THE JOURNAL OF PHYSICAL CHEMISTRY B

ARTICLE

pubs.acs.org/JPCB

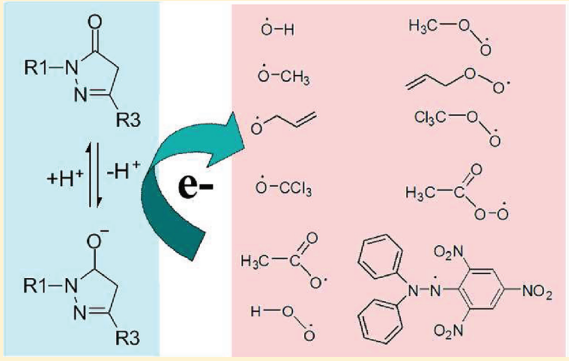
On the Outstanding Antioxidant Capacity of Edaravone Derivatives through Single Electron Transfer Reactions

Adriana Pérez-González and Annia Galano*

Departamento de Química, División de Ciencias Básicas e Ingeniería, Universidad Autónoma Metropolitana-Iztapalapa, Av San Rafael Atlixco No.186, Col.Vicentina C.P.09340, México D.F.

Supporting Information

ABSTRACT: The single electron transfer (SET) reactions from the neutral and anionic forms of 27 edaravone derivatives to 11 free radicals have been studied using density functional theory and the Marcus theory. All of the studied compounds were found to be able to efficiently scavenge at least some of the studied radicals. More than half of them were found to be excellent free radical scavengers, via SET, under physiological conditions. Their SET reactions with all the studied radicals were found to have rate constants ranging from 10^6 to 10^9 M^{-1} s^{-1} (diffusion limited). Therefore, they are predicted to be versatile scavengers, able to deactivate free radicals of different nature. Functionalizing the R1 and R3 sites of the pyrazol-5-one ring with the NO group is not recommended for edaravone derivatives designed as free radical scavengers through the SET mechanism. In general, this family of compounds was found to be exceptionally good for scavenging free radicals by transferring one electron. Moreover they are predicted to be outstanding scavengers, even if they would only react by SET. In addition, the acid−base equilibrium was found to play an important role in their activity.



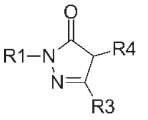
INTRODUCTION

In healthy organisms, there is a delicate balance between the production and the removal of free radicals, which warrants that they remain in low/moderate concentrations. Under such conditions, free radicals have beneficial effects. However, at high concentrations free radicals can be very harmful to living organisms. Such high concentrations are caused by an imbalance between the production and the consumption of free radicals, which is commonly referred to as oxidative stress (OS). This chemical stress is a major health problem currently associated to the development of several diseases such as cancer,[1] cardiovascular disorders,[2] atherosclerosis,[3] and Alzheimer's disease.[4] Therefore, the study of compounds that can efficiently act as free radical scavengers is an important and active area of research.

Edaravone (EDA, 3-methyl-1-phenyl-2-pyrazolin-5-one, Scheme 1), also known as MCI-186, is a recently developed neuroprotective drug that has been successfully used for treating acute stroke caused by cerebral thrombosis and embolism.[5] Its beneficial effects have been associated with its ability to scavenge free radicals.[6−10] Moreover, there is an increasing interest in the synthesis of edaravone derivatives designed to potentiate the free radical scavenging activity of this compound. Some of these derivatives also have been reported to present other beneficial properties, such as antitumor activity,[11,12] antiviral activity,[13,14] inhibition of the agent of tuberculosis,[15] and helpful effects for medical treatment of cancer and related diseases.[16]

It has been proposed that single electron transfer (SET) is one of the main antioxidant mechanisms of edaravone and its derivatives in aqueous solution and that their anionic forms have higher activity than the neutral ones.[6,8,9,17] On the basis of this evidence, a study on the electron-donating capability and the ease of deprotonation of a large series of edaravone derivatives has been recently reported.[18] In that work, the ionization energies, the pK_a's, and the anionic fractions at physiological pH were estimated, and some derivatives were proposed as ideal candidates for scavenging free radicals via SET. However, there are no previous reports on the relative antioxidant activity of different edaravone derivatives. There is also a lack of information on the relative antioxidant activity of the neutral and anionic forms of these compounds. Accordingly, it is the main goal of the present work to address these points. To that purpose, we have studied the kinetics of the SET reactions between 27 edaravone derivatives and their monoanions, with 11 free radicals of different

Scheme 1. Pyrazol-5-one Ring[a]



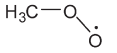
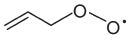
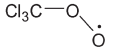
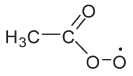
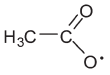
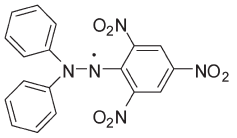
[a] Edaravone: R1 = Ph, R3 = CH_3, and R4 = H.

Received: October 15, 2011
Revised: December 17, 2011
Published: December 21, 2011

Table 1. Edaravone Derivatives Studied in This Work

	R1	R3		R1	R3
A1	Ph-	$-CH_3$	A2	2-pyridinyl−	$-CH_3$
B1	*p*-OCH_3−Ph−	$-CH_3$	B2	Ph−	$-OCH_3$
C1	*p*-$O(CH_2)_3$ ONO_2−Ph−	$-CH_3$			
D1	*p*-NH_2−Ph−	$-CH_3$	D2	Ph−	$-NH_2$
E1	*p*-CH_3−Ph−	$-CH_3$	E2	Ph−	−H
F1	*p*-Cl−Ph−	$-CH_3$	F2	Ph−	−Cl
G1	*p*-OH−Ph−	$-CH_3$	G2	Ph−	−OH
H1	*p*-$CH{=}CH_2$−Ph−	$-CH_3$	H2	Ph−	$-CH{=}CH_2$
I1	*p*-SH−Ph−	$-CH_3$	I2	Ph−	−SH
J1	*p*-CHO−Ph−	$-CH_3$	J2	Ph−	−CHO
K1	*p*-CN−Ph−	$-CH_3$	K2	Ph−	−CN
L1	*p*-NO_2−Ph−	$-CH_3$	L2	Ph−	$-NO_2$
M1	*p*-CF_3−Ph−	$-CH_3$	M2	Ph−	$-CF_3$
N1	*p*-NO−Ph−	$-CH_3$	N2	Ph−	−NO

Table 2. Free Radicals Studied in This Work

Acronym	Structure	Acronym	Structure
•R1		•R7	
•R2		•R8	
•R3		•R9	
•R4		•R10	
•R5		•R11	
•R6			

nature. This study has been performed in aqueous solution considering the acid−base equilibria.

