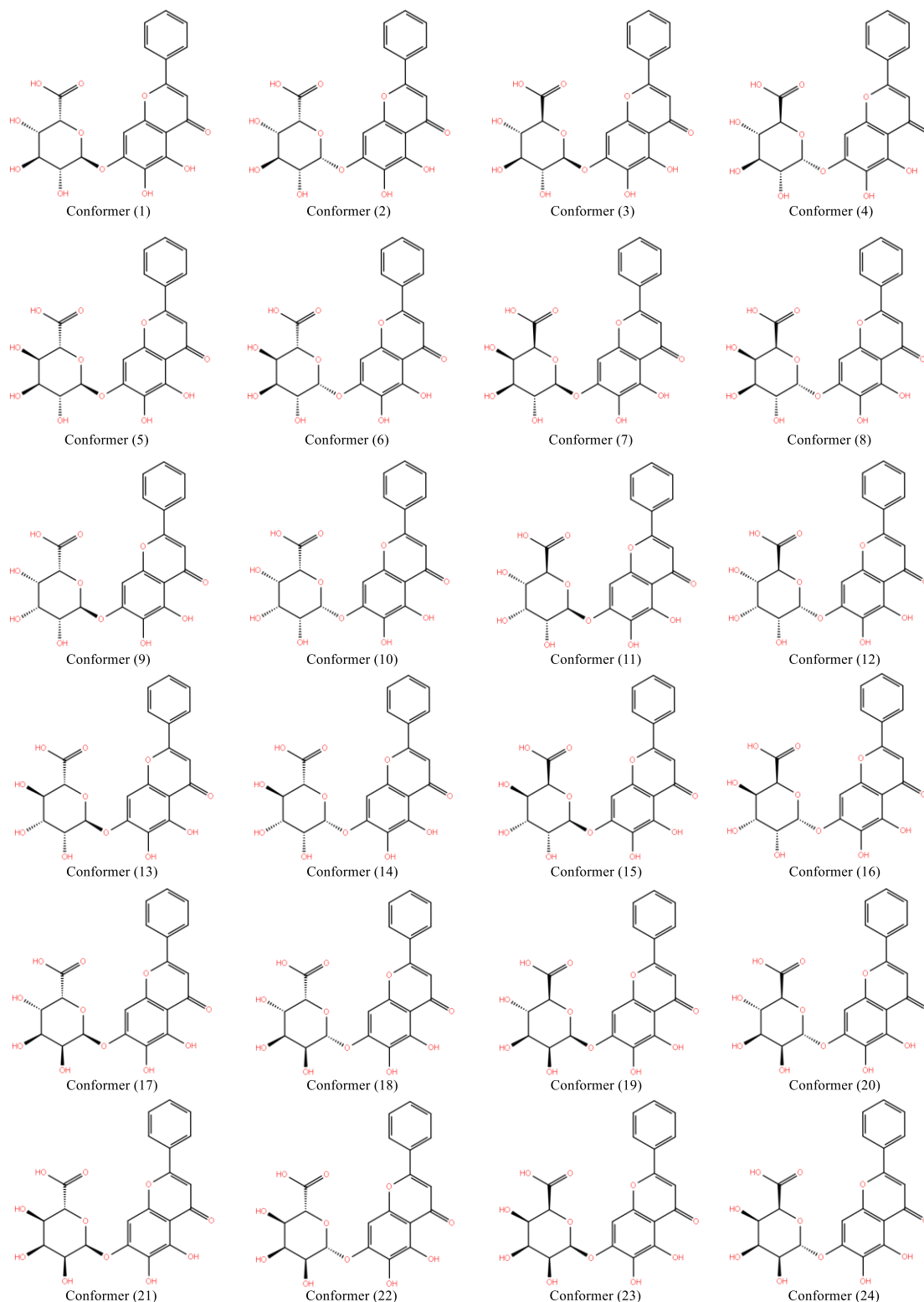
3. Results and Discussion

3.1. Conformer analysis and optimization of baicalin

Baicalin is pre-optimized at UFF method and the conformer analyses are completed at OPLS3e method by using Maestro 11.9 program at neutral (pH=7) conditions. The related conformers belong to baicalin are given in Scheme 1. Additionally, the energies of the related conformers are given in Table 1.

