J Mol Model (2014) 20:2541
DOI 10.1007/s00894-014-2541-9

ORIGINAL PAPER

Understanding the cytotoxicity or cytoprotective effects of biological and synthetic quinone derivatives by redox mechanism

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Received: 7 June 2014 / Accepted: 17 November 2014 / Published online: 11 December 2014

Abstract Quinones represent an important class of biological compounds, but are also involved with toxicological intermediates and among their hazardous effects include cytotoxicity, immunotoxicity, and carcinogenesis. The structure–toxicity relationship for quinone derivatives has been used to cytotoxicity or cytoprotective effects by redox mechanism is determined using quantum chemical calculations through the density functional theory (DFT). According to our DFT study, the electron acceptance is related with LUMO, electron affinity, and stabilization energy values. The highest spin density distribution in the heteroatoms is more favored for the more cytotoxic compounds. The electrophilic capacities of these compounds have been related with LUMO values. The cytotoxic properties of quinones are related to the stabilization energy after electron accepting by redox mechanism. Electron affinity is the most relevant parameter related to toxicity mechanism. Regioisomers has different electrophilic capacity. The electrophilicity increases on molecules containing electron-withdrawing groups (EWG) and reduces on molecules containing electron-donating groups (EDG). These results explain the toxic difference between natural and synthetic quinone derivatives and can be used in the design and study of new drugs.

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Keywords Quinone · ADMET · DFT · NAPQI · Quinone · Reactivity · Redox · Toxicity

Introduction

The toxicity related with cytotoxic and/or genotoxic effects produced by environmental chemicals and innumerable other xenobiotics as well as endogenous compounds are frequently due to intracellular reactions of electrophilic or free radical metabolites [1]. A few of the best known examples of toxic electrophiles include epoxides from polycyclic aromatic hydrocarbons [2] and α,β-unsaturated carbonyl compounds such as acrolein that serve as Michael acceptors [3]. These species alkylate nucleophilic sites on peptides, proteins, and/or nucleic acids, forming covalent adducts that can significantly compromise cellular integrity and function [4]. However, the radicals can cause a variety of deleterious effects in cells such as oxidation of proteins, lipids, and DNA as well as activation of numerous signaling pathways involved in several human pathologies, including the aging process and initiation, promotion, and progression of carcinogenesis [5, 6].

Biphenol derivatives with other hydroxyl substituents at the *ortho* or *para* positions also have been extensively studied, such as catechol and hydroquinones, all of which can be converted to quinones by monooxygenase or peroxidase enzymes, metal ions, and in some cases molecular oxygen [7]. Quinones are a general term for a ubiquitous class of compounds which are common in several natural products and endogenous biochemicals or generated through metabolism of biphenols. Generally, quinones are named as derivatives of their parent aromatic system. As a result, benzoquinones are derived from benzene, naphthoquinones from naphthalene, and anthraquinones

from anthracene to name a few examples. Some quinones are potent redox active compounds. They are subject to enzymatic (i.e., P450/P450 reductase) and nonenzymatic redox cycling with their corresponding semiquinone radical and as a result generate superoxide anion radicals [7–9]. Among the main known drugs of these classes are dopamine, adrenaline, noradrenaline, hydroquinone, atovaquone, mitomycin C, doxorubicin, lapachol, vitamin K, coenzyme Q.

Quinones are also Michael acceptors; therefore, damage due to these species sometimes results from covalent binding with cellular nucleophiles. For example, *N*-acetyl-p-benzoquinone-imine (NAPQI) reacts readily with sulfur nucleophiles, such as (glutathione) GSH or cysteine residues on proteins, leading to depletion of cellular GSH levels and/or protein alkylation [10–12]. In addition, some quinones can react with nucleophilic amino groups on proteins or DNA [13–16]. *p*-Benzoquinone is known to form a DNA adduct that supports this hypothesis [17], although the genotoxic mechanism also may involve the formation of reactive oxygen species (ROS) which cause single-strand breaks as well as oxidation of DNA bases. Nevertheless, some endogenous or exogenous quinones exert a crucial function and also have been implicated on several biological mechanisms contributing to the many biological functions in basic metabolic processes as respiration and photosynthesis [18, 19]. Less clear are the conditions which lead to loss of the normal metabolic functions of quinones, often resulting in the generation of ROS.