COMPUTATIONAL DETAILS

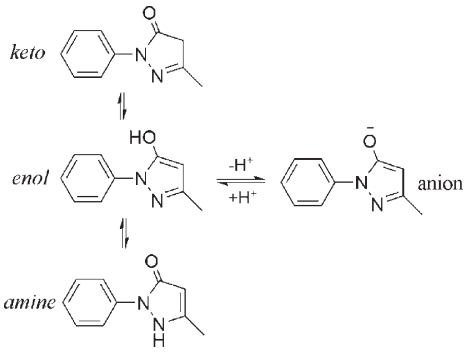
All the electronic calculations have been carried out with the Gaussian 09 package of programs,[19] using the M05-2X functional[20] and the 6-311++G(d,p) basis set, in conjunction with the SMD continuum model.[21] The reliability of this functional has been extensively proven.[22−30] Full geometry optimizations, without any symmetry constraints, and frequency calculations were performed for all the species, in aqueous solution, and local minima were identified by the absence of imaginary frequencies.

The rate constants (k) were calculated using Conventional Transition State Theory (TST)[31] and the 1 M standard state as

$$k = \frac{k_B T}{h} e^{-(\Delta G^{\ddagger})/RT} \quad (1)$$

where k_B and h are the Boltzmann and Planck constants and $\Delta G^{\ddagger}$ is the Gibbs free energy of activation, which was calculated using

Scheme 2. Anionic and Tautomeric Forms of Edaravone



the Marcus theory[32] as

$$\Delta G^{\ddagger} = \frac{\lambda}{4}\left(1 + \frac{\Delta G}{\lambda}\right)^2 \quad (2)$$

where ΔG is the free energy of reaction and λ is a reorganization term.

Most of the calculated rate constants (k) are close to the diffusion limit. Accordingly, the apparent rate constant (k_{app}) cannot be directly obtained from TST calculations. In the present work, the Collins−Kimball theory is used to that purpose[33]

$$k_{app} = \frac{k_D k_{act}}{k_D + k_{act}} \quad (3)$$

where k_{act} is the thermal rate constant, obtained from TST calculations (eq 1), and k_D is the steady-state Smoluchowski[34] rate constant for an irreversible bimolecular diffusion-controlled reaction

$$k_D = 4\pi R D_{AB} N_A \quad (4)$$

where R denotes the reaction distance; N_A is the Avogadro number; and D_{AB} is the mutual diffusion coefficient of the reactants A (free radical) and B (antioxidant). D_{AB} has been calculated from D_A and D_B according to ref 35, and D_A and D_B have been estimated from the Stokes−Einstein approach[36]

$$D = \frac{k_B T}{6\pi\eta a} \quad (5)$$

where k_B is the Boltzmann constant; T is the temperature; η denotes the viscosity of the solvent, in our case water ($\eta = 8.91 \times 10^{-4}$ Pa s); and a is the radius of the solute.

RESULTS AND DISCUSSION

The edaravone derivatives studied in this work are presented in Table 1. They have been constructed by replacement of the R1 (series 1) and R3 (series 2) moieties of edaravone (A1) with several groups. The substitute groups have different chemical nature, with their Hammett sigma constants ranging from −0.66 for the $-NH_2$ group to 0.91 for −NO. In addition, the A2 and C1 derivatives have been included since they have been already synthesized[9,37] and proposed as better antioxidants than edaravone itself.[9,37] The single electron transfer reaction from these compounds, and from their monoanions, to different free radicals (Table 2) has been studied. They have been modeled only in aqueous solution since nonpolar environments do not promote the necessary solvation of the ionic species involved in the SET

dx.doi.org/10.1021/jp209930y |J. Phys. Chem. B 2012, 116, 1180–1188

mechanism

$$HX + R^{\bullet} \rightarrow HX^{\bullet +} + R^{-}$$

$$X^{-} + R^{\bullet} \rightarrow X^{\bullet} + R^{-}$$

where HX represents the neutral form of the edaravone derivatives; X^{-} represents their monoanions; and $R^{\bullet}$ is the free radical.

Three nonionic tautomeric forms of edaravone have been previously proposed.[38,39] They are the *keto*, the *enol*, and the *amino* forms (Scheme 2). Their relative abundance has been estimated,[17] and it was found that more than 97% of edaravone is in its keto form, regardless of the polarity of the environment. Therefore, this is the only nonionic form considered in the present work. Regarding the monoanion we have used the structure previously reported,[38−43] which is shown in Scheme 2. The equivalent structures were also used for the studied derivatives.

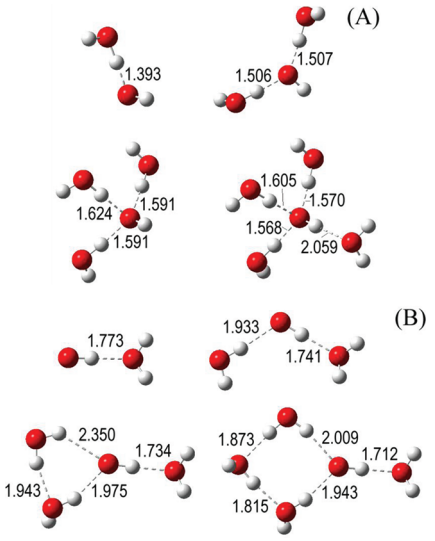


Figure 1. Optimized geometries of the (A) OH anion and (B) OH radical, with 1 to 4 explicit water molecules.

Regarding the conversion of free radicals into anions, via SET, there is an extra computational challenge, the proper description of the solvation of the anions. It has been previously reported that the largest errors derived from using solvent continuum models to that purpose arise when studying anions which concentrate charge on a single exposed heteroatom.[44] From the studied species, the OH anion is the only one in this situation. Therefore, we have analyzed the description of the solvation of this species in detail. The OH^{-} Gibbs free energy of solvation obtained from using the SMD model, without any explicit water molecules, is −97.5 kcal/mol. The experimental value recommended by Pliego and Riveros is −105 ± 0.5 kcal/mol.[45] Therefore, even when SMD accounts for 92.8% of the solvation, there are 7.5 kcal/mol that are not included in the description. This difference is attributed to strong short-range hydrogen bonding interactions between the anion and the solvent. As a result, a recommended strategy to improve the performance of continuum models is to combine them with explicit water molecules.[44,46]

We have tested this strategy for the $^{\bullet}OH/OH^{-}$ pair, including up to four water molecules (Figure 1). The rate constants (calculated using eq 6), for the reactions with edaravone, were found to be 1.09×10^{7}, 6.02×10^{9}, 6.15×10^{9}, 6.75×10^{9}, and 6.48×10^{9} M^{-1} s^{-1} for 0, 1, 2, 3, and 4 explicit water molecules, respectively. These values show that including the first water molecule has a huge effect on the rate constant, which becomes more than 550 times larger. However, the effect of the inclusion of the subsequent water molecules is almost negligible. These results support the importance of adding at least one water molecule to the continuum for properly describing the solvation of OH^{-}, in agreement with the proposal of Kelly, Cramer, and Truhlar.[44] Nevertheless, since it is generally accepted that the first solvation shell of OH^{-} contains four water molecules, we have used this particular cluster for estimating all the related data

