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Correlations between theoretical calculations and experimental photochemical reactivity of hydroxyanthraquinone drugs present in *Aloe vera*

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Abstract

The phototoxic drugs (S) (aloe-emodin (**1**), emodin (**2**), and rhein (**3**)) were studied with the parametric method CATIVIC in order to find correlations between calculated theoretical properties and the experimental photodegradation rate. These correlations can be explained through the formation of free radical intermediates, singlet oxygen and stable photoproducts. A correspondence between calculated dipolar moment and heat of formation with photolysis rate and quantum yield (ϕ_{fl}) of anthraquinones (**1**, **2** and **3**) was found. In addition, HOMO energy correlates with the wavelength of excitation (λ_{exc}). Formation of S^-, SH°, and $^1O_2$ intermediates were evaluated and confirmed as feasible. The O_2^- anion is found to be the most probable species in the photooxidation of biological substrates.

Key words: anthraquinones, *Aloe vera*, photolability, CATIVIC, theoretical correlations, photochemical reactivity.

Correlaciones entre cálculos teóricos y la reactividad fotoquímica experimental de drogas hidroxiantraquinonas presentes en la *Aloe vera*

Resumen

Las drogas fototóxicas (S) aloe-emodina (**1**), emodina (**2**) y rhein (**3**) fueron estudiadas con el método paramétrico CATIVIC con la finalidad de encontrar las correlaciones entre las propiedades calculadas teóricamente y la velocidad de fotodegradación experimental. Estas coorrelaciones pueden explicarse a través de la formación de intermediarios de radicales libres, oxígeno singlete y fotoproductos estables. Se encontró una correspondencia entre el momento bipolar y el calor de formación, calculados con la velocidad de fotólisis y el rendimiento cuántico (λ_{exc}) de las atraquinonas (**1**, **2** y **3**). La formación de los intermediarios S^-, SH°, y $^1O_2$ fue evaluada y confirmada como factible. Se encontró que el anión es la especie más probable en la fotoionización de los sustratos biológicos.

Palabras claves: antraquinonas, *Aloe vera*, fotolabilidad, CATIVIC, correlaciones teóricas, reactividad fotoquímica.

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1. Introduction

Anthraquinones (1,8-dihydroxyanthra quinones, (DHA)) are present in several plants mainly as glycosides. These compounds have both therapeutic and cytotoxic properties related with diverse types of human affections. For example, aloe-emodin (1,8-dihydroxy-3-hydroxy-methylanthra quinone, (**1**)) is a compound present in *Aloe vera* leaves, which exhibits antifungal (1), mutagenic (2), and tumorigenic properties (3). Although in a recent report aloe-emodin was postulated as a new lead antitumor drug (4); emodin (1,3,8-trihydroxy-6-methylan thraquinone, (**2**)) possesses anticancer, diuretic, antibacterial, vasorelaxant (5) and anti-inflammatory effects (6); and rhein (1,8-dihydroxyanthraquinone-3-carboxilic acid, (**3**)) is the active metabolite of diacetylrhein that can be used as a drug for the treatment of patients with osteoarthritis.

On the other hand, some synthetic and vegetable-origin anthraquinones have shown to be able to produce free radicals and singlet oxygen highly cytotoxic, when they are irradiated with visible light (7). Specifically, phototoxicity indications have been detected *in vitro* in Chinese hamster V79 cells irradiated with light UVA and UVB in the presence of emodin (8). These findings suggest, in general terms, that the irradiation of DHAs can lead to the production of reactive oxygen species able to produce toxic effects on diverse cellular systems. Also, some evidences *in vivo* confirm the importance of discoveries *in vitro*. For example, two cases of photodermatitis have been reported: the first one (9), caused by anthraquinone (9,10-anthracenedione) and the other one by a preparation coming from *Aloe vera* (10).

