Hindawi
Journal of Chemistry
Volume 2018, Article ID 1958047, 10 pages
https://doi.org/10.1155/2018/1958047

Research Article

The Substitution Effect on Reaction Enthalpies of Antioxidant Mechanisms of Juglone and Its Derivatives in Gas and Solution Phase: DFT Study

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Received 21 October 2017; Revised 27 December 2017; Accepted 9 January 2018; Published 16 April 2018

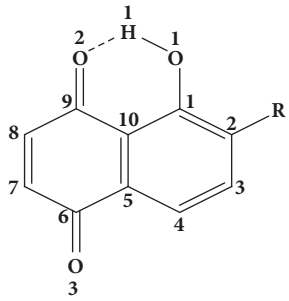
Academic Editor: Dario Pasini

We examined the structure-reaction enthalpies-antioxidant activity relationship of the molecule library built around juglone and its derivatives at B3LYP/6-31+G(d,p) level. Three major antioxidant mechanisms (hydrogen atom transfer (HAT), single electron transfer-proton transfer (SET-PT), and sequential proton loss electron transfer (SPLET)) have been investigated in five solvents and in the gas phase. The delocalization of the unpaired electrons in the radicals or cation radicals has been explored by the natural bond orbital analysis and the interpretation of spin density maps. The results obtained have proven that the HAT mechanism is the thermodynamically preferred mechanism in the gas phase. But, in the solution phase, the SPLET mechanism has been shown to be more predominant than HAT. The reactivity order of compounds towards selected reactive oxygen species has also been studied.

1. Introduction

5-Hydroxy-1,4-naphthoquinone, ordinarily called juglone, has been isolated from many plants in the walnut family [1, 2]. Investigations demonstrated that the principal chemical responsible for the walnut allelopathy is juglone. Walnut has then been reported to be toxic to both herbaceous and woody plants [3, 4]. Hydrojuglone is found in leaves, stems, fruit hulls, inner barks, and roots. When exposed to air or soil compounds, hydrojuglone is oxidized into the allelochemical juglone, which is highly toxic [5]. Rain washes juglone from the leaves and carries it into the soil. Thus, neighbouring plants of the walnut are affected by absorbing juglone through their roots [3, 4]. To the best of our knowledge, the literature does not contain any reports of growth-inhibiting effect of juglone. The pretreatment of seeds of plants (tomato and wheat) by the combination of gibberellic acid (GA3) and kinetin (KIN) has been shown to effectively overcome the effects of juglone stress on neighbouring plants of the walnut [6].

Walnut leaves have widely been used in folk medicine for treatment because of many medicinal properties (antidiarrheic, antihelminthic, and depurative) and biological activities (hypotensive, antimicrobial, anticancer, and sedative activities) [7, 8]. It is reported that walnut is one of the most enriched dietary plants in the antioxidants, ranked at the top of the scale just after dog rose and before pomegranate [9]. These higher antioxidant properties have been proven by experimental analysis [10]. This explained why walnut had the greatest antioxidant activity among commonly analyzed foods and drinks in Turkey [11]. The interest in juglone has increased because of several further studies that revealed that juglone has cytotoxic and genotoxic effects against cultured melanoma tumor cell [12]. In addition, juglone has been shown to be a potential anticancer drug due to its strong inhibitor properties of peptidyl-prolyl isomerase (PIN1)



R	Name
H	J1
NMe_2	J2
NHMe	J3
NH_2	J4
OH	J5
OMe	J6
t-bu	J7
C_2H_5	J8
F	J9
Cl	J10
Br	J11
Phen	J12
C_2H_3	J13
CHO	J14
COOH	J15
CN	J16
NO_2	J17
CF_3	J18

Figure 1: Numbering system used to designate specific atom of juglone and its derivatives followed by specification of electron donating or withdrawing substituent used.

(a therapeutic target for anticancer research) with anti-inflammatory and antifibrotic properties [13]. As antioxidant, juglone appears to play an important role in the pathogenesis of many neurodegenerative processes (Alzheimer's and Parkinson's diseases) [14]. Moreover, the literature reports the structure-activity relationship of the multitarget anti-Alzheimer compounds designed by combining a tacrine and a juglone [15]. Besides the potent inhibitory activity, this ligand displays interesting abilities to block amyloid-β aggregation and antioxidant proprieties in vitro [16]. This effectively protects neurons from the oxidative stress damage occurring in Alzheimer's disease. This explains the motivation to investigate the structure-activity relationships of juglone and its derivatives using experimental [17] and theoretical [18] tools. As shown in Figure 1, juglone and its derivatives possess an intramolecular hydrogen bond between hydroxyl and keto groups. The importance of these intramolecular hydrogen bonds has been shown in phenolic constituents [19–22]. The calculations of antioxidant activity of juglone and its derivatives have been earlier performed only on two descriptors: hydrogen atom transfer (HAT) and ionization potential (IP) by Jin [18].

In general, three different mechanisms are involved in the description of the antioxidant action [23]: hydrogen atom transfer (HAT) mechanism (see (1)), electron transfer-proton transfer (ET-PT) mechanism (see (2)-(3)), and sequential proton loss-proton transfer (SPLET) mechanism (see (4)-(5)):

$$RX - H \longrightarrow RX^{\bullet} + H^{\bullet} \quad (1)$$

$$RX - H \longrightarrow RX - H^{\bullet+} + e^{-} \quad (2)$$

$$RX - H^{\bullet+} \longrightarrow RX^{\bullet} + H^{+} \quad (3)$$

$$RX - H \longrightarrow RX^{-} + H^{+} \quad (4)$$

$$RX^{-} \longrightarrow RX^{\bullet} + e^{-} \quad (5)$$

In the present work, we have performed extensive density functional calculations of thermodynamic energies of reactions (1)–(5). The detailed comparison between the reaction enthalpies of these different antioxidant mechanisms of the juglone and its derivatives and those of the classical antioxidants has been done. The survey of the literature indicates that such an analysis has not been done previously for juglone and its derivatives.