Table 1. The energy of mentioned conformers of baicalin

Conformers	Energy (kcal/mol)	Conformers	Energy (kcal/mol)	Conformers	Energy (kcal/mol)
(1)	41.377	(9)	36.543	(17)	35.815
(2)	36.429	(10)	34.035	(18)	31.702
(3)	37.052	(11)	35.645	(19)	37.124
(4)	36.937	(12)	38.274	(20)	38.962
(5)	36.356	(13)	38.184	(21)	39.386
(6)	39.096	(14)	39.014	(22)	37.461
(7)	32.605	(15)	32.228	(23)	34.571
(8)	33.996	(16)	36.113	(24)	37.788



Schema 1. The most possible 24 conformer structures of baicalin

According to Table 1, the most stable conformer is determined as conformer (15) by using Maestro 11.9 program. The energy values are positive due to the program outputs. In this step, the lowest energy is selected as the most stable one. The optimized

structures in both gas and water phases of the conformer (15) are given in Figure 1.

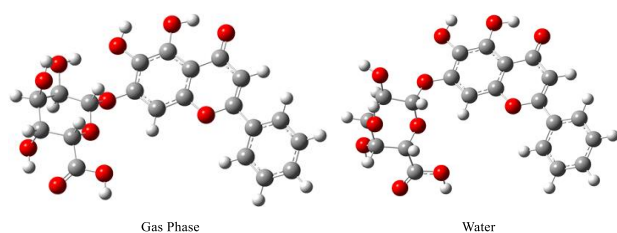


Figure 1. The optimized structures of conformer (15) in gas phase and water.

3.2. Optimized structures of vanadium (iv) complexes at ground state

Oxovanadium (IV) – baicalin complex are optimized at B3LYP/LANL2DZ level in gas phase and water. The optimized structures of it and structural parameters of environment of metal atom are given in Figure 2 and Table 2, respectively.

Table 2. Structural parameters of studied complex in gas phase and water

Assignments	Gas Phase	Water
Bond Lengths (Å)		
V95–O24	2.022	1.979
V95–O25	1.976	1.961
V95–O71	2.022	1.979
V95–O72	1.976	1.961
V95–O96	1.610	1.626
Bond Angles (deg)		
O24–V95–O25	79.5	80.6
O24–V95–O71	152.0	146.1
O24–V95–O72	90.2	89.0
O24–V95–O96	104.0	106.9
O25–V95–O71	90.2	89.0
O25–V95–O72	136.6	143.9
O25–V95–O96	111.7	108.0
O71–V95–O72	79.5	80.6
O71–V95–O96	104.0	106.7
O72–V95–O96	111.7	108.0

According to Table 2, bond lengths between vanadium metal and oxygen atoms in baicalin ligands are calculated in the range of 1.96 – 2.02 Å while the bond length between vanadium and oxo ligand is calculated nearly 1.62 Å. In published papers, the bond lengths between V–O and V–(oxo) have been reported in the range of 1.96 – 2.00 Å and 1.59 – 1.65 Å, respectively [24-26]. According to these reported values, the

calculated results are in agreement with experimental values. From bond angles, it is determined that the geometry of studied complex is distorted square pyramidal.

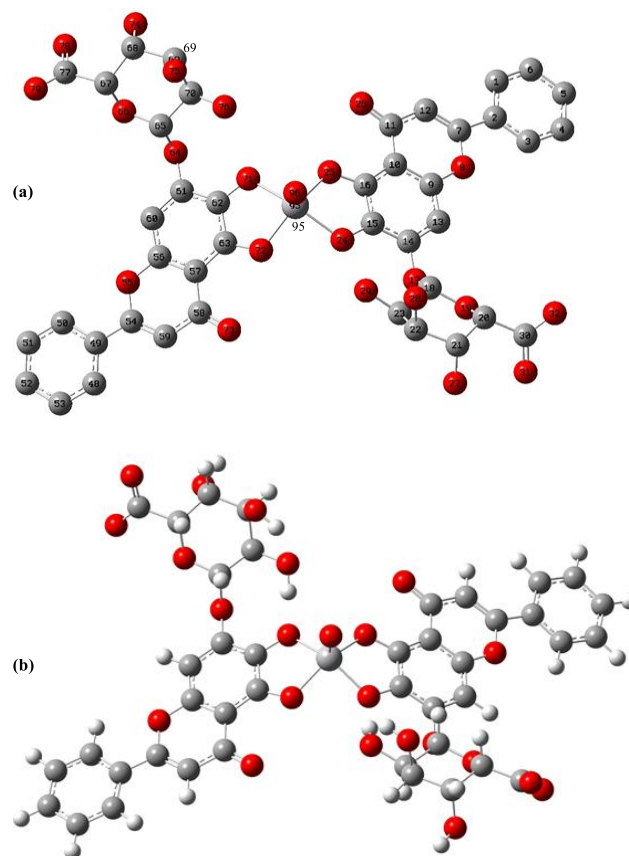


Figure 2. Optimized structure of studied oxo-vanadium(IV) complexes in gas phase (a) and water (b). Hydrogen atoms were omitted for clarity in gas phase structure.