Recent photochemical works have shown a comparative study of the photostability and phototoxicity (photohemolysis on human erythrocytes) (11). Other researches have also shown that emodic acid is potentially phototoxic through photogeneration of reactive oxygen species or nucleic acids and amino acids oxidation by the excited triplet state specie (12), as also it photoinduces cleavage on DNA by aloe-emodin (13). Phototoxicity due to occasional or therapeutical contact with chemicals is attracting clinical and research interest because of its increasing relevance. Progress in this field has probably been hindered by its intrinsic complexity; therefore, the need for an interdisciplinary approach and the lack of reliable *in vitro* tests for assaying the photosensitizing capability of xenobiotics in general.

In connection with these facts, the correlation between experimental data of UV-A and visible irradiations on aloe-emodin, emodin, and rhein molecules and electronic properties of these drugs and their free radical intermediates formed during its photodegradation may be of great importance to establish the molecular bases of their photostability and their phototoxicity.

Theoretical calculations with the parametric method CATIVIC were carried out to understand electronic and structural aspects of **1**, **2** and **3** molecules and their respective radicals; see fig. 1. Correlation between electronic structure and reactivity has been used to understand some details of these complex systems. A simple method and new theoretical tools were employed to try to explain the behavior of the above mentioned molecules.

The present work is organized in the following manner. A brief description of the basis of the method employed is presented in section 2 with the corresponding tools to evaluate properties of interest. Section 3 deals with the discussion of experimental results and interpretation of theoretical calculations in order to propose an explanation of experimental facts. Finally conclusions and comments are presented in Section 4.

2. Theoretical method

The theoretical calculations were carried out in the program CATIVIC (14) based

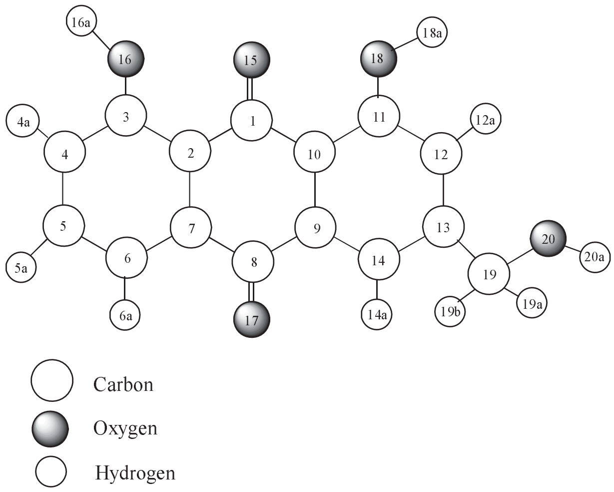

Figure 1. Structure of anthraquinones aloe-emodin **(1)**, emodin **(2)** and rhein **(3)** molecules.

on simulation techniques of parametric methods (15-17). For example, the binding energy functional for a molecular system of *N* atoms can be defined as,

$$\min_{\Delta E^{I}_{pa} \in \langle f \rangle} \left(\sum_{I \in S} \left| E^{I}_{exa} - E^{I}_{pa} \right|^{2} \right)^{1/2} \qquad [1]$$

$$E^{I}_{pa} = f^{1}\Big(\left\{ j_{X_{\mu\nu}} \right\}, \left\{ k_{X_{\mu\nu}} \right\}, \left\{ U_{X_{\mu\nu}} \right\}, \left\{ Res_{XY} \right\}, \left\{ Rep_{XY} \right\}, \left\{ V_{X_{\mu}Y_{\nu}} \right\}, \left\{ \gamma_{X_{\mu}Y_{\nu}} \right\}, \left\{ R_{XY} \right\} \Big) \qquad [2]$$