In addition, studies with estradiol, which subjected the possible quinone production after hydroxylation, were interesting and produced two hydroxylated metabolites, 2-hydroxyestradiol and 4-hydroxyestradiol. It has been shown that 2-hydroxylation of estradiol to its catechol derivative is a major metabolic pathway in rodent and human livers, whereas 4-hydroxylation to a different catechol represents a minor pathway in the liver [20, 21].

However, the reactivity parameters of quinone derivatives and their importance on the toxicity by redox mechanism have not been clarified using theoretical methods. The failure due to deficiencies in theoretical toxicity properties during the development, a set of *in vitro* and *in silico* screening has been implemented in most pharmaceutical companies for predicting drug-likeness with the aim of discarding compounds in the discovery phase that are likely to fail further down the lane [1]. Therefore, in this work, we showed the first toxicity mechanism using theoretical calculations of the electron transfer in the redox and electrophilic reactivity of quinone derivatives. Our purpose here is to contribute to a better understanding of the mechanistic features of this process and development of the toxicity model for quinone derivatives.

Methods

All quantum chemical calculations were performed with the Gaussian 03 molecular package [22]. Prior to any DFT [23] calculation all structures were initially submitted to a PM3 [24] geometry conformational search. Only the most stable conformation for a given compound was used to perform the quantum chemical calculations. These PM3 geometries of lower energy were re-optimized using the B3LYP hybrid density functional theory [25, 26] along with the 6-31+G(d,p) basis sets [27].

The ionization potential (IP) was calculated as the energy difference between a neutral molecule and the respective cation free radical (Eq. 1). The electron affinity (EA) was calculated as the energy difference between a neutral molecule and the respective anion free radical (Eq. 2).

$$IP = EQO_2^{\bullet+} - EQO_2 \quad (1)$$

$$EA = EQO_2^{\bullet-} - EQO_2 \quad (2)$$

Radical stability is usually calculated by stabilization energies (ΔEiso) [28–30]. The ΔEiso values were calculated by energy difference between quinone derivatives related with the superoxide radical quenching, as shown in Eq. 3 for the electron transfer, where the quinone derivatives are QO_2 and the superoxide radical is $O_2^{\bullet-}$ (Eq. 3).

$$\Delta Eiso = (EQO_2^{\bullet-} + EO_2) - (EQO_2 + EO_2^{\bullet-}) \quad (3)$$

However, the quenching of the superoxide anion gives semiquinone as reactive groups. Hence, in the present article we aimed to explore the quinone derivatives for the toxic mechanism identification by electron transfer. In the Figs. 1 and 2, the compounds studied were *ortho*- and *para*-quinone derivatives formed by the molecular addiction of benzene rings (1–6), quinone-imine (7), methylation and/or

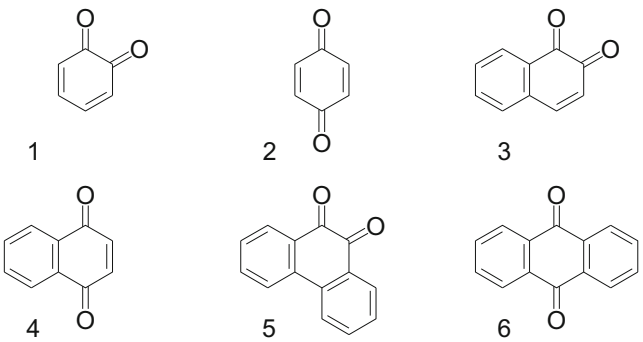

Fig. 1 Chemical structures of the 1,2 and 1,4-quinone derivatives

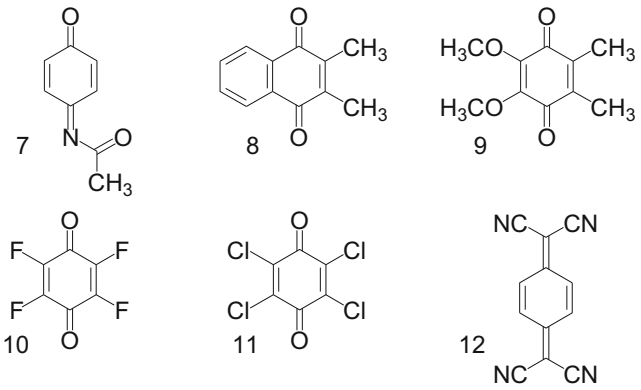

Fig. 2 Chemical structures of analogous and substituted 1,4-quinone derivatives

methoxylation addition on quinone structure (8 and 9), and halogenation (10 and 11) or electron-withdrawing group, such as nitrile (12).