3.3. Analyses of infrared (IR) and NMR spectra

The IR spectrum is important in the determination of some specific and functional groups in structure. This spectral technique is vital in characterization of geometric structure. The IR spectrum of related complex is calculated in gas phase and water. There is no imaginary frequency in simulated IR spectrum. The calculated IR spectrum is analyzed by potential energy distribution (PED) analyses in VEDA 4XX program. The calculated IR spectrum in gas and water phase are represented in Figure 3. Additionally, PED analyses are given in Table 3.

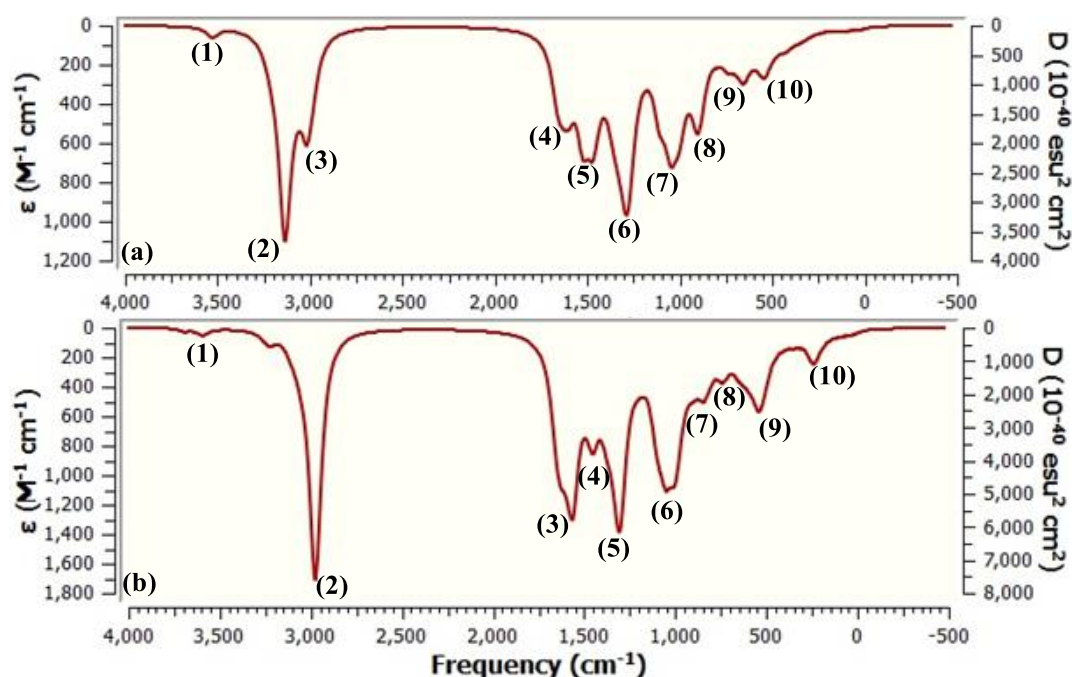


Figure 3. Calculated IR spectrum of studied V(IV) complex in gas phase (a) and water (b).

Table 3. PED analyses of IR spectrum of studied complex in gas phase and water

Assignments	Gas Phase		Water	
	Frequency (cm ⁻¹)	Mode ^a	Frequency (cm ⁻¹)	Mode ^a
1	3528	STRE (OH)	3593	STRE (OH)
2	3136	STRE (OH)	2975	STRE (OH)
3	3017	STRE (OH), STRE (CH)	1588	STRE (C=O), STRE (CC) aromatic ring
4	1629	STRE (CC) aromatic ring	1452	STRE (CC) aromatic ring
5	1523	STRE (C=O), BEND (HOC)	1317	BEND (HCC)
6	1300	BEND (HCO),	1046	STRE (CC)
7	1039	STRE (CO), TORS (HCCC)	842	TORS (HOCC)
8	901	TORS (HOCC)	755	BEND (OCO)
9	660	TORS (HOCC)	550	STRE (VO)
10	545	STRE (VO)	242	TORS (HOCC), TORS (COCC)

^a Vibration Modes: STRE: Stretching; BEND: Bending; TORS: Torsion

Nuclear magnetic resonance (NMR) spectrum is significant another technique in the characterization of structures. The ¹H- and ¹³C-NMR spectrum of studied complex are calculated in gas phase and water. Tetramethylsilane (TMS) is selected as a reference

substance. Chemical shift values of hydrogen and carbon atoms are recalculated and given in Table 4 and 5, respectively.