where $\langle f \rangle$ is a family of functionals of binding energy. *I* is associated to the state Ψ_I that belongs to an orthonormal set of eigenfunctions $\{\Psi\}$ of H_{exa} that is complete in a subspace *S* of the Hilbert space (*H*). The E^{I}_{pa} and E^{I}_{exa} variables are parametric and exact energy functionals for the state *I*, respectively. The term E^{I}_{pa} depends on elementary of one-center $\left\{ j_{X\mu\nu} \right\}, \left\{ k_{X\mu\nu} \right\}, \left\{ U_{X\mu\nu} \right\}$, two-centers $\left\{ V_{X\mu Y\nu} \right\}, \left\{ \gamma_{X\mu Y\nu} \right\}, \left\{ Res_{X\mu Y\nu} \right\}, \left\{ Rep_{X\mu Y\nu} \right\}$ parametric functionals, and the set of interatomic distances $\left\{ R_{XY} \right\}$. These one-center functionals correspond to electronic repulsion, exchange, and kinetic and attractive energy, respectively. On the other hand, two-center functionals are electron-core attraction, electron-electron repulsion, resonance, and core-core repulsion, respectively (15). It is easy to see that the total energy for a molecular system (*E*) is divided in diatomic (ε_{XY}) and monoatomic (ε_{X})energy terms

$$E = \sum_{X} \varepsilon_{X} + \sum_{X>Y} \varepsilon_{XY} \qquad [4]$$

The molecular and atomic parameters come from the semi-empirical method MINDO/SR (18) that is based on MINDO/3 (19). The bond strength was analyzed using different tools: bond orders, diatomic energies (*DE*) (20) and diatomic bonding energies (*DBE*) (21). In the case of *DBE*, the X-Y bond strength is may be defined as,

$$DBE(X-Y) = \varepsilon_{XY} + f_{X}(X-Y)\varepsilon_{X} + f_{Y}(X-Y)\varepsilon_{Y} \qquad [5]$$

and

$$f_{X}(X-Y) = \varepsilon_{XY} \Big/ \sum_{Y \neq X} \varepsilon_{XY} \qquad [6]$$

3. Investigations and results

There is sufficient evidence that ethanolic solutions of 1-3 compounds, shown in fig. 1 are photolabile under aerobic conditions by irradiation with visible light (340-500 nm). The photolysis of the drugs **1**-**3** was reported by Vargas et ál. (11) under these conditions and was followed by monitoring the changes of their absorption and emission bands. These authors concluded that the photolability of ethanolic solutions of aloe-emodin and emodin are higher than rhein under visible light and aerobic conditions (i.e., **1** > **2** > **3**). Fig. 2 shows an experimental comparison of the photodegradation velocity of the three anthraquinones studied by measuring the absorbance at 430 nm as a function of the time.

In order to understand from the molecular point of view the order of photodegradation velocity, we calculate energetic and electronic properties of selected molecules of 1,8-dihydroxyanthraquinones aloe-emodin (**1**), emodin (**2**) and rhein (**3**) shown in fig. 1. Correlation between theoretical and experimental data were analyzed in terms of photodegradation velocity and calculated global molecular properties, such as, total dipolar moment (*DP*), highest occupied molecular orbital (*HOMO*), lowest occupied molecular orbitals (*LUMO*), Δ(|*HOMO-LUMO*|) energies (Δ(|*H-L*|)), and heat of formation (*HF*). Calculated values of these properties are in Debye, au, and kcal/mol, as shown in table 1. The magnitude of molecular *DM* follows the order **1** < **2** < **3**, in inverse order withexperimental photodegradation findings. A possible correlation of these results with experimental findings can be explained in terms of the microenvironment effects on the spectroscopic properties of the molecules. Absorption spectra change dramatically with solvent properties, such as polarity, polarizability, hydrogen-bonding capacity, PH, and viscosity. For example, molecule **3** has the lowest photoreactivity because of the high polarity of this anthraquinone produces a water solvation layer from the surrounding microenvironment. This effect generates a sort of protection to absorbants, creating an obstacle in the formation of photoproducts and also enhances recombination of dissociated radical fragments.