2. Computational Details

All the calculations were performed using the Gaussian 09 software package [24]. The geometry of molecular structures (neutral, radical, ionic, and cationic structures) was optimized using DFT method at B3LYP/6-31+G(d,p) level. The optimized structures were confirmed to be real minima by the frequency calculations (no imaginary frequency). The natural bond orbital (NBO) analysis of charge and the spin density of radicals of the molecular system studied were computed at B3LYP/6-31+G(d,p) level of the theory. Solvent contribution at 298.15 K to reaction enthalpies was computed employing integral equation formalism of the polarized continuum model IEF-PCM method [25].

The scavenging activity of juglone and its derivatives is related to O-H bond dissociation enthalpy (BDE), ionization potential (IP), proton dissociation enthalpy (PDE), proton affinity (PA), and electron transfer enthalpy (ETE). These five thermodynamic parameters are, respectively, defined according to the following relations:

$$\mathrm{BDE} = H\left(H^{\bullet}\right) + H\left(R^{\bullet}\right) - H\left(RX - H\right) \quad (6)$$

$$\mathrm{IP} = H\left(RX - H^{\bullet+}\right) + H\left(e^{-}\right) - H\left(RX - H\right) \quad (7)$$

$$\mathrm{PDE} = H\left(RX^{\bullet}\right) + H\left(H^{+}\right) - H\left(RX - H^{\bullet+}\right) \quad (8)$$

$$\mathrm{PA} = H\left(RX^{-}\right) + H\left(H^{+}\right) - H\left(RX - H\right) \quad (9)$$

$$\mathrm{ETE} = H\left(RX^{\bullet}\right) + H\left(e^{-}\right) - H\left(RX^{-}\right) \quad (10)$$

The calculated gas enthalpies of a proton ($H(H^+)$) and an electron ($H(e^-)$) are, respectively, 6.197 kJ/mol and 3.145 kJ/mol [26]. The reaction free energies of reactions (1)–(5), ordinary denoted BDFE (bond dissociation free energy), IPFE (ionization potential free energy), PDFE (proton dissociation free energy), PAFE (proton affinity free energy), and ETFE (electron transfer free energy) are, respectively, calculated according to relations (6)–(10). In the same vein, the calculated gas free energies of a proton ($H(H^+)$) and an electron ($H(e^-)$), are respectively, −26.28 kJ/mol [27] and −3.72 kJ/mol [28]. Proton and electron solvation enthalpies and free energies were taken from the literature [29, 30]. The hydrogen atom solvation reaction enthalpies and free energies were also taken from earlier researches [30].

3. Results and Discussion

3.1. General Considerations. Seventeen derivatives **(J2–18)** with electron donating or withdrawing substituents on the

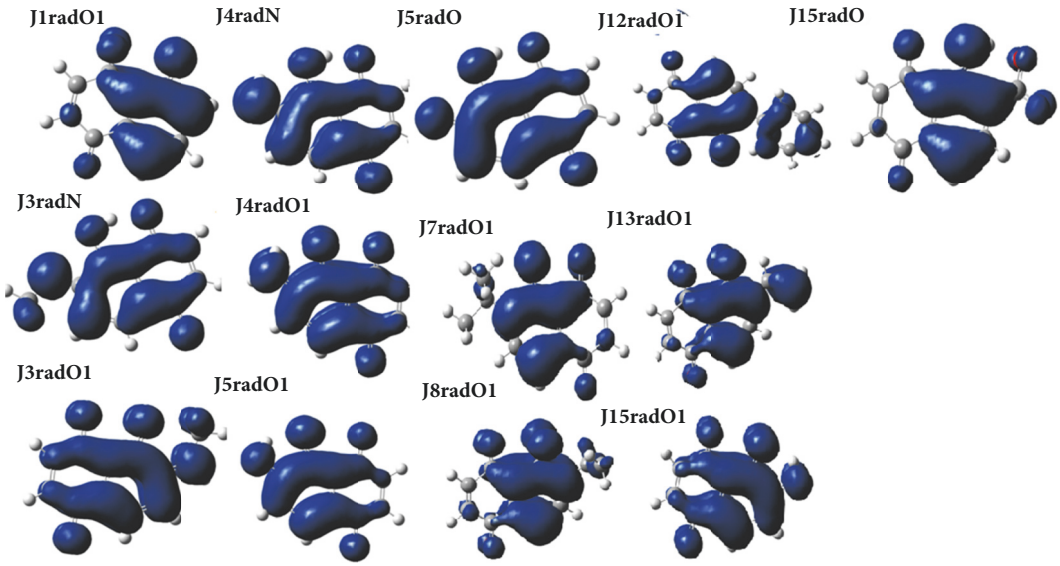


Figure 2: Plots of spin density for various hydrogen atom-abstracted radicals of juglone and selected derivatives.