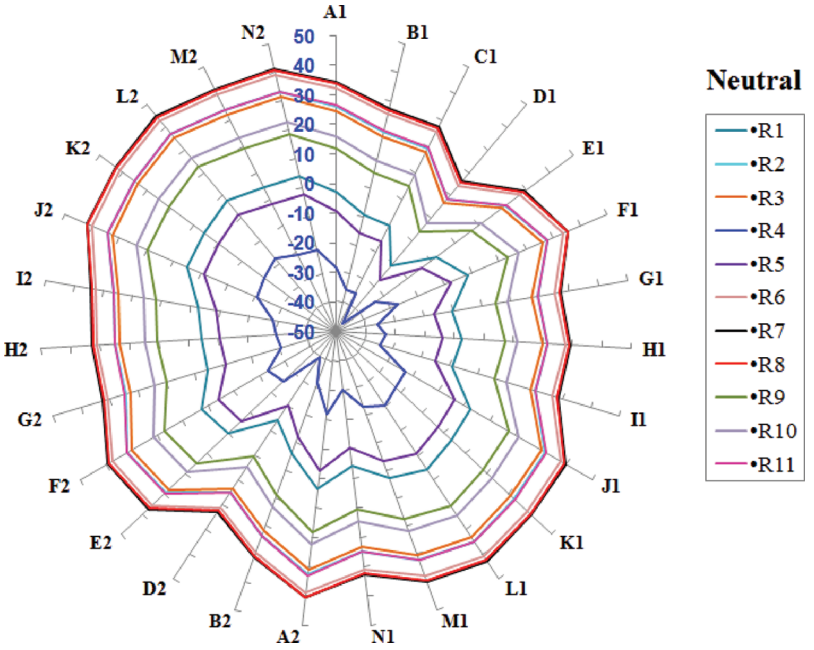


Figure 2. Gibbs free energies of reaction (kcal/mol) for the SET processes involving edaravone deriviatives, in their neutral form, and the studied free radicals.

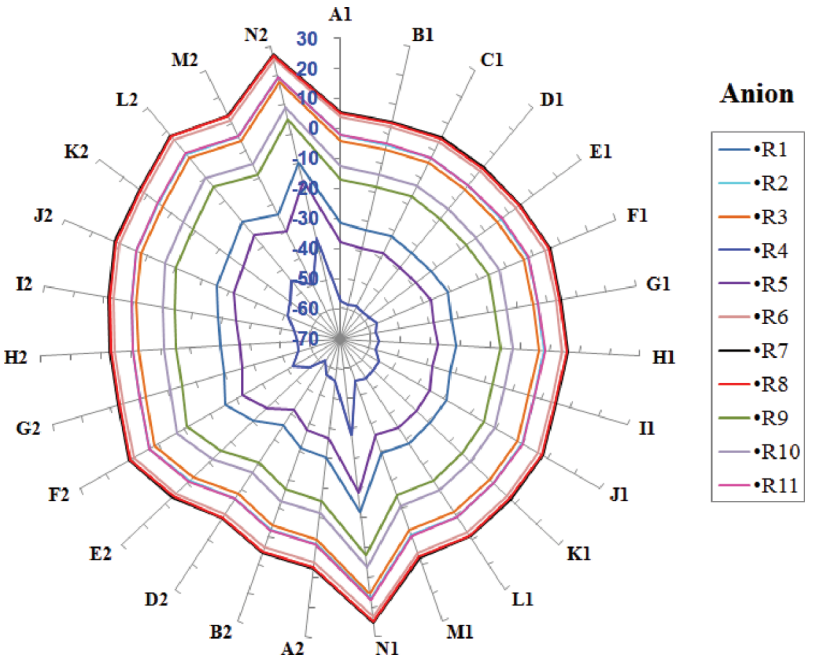


Figure 3. Gibbs free energies of reaction (kcal/mol) for the SET processes involving edaravone deriviatives, in their monoanionic form, and the studied free radicals.

reported in this work. A similar analysis was performed for the reactions with $^{\bullet}$OOH, using up to three water molecules (Figure 1S, Supporting Information). However, in this case the inclusion of explicit water molecules has only minor effects on the calculated rate constants. Accordingly, for all the other radical/anion pairs studied in this work, the solvation has been modeled using only SMD.

The Gibbs free energies of the reactions (ΔG) between the studied radicals and the edaravone derivatives, in their neutral and monoanionic forms, are provided in Tables 1S and 2S (Supporting Information). Since the calculated data are numerous, they have also been plotted in Figures 2 and 3 to facilitate direct comparisons. The electron acceptor capability of the studied radicals was found to follow the trend: $^{\bullet}$R4 > $^{\bullet}$R5 > $^{\bullet}$R1 > $^{\bullet}$R9 > $^{\bullet}$R10 > $^{\bullet}$R3 > $^{\bullet}$R2 > $^{\bullet}$R11 > $^{\bullet}$R6 > $^{\bullet}$R8 > $^{\bullet}$R7. For the electron transfer from the neutral form of edaravone derivatives, those involving radicals $^{\bullet}$R2, $^{\bullet}$R3, $^{\bullet}$R6, $^{\bullet}$R7, $^{\bullet}$R8, and $^{\bullet}$R11 were all found to be endergonic. Most of the reactions involving $^{\bullet}$R9 and $^{\bullet}$R10 were also found to be endergonic, except D1 + $^{\bullet}$R9, and D1 + $^{\bullet}$R10, while about half of the reactions with $^{\bullet}$R1 are exergonic. On the other hand, the SET processes involving $^{\bullet}$R4 and $^{\bullet}$R5 are all exergonic, except L2 + $^{\bullet}$R5. In general, edaravone derivatives D1 and D2 are those with the lowest values of ΔG when transferring an electron from their neutral forms (Figure 2). However, the nature of the reacting free radical seems to be more important to the thermochemical feasibility of the studied processes than the specific derivative involved in the reaction. While electron transfers from neutral derivatives to $^{\bullet}OCCl_3$ (R4) and $CH_3COO^{\bullet}$ (R5) are thermodynamically viable, most of the processes involving the other radicals are endergonic.