In fact, we are interested in the understanding of the role played by different structural features of the quinone compounds studied here on toxicity mechanism. Thus, we have therefore undertaken a systematic study of the influence of the *ortho*- or *para*-positions of carbonyl moieties, benzene group, and/or methyl and methoxy radicals on the electron transfer properties of quinone derivatives. To this aim, we have calculated: (i) the highest occupied molecular orbital (HOMO); (ii) the lowest unoccupied molecular orbital (LUMO); (iii) the ionization potential (IP); (iv) the electron affinity (EA); (v) the stabilization energy (ΔEiso); (vi) the spin density.

Results and discussion

Molecular orbitals: HOMO and LUMO

The redox activities of 12 different quinone derivatives were theoretically measured for toxicity mechanism. These compounds were selected based on their chemical structure characteristics and some compounds were naturally occurring and other were drugs or industrial compounds.

The energy of the frontier orbitals HOMO and LUMO are important parameters of the molecular electron structure to study the electron transfer. The molecule which has the highest ε_{HOMO} has the strongest electron-donating ability. Nonetheless, the lowest ε_{LUMO} implies that the molecule is a good electron acceptor [28]. The calculated HOMO and LUMO values for the molecules studied in this work are shown in Table 1.

In general, the quinone derivatives with C=O groups *ortho* related showed the higher HOMO values, such as 1,2-benzoquinone 1, 1,2-naphthoquinone 3, and phenanthrene-9,10-dione 5. Similar results were obtained for the 1,4-naphthoquinones linked to electron donating groups (EDGs) such as methyl 8 and methoxy 9 groups. On the contrary, the quinone derivatives with C=O groups *para* related showed the lower HOMO values, such as 1,4-benzoquinone 2, 1,4-naphthoquinone 4, and 9,10-anthraquinone 6. However, 1,4-benzoquinones linked to electron withdrawing groups (EWGs) such as fluoro 10, chloro 11, and nitrile 12 groups showed the lowest HOMO values.

The quinones with C=O groups *ortho* related showed the lower LUMO values, compounds such as 1,2-benzoquinone 1, 1,2-naphthoquinone 3, and phenanthrene-9,10-dione 5 compounds. Similar results were obtained for the 1,4-benzoquinones linked to EWGs such as fluoro 10, chloro 11, and nitrile 12. Therefore, these benzoquinones (compounds 10, 11, and 12) studied here are the most electrophilic compounds. In fact, the obtained results in the present work have indicated that the EWGs are essential for the increase of electrophilic capacity. On the contrary, the quinones with C=O groups *ortho* related have higher LUMO values, such as 1,4-benzoquinone 2, 1,4-naphthoquinone 4, and 9,10-anthraquinone 6. A similar result was obtained for the 1,4-naphthoquinones linked to EDGs such as methyl 8 and methoxy 9. Consequently, these compounds have less electron-accepting ability. The contribution from the carbonyl position also cannot be neglected. These results are in accordance with experimental works for the evaluation of quinones in several models of cytotoxicity and cancer [13, 29, 30].

The LUMO disposition of the quinone derivatives can indicate qualitatively the possible reactive site for electron acceptation of free-radicals. The results presented here have a direct influence in the resonance effect between *ortho* and *para* quinones after electron acceptance as shown in Fig. 3. The number of resonance structures can be related to the electrophilicity and the most electrophilic positions are determined by the LUMO contribution for the carbonyl and double bond moieties on the quinones compounds studied here (Fig. 3). Additional contributions were observed by the EDGs and EWGs. The reactivity increased due to these compounds showed a coplanar orbital structure between carbonyl and double-bonds or benzene-rings.

Ionization potential (IP)

The ionization potential (IP) represents the easiness for an electron donation of a compound, in our case the quinone derivatives. The electron abstraction is one of the mechanisms for toxicity by redox property. Therefore, molecules with lower IP are better electron-donating compounds. The calculated IP values are shown in Table 1.

