THE JOURNAL OF PHYSICAL CHEMISTRY B

ARTICLE

pubs.acs.org/JPCB

Ionization Energies, Proton Affinities, and pK_a Values of a Large Series of Edaravone Derivatives: Implication for Their Free Radical Scavenging Activity

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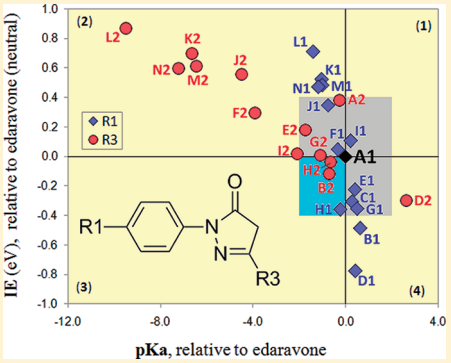
Supporting Information

ABSTRACT: The electron-donating capability (EDC) and the ease of deprotonation (ED) of 26 edaravone derivatives have been evaluated. Their first ionization energies have been used to assess their EDC. Four different approaches to obtain vertical ionization energies were tested, using a set of structurally related compounds. Those based on the electron propagator theory (EPT) were identified as the best ones. In particular, the partial third order (P3) approximation led to the lowest mean unsigned error (MUE = 0.10 eV). Two descriptors were used to evaluate ED: the proton affinity (PA) and the pK_a. It was found that pK_a values are better descriptors than PA values. Ideal candidates to perform as efficiently as, or even better than, edaravone itself are proposed. The recommendations were based on the simultaneous analyses of EDC and ED, and they should be particularly valid when the electron transfer mechanism plays an important role in the antioxidant activity of the studied compounds.



INTRODUCTION

Edaravone (EDA, 3-methyl-1-phenyl-2-pyrazolin-5-one, Scheme 1), also known as MCI-186, is a neuroprotective drug developed in Japan, where it was approved for treating acute stroke caused by cerebral thrombosis and embolism.[1] Its beneficial effects have been attributed to its free radical scavenging ability[2−6] because it has been reported to be very reactive toward reactive oxidative species (ROS) such as hydroxyl[4,6] and peroxyl radicals. This high reactivity toward ROS has drawn attention to the potential use of this compound as a radioprotector.[7,8] It has been shown that repeated treatment with edaravone reduces oxidative cell damage in rat brains.[9] Its beneficial effects on the atherosclerotic process in patients with cardiovascular diseases have been reviewed.[10] Edaravone has been proven to protect against retinal damage caused by oxidative stress, both *in vitro* and *in vivo*,[11] and to attenuate OH radical stress in diabetic rats.[12,13] It has been demonstrated that edaravone efficiently suppresses lipid peroxidation[14,15] and oxidative DNA damage.[14] It has also been proven to effectively block free radicals in the liver.[16]

Accordingly, the increasing interest in the synthesis of edaravone derivatives designed to potentiate the free radical scavenger activity of this compound is not surprising. Moreover, it has been reported that edaravone derivatives, obtained by the functionalization of the pyrazol-5-one ring (Scheme 1), offer a wide variety of synthetic and pharmacological possibilities. For example, some of them have been proven to have excellent antiviral activity,[17,18] to inhibit the agent of tuberculosis,[19] to act as antitumor agents,[20,21] and to be helpful for the medical treatment of cancer and related diseases.[22]

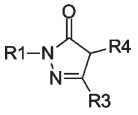
Nakagawa et al.[5] synthesized a large series of edaravone derivatives with substituents of different natures (electron-withdrawing groups, electron-donating groups, and π-conjugated groups) at sites 1, 3, and 4 of the pyrazolone ring (Scheme 1). They found one derivative (R1 = 2-pyridinyl, R3 = CH_3, R4 = H) with better antioxidant activity than that of edaravone when reacting with OH by the single electron transfer mechanism (SET) in aqueous solution. They also proposed that there are two factors influencing such activity: the oxidation potential and the amount of the anionic form. This is in line with other reports proposing that the anionic form has higher antioxidant activity than the neutral form of edaravone when reacting with free radicals through SET in polar media.[2,4,23] Chegaev et al.[24] obtained a series of edaravone derivatives with NO-donor moieties and found them to have high antioxidant powers and NO-dependent vasodilator properties. They proposed that the antioxidant activity is mainly modulated by lipophilicity.