When the electron transfer takes place from the monoanions, the thermochemical feasibility of the processes logically increases. The only SET reactions that remain endergonic in this case are those involving radicals $^{\bullet}$R6 (except for its reaction with D2), $^{\bullet}$R7, and $^{\bullet}$R8. However, even for these radicals, the thermochemical feasibility is significantly increased with respect to the reactions involving the neutral antioxidants. Most of the other reactions are exergonic, or rather isoergonic, and most of the exceptions correspond to the electron transfers from N1 and N2 anions, which were found to be the edaravone derivatives that systematically produce higher values of ΔG when transferring an electron from their anionic forms (Figure 3). This is a logical finding since −NO is the strongest electro-acceptor group, among the studied substituents. However, as was described for the neutral species, in the case of the anions the thermochemical feasibility of the SET reactions is largely influenced by the nature of the reacting free radical and only moderately influenced by the different derivatives.

It should be noticed that positive values of ΔG do not necessarily mean that the corresponding SET reaction would not occur, especially if they are small values. Such processes can still take place at significant rates, and if their products rapidly react further, through reactions that are sufficiently exergonic to provide a driving force, they might still represent significant channels. Moreover, endergonic processes might play important roles in biological systems when there are not parallel reactions that are more energetically favored.

The Gibbs free energies of activation ($\Delta G^{\ddagger}$) are reported in Tables 3S and 4S (Supporting Information) for the reactions involving neutral and anionic derivatives, respectively. Some of the reactions involving the anionic derivatives of edaravone have high barriers, despite the fact that they are highly exergonic. This is particularly evident for the reactions of radicals $^{\bullet}$R4 and $^{\bullet}$R5, for which the $\Delta G^{\ddagger}$ values of the reactions with the derivative anions are significantly higher than those of the reactions with the neutral derivatives. Since it would be expected that the electrodonor capability of the anions would be higher than that of the corresponding neutral compound, this behavior is contra-intuitive. However, it can be explained based on the fact that these reactions correspond to the inverted region of the Marcus theory ($\Delta G < -\lambda$)[32a,47] and have the characteristic that ΔG is not only

dx.doi.org/10.1021/jp209930y |J. Phys. Chem. B 2012, 116, 1180–1188

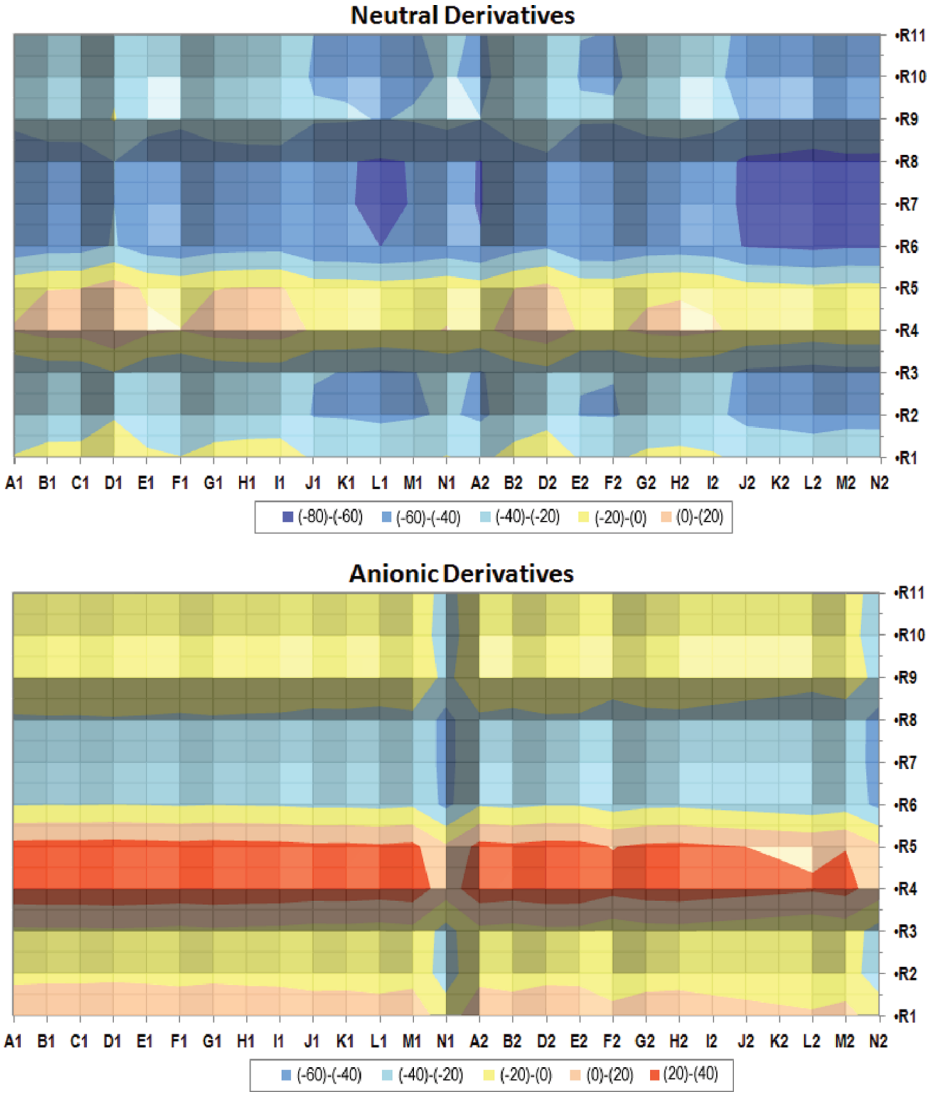


Figure 4. Difference between $-\lambda$ and ΔG (kcal/mol).

lower, but much lower, than $-\lambda$ (red zones, Figure 4). The λ values are provided in Tables 5S and 6S (Supporting Information). There are other reactions that, while located in the inverted region, are very close to the vertex of the parabola, and therefore their barrier remains low. This corresponds to the cases where the difference $(-\lambda) - \Delta G$ is positive but relatively small (pink regions, Figure 4). For the other radicals ($^{\bullet}$R2, $^{\bullet}$R3, and $^{\bullet}$R6 to $^{\bullet}$R11), on the other hand, the expected behavior was found, and the barriers of their reactions with the anionic derivatives are lower than those of the reactions with the neutral species.

Logically, the $\Delta G^{\ddagger}$ values are directly reflected on the rate constants (Tables 7S and 8S, Supporting Information). Therefore, the rate constants of radicals $^{\bullet}$R4 and $^{\bullet}$R5 are, in general, higher for the reactions with the neutral derivatives, compared to those involving the anionic species. For the rest of the radicals the general trend is that the rate constants of the reactions with the monoanions are higher.

It is very interesting that, except in a few cases, for every pair free radical−edaravone derivative at least one of the rate constants (with the anionic or with the neutral forms) is significantly high ($>10^6$ M^{-1} s^{-1}). This has important implications for the free radical scavenging activity of this family of compounds. Since the pK_a values of most of the studied derivatives have been estimated to be near the physiological pH,[18] under such conditions significant amounts of both their anionic and neutral forms are expected to be present. This means that the most reactive one would donate one electron to the free radical, deactivating it, and its population would be restored through the acid−base equilibrium.