phenyl ring of 5-hydroxy-1,4-naphthoquinone as shown in Figure 1 have been designed in order to investigate the substituent effects. The optimized structures of neutral molecules obtained possess 5-hydroxy-1,4-naphthoquinone moiety that is completely planar. These optimized structures are characterized by the formation of hydrogen bond between hydroxy-H and oxygen atom of carbonyl group. From Table 1S, it can be seen that the O_1-$H_1 \cdots O_2$ bond's length ranges from 1.621 Å to 1.709 Å in gas phase. We also investigated the formation of other hydrogen bonds between oxygen atom of carbonyl group and hydrogen atom of the substituent (H-X: X = O, N) using the cut-off definition of X-H$\cdots O_2$ hydrogen bond (H$\cdots O_2$ < 3.0 Å and X-H$\cdots O_2$ angles > 110°) [31]. Our B3LYP results then indicated that another hydrogen bond can only be obtained for **J5**. Conversely, we registered 104.6° **(J3)** and 101.3° **(J4)** for X-H$\cdots O_2$ angle (X = N). For **J17**, two conformations are found, **J17A** and **J17B**, corresponding, respectively, to the formation of O_1-$H_1 \cdots O_2$ and O_1-$H_1 \cdots$O (O: oxygen atom of NO_2 substituent). Structure **J17A** (E_T = −814.87830035 hartree) has been shown to be slightly more stable than **J17B** (E_T = −814.87466923 hartree) in gas phase. The minor total energy difference (2.3 kJ/mol) explained why we did not take into account the configuration **J17** in this paper. In the whole, the substitution on the phenyl ring of 5-hydroxy-1,4-naphthoquinone leads to the sensitive shortening of the O_1-$H_1 \cdots O_2$ bond distances. This fact is in accordance with the elucidation on the enhancement of the interaction strength of the hydrogen bond by the introduction of the electron-donation or electron-withdrawing group in **J1** [18]. The difference average is about 0.038 Å in gas phase. The comparison between O_1-H_1 bond distances of **J2–18** and those in **J1** indicated that the introduction of substituent groups provokes an elongation of the O_1-H_1 distances. Although solvation of these molecules does not give any additional information on O_1-$H_1 \cdots O_2$ interaction, it augments this elongation. Because of the absence of experimental geometrical parameters of the molecular library analyzed, a verification of the optimized structures cannot be done. Nevertheless, we have compared experimental gas phase FT-IR frequencies of some functional group of juglone to theoretical values [32, 33] (Table 2S and Figure 1S). For juglone, we have obtained the following linear dependence between experimental frequencies (υ_{Exp}) and theoretical frequencies (υ_{Theo}):

$$\upsilon_{Exp} = 0.8908\upsilon_{Theo} + 238.89. \quad (11)$$

The correlation coefficient (R^2 = 0.998) obtained confirms the suitability of the theoretical method employed for geometry optimization.

3.2. HAT Mechanism. In order to clarify the geometries and the energetic aspects of different radical species obtained, we adopted the notation **Jn-RaX** (n = 1–18) for radical species in order to denote where the abstraction of an H atom from X-H bond occurs. The OH BDE values were calculated in various media (for each substituent) and reported in Table 1 and Table 3S. The spin density plots for analyzed radicals are presented in Figure 2. The diminution of BDE values compared to that of **J1** observed for electron donating substituent is in good agreement with previous researches [34]. Lower BDE values are obtained for amino substituents **(J2–4)**. The difference between BDE values of **J1** and those of **J2–4** ranges from 25 to 47 kJ/mol. In the case of **J3**, the abstraction of hydrogen atom leads to the formation of **J3radO1** and **J3ranN**. The latter is slightly more stable than the former by 2,04 kJ/mol. The BDE values of 392 and 380 kJ/mol, respectively obtained, for **J3radO1** and **J3radN** provide an indication that H atom removal on an amino group is preferred to H atom removal on a 5-hydroxy-1,4-naphthoquinone moiety. The spin distribution shows an

Table 1: Thermodynamic energies in kJ/mol: bond dissociation energies, ionization potential, proton dissociation energies, proton affinities, and electron transfer energies in gas phase and in water at B3LYP/6-31+G(d,p) level.

Molecules		BDE (kJ/mol)		IP (kJ/mol)		PDE (kJ/mol)		PA (kJ/mol)		ETE (kJ/mol)	
Denotations	Substituents	Gas	Water	Gas	Water	Gas	Water	Gas	Water	Gas	Water
J1	H	417	400	834	538	899	41	1422	192	312	386
J2	NMe_2	370	344	680	422	987	100	1480	194	266	328
J3	NHMe	392	343	721	439	988	82	1448	219	261	302
		380[a]	377[a]			986[a]	108[a]	1439[a]	229[a]	263[a]	330[a]
J4	NH_2	372	350	743	452	946	76	1413	184	276	343
		372[a]	377[a]			946[a]	103[a]	1415[a]	221[a]	277[a]	334[a]
J5	OH	380	367	805	510	892	36	1377	163	319	382
		359[b]	348[b]			871[b]	16[b]	1361[b]	151[b]	314[b]	374[b]
J6	OMe	397	387	773	495	940	71	1423	188	297	372
J7	t-bu	409	394	798	519	928	53	1417	200	308	375
J8	C_2H_5	410	394	806	521	921	50	1423	196	303	397
J9	F	410	393	845	547	881	24	1398	174	434	398
J10	Cl	412	396	834	542	888	31	1395	175	336	399
J11	Br	412	397	827	539	902	35	1394	176	335	376
J12	Phen	405	390	763	500	959	68	1408	192	314	375
J13	C_2H_3	401	386	786	501	934	63	1408	189	309	405
J14	CHO	420	407	863	565	873	19	1403	179	333	448
J15	COOH	406	398	883	575	840	1	1322	127	401	423
									129[c]		
J16	CN	**472**	477	874	571	864	13	1366	161	371	432
J17	NO_2	421	406	884	581	861	7	1358	155	387	414
J18	CF_3	428	410	867	567	870	18	1381	171	359	372

[a]Relative to N-H thermodynamic parameter values. [b]O-H thermodynamic parameter values. [c]Related to H-OOC thermochemical parameter values.