Radical formation may be related with values of *HOMO*, *LUMO*, and energy differences (Δ(|*H-L*|)). For example, a high *HOMO* absolute value (a very negative and stable *HOMO*) implies more difficulty to excite the molecule. Thus, the lowest *HOMO* value (-0.3279 au for **3**) corresponds to the least active anthraquinone. However, **1** and **2** molecules show very close *HOMO* values, but they present a converse behavior. It means, |(*HOMO*(**1**)| > |*HOMO*(**2**)|) and the order should be |(*HOMO*(**1**)| < |*HOMO*(**2**)| < |(*HOMO*(**3**)|.

With respect to *LUMO* values, negative quantities indicate that these molecular systems have a non negligible electronic affin-

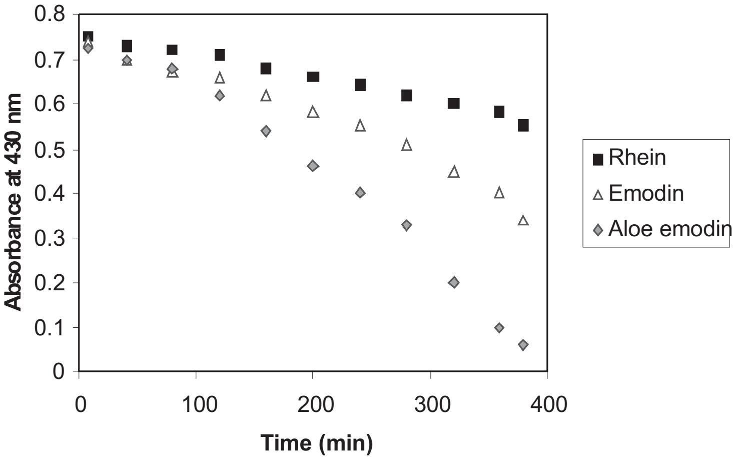

Figure 2. Experimental photodegradation velof the anthraquinones **(1)**, **(2)** and **(3)** (λ= 430 nm).

Table 1
Global properties of dihydroxyanthraquinones (**1**, **2** and **3**): dipolar moment (*DM*), highest occupied molecular orbitals (*HOMO*), lowest occupied molecular orbitals (*LUMO*), (|*HOMO-LUMO*|) energy difference (Δ| *H-L*|) and heat of formation (*HF*).

Molecule	*DM* (D)	*HOMO* (au)	*LUMO* (au)	Δ| *H-L*| (au)	*HF* (kcal/mol)
Aloe-emodin **(1)**	3.6259	-0.3171	-0.0222	0.2949	-161.1
Emodin **(2)**	3.6508	-0.3150	-0.0204	0.2946	-174.1
Rhein **(3)**	7.9787	-0.3279	-0.0339	0.2940	-197.1

ity. This suggests that electronic transfer from electron donator groups to these molecules is possible during the electronic excitation processes. However, there is not a correlation between LUMO energy and the photodegradation velocity. Note that a single determinant function does not represent correctly unoccupied orbitals and the use of multiconfigurational approaches is required (22) to calculate electron affinity. On the contrary, the $\Delta|H\text{-}L|$ energy difference presents very close values and follows the order **1** > **2** > **3**. The possibility to excite an electron from HOMO to LUMO shows an inverse trends that the experimental photoreactivy rate; i.e., the less reactive compound **3** has the lowest $\Delta|H\text{-}L|$ energy.

Thermodynamic stability of these molecules is associated with the heat of formation. A very stable molecule would be more difficult to transform in the corresponding radical. In this case, the order of photolability: *HF*(**1**) < *HF*(**2**) < *HF*(**3**) is in concordance with the order of photoreactivity (higher *HF* less photoreactive). Similar theoretical trends were found in previous theoretical work with hyperlipoproteinemic drugs (fibrates) (23).