In general, the IP calculation showed that quinone compounds *ortho* related (1, 3, and 5) have more electron donating capacity than quinone derivatives *para* related (2, 4, and 6). Quinones with EDG moieties (8 and 9 compounds) decrease the IP values. Moreover, quinones with EWG groups (10 and

Table 1 Calculated theoretical properties for the quinone derivatives

Compound	Toxicity	HOMO (eV)	LUMO (eV)	IP (kcal mol^{-1})	EA (kcal mol^{-1})	ΔEiso (kcal mol^{-1})
1	Toxic	−7.20	−4.01	217.83	−45.33	−18.71
2	Toxic	−7.79	−3.95	229.61	−43.83	−17.20
3	Toxic	−7.02	−3.59	206.90	−41.70	−15.08
4	Toxic	−7.56	−3.56	218.17	−40.71	−14.09
5	Toxic	−6.91	−3.38	196.60	−40.32	−13.70
6	Nontoxic	−7.36	−3.17	208.84	−36.70	−10.07
7	Very toxic	−7.29	−4.08	211.04	−52.20	−25.57
8	Nontoxic	−7.30	−3.29	210.22	−36.74	−10.11
9	Nontoxic	−6.38	−3.40	188.85	−36.86	−10.23
10	Very toxic	−8.59	−4.76	247.17	−61.92	−35.29
11	Very toxic	−7.94	−4.55	223.17	−63.89	−37.26
12	Very toxic	−7.62	−5.12	210.15	−82.98	−56.36

11 compounds) have the highest IP values. However, the increase of double-bonds (C=C or C=N) are important for the electron-donating capacity, such as molecules 7 and 12. Therefore, all molecules with low electron donating capacity have high IP values.

Electron affinity (EA)

The electron affinity (EA) represents the easiness for electron-accepting of the quinone derivatives. The electron abstraction is another mechanism for toxicity by redox property. Therefore, molecules with a high EA are better electron accepting compounds. The calculated EA values are shown in Table 1.

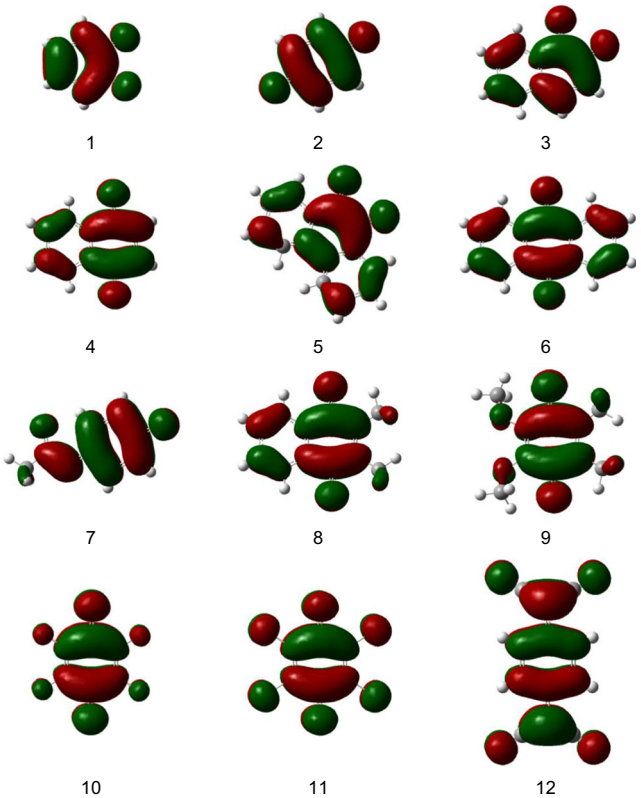

Fig. 3 Structure of LUMO for the quinone derivatives

From Table 1, it can be seen that the EA values for *ortho*-quinones, such as 1,2-benzoquinone 1, 1,2-naphthoquinone 3, and phenanthrene-9,10-dione 5 are higher when compared with their respective regioisomers. In fact, *para*-quinones such as 1,4-benzoquinone 2, 1,4-naphthoquinone 4, and 9,10-anthraquinone 6 have the lower values. Nonetheless, all molecules with EDG decreased the EA values, such as methyl 8 (−36.74) and methoxy 9 (−36.86). Moreover, all molecules with EWGs increased the EA values, such as fluoro 10 (−61.92), chloro 11 (−63.89), and nitrile 12 (−82.98).