almost identical involvement of atoms of 5-hydroxy-1,4-naphthoquinone moiety and those of the amino substituent for both radicals. The $n_{O_2} \rightarrow \sigma^*_{O_1\text{-}H_1}$ orbital interaction ($E^{(2)}$ = 2.73 kcal/mol) may be the plausible explanation of the higher stability of **J3radN**. In contrast, the energy difference of 0.55 kJ/mol between the **J4radO1** and **J4radN** radical species in favor of the former suggested that despite the identical BDE values obtained (372 kJ/mol) for both corresponding radical species, the H atom removal on 5-hydroxy-1,4-naphthoquinone moiety is almost the most preferred. This former is stabilized by the N-H$\cdots$O$_2$ intramolecular hydrogen bond with the second-order perturbation energy of 0.35 kJ/mol. The presence of two intramolecular hydrogen bonds N-H$\cdots$O$_1$ ($E^{(2)}$ = 0.62 kJ/mol) and O$_1$-H$_1\cdots$O$_2$ ($E^{(2)}$ = 2.81 kcal/mol) in **J4radN** radical does not affect the N center. An increase of the total energy difference observed in the same sense with the increase of the dielectric constant of the solvent (3.160 (benzene), 3.280 (toluene), 6.842 (methanol), 6.875 (acetonitrile), and 7.075 kJ/mol (water)) clearly proved that this H atom abstraction site is more preferred in solution phase. Contrary to amino substituents, the difference in OH BDE values (21 kJ/mol) found for the **J5radO1** and **J5radO** radical species revealed that the H abstraction on 5-hydroxy-1,4-naphthoquinone moiety is less favored for OH group **(J5)**. The **J5radO** radical displays $n_O \rightarrow \sigma^*_{C_2\text{-}C_3}$ ($E'^{(2)}$ = 8.48 kcal/mol), $n_O \rightarrow \sigma^*_{Cl\text{-}C_2}$ ($E'^{(2)}$ = 11.01 kJ/mol), and O$_1$-H$_1\cdots$O$_2$ intramolecular hydrogen bond with second-order perturbation energy of 2.64 kJ/mol, whereas **J5radO1** radical centre is stabilized by $n_{O_1} \rightarrow \sigma^*_{C_1\text{-}C_{10}}$ ($E^{(2)}$ = 0.72 kJmol), $n_{O_1} \rightarrow \sigma^*_{C_1\text{-}C_2}$ ($E^{(2)}$ = 8.05 kJ/mol), and O-H$\cdots$O$_1$ hydrogen bond ($E^{(2)}$ = 0.63 kJ/mol). For **J5** molecule in gas phase, the O$_1$-H$_1$ BDE difference between the value calculated from monodeprotonated form (anion) and that obtained from neutral form equal to 49 kJ/mol demonstrates the fact that the deprotonation of the parent molecule severely alters the BDE values. This fact is in accordance with the previous investigation of the impact of the deprotonation of sixteen flavonoids on the OH BDE values carried by Klein et al. [35]. The substitution of OH group by the OMe **(J6)** leads to a 17 kJ/mol increase in the O$_1$-H$_1$ BDE. Similar results have been observed in the case of hydroxyl daidzein and glycitein by Lengyel et al. [36]. The substitution of hydrogen atom **(J1)** with ethyl group **(J8)** or with t-butyl group **(J7)** induces a slight decrease in BDE (8 kJ/mol and 7 kJ/mol, resp., for **J8** and **J7**). The values agree with earlier researches [37] that demonstrated that the influence of the side chain on the antioxidant is more pronounced when the number of carbon atoms of the alkyl substituent exceeds five. But it is difficult to expand such a comparison between linear and branched substituents in *ortho* position due to the steric

effects. The difference that is about 1 kJ/mol may therefore be attributed to the error bars of the method used. These two substituents (R = C_2H_5 and t-but) do not contribute to the spin density distribution (Figure 2). Close result obtained for F **(J9)**, Cl **(J10)**, and Br **(J11)** substituents revealed that the variation of the influence of the electronegativity of halogen substituent has a minor effect on the BDE values. Besides the electronegativity, an increase of the C-halogen bond length was also observed when the atomic radius of halogen atom augmented regardless of the media: in water, the C-halogen bond lengths were 1.352 Å (C-F), 1.746 Å (C-Cl), and 1.846 Å (C-Br). In contrast, a sensitive decrease of BDE values is obtained for the unsaturated double bond ($CH{=}CH_2$ **(J13)** and C_6H_5 **(J12)**) substituents that extend the system conjugation. Figure 2 clearly indicates that spin density distribution for the radicals generated from **J12-13** involves all atoms of a ring and those of the substituents around the substitution site. The removal of a hydrogen atom on the **J15** molecule gives two radical species: **J15radO1** and **J15radO**. The respective values of BDE obtained, 406 and 472 kJ/mol, expose the easier removal of the H_1 hydrogen atom on 5-hydroxy-1,4-naphthoquinone moiety. The O-H_1 BDE of structure with COOH **(J15)** was smaller than BDE value of **J1**, despite the electron-withdrawing effect. The BDE difference (10 kJ/mol) displays the importance of the presence of $O_1 \cdots$H-O intramolecular hydrogen bond to the stability of the radical. This fact is in agreement with prior researches [38–40]. For other withdrawing substituents, augmentation of O-H_1 BDE ranging from 3 to 11 kJ/mol compared to that of **J1** molecule is obtained. Figure 3 showed that the solvation of molecules provokes a diminution of BDE values with the exception of **J15** in methanol and acetonitrile. The BDE difference averages obtained in various media are 7.14 (benzene), 7.33 (toluene), 14.28 (methanol), 14.71 (acetonitrile), and 15.21 kJ/mol (water). This confirms the fact that the higher polarity of the solvent, the easier the HAT mechanism [19]. Fifen et al. [20] explained through the analysis of spin density distribution of polyphenolic deoxybenzoins in solvents that the reduction of BDE in polar media is related to the greater stabilization of the corresponding radical species in polar solvents. The BDE values (Figure 3) confirm that abstraction of the hydrogen atom is easier in polar media. In the whole, one can also observe from Table 4S that the HAT mechanism is endergonic.