Table 4. Calculated carbon chemical shift values (ppm) of V(IV) complex

Assignments	Gas Phase	Water	Assignments	Gas Phase	Water
C1	126.0	128.9	C48	126.0	128.9
C2	144.1	134.5	C49	144.1	134.5
C3	132.4	131.0	C50	132.4	131.0
C4	130.2	133.4	C51	130.2	133.4
C5	124.4	135.6	C52	124.4	135.6
C6	127.5	133.0	C53	127.5	133.0
C7	156.7	167.7	C54	156.7	167.7

C9	153.7	166.7	C56	153.7	166.7
C10	116.1	117.1	C57	116.1	117.1
C11	183.1	188.5	C58	183.1	188.5
C12	115.9	114.9	C59	115.9	114.9
C13	104.5	106.8	C60	104.5	106.8
C14	152.2	152.1	C61	152.2	152.1
C15	161.4	154.2	C62	161.4	154.2
C16	173.2	166.7	C63	173.2	166.7
C18	126.5	124.3	C65	126.5	124.3
C20	89.0	89.0	C67	89.0	89.0
C21	78.4	79.9	C68	78.4	79.9
C22	82.2	80.9	C69	82.2	80.9
C23	75.9	76.8	C70	75.9	76.8
C30	191.7	191.0	C77	191.7	191.0

Table 5. Calculated hydrogen chemical shift values (ppm) of studied complex

Assignments	Gas Phase	Water	Assignments	Gas Phase	Water
C1H	8.0	8.4	C48H	8.0	8.4
C3H	9.1	9.0	C50H	9.1	9.0
C4H	7.5	8.3	C51H	7.5	8.3
C5H	7.1	8.3	C52H	7.1	8.3
C6H	7.3	8.2	C53H	7.3	8.2
C12H	6.0	7.0	C59H	6.0	7.0
C13H	7.1	7.5	C60H	7.1	7.5
C18H	4.6	5.2	C65H	4.6	5.2
C20H	3.9	4.7	C67H	3.9	4.7
C21H	3.4	4.4	C68H	3.4	4.4
C22H	3.9	4.1	C69H	3.9	4.1
C23H	4.2	4.2	C70H	4.2	4.2
O27H	9.1	9.3	O74H	9.1	9.3
O28H	4.1	3.8	O75H	4.1	3.8
O29H	8.6	9.4	O76H	8.6	9.4

According to Table 4, chemical shift values of aromatic and aliphatic carbon atoms in gas phase are calculated in the range of 104 – 173 ppm and 76 – 127 ppm, respectively. As for the water, chemical shift values of aromatic carbon atoms are calculated among 107 – 167 ppm while 76 – 124 ppm for aliphatic carbon atoms. Chemical shift values hydrogen atoms in cyclohexane ring are calculated in the range of 3.9 – 4.6 ppm; 4.1 – 9.1 ppm for hydrogen on oxygen atoms and 6.0 – 9.1 ppm in aromatic ring. As for the water phase, chemical shifts are calculated between 4.1 – 5.2 ppm for on cyclohexane; 3.8 – 9.4 ppm for on oxygen atoms and 7.0 – 9.0 ppm for on aromatic rings.

3.5. Molecular orbital energy diagram (moed), molecular electrostatic potential (mep) map, contour plots of frontier molecular orbital, density of state (dos) spectrum

Some diagrams which are MOED, MEP map, contour plots and DOS spectrum are so important in the determination of electronic properties. MOEDs of baicalin and its vanadium(IV) complexes in water are represented in Figure 4. Additionally, contour plots of frontier molecular orbitals, HOMO and LUMO, are represented in Figure 4, too.