These results showed that the electron-accepting properties of the quinone derivatives can be determined mainly by the stability of the anion free-radical, generated after the electron transfer. The anion free-radical in molecules with carbonyl groups at *para* position or substituted by EWGs are formed with a lower energy than the molecules with carbonyl group at *ortho* position or substituted by EDGs. The highest electron transfer found for molecules with carbonyl moieties at *para* position or substituted by EWGs is facilitated by the existence of the π-delocalized system (Fig. 4). The same results were obtained for the electron transfer in molecules with carbonyl moieties at *ortho* position or substituted by EDG. In fact, these molecules showed a similar number of resonance structures (Fig. 5).

Thus, the EA values can be used for separation of toxic or non-toxic molecules, for example anthraquinone 6, a non-toxic molecule that has the lowest EA value (−36.70 kcal mol^{-1}) [19]. However, we have an increase of EA values in toxic molecules such as *N*-acetyl-p-benzoquinone-imine 7 (−52.20 kcal mol^{-1}). Note that *N*-acetyl-p-benzoquinone-imine (NAPQI) is a known toxic molecule [10–12].

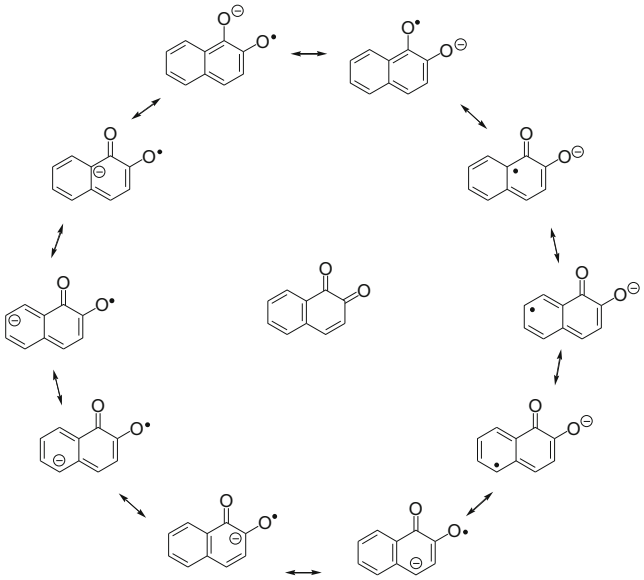

Fig. 4 The resonance structures of anion the free-radicals for 1,2-quinone

Stabilization energies (ΔEiso)

The electron abstraction has importance because free-radicals, such as the superoxide anion, can be inhibited in the presence of various quinone derivatives which can act at different processes [31]. The chain-breaking is one of the redox mechanisms for several biological processes such as the electron transport chain in cellular respiration. Nonetheless, the reaction between some quinone derivatives with superoxide anion gives an anion free-radical, responsible for oxidative stress and lipoperoxidation [32]. This reaction is shown in Fig. 6.