To provide more insight into the antioxidant properties, we analyzed the capacities of **J1–18** as a quencher of radicals ($R' = {}^{\bullet}OR_i$, ${}^{\bullet}OOR_i$ (i = 1 (R = H), 2 (R = CH_3), 3 (R = CCl_3), and 4 (R = $CH_2CH{=}CH_2$)), and ${}^{\bullet}OO^{-}$) through a hydrogen atom transfer:

$$RX - H + R'^{\bullet} \longrightarrow RX^{\bullet} + R'H \quad (12)$$

The reaction free energies values (ΔG) for (O1-H1) HAT (12) calculated at 298.15 K in gas phase are reported in Table 5S. It can be observed that the HAT mechanism towards OR_i radicals is exergonic except for reactions towards OR_3 (**J14** (ΔG = 0), **J15** (ΔG = 531 kJ/mol), **J17** (ΔG = 11 kJ/mol), and **J18** (ΔG = 3 kJ/mol)) and that towards OR_4 (**J15** (ΔG = 511 kJ/mol) and **J18** (ΔG = 1 kJ/mol)) and that towards OR_2

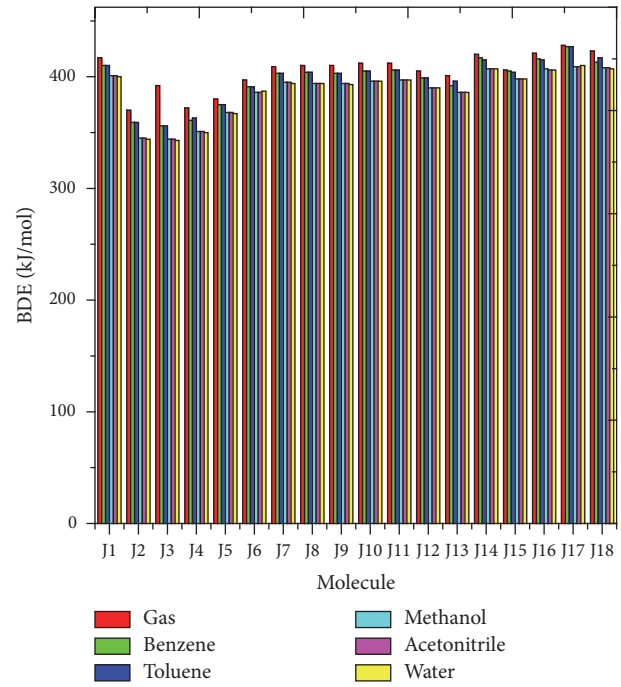


Figure 3: Bond dissociation energies of Jn (in kJ/mol) at B3LYP/6-31+G(d,p) level in various media.

(**J18** (ΔG = 38 kJ/mol)). In addition, it emerges that the Gibb free energy values are considerably lower towards hydroxyl radicals (ΔG_{OH} from −129 to −19 kJ/mol). This finding supports the higher reactivity of ${}^{\bullet}OH$ [40, 41]. However, the HAT mechanism is endergonic towards all other radicals (except for the ${}^{\bullet}OO^{-}$ scavenging activity of the analyzed molecules **(J1–18)** that is less thermodynamically preferred). The free energy value was in the range of 104–214 kJ/mol towards ${}^{\bullet}OO^{-}$ radical and the range of −1–78 kJ/mol towards ${}^{\bullet}OOR_i$. This confirms the least reactivity of ${}^{\bullet}OO^{-}$ radicals. Our data showed that the hydrogen atom abstraction from O_1-H_1 hydroxyl group of the molecules studied **(J1–18)** is more exergonic than the hydrogen atom abstraction from the substituent for the compounds **J4** and **J15**. Meanwhile, **J3** and **J5** calculations yielded contrasting results.

3.3. SET-PT Mechanism. The ionization potentials of the compounds investigated lie in a range from 680 to 884 kJ/mol in the gas phase. Figure 4 shows the spin density distribution for investigated radical cations. For the sake of clarity, we used the abbreviation **CatJn** (n = 1–18) to denote cation of the corresponding investigated molecules Jn (n = 1–18). The IP values of **J1–18** in the solution phase decreased significantly compared with those in the gas phase. The average of the calculated drop in IP values which is 111.94 kJ/mol for benzene, 115.72 kJ/mol for toluene, 266.22 kJ/mol for methanol, 277.27 for acetonitrile, and 285.55 kJ/mol for water corroborates the sensitivity of the cation radical forms of compounds to the polarity of different solvents used [39]. We concluded that the relative order of IP is water < acetonitrile < methanol < toluene < benzene < gas (Figure 5). It emerges that IP values

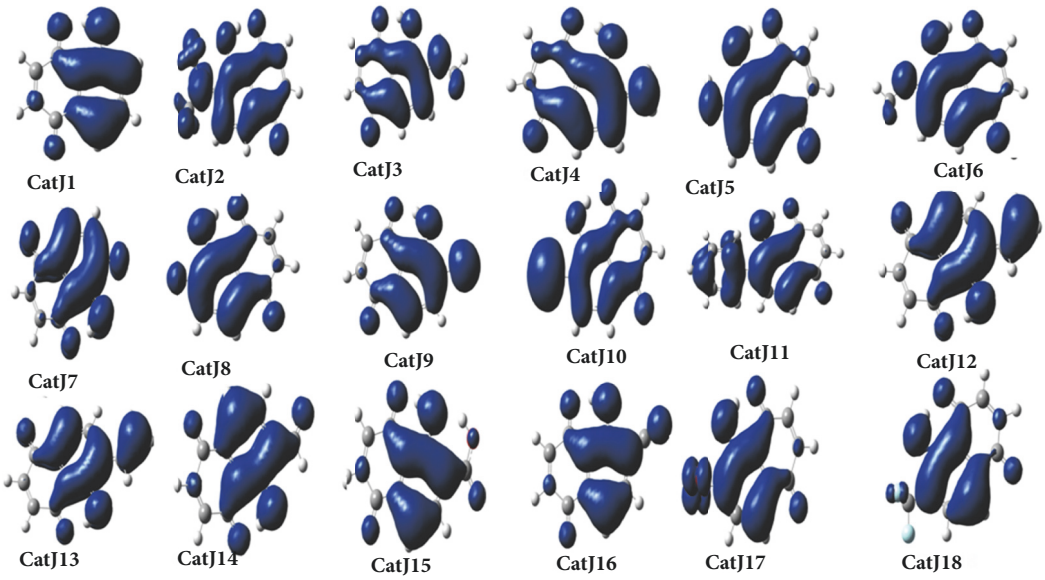


Figure 4: Plots of spin density for various hydrogen atom-abstracted cation radicals of juglone and derivatives.