Fluorescence spectra of **1**, **2** and **3** compounds given by Vargas et al. (11) have maxima wavelengths for excitation, λ_{exc}= 451, 465, and 437 nm, see table 2. In that Table, energy *HOMO* values, λ_{exc}, $\Delta|\ H\text{-}L|$, λ_{emi}, and *DM* are also displayed in order to make easier comparisons with photoreactivity. We found that the λ_{exc} values (451, 465, and 437 nm) may be related with the corresponding *HOMO* energies (-0.3171, -0.3150, and -0.3279 au), respectively. In addition, a good correlation between excitation energies (ε_{exc} = h/λ_{ex}) and *HOMO* energies is found, i.e. ε_{exc}(**3**) > ε_{exc}(**1**) > ε_{exc}(**2**) and HOMO(**3**) > HOMO(**1**) > HOMO(**2**). Note that high values of excitation wavelengths are associated to low excitation energies and viceverse.

On the other hand, experimental maxima wavelengths of emission (11) are: λ_{emis}= 537, 535, and 513 nm, correlate with the photoreactivity of **1**, **2**, and **3** compounds. The quantum yield (ϕ_{f1}= (λ_{emis}+λ_{exc})/λ_{emis}) is calculated as: 0.16, 0.14, and 0.04 for the above compounds, respectively. It was found a direct correlation between the photolabilitiy and quantum yield of fluorescence: ϕ_{fl}(**1**) > ϕ_{fl}(**2**) > ϕ_{fl}(**3**) in inverse order of dipolar moments, as shown in table 2 (*DM*(**1**) < *DM*(**2**) < *DM*(**3**)). This also is coherent with the fact that the microenvironment may have an important influence in the quantum yield.

The phototoxicity mechanism most probably involves reactions of electronic excited states of sensitizer molecules (S), (**1**, **2**, and **3)** that normally have a short-lived

Table 2
Correlation between wavelength of excitation (λ_{exc}), wave length of emission (λ_{emi}), and quantum yield of fluorescence data (Φ_{fl}) and calculated properties of dihydroxyanthraquinones.

Molecule	*HOMO* (au)	λ_{exc} (nm)	$\Delta(\lvert H\text{-}L\rvert)$ (au)	λ_{emi} (nm)	*DM* (D)	Φ_{fl}
Aloe-emodin **(1)**	-0.3171	451	0.2949	537	3.6259	0.16
Emodin **(2)**	-0.3150	465	0.2947	535	3.6508	0.14
Rhein **(3)**	-0.3279	437	0.2939	513	7.9787	0.04

singlet excited states. These states can overcome an intersystem crossing process to produce long-lived triplet states (24). Triplet sensitizer states can undergoes interactions with molecules in their vecinities. An energy transfer may occur to the oxygen molecule ground state (triplet state) to the excite state (singlet state). Singlet state of molecular oxygen is highly reactive and it is involved in photodynamic reactions that result in a fully oxidized form of biological systems (substrate). Thus, we evaluate also total energies of the triplet and singlet states for the O_2 molecule. The calculated excitation energy triplet → singlet ($^1\Delta_g$) was about 27 kcal/mol that compares reasonable well with experimental data of 22 kcal/mol (25).

It would be expected that the energy required to form the triplet state would be related with the formation of oxygen singlet. In order analyze these values excited triplet states of **1**, **2**, and **3** sensitizers were calculated with respect to the correspondent singlet states (ground states). Energy values of 40.2, 43.5, and 40.2 kcal/mol are displayed in the second row of table 3. The order found (**2** > **1** ≈ **3**) is contrary to that experimentally observed. Therefore, there is not a correlation between energies of triplet states formed from the photoactive molecule and the photodegradation velocity. These triplet states are close in energy to another oxygen singlet excited state ($^1\sum_g^+$) at about 38 kcal/mol (25). This suggests that a faster energy transfer of the triplet sensitizer could be first to the $^1\sum_g^+$ state and then it decay to the longest live state $^1\Delta_g$ (45 min) through internal conversion process.