The rate constants (k_{app}) of the SET reactions between the studied free radicals and the neutral form of the edaravone derivatives have been plotted in Figure 5 to facilitate direct comparisons among all the reported data. As this figure shows, the reactions involving $^{\bullet}$R4 and $^{\bullet}$R5 are all within the diffusion-limit regime, or close to it ($k_{app} \geq 10^8$ M^{-1} s^{-1}). This is also the case of the $^{\bullet}$R1 reactions with most derivatives and of the $^{\bullet}$R9 + D1, $^{\bullet}$R9 + D2, and $^{\bullet}$R10 + D1 reactions. For the SET processes involving the monoanions of edaravone derivatives (Table 8S (Supporting Information) and Figure 6), most of the reactions with $^{\bullet}$R4 and $^{\bullet}$R5 have k_{app} values lower than 10^8 M^{-1} s^{-1}. The exceptions are the SET processes from N1, K2, L2, and N2 to $^{\bullet}$R4 and from N1, L2, and N2 to $^{\bullet}$R5. On the other hand, most of the reactions

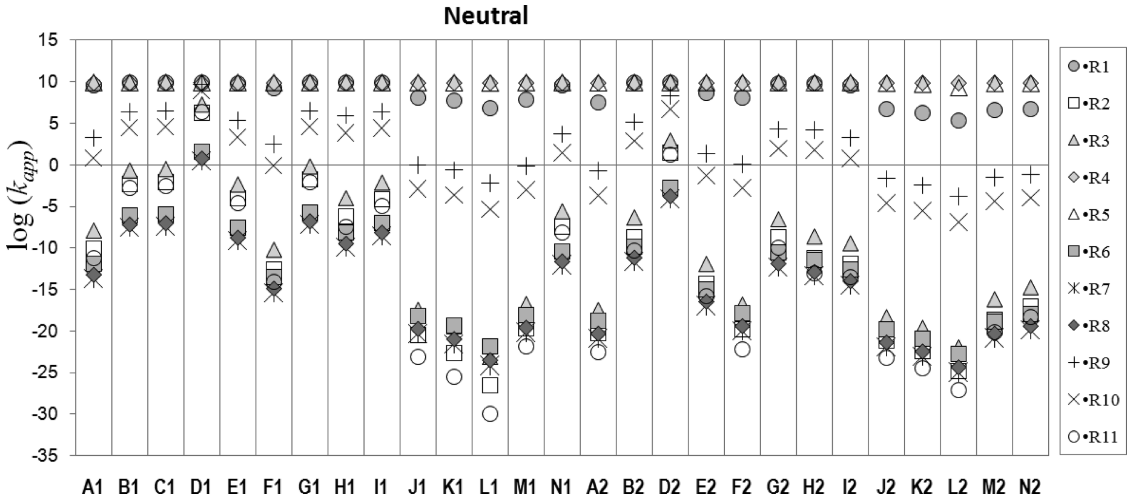


Figure 5. Rate constants of the SET reactions involving the neutral form of the edaravone derivatives.

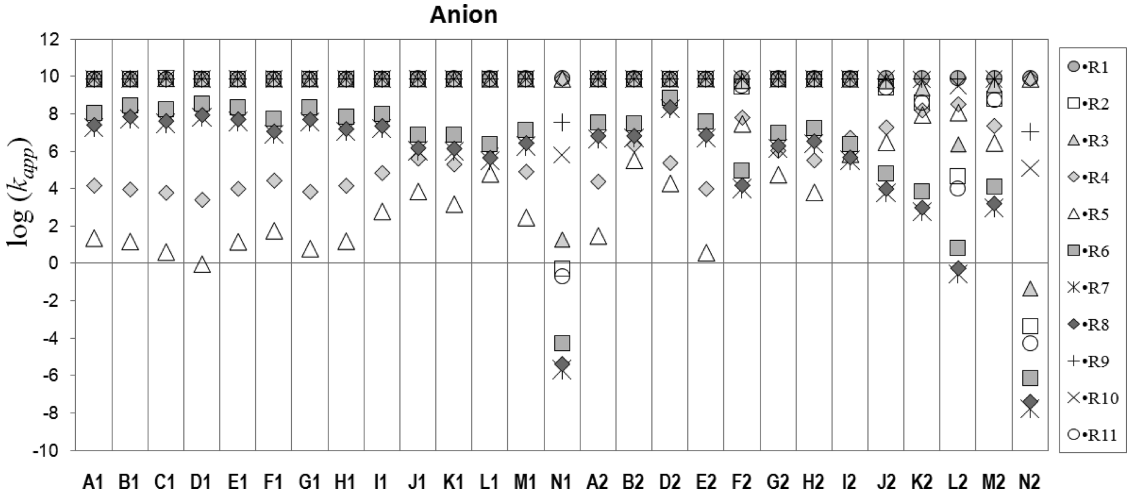


Figure 6. Rate constants of the SET reactions involving the anionic form of the edaravone derivatives.

involving •R1, •R2, •R3, •R9, •R10, and •R11 have values of k_{app} that are within, or close to, the diffusion-limited control.

Since the efficiency as a free radical scavenger of the studied compounds would be particularly important under physiological conditions, we have also calculated the corresponding total rate constant according to

$$k_{app}^{total} = p^N k_{app}^N + p^A k_{app}^A \quad (6)$$

where p^N and p^A account for the fractions of the neutral and the anionic forms of the edaravone derivatives, respectively, and k_{app}^N and k_{app}^A are their SET rate constants. The values of these total rate constants are reported in Table 9S (Supporting Information) and plotted in Figure 7. In this figure, a red line has been drawn at 10^6 M^{-1} s^{-1} to divide the plot into two separated regions: above the red line are located the free radical scavenging processes that are considered particularly efficient, and below the red line are those that are not expected to be very effective.

As Figure 7 shows, most of the studied edaravone derivatives are very efficient for scavenging a wide variety of free radicals (all those studied in this work), through the SET mechanism. In fact, the SET reactions that were found to have rate constants lower than 10^6 M^{-1} s^{-1}, under physiological conditions, are the exceptions. Edaravone derivatives A1 to J1, M1, A2, B2, and H2 are excellent for scavenging all the studied free radicals by donating one electron. These results are in agreement with the high efficiency as antioxidants previously proposed for compounds C1 and A2.[9,37] They are also in general agreement with the predictions derived from ionization energies and pK_a's.[18] According to them, derivatives A1, C1 to J1, A2, B2, E2, G2, H2, and I2 were identified as the best candidates for scavenging oxygenated free radicals through the SET mechanism. It should be noticed that a more detailed study, including kinetics, is needed to make more accurate predictions. After such study, B1 and M1 are also included in the ideal list, while E2, G2, and I2 are no longer among the best candidates for scavenging free radicals via SET. However, it is interesting that the overlap between the predictions made based only on chemical descriptors and those made based on kinetic consideration is wide. In fact, they agree for most of the studied species (more than 80%).