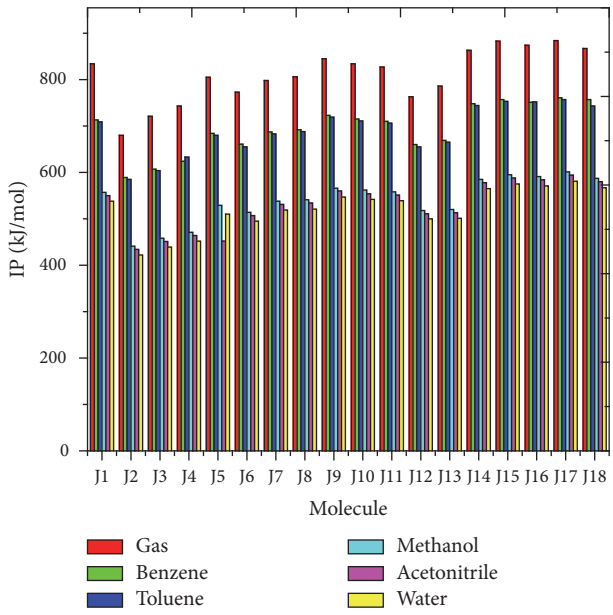


Figure 5: Ionization potentials of J*n* (in kJ/mol) at B3LYP/6-31+G(d,p) level in various media.

are higher than the BDE values regardless of the solvent considered. The HAT mechanism is clearly dominant thermodynamically over the SET mechanism. Such a result has previously been obtained for phenolic-4-En-1-Yne derivatives isolated from *Hypoxis rooperi* [22] for natural phenolic acids and their derivatives [38]. For the six environments, the substitution by the electron donating groups leads to the reduction of the IP values. Figure 5 also shows that lowest IP values are obtained for **J2** (R = NMe_2) in various media. The comparison of the IP values obtained to those of classical antioxidants (vanillic acid, gallic acid, and ascorbic acid) reveals that the more powerful antioxidant can be expected only for electron donating groups. From Table 1, it should be noticed that the compounds with lower IP values than those of the vanillic acid (777 kJ/mol) and gallic acid (763 kJ/mol) at B3LYP/6-311++G(d,p) level are, respectively, **J2–4**, **J6**, and **J12** and **J2–4** [38]. In addition, the IP values for **J2–4** and **J6-7** substituents are lower than that of the ascorbic acid (804 kJ/mol at B3LYP/6-311++G(2d,2p)//B3LYP/6-31G(d,p)) [19]. It is also noteworthy that IP values calculated for amino substituents are lower than that of Trolox calculated at the same level (763 kJ/mol) [19]. We then concluded that, despite the basis set, the SET mechanism for the amino substituent is stronger in the gas phase than that of the natural phenolic acid derivatives (vanillic acid and gallic acid), ascorbic acid, and Trolox. From Table 1, it is noticeable that, for electron withdrawing substituents **(J14–18)**, the IP values obtained are higher than those of classical antioxidants selected. All the free energies are positive (Table 6S), showing that the ET is not spontaneous regardless of the environment considered.

Table 1 also displays the similarity between the trends observed in PDE values of **Jn-RaX** radical species and those of BDEs. Such a similarity observed by other authors [19, 34] is attributed to the fact that the second stage of SET-PT mechanism also ends with the formation of **Jn-RaX** radical species. It is noticeable that the substitution by electron donating groups in the molecule reference provokes a decrease in 1-OH PDE. The differences are in the 22–88 kJ mol^{-1} range. A notable exception is observed for two halogen substituents (**J9** (R = F) and **J10** (R = Cl)) and for O-H hydroxyl group **(J5)**. This latter case, regardless of position of the proton abstracted, is confirmed by the augmentation of O-H PDE value of phenyl ring attached to heterocyclic pyran ring of daidzein compared to that of its homolog in 6-hydroxydaidzein [36] in the gas phase. In the whole, the substitution of electron withdrawing group leads to an increase of PDE values in this phase. The solvation

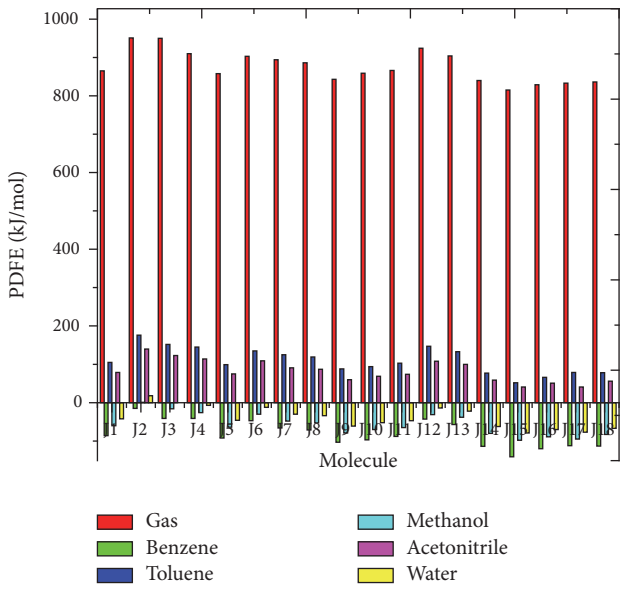


FIGURE 6: Proton dissociation free energies of J*n* (in kJ/mol) at B3LYP/6-31+G(d,p) level in various media.