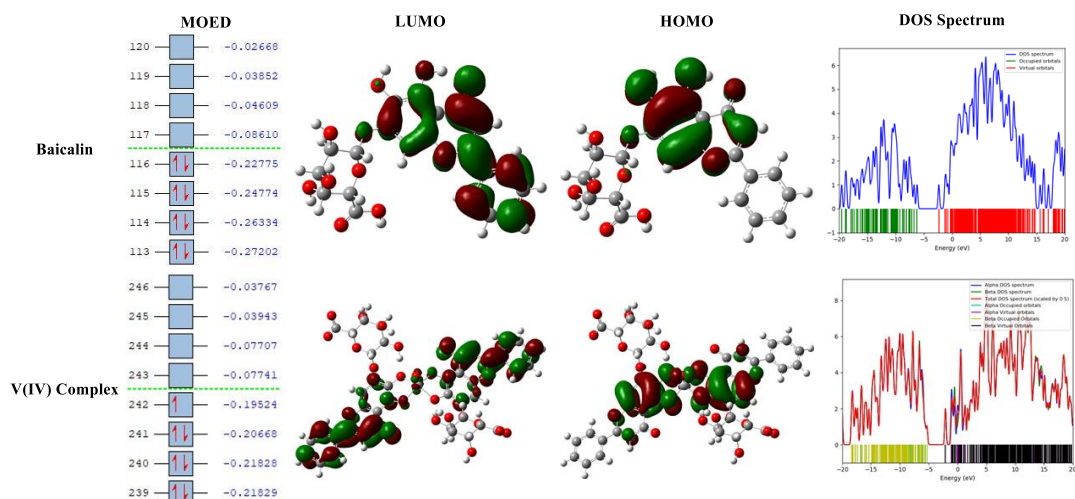


Figure 4. MOED and contour plots of baicalin and its vanadium(IV) complex.

The whole electrons are paired in baicalin while there is a single occupied molecular orbital (SOMO) in V(IV) complex. In this stage, SOMO in studied complex is accepted as the HOMO in the determination of electronic properties. Electrons in HOMO of baicalin are delocalized on the middle of the structure while SOMO electron is delocalized on the benzene rings of the ligands. These regions can be proposed as the active regions in any interactions. As for the LUMOs, if studied compounds get electrons, these electrons will be delocalized on the benzene rings. DOS spectrum is plotted for each compound. The energy range is determined between $-20 - 20$ eV. According to DOS spectrum, the energy gap values are similar to each other. However, peak intensity of both occupied and virtual molecular orbitals in studied complex is more than that of baicalin. It implies that there are more molecular orbitals in this range in V(IV) complex. This result shows that there is more opportunity in electron transition in vanadium complex. It is expected that chemical reactivity of V(IV) complex is more than that of the other one.

Another significant tool is molecular electrostatic potential (MEP) map. This diagram shows the active regions on molecular surface via calculation of electrostatic potential (ESP) charges. These charges where on molecular surface so important in the determination of coulomb interaction energies. The calculated MEP maps of baicalin and its vanadium complex are represented in Figure 5.

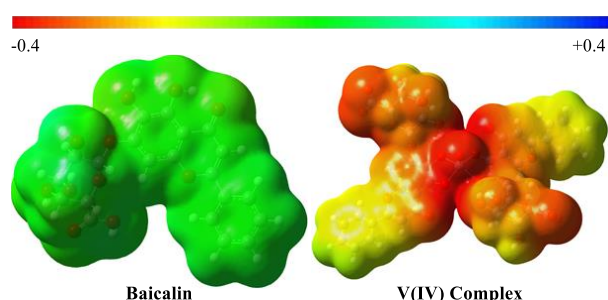


Figure 5. Molecular electrostatic potential maps of baicalin and its V(IV) complex.

Red color implies the electro-rich site while dark blue color implies the electro-poor sites. Red regions are appropriate for nucleophilic attack while dark blue region is appropriate for electrophilic attack. According to Figure 5, red and yellow colors are dominant in studied metal complex while the just green color is dominant in baicalin. According to MEP maps, it is expected that the chemical and biological reactivity of V(IV) complex is more than that of baicalin. Because electro-rich regions in studied complex is more than that of baicalin.

3.6. Determination of antioxidant and biological reactivity

Antioxidant and biological properties of compounds can be proposed by some quantum chemical descriptors (QCDs) [27-30]. The related quantum chemical descriptors are calculated by using Eq. (1) – (11). In these calculations, Koopmans theorem is taken into account. The calculated QCDs are given in Table 6. Additionally, cisplatin is optimized and same quantum chemical descriptors are calculated for cisplatin. These results are given in Table 6, too.