Beside the mechanism of singlet oxygen photooxidation, S molecules may undergo reactions of electron transfer from the substrate (amino acids, proteins, nucleic acids, and other biological substances). The reduced sensitizer (S^-) can react with O_2 to produce superoxide radical (O_2^-) that is highly active for oxidation of substrates (24). Thus, energy of negatively charged **1**, **2** and **3** anthraquinones in the lowest doublet state ($^2S^-$) were evaluated. Energy differences between charged anthraquinones and neutral ones ($\Delta E(^2S^- - {}^1S)$) show that anions are more stable than neutral systems, as displayed in the third row of Table 3. This result may be explained by the electronic delocalization in these aromatic compounds. Similar results were reported in theoretical studies of the anionic π-radicals formation from polyaromatic starting materials used for the carbonization process (26).

Electron transfer from $^2S^-$ to $^3O_2$ is not feasible from the thermodynamic point of view because the energy gain of $^3O_2 + e \rightarrow {}^2O_2^-$ is only -10 kcal/mol (27) compared with -31

Table 3

Energy differences (ΔE) of triplet excited state (^3S), the negatively charged sensitizer ($^2S^-$), the hydrogenated radical in a doublet ($^2SH°$), and the quadruplet ($^4S^-$) excited states with respect to the singlet (^1S) ground state of sentitizers. In addition, excitation energies for $^4S^-$ and $^4SH°$ radicals to their respective excited states $^2S^-$ and $^2S^-$. Energy values are in kcal/mol.

ΔE Energy Difference	(^3S - ^1S)	($^2S^-$ - ^1S)	($^4S^-$ - $^2S^-$)	($^4S^-$ - ^1S)	($^2SH°$ - ^1S)	($^4SH°$ - $^2SH°$)
Aloe-emodin **(1)**	40.2	-31.1	54.1	23.0	-63.1	53.9
Emodin **(2)**	43.5	-31.4	46.1	14.7	-62.6	48.1
Rhein **(3)**	40.2	-41.7	50.0	9.3	-63.6	40.9

kcal/mol for the $^1S + e \rightarrow {}^2S^-$. Because the $^2S^-$ systems are stable, excitations of the double ground state to another doublet state of higher energy may occur and then an intersystem crossing mechanism leads to a quadruplet excited state, see values in column forth of table 3. On the other hand, results of total energy differences ($\Delta(^4S^- - {}^1S)$) between the excited quadruplet sensitizer ($^4S^-$) and the ground state ^1S may be the driving force for the electron transfer reaction $^4S^- + {}^3O_2 \rightarrow {}^1S + {}^2O_2^-$. Results for the $^4S^- \rightarrow {}^1S$ process are presented in column five of table 3. The order of these values correlates with the experimental photoreactivity. It means that $^4S^-$, surrounded by O_2 molecules, releases an electron as decays to ^1S and as more energy is liberated more probability that an electron transfer to O_2 occurs. The excited state $^4S^-$ may also transfer an electron by and intermediate excited state as the following process ($^4S^- \rightarrow {}^3S + e$), but it requires energy because $^4S^-$ is more stable than ^3S. If $^1O_2$ exists in some concentration, the formation of $^2O_2^-$ is also feasible because the energy difference of the $^1O_2 \rightarrow {}^2O_2^-$ process would be about 32 kcal/mol (25, 27). Thus the correlation between experimental data and theoretical findings results suggest that the formation of $^2O_2^-$ maybe a controlling step in the photodynamics process of these S compounds.

Another process for the photodynamics of these studied compounds may involve an H transfer from the substrate to the sensitizer to produce $^2SH°$ radical. Then, it reacts with O_2 to give hydrogen peroxide (H_2O_2). Calculations were carried out for $^2SH°$ compounds shown in fig. 1 adding H atoms to O(15), O(17) in **1** and **3** and to O(15), O(18) in **2**, respectively. Results, displayed in column six of table 3, indicate that formation of S-H bond is very favorable (about -63 kcal/mol) with respect to the ^1S sensitizer, because of the formation of a new O-H bond.