causes an enormous decrease of PDEs in comparison to the gas phase values because of high solvation enthalpies [30]. The average decrease in PDEs reached approximately 874.5 kJ/mol. The average decrease in PDEs for different solvents used (benzene (902 kJ/mol), toluene (837 kJ/mol), methanol (886 kJ/mol), acetonitrile (875 kJ/mol), and water (865 kJ/mol)) shows that lowest PDE values are registered in benzene (Table 1 and Table 6S). Our B3LYP data therefore confirm the fact that aprotic solvents have good capability of proton solvation [29, 42]. In the whole, our results showed that, for electron withdrawing substituents **(J14–18)**, PDEs are lower than that of Trolox in benzene (37 kJ/mol) and water (21.2 kJ/mol) at B3LYP/6-311++G(2d,2p)//B3LYP/6-31G(d,p) [19]. We then concluded that proton dissociation ability of **J14–18** is significantly higher than that of Trolox in benzene and water. In the same vein, the PDEs in benzene are significantly lower than that of ascorbic acid (8.5 kJ/mol at B3LYP/6-311++G(2d,2p)//B3LYP/6-31G(d,p) in benzene) with the exception of **J2–4** and **J6-7** [13]. This indicated that the proton donation ability of the molecules analyzed from RX-H^+ cation is stronger than that of ascorbic acid in benzene. In the whole, Table 7S and Figure 6 showed that PDFE values are positive in the gas phase and in two solvents (toluene and acetonitrile). Consequently, PT mechanism is not spontaneous in these media. Nevertheless, negative values are obtained for other solvents, with exception made for few molecules: **J2** (in water) and **J4** (in methanol). Subsequently, we concluded that the PT mechanism is then spontaneous in these solvents.

3.4. SPLET Mechanism. Computational results of PA and ETE in vacuum and in various media are compiled in Table 1 and Table 8S. The substitution of the hydrogen atom by various electron donor substituents leads to augmentation of PA values ranging from 17 to 58 kJ/mol for **J2–4** in the gas phase. Such an increase is attributed to donor inductive effect of corresponding substituents (-NMe_2 and -NHMe) which strengthens the O_1-H_1 bonds. Owing to the mesomeric effect of other donor substituents, a reduction of PAs in the range of 1–64 kJ/mol is observed for **J4–13** in the gas phase. The difference of 2 kJ/mol obtained between the N-H PAS and O_1-H_1 homolog in the favor of the latter points out this effect which is due to nearness of the carbonyl function. Nevertheless, contrary result obtained for **J3** is related to the simultaneous contribution of the mesomeric effect previously evoked and the donor inductive effect of the methyl group that has substituted the hydrogen atom of the amino group of **J4**. It is noteworthy to mention that the difference of 16 kJ/mol between the O-H PA and O_1-H_1 PA (J**5**) in the benefit of the former discloses the fact that the hydrogen atom hampers the proton donation ability. The drop of the PAs in the range of 41–100 kJ/mol for molecular system **(J15–J18)** with withdrawing substituents is also related to the mesomeric effect that weakens the O_1-H_1 bonds. Our data showed a drastic drop of PAs when passing from gas phase to solution phase. The average drop in PA value approximated to 1107 (benzene), 1039 (toluene), 1039 (methanol), 1234 (acetonitrile), and 1223 kJ/mol (water) sheds light on the intensification of the deprotonation process by the solvation and its sensibility to the dielectric constant of the solvent used. This latter point is consistent with the claim of other researchers [42]. Table 1 and Table 8S display the fact that O_1-H_1 PA values are slightly smaller than H-OOC PA ones (J15) in water, toluene, and acetonitrile. This is an indication of easier monodeprotonation of **J15** from O_1-H_1 site in these media. Overall, the positive sign of PAs (Table 1 and Table 8S) and PAFEs (Table 9S) discloses the fact that the proton loss (PL) mechanism is endothermic but not spontaneous, independently of the environment. The comparison of the PAs of these molecules with those of classical antioxidants revealed that our data are slightly lower than those of Trolox in water (237 kJ/Mol), benzene (457 kJ/mol), and in the gas phase (1450 kJ/mol) at B3LYP/6-311++G(2d,2p)//B3LYP/6-31G(d,p) level with the exception of **J2** in the gas phase [19]. Consequently, the deprotonation of X-H (X = N, O) for molecular systems analyzed is easier than Trolox. In the whole, the majority of PAs in benzene are lower than those of ascorbic acid (367 kJ/mol at B3LYP/6-311++G(2d,2p)//B3LYP/6-31G(d,p) [19]) and those of a few natural phenolic acids: ferulic acid (388 kJ/mol) and vanillic acid (400 kJ/mol) at B3LYP/6-311++G(d,p) level [19]. The deprotonation process has been afterwards shown to be more predominant for these molecules in this medium. In the solution phase, electron transfer enthalpies are higher than the corresponding gas phase values. The average differences between ETE in the gas phase and different solvent are 83.4 (benzene), 72.4 (toluene), 71.6 (methanol), 61.04 (acetonitrile), and 60.4 kJ/mol. This means that electron transfer from anion (RX^-) is not favored enough in the solution phase. The positive values obtained for gas phase and solution phase ETFEs (Table 9S) illustrate the nonspontaneity of the ET mechanism from anions.

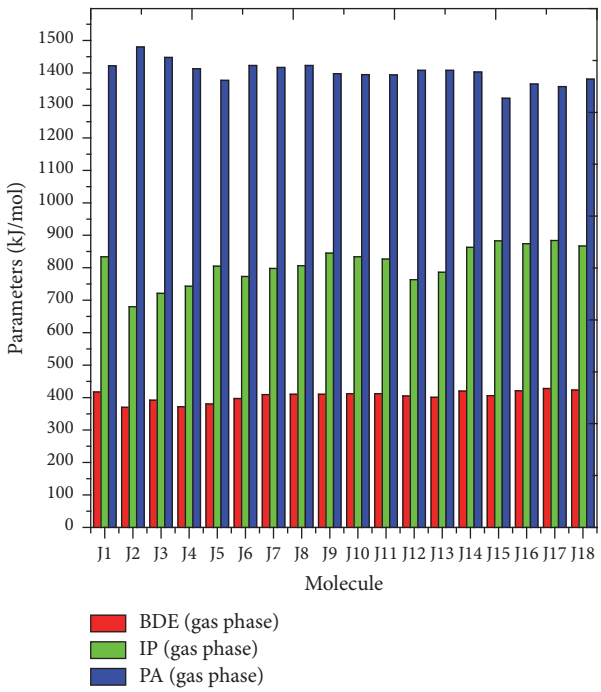


FIGURE 7: Thermodynamic energies of J*n*: bond dissociation energy (in kJ/mol), ionization potential of J*n* (in kJ/mol), and proton affinities (in kJ/mol) at B3LYP/6-31+G(d,p) level in gas phase.