Derivatives J1, K1, L1, and I2 were found to be also excellent for scavenging most free radicals, and the exceptions correspond

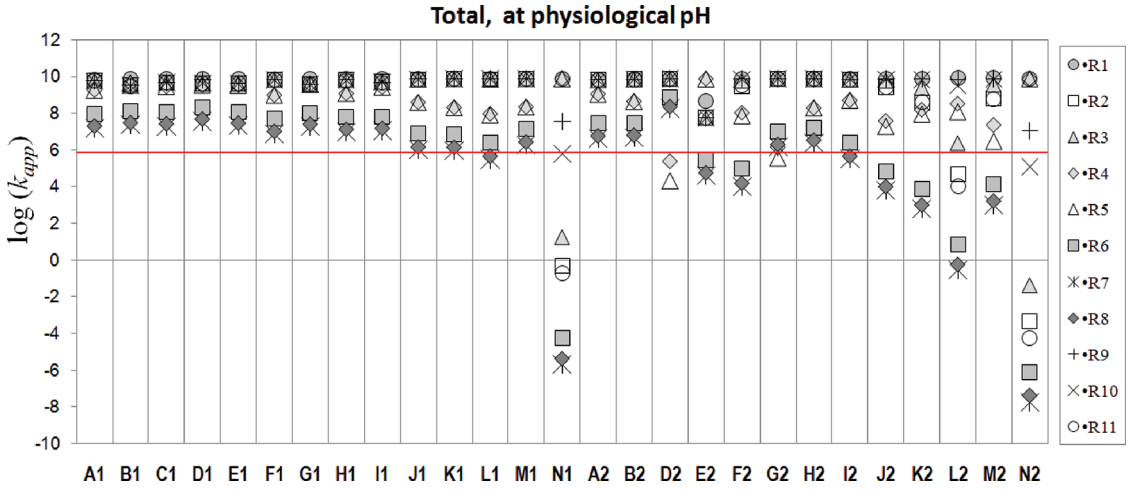


Figure 7. Total rate constants of the SET reactions, considering the molar fractions of neutral and anionic derivatives, at physiological pH.

to the reactions involving radicals •R7 and •R8, against which their protective activity is only good. The efficiency of the other derivatives as free radical scavengers, via SET, is largely influenced by the nature of the reacting radical. The worst scavengers were found to be N1 and N2. They would be unable to transfer an electron to •R2, •R3, •R6, •R7, •R8, •R9, and •R10 at significant rates under physiological conditions. Therefore, functionalizing the R1 and R3 sites of the pyrazol-5-one ring with the NO group is not recommended for designing compounds intended to act as free radical scavengers through the SET mechanism. In addition, derivatives obtained by functionalizing site R3 in the pyrazol-5-one ring generally produce derivatives with poorer electron-donor capabilities than those with the same functional group at site R1.

To put in perspective the efficiency of the studied compounds as free radical scavengers, some comparisons with other antioxidants have been performed. To that purpose it is recommended to compare different scavengers using their reactions with free radicals that are not particularly reactive. For example, if we use their reactions with •OH, we might conclude that they all have similar reactivity since the reactions with this radical often are diffusion-controlled.[48,49] Since such comparison might be misleading, we prefer to use one of the less reactive radicals; therefore, we have chosen •OOH. Moreover, precisely because of the relatively low reactivity of this radical, overall rate coefficients in the order of $10^5\ M^{-1}\ s^{-1}$ indicate that a chemical compound is a good radical scavenger, while rate coefficients in the order of $10^7\ M^{-1}\ s^{-1}$ or higher imply an outstanding antioxidant activity.[50]

It was found that, in aqueous solution, under physiological conditions, the reactions of •OOH with derivatives B1, C1, D1, E1, G1, and D2 (through SET processes) have rate constants in the order of $10^8\ M^{-1}\ s^{-1}$ (Table 9S, Supporting Information). This means that these reactions are faster than those involving most of the known antioxidants and only comparable to that of sesamol ($\sim 2.4 \times 10^8\ M^{-1}\ s^{-1}$).[51] The rate coefficients for the reactions of derivatives A1, F1, H1, I1, M1, A2, B2, and H2 were found to be slightly lower and similar to those of 2-propenesulfenic acid ($\sim 2.6 \times 10^7\ M^{-1}\ s^{-1}$)[51] and glutathione ($\sim 2.7 \times 10^7\ M^{-1}\ s^{-1}$),[52] which have been reported to be excellent for scavenging •OOH. Accordingly, 14 of the studied edaravone derivatives are among the best of the known •OOH scavengers. In addition, their efficiency for deactivating this radical was found to be much higher than that of carotenes ($\sim 10^5 - 10^6\ M^{-1}\ s^{-1}$),[53] allicin ($\sim 8 \times 10^3\ M^{-1}\ s^{-1}$),[54] melatonin ($\sim 2 \times 10^1\ M^{-1}\ s^{-1}$),[55] and caffeine ($3.3 \times 10^{-1}\ M^{-1}\ s^{-1}$). Derivatives J1, K1, L1, G2, and I2 also react with •OOH faster than allicin, melatonin, and caffeine and at rates ($\sim 10^6\ M^{-1}\ s^{-1}$) similar to the most reactive carotenes. Therefore, they also are very good •OOH scavengers. The efficiency of derivatives E2, F2, J2, K2, and M2 was found to be moderate ($k_{app} \sim 10^4 - 10^5\ M^{-1}\ s^{-1}$) but still better than that of allicin, melatonin, and caffeine and similar to those of some carotenes. Only derivatives N1, L2, and N2 were found to have negligible •OOH scavenging activity.

In addition, it should be noted that we are considering only the SET mechanism for the reactions of the edaravone derivatives, while other mechanisms were included in the estimations of the rate constants of the other antioxidants mentioned above. Therefore, the rate constants of the studied derivatives are only lower limits, and including other reaction mechanisms in the study of their antioxidant activity would lead to higher overall rate coefficients. This means that they are at least as good as predicted in this work for scavenging free radicals.

CONCLUSIONS

The SET reactions from the neutral and anionic forms of 27 edaravone derivatives to 11 free radicals, in aqueous solution, have been studied using density functional theory and the Marcus theory. Their relative order of reactivity is proposed for the first time. It is demonstrated that the most active form is not always the anion but depends on the particular derivative that is reacting and also on the nature of the involved free radical.