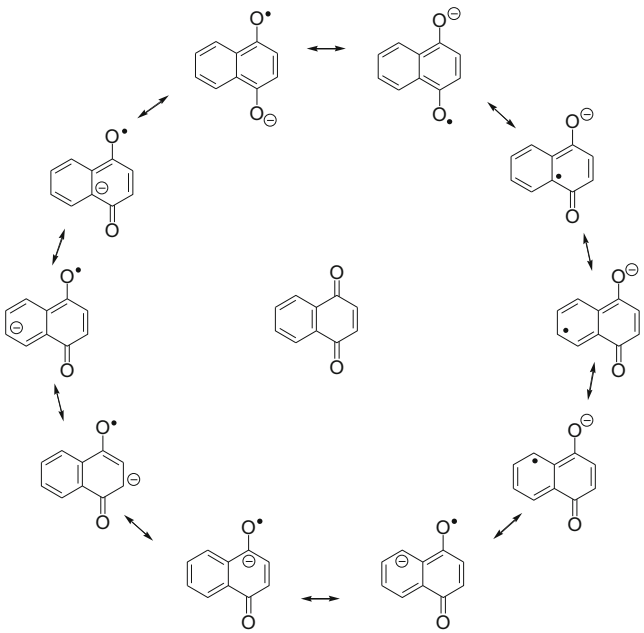

Fig. 5 The resonance structures of the free-radicals for 1,4-quinone

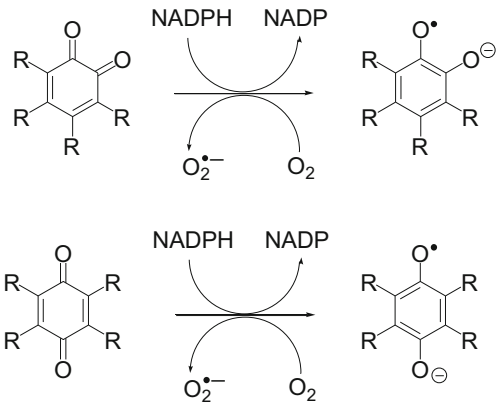

Fig. 6 Structures and reactions between quinone derivatives and the superoxide anion

The electron transfer reaction can be calculated by using the stabilization energies (ΔEiso) of the quinone derivatives related with the superoxide anion. The ΔEiso are shown in Table 1. According to these values, it is possible to establish the relative stability for the involved groups in toxicity properties of quinone derivatives.

In previous works, the stabilization energies are frequently used as a simple method to predict the redox ability to trap free-radicals or scavenging effects of organic compounds [33–35]. This approach provides additional evidence for the regioisomerism and electronic effect on quinone derivatives in the stabilization of radical species by electron transfer. The obtained ΔEiso results have demonstrated a clear classification between these two different classes. In the molecules with carbonyl groups in *ortho* position we observed an increase of ΔEiso for the compounds 1,2-benzoquinone 1, 1,2-naphthoquinone 3, and phenanthrene-9,10-dione 5 (−18.71, −15.08, and −13.70 kcal mol^{-1}, respectively) when compared with molecules with carbonyl groups in *para* position that showed low ΔEiso values for the compounds 1,4-benzoquinone 2, 1,4-naphthoquinone 4, and 9,10-anthraquinone 6 (−17.20, −14.09, and −10.07 kcal mol^{-1}, respectively).

All substituted quinone derivatives with EDG showed lower ΔEiso values. In fact, the ΔEiso for the compounds methyl 8 and methoxy 9 are −10.11 and −10.23 kcal mol^{-1}, respectively. Nevertheless, the presence of EWGs in the double bond C=C of the quinone derivatives increased ΔEiso in the compounds fluoro 10, chloro 11, and nitrile 12. These compounds showed the lowest values of ΔEiso (−35.29, −37.26, and −56.36 kcal mol^{-1}, respectively).

Therefore, the alkenes, phenyl rings, and EWGs may stabilize the radical formed during oxidation by extension of the conjugation via resonance effect, contributing to the increase of ΔEiso. These results showed that these EWGs are determinant for the increase of the toxicity of the quinone derivatives. Consequently, the anthraquinone 6, a non-toxic molecule has the lowest ΔEiso value (−10.07 kcal mol^{-1}).

However, the NAPQI 7, a known toxic molecule, has an increase of the ΔEiso value to −25.57 kcal mol^{-1}.

Spin density and unpaired electron distribution of radicals

The resonance structures of the anion free-radicals by electron abstraction of the redox process can be observed by the spin density contributions for the quinone derivatives. Figure 7 shows the spin density distribution for the anion free-radicals of the quinone derivatives (all structures have one additional electron).

The calculated spin density contributions to initial electron abstraction at the *ortho* quinone derivatives (1,2-benzoquinone 1, 1,2-naphthoquinone 3, and phenanthrene-9,10-dione 5) show a main contribution from the phenoxyl position (20.0–20.8) and a medium contribution for the aromatic rings (7.46–10.18). However, the calculated spin density contributions at the *para* quinone derivatives (1,4-benzoquinone 2, 1,4-naphthoquinone 4, and 9,10-anthraquinone 6) show a main contribution from the phenoxyl position (19.3–22.5) and a medium contribution for the aromatic rings (5.92–9.51).

Moreover, their related molecules are observed in the biological molecules (methyl 8 and methoxy 9) showing a spin density contribution in the phenoxyl groups (20.9–21.4) and a smaller contribution for methyl and methoxyl groups (0.12–0.43). Apparently, these compounds are not toxic for the biologic cells. Nevertheless, other related molecules that are known by their toxicity (fluoro 10, chloro 11, and nitrile 12) show a higher spin contribution for the phenoxyl or related position (23.9, 22.5, and 29.1, respectively). The spin contribution for the heteroatoms has also increased for 0.15, 0.85, and 10.5. These compounds we found to be highly toxic for life organisms.