From Figure 7, it is noticeable that calculated gas phase PAs are higher than corresponding values of IPs (that are approximately twice as high as gas phase BDEs). This demonstrates that the thermodynamically favored mechanism in the gas phase can be classified in the following increasing order: HAT < SET-PT < SPLET. Nevertheless, the drastic drop in solution phase PAs mentioned earlier justifies the fact that these are importantly lower than corresponding solution phase BDEs and IPs. We then assume that SPLET mechanism is more predominant than HAT and its SET-PT homolog in the solution phase. This general trend confirms the importance of this mechanism in polar solvents enlightened by experimental and theoretical studies [38, 43, 44].

4. Conclusions

The antioxidant mechanisms of juglone and its derivatives in gas and solution phase have been studied using computational methods. The main purpose is to evaluate thermodynamically the impact of the substitution effect on these mechanisms. A molecule library of eighteen molecules has then been built. Three major antioxidant mechanisms (HAT, SET-PT, and SPLET) have been analyzed. The optimized geometries obtained are characterized by the formation of hydrogen bond between hydroxy-H and oxygen atom of keto (O_1-$H_1 \cdots O_2$). The introduction of the electron-donation or electron-withdrawing group in juglone provokes an enhancement of the interaction strength of this hydrogen bond.

In the gas phase, the HAT mechanism is thermodynamically more predominant followed by SET-PT and SPLET. But the SPLET mechanism is the most preferred in the solution phase. This general trend is in agreement with previous experimental and theoretical studies for phenolic antioxidants. Our data demonstrate that the three mechanisms analyzed are endothermic but not spontaneous with exception of PT mechanism (for benzene, methanol, and water).

Conflicts of Interest

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

Acknowledgments

The authors are grateful to Bénoît Champagne (Université de Namur, Belgium) for his support. This work has been supported by the Ministry of Higher Education of Cameroon.

Supplementary Materials

From Crystallographic parameters obtained from the optimized structures of juglone and its derivatives (Table 1S), it is clearly shown that the length of the O_1-$H_1 \cdots O_2$ hydrogen bonding (HB) decreases with the substitution. Such an observation corroborates the increment observed in O_1-H_1 bond length due to the substitution of the H atom. The agreement between vibrational frequencies of optimized structures (J1–18) and that obtained experimentally (Table 2S) is confirmed by the value of the correlation coefficient (R^2 = 0.998) obtained between the two sets of data (Figure 1S). The diminution of BDE values for O_1-H_1 bond is presented in Table 3S when the polarity of the study medium increases. This fact is in good agreement with the increase in O_1-H_1 bond length observed in polar solvents (methanol, acetonitrile, and water). The positive BDFE values of the compounds (Table 4S) show that the HAT from all the molecules is nonspontaneous. Table 5S clearly shows that all reactions involving hydroxyl radical are spontaneous. This fact corroborates with the high reactivity of that radical. In addition, a huge decrease in IP values is observed (Table 6S) for polar media, agreeing with low values of electron solvation enthalpy in polar solvents IP. PDE values for molecules containing electron withdrawing groups are almost all negative (Table 6S) (except in toluene), showing that the proton transfer reaction from those radicals is exothermic. For all study compounds, PDFE values (Table 7S) are negative in benzene, meaning that the proton transfer reaction from the molecules is thermodynamically spontaneous in that solvent. In water and methanol, the same observation is made for almost all molecules herein studied. PA and ETE values (Table 8S) are positive for all molecules and in all the media. This means that the involved reactions are exothermic. The free energy values (PAFE and ETFE, Table 9S) for these reactions are also positive, meaning that the reactions are nonspontaneous in standard conditions. Table 1S: optimized geometrical parameters (bond lengths (Å) and bond angles (°)) in various media at B3LYP/6-31+G(d,p) level. Table 2S: experimental and calculated

vibrational frequencies (cm^{-1}) at the B3LYP/6-31+G(d,p) level. Table 3S: B3LYP/6-31+G(d,p) total energies of radical (E_T in a.u) and bond dissociation enthalpies (BDE in kJ/mol) in solution phase. Table 4S: bond dissociation free energy of J*n* (in kJ/mol) at B3LYP/6-31+G(d,p) level in solution phase. Table 5S: thermochemical parameters for interaction of investigated juglone derivatives with some of oxygen species obtained ($\Delta G_{R'}$ in kJ/mol) at B3LYP/6-31+G(d,p) level ($\Delta G_{R'}$ in kJ/mol). Table 6S: thermodynamic energies of J*n* (in kJ/mol) at B3LYP/6-31+G(d,p) level in various media: ionization potentials (IP) and proton dissociation enthalpies (PDE). Table 7S: thermodynamic energies of J*n* (in kJ/mol) at B3LYP/6-31+G(d,p) level in various media: ionization potential free energies (IPFE) and proton dissociation free energies (PDFE). Table 8S: thermodynamic energies of J*n* (in kJ/mol) at B3LYP/6-31+G(d,p) level in various media: proton affinities (PA) and electron transfer enthalpies (ETE). Table 9S: thermodynamic energies of J*n* (in kJ/mol) at B3LYP/6-31+G(d,p) level in various media: proton affinity free energies (PAFE) and electron transfer free energy (ETFE). Figure 1S: dependence of experimental and calculated gas phase FT-IR frequencies (cm^{-1}) at B3LYP/6-31+G(d,p) level. *(Supplementary Materials)*

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