In general, the nature of the reacting free radical was found to be more important, to the thermochemical feasibility of the studied reactions, than the particular derivative that is involved in the process. This does not mean that the nature of the derivatives is unimportant. In fact, two derivatives (N1 and N2) were found to be significantly less efficient than the rest as free radical scavengers, based on their versatility. Therefore, functionalizing the R1 and R3 sites of the pyrazol-5-one ring with the NO group is not recommended for designing edaravone derivatives intended to act as free radical scavengers through the SET mechanism.

For every pair free radical−edaravone derivative, at least one of the rate constants (with the anionic or with the neutral forms) was found to be larger than $10^6\ M^{-1}\ s^{-1}$. This has important implications for the free radical scavenging activity of this family

of compounds since according to their pK_a values both forms should be present in significant amounts under physiological conditions for most of the studied compounds. Thus, this distribution warrants the presence of at least one active species under such conditions.

All of the studied compounds were found to be able to efficiently scavenge at least some of the studied radicals. More than half of them (A1, B1, C1, D1, E1, F1, G1, H1, I1, J1, K1, L1, M1, A2, B2, D2, G2, H2, and I2) were found to be excellent free radical scavengers, via SET, in aqueous solution under physiological conditions. Their SET reactions with all the studied radicals were found to have rate constants ranging from 10^6 to 10^9 M^{-1} s^{-1}. Therefore, they are predicted to be versatile scavengers, able to rapidly deactivate free radicals of different nature in aqueous solution.

In general, this family of compounds was found to be exceptionally good for scavenging free radicals, even if they would only react by SET, and the acid−base equilibrium was found to play an important role in their activity.

■ ASSOCIATED CONTENT

Supporting Information. Gibbs free energies of reaction, Gibbs free energies of activation, reorganization energies, and rate constant values. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: agalano@prodigy.net.mx.

■ ACKNOWLEDGMENT

The authors thank Laboratorio de Visualización y Cómputo Paralelo at UAM - Iztapalapa for the access to its computer facilities. A.P.-G. acknowledges CONACyT for a Doctoral fellowship.

■ REFERENCES

(1) (a) Boyd, N. F.; McGuire, V. *Free Radical Biol. Med.* **1991**, *10*, 185–190. (b) Nelson, R. L. *Free Radical Biol. Med.* **1992**, *12*, 161–168. (c) Knekt, P.; Reunanen, A.; Takkunen, H.; Aromaa, A.; Heliovaara, M.; Hakuunen, T. *Int. J. Cancer* **1994**, *56*, 379–382. (d) Omenn, G. S.; Goodman, G. E.; Thornquist, M. D. *N. Engl. J. Med.* **1996**, *334*, 1150–1155.

(2) (a) Riemersma, R. A.; Wood, D. A.; Macintyre, C. C. A.; Elton, R. A.; Gey, K. F.; Oliver, M. F. *Lancet* **1991**, *337*, 1–5. (b) Salonen, J. T.; Nyyssoner, K.; Korpela, H.; Tuomilehto, J.; Seppanen, R.; Salonen, R. *Circulation* **1992**, *86*, 803–811. (c) Street, D. A.; Comstock, G.; Salkeld, R.; Klag, M. *Circulation* **1994**, *90*, 1154–1161. (d) Kushi, L. H.; Folsom, A. R.; Prineas, R. J.; Mink, P. J.; Wu, Y.; Bostick, R. *N. Engl. J. Med.* **1996**, *334*, 1156–1162. (e) Stephens, N. G.; Parsons, A.; Schofield, P. M.; Kelly, F.; Cheesman, K.; Mitchinson, M. J.; Brown, M. J. *Lancet* **1996**, *347*, 781–786.

(3) (a) Panasenko, O. M.; Nova, T. V.; Azizova, O. A.; Vladimirov, Y. A. *Free Radical Biol. Med.* **1991**, *10*, 137–148. (b) Steinberg, D. *Circulation* **1991**, *84*, 1421–1425. (c) Janero, D. R. *Free Radical Biol. Med.* **1991**, *11*, 129–144. (d) Hodis, H. N.; Mack, W. J.; LaBree, L.; Cashin-Hemphill, L.; Sevanian, A.; Johnson, R.; Azen, S. *J. Am. Med. Assoc.* **1995**, *273*, 1849–1854.

(4) (a) Butterfield, D. A.; Hensley, K.; Harris, M.; Mattson, M.; Carney, J. *Biochem. Biophys. Res. Commun.* **1994**, *200*, 710–715. (b) Hensley, K.; Carney, J. M.; Mattson, M. P.; Aksenova, M.; Harris, M.; Wu, J. F.; Floyd, R. A.; Butterfield, D. A. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 3270–3274. (c) Butterfield, D. A.; Martin, L.; Carney, J. M.; Hensley, K. *Life Sci.* **1996**, *58*, 217–228. (d) Butterfield, D. A. *Chem. Res. Toxicol.* **1997**, *10*, 495–506. (e) Fay, D. S.; Fluet, A.; Johnson, C. J.; Link, C. D. *J. Neurochem.* **1998**, *71*, 1616–1625.

(5) Watanabe, T.; Tahara, M.; Todo, S. *Cardiovasc. Ther.* **2008**, *26*, 101–114.

(6) Yamamoto, Y.; Kuwahara, T.; Watanabe, K.; Watanabe, K. *Redox Rep.* **1996**, *2*, 333–338.

(7) Wang, L. F.; Zhang, H. Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3789–3792.

(8) Abe, S.; Kirima, K.; Tsuchiya, K.; Okamoto, M.; Hasegawa, T.; Houchi, H.; Yoshizumi, M.; Tamaki, T. *Chem. Pharm. Bull.* **2004**, *52*, 186–191.

(9) Nakagawa, H.; Ohyama, R.; Kimata, A.; Suzuki, T.; Miyata, N. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5939–5942.

(10) Lin, M.; Katsumura, Y.; Hata, K.; Muroya, Y.; Nakagawa, K. *J. Photochem. Photobiol. B* **2007**, *89*, 36–43.

(11) Tripathy, R.; Ghose, A.; Singh, J.; Bacon, E. R.; Angeles, T. S.; Yang, S. X.; Albom, M. S.; Aimone, L. D.; Herman, J. L.; Mallamo, J. P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1793–1798.

(12) Markovic, V.; Eric, S.; Juranic, Z. D.; Stanojkovic, T.; Joksovic, L.; Rankovic, B.; Kosanic, M.; Joksovic, M. D. *Bioorg. Chem.* **2011**, *39*, 18–27.

(13) Sujatha, K.; Shanthi, G.; Selvam, N. P.; Manoharan, S.; Perumal, P. T.; Rajendran, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4501–4503.

(14) Fan, X.; Zhang, X.; Zhou, L.; Keith, K. A.; Kern, E. R.; Torrence, P. F. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3224–3228.