Therefore, the NAPQI 7, a known toxic metabolite of acetaminophen, shows an additional spin contribution on the aromatic ring (12.9, 16.5, and 17.5). These spin contributions are the highest localization of the unpaired electron on the phenyl ring. Other important spin contributions are located on the acetyl group (6.60 and 8.70).

Then, the highest spin density distribution on phenoxyl, heteroatom, and aromatic groups are more favored in toxic compounds. It appears that symmetric molecules are less reactive.

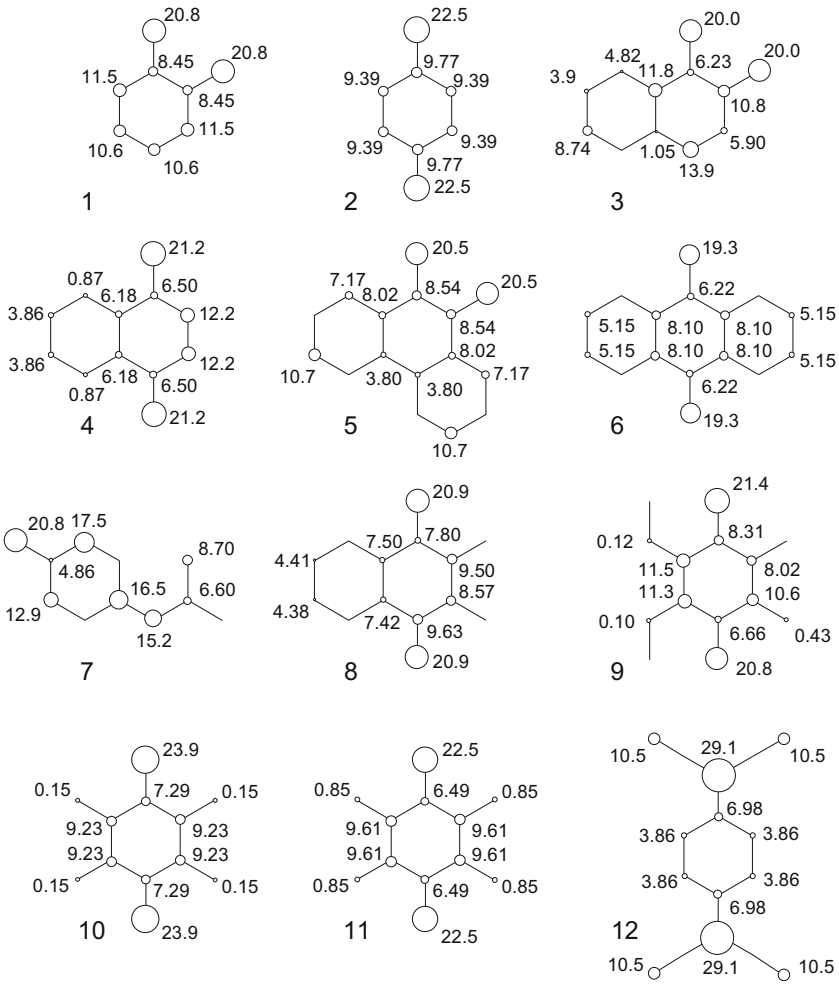

Fig. 7 Structure and calculated spin density contributions for the quinone derivatives

Conclusions

Our results showed that LUMO, electron affinity, and stabilization energies are important theoretical parameters for the toxicity mechanism of quinone derivatives. The calculated electron affinity is the most relevant parameter related to toxicity or protective property of quinone derivatives. The *ortho*-quinones were more electrophilic when compared with their respective regioisomers. The electrophilicity was increased by molecules containing electron-withdrawing groups (EWG) and the same was reduced by molecules containing electron-donating groups (EDG). These results explain the toxicity of *N*-acetyl-p-benzoquinone-imine (NAPQI) and protective effects of anthraquinone. The potential toxicity of these derivatives is related with electron transfer and chemical stability of the anion free-radicals. The resonance structures in which the unpaired electron is mainly distributed on the phenoxyl, heteroatom, and phenyl rings were observed by prevalent spin density contributions. Quinones more reactive with superoxide anion are more toxic. The toxicity mechanism performed here using theoretical approach can be easily used for the toxicity prediction in the design, study, and selection of safer drugs.

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