Table 6. Calculated quantum chemical descriptors in water

In gas phase						
	E_{HOMO}^1	E_{LUMO}^1	E_{GAP}^1	η^1	σ^2	S^2
Baicalin	-6.369	-2.512	3.857	1.928	0.519	0.259
V(IV) Complex	2.858	4.440	1.582	0.791	1.264	0.632
cis-Platin	-6.271	-1.900	4.371	2.185	0.458	0.229
	χ^1	CP ¹	ω^1	N ²	ΔN_{max}	
Baicalin	4.441	-4.441	5.113	0.196	2.303	
V(IV) Complex	3.649	-3.649	8.415	0.119	4.612	
cis-Platin	4.086	-4.086	3.819	0.262	1.870	
In water						
	E_{HOMO}^1	E_{LUMO}^1	E_{GAP}^1	η^1	σ^2	S^2
Baicalin	-6.197	-2.343	3.855	1.927	0.519	0.259
V(IV) Complex	-5.313	-2.106	3.206	1.603	0.624	0.312
cis-Platin	-6.507	-1.805	4.702	2.351	0.425	0.213
	χ^1	CP ¹	ω^1	N ²	ΔN_{max}	
Baicalin	4.270	-4.270	4.731	0.211	2.216	
V(IV) Complex	3.710	-3.710	4.292	0.233	2.314	
cis-Platin	4.156	-4.156	3.673	0.272	1.768	

¹in eV, ²in eV⁻¹,

In many published papers, the effects of QCDs on biological and antioxidant properties have been discussed, used and reported [21,26]. The reactivity ranking of studied compounds are given as following,

According to E_{HOMO}	V(IV) Complex > cis-Platin > Baicalin	Gas Phase
	V(IV) Complex > Baicalin > cis-Platin	Water
According to E_{LUMO}	Baicalin > cis-Platin > V(IV) Complex	Gas Phase
	cis-Platin > V(IV) Complex > Baicalin	Water
According to E_{GAP}	V(IV) Complex > Baicalin > cis-Platin	Gas Phase
	V(IV) Complex > Baicalin > cis-Platin	Water
According to η	V(IV) Complex > Baicalin > cis-Platin	Gas Phase
	V(IV) Complex > Baicalin > cis-Platin	Water
According to σ	V(IV) Complex > Baicalin > cis-Platin	Gas Phase
	V(IV) Complex > Baicalin > cis-Platin	Water
According to S	V(IV) Complex > Baicalin > cis-Platin	Gas Phase
	V(IV) Complex > Baicalin > cis-Platin	Water
According to χ	V(IV) Complex > cis-Platin > Baicalin	Gas Phase
	V(IV) Complex > cis-Platin > Baicalin	Water
According to CP	V(IV) Complex > cis-Platin > Baicalin	Gas Phase
	V(IV) Complex > cis-Platin > Baicalin	Water
According to ω	cis-Platin > Baicalin > V(IV) Complex	Gas Phase
	cis-Platin > V(IV) Complex > Baicalin	Water
According to N	cis-Platin > Baicalin > V(IV) Complex	Gas Phase

According to ΔN_{\max}	cis-Platin > V(IV) Complex > Baicalin	Water
	V(IV) Complex > Baicalin > cis-Platin	Gas Phase
	V(IV) Complex > Baicalin > cis-Platin	Water

According to above rankings, it can be said that biological activities of studied compounds are mainly more than that of cis-platin. Therefore, baicalin and its vanadium(IV) complex can be used instead of cis-platin. The further researches should be performed to learn more precise result. As for the antioxidant activity, baicalin which is member of flavonoid compounds is known as antioxidant molecule. However, the effect of complexing on antioxidant properties is almost never investigated. The above rankings show that the antioxidant activity of baicalin is increased with the complexing of it. Therefore, the complexing effect on antioxidant properties should be more investigated both experimental and computational techniques.

4. Conclusions

In this study, baicalin and its vanadium complex were investigated in detail. The conformer analyses of baicalin were performed at neutral condition by using Maestro 11.9 program. The most stable one is determined and optimized at B3LYP/6-31G+G(d) level in gas phase and water. The optimized structure of baicalin – vanadium (IV) complex was obtained at B3LYP/LANL2DZ level. Spectral (IR and NMR) analyses were performed in detail. Molecular orbital energy diagram, contour plots of frontier molecular orbitals, density of state spectrum and molecular electrostatic potential map were calculated and examined in detail. Especially, active sites on molecular surface and activity of compounds were proposed via these analyses. Some quantum chemical descriptors/parameters were calculated. The obtained results were compared with cis-platin result. It is found that, vanadium complex has the most active compound. The antioxidant activity of baicalin is increased with the complexing of baicalin.

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Conflicts of interest

The authors state that did not have conflict of interests

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