(15) Castagnolo, D.; Manetti, F.; Radi, M.; Bechi, B.; Pagano, M.; De Logu, A.; Meleddu, R.; Saddi, M.; Botta, M. *Bioorg. Med. Chem.* **2009**, *17*, 5716–5721.

(16) Kakiuchi, Y.; Sasaki, N.; Satoh-Masuoka, M.; Murofushi, H.; Murakami-Murofushi, K. *Biochem. Biophys. Res. Commun.* **2004**, *320*, 1351–1358.

(17) Pérez-González, A.; Galano, A *J. Phys. Chem. B* **2011**, *115*, 1306–1314.

(18) Pérez-González, A.; Galano, A. *J. Phys. Chem. B* **2011**, *115*, 10375–10384.

(19) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A., et al. *Gaussian 09*, Revision A.08; Gaussian, Inc.: Wallingford, CT, 2009.

(20) Zhao, Y.; Schultz, N. E.; Truhlar, D. G. *J. Chem. Theory Comput.* **2006**, *2*, 364–382.

(21) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378–6396.

(22) Zavala-Oseguera, C.; Alvarez-Idaboy, J. R.; Merino, G.; Galano, A. *J. Phys. Chem. A* **2009**, *113*, 13913–13920.

(23) Velez, E.; Quijano, J.; Notario, R.; Pabón, E.; Murillo, J.; Leal, J.; Zapata, E.; Alarcón, G. *J. Phys. Org. Chem.* **2009**, *22*, 971–977.

(24) Vega-Rodriguez, A.; Alvarez-Idaboy, J. R. *Phys. Chem. Chem. Phys.* **2009**, *11*, 7649–7658.

(25) Galano, A.; Alvarez-Idaboy, J. R. *Org. Lett.* **2009**, *11*, 5114–5117.

(26) Black, G.; Simmie, J. M. *J. Comput. Chem.* **2010**, *31*, 1236–1248.

(27) Furuncuoglu, T.; Ugur, I.; Degirmenci, I.; Aviyente, V. *Macromolecules* **2010**, *43*, 1823–1835.

(28) Galano, A.; Macías-Ruvalcaba, N. A.; Campos, O. N. M.; Pedraza-Chaverri, J. *J. Phys. Chem. B* **2010**, *114*, 6625–6635.

(29) Galano, A.; Francisco-Marquez, M.; Alvarez-Idaboy, J. R. *Phys. Chem. Chem. Phys.* **2011**, *13*, 11199–11205.

(30) Galano, A. *Theor. Chem. Acc.* **2011**, *130*, 51–60.

(31) (a) Eyring, H. *J. Chem. Phys.* **1935**, *3*, 107–115. (b) Evans, M. G.; Polanyi, M. *Trans. Faraday Soc* **1935**, *31*, 875–894. (c) Truhlar, D. G.; Hase, W. L.; Hynes, J. T. *J. Phys. Chem.* **1983**, *87*, 2664–2682.

(32) (a) Marcus, R. A. *Annu. Rev. Phys. Chem.* **1965**, *16*, 155–196. (b) Marcus, R. A. *Rev. Mod. Phys.* **1993**, *65*, 599–610. (c) Marcus, R. A. *Pure Appl. Chem.* **1997**, *69*, 13–30.

(33) Collins, F. C.; Kimball, G. E. *J. Colloid Sci.* **1949**, *4*, 425–437.

(34) Smoluchowski, M. *Z. Phys. Chem.* **1917**, *92*, 129–168.
(35) Truhlar, D. G. *J. Chem. Educ.* **1985**, *62*, 104–106.
(36) (a) Einstein, A. *Ann. Phys. (Leipzig)* **1905**, *17*, 549–560. (b) Stokes, G. G. *Mathematical and Physical Papers*; Cambridge University Press: Cambridge, 1903; Vol. 3, p 55.
(37) Chegaev, K.; Cena, C.; Giorgis, M.; Rolando, B.; Tosco, P.; Bertinaria, M.; Fruttero, R.; Carrupt, P. A.; Gasco, A. *J. Med. Chem.* **2009**, *52*, 574–578.
(38) Ono, S.; Okazaki, K.; Sakurai, M.; Inoue, Y. *J. Phys. Chem. A* **1997**, *101*, 3769–3775.
(39) Lin, M.; Katsumura, Y.; Hata, K.; Muroya, Y.; Nakagawa, K. *J. Photochem. Photobiol. B: Biol.* **2007**, *89*, 36–43.
(40) Abe, S.; Kirima, K.; Tsuchiya, K.; Okamoto, M.; Hasegawa, T.; Houchi, H.; Yoshizumi, M.; Tamaki, T. *Chem. Pharm. Bull.* **2004**, *52*, 186–191.
(41) Higashi, Y.; Jitsuikia, D.; Chayamab, K.; Yoshizumia, M. *Recent Pat. Cardiovasc. Drug Discovery* **2006**, *1*, 85–93.
(42) Ohara, K.; Fujii, A.; Ichimura, Y.; Sato, K.; Mukai, K. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 421–426.
(43) Watanabe, T.; Tahara, M.; Todo, S. *Cardiovasc. Ther.* **2008**, *26*, 101–114.
(44) Kelly, C. P.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. A* **2006**, *110*, 2493–2499.
(45) Pliego, J. R.; Riveros, J. M. *Chem. Phys. Lett.* **2000**, *332*, 597–602.
(46) Cramer, C. J.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 760–768.
(47) See for example: (a) Ulstrup, J.; Jortner, J. *J. Chem. Phys.* **1975**, *63*, 4358–4368. (b) Marcus, R. A.; Sutin, N. *Biochim. Biophys. Acta* **1985**, *811*, 265–322. (c) Marcus, R. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1111–1121.
(48) Rose, R. C.; Bode, A. M. *FASEB J.* **1993**, *7*, 1135–1142.
(49) Galano, A.; Tan, D. X.; Reiter, R. J. *J. Pineal Res.* **2011**, *51*, 1–16.
(50) Vaidya, V.; Ingold, K. U.; Pratt, D. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 157–160.
(51) Galano, A.; Alvarez-Idaboy, J. R.; Francisco-Márquez, M. *J. Phys. Chem. B.* **2011**, *115*, 13101–13109.
(52) Galano, A.; Alvarez-Idaboy, J. R. *RSC Adv.* **2011**, *1*, 1763–1771.
(53) Galano, A.; Francisco-Márquez, M. *J. Phys. Chem. B* **2009**, *113*, 11338–11345.
(54) Galano, A.; Francisco-Márquez, M. *J. Phys. Chem. B* **2009**, *113*, 16077–16081.
(55) Galano, A. *Phys. Chem. Chem. Phys.* **2011**, *13*, 7147–7157.