The formation of H_2O_2 by H° transfer to O_2 from the hydrogenated sensitizer may be produced in two steps: $H° + O_2 \rightarrow O_2H°$ and $O_2H° + H° \rightarrow H_2O_2$. The energy (E) gained in the formation of $O_2H°$ ($E(^2HO_2) - E(^3O_2) - E(H°)$) is only -51.1 kcal/mol. This is smaller than that obtained from the formation of S-H bond. Therefore excitation of $^2SH°$ to another doublet state or $^3O_2 \rightarrow {}^1O_2$ must occur to assure H transfer. Excited $^2SH°$ can overcome intersystem crossing to a $^4SH°$. Results of ($^4SH°$ - $^2SH°$) energy differences are presented in the last column of table 3. The order is concordant with experimental findings; i.e., higher release of energy implies higher photolability. Nevertheless, the energy released in going from $^4SH°$ to $^2SH°$ is not enough to overcome the stability of $^2S^-H$ bond. The whole process, however, is thermodynamically feasible because the formation of O-H bonds in $H^\circ + O_2 \rightarrow O_2H^\circ$ process contribute with about -51 kcal/mol. Nonetheless, the formation of H_2O_2 is less probable than the formation of $^2SH^\circ$, because it requires the transfer of two H° atoms.

Finally energy formation of radicals and bond strengths (diatomic binding energies from Eq. (5)) for all O-H bonds in the anthraquinones were evaluated. For example, the strength of O(16)-H, O(18)-H, O(20)-H bonds in compound **1** (see labels shown in fig. 1) were calculated. No correlations between the photodegradation rate and the radical stability and O-H bond strengths were found.

4. Conclusions and comments

1) Qualitative parametric methods can be used, for establishing correlation between experimental data of phototoxicity of aloe-emodin, emodin, and rhein and some theoretical calculated properties.

2) Calculated total dipolar moment and heat of formation of the compounds **1**, **2**, and **3**, used as sensitizers, correlate with experimental photodegradation velocity. It was found that a higher stability and polarity of the sensitizer implies less photoactivity. High stability of sensitizer means more difficulty to generate the correspondent radical and high dipolar moment signifies a less effective radical formation because of solvation effects.

3) Correlation of calculated HOMO energy of compounds **1**, **2** and **3** and experimental wavelength of excitation (λ_{exc}) is observed.

4) Different mechanisms of photoxidation were explored: formation of singlet oxygen, hydrogen transfer, and creation of negatively charged sensitizer. Singlet oxygen formation energy does not correlate with the photolability experimental findings. A mechanism of intersystem crossing between ^3S and ^3O to give ^1O in the ${}^1\sum_g^+$ state and it decays to the longest life state, ${}^1\Delta_g$.

5) Formation of a $^2S^-$ intermediate is feasible because the electronic charge can be delocalized in the aromatic systems. Excitation of this species to doublet and through an intersystem crossing process to generate $^4S^-$ is required to energetically allow the electron transfer to the $^3O_2$ to form $^2O_2^-$. There is a correlation between excitation energies and experimental findings and therefore, maybe the formation of $^2O_2^-$ is an intermediate in the photodynamic of these sensitizers. If $^1O_2$ exists in some concentration around S^- radicals, it also would contribute to the formation of $^2O_2^-$.

6) Hydrogen transfer mechanism to form $^2SH^\circ$ radicals is highly probable for substrates that have weak H atoms because the stability of these radicals. Excitation of $^2SH^\circ$ to doublets and the decay to quadruplets may occur in order to make possible the transference of H to $^3O_2$ to form O_2H°. There is concordance with experimental findings; i.e., a high excitation energy entails high photolability. However, this mechanism involves the transfer of two H atoms to form H_2O_2 and for that reason it is less probable.

7) Calculations of relative stability of radicals from **1**, **2** and **3** and O-H bond strength do not correlate with the photolysis rate of these anthraquinones.

8) It is good to note that one single determinant and parametric methods are quite approximated approaches. Therefore, results shown are qualitative and further studies of excited states are required in order to gain a deeper understanding of the photodynamic processes of these anthraquinones.

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