However, to our best knowledge, there are no previous reports on the ionization energies of the edaravone derivatives. For edaravone itself, there is one experimental value of ionization energy (IE) previously reported, 8.00 eV.[25] There is also a

Received: May 20, 2011
Revised: July 27, 2011
Published: July 28, 2011

dx.doi.org/10.1021/jp2047163 | *J. Phys. Chem. B* 2011, 115, 10375–10384

Scheme 1. Pyrazol-5-one Ring, Edaravone: R1= Ph, R3 = CH_3, and R4 = H



theoretical estimation,[26] but it is 0.86 eV larger than the experimental value. Because the SET seems to play an important role in the antioxidant activity of this family of compounds, with the electron transfer taking place from the edaravone derivatives to the free radicals, the IE values become important magnitudes to characterize their reactivity. Therefore, it is one of the main goals of the present work to propose reliable IE values for the neutral and anionic forms of a large series of edaravone derivatives, functionalized with groups of various natures. To that purpose, the accuracy of four different approaches has been tested against the experimental values of vertical IE using a reference set of molecules that are structurally similar to edaravone derivatives and for which there is experimental data available.

There is also a lack of information on the proton affinities and pK_a values of edaravone derivatives. Because they are key descriptors to evaluate the ease of deprotonation and, therefore, the fraction of the anionic form (fa), it is another of the main goals of the present work to estimate their proton affinity (PA) and pK_a values, as well as the fa.

COMPUTATIONAL DETAILS

All the electronic calculations have been carried out with the Gaussian 09 package of programs,[27] using the M05-2X functional[28] and the 6-311++G(d,p) basis set. The reliability of this functional has been extensively proven.[29−37] Full geometry optimizations, without any symmetry constraints, and frequency calculations were performed for all the species, and local minima were identified by the absence of imaginary frequencies. For ionization energies and proton affinities, all the calculations were performed in vacuum. For the estimations of pK_a values, all the calculations were carried out in solution, using the solvent model density (SMD) continuum model[38] and water as solvent. In this model, the full solute electron density is used without defining partial atomic charges, and the solvent is not represented explicitly but by a dielectric medium with surface tension at the solute−solvent boundary. SMD is considered a universal solvation model because of its applicability to any charged or uncharged solute in any solvent or liquid medium for which a few key descriptors are known. More details on this model can be found elsewhere.[38]

Four different approaches have been used to estimate the electron detachment energies (vertical ionization energies) of the studied compounds. They are referred to as the following: electronic, Perdew−Levy, OVGF, and P3.

Electronic. The geometry relaxation of the $(N-1)$-electron species after the electron transfer is ignored and the ionization energies are calculated as

$$\mathrm{IE}^{E} = E_{N-1}(g_N) - E_N(g_N) \quad (1)$$

where E_N (g_N) is the energy of the N-electron system calculated at the geometry g_N and E_{N-1} (g_N) is the energy of the $(N-1)$ electron system calculated at the geometry g_N.

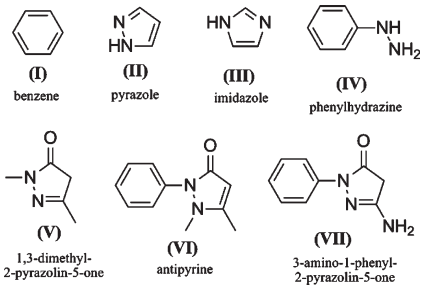


Figure 1. Set of reference molecules.

Perdew−Levy. This is the analogue to Koopman's theorem approximation[39] for the DFT framework and represents a particular case of vertical IE. Perdew et al.[40,41] demonstrated that, in exact DFT, the ionization energy is

$$\mathrm{IE}^{P-L} = -E_{\mathrm{HOMO}}(g_N) \quad (2)$$

where E_{HOMO} (g_N) represents the energy of the highest occupied molecular orbital (HOMO) of the N-electron system, from which an electron is removed.

OVGF and P3. The outer valence Green's function (OVGF)[42] and the partial third order (P3)[43] approximations are electron propagator theory (EPT)[42,44−46] -based methods. They are based on the Dyson equation,[45,47] which can be written as one-electron equations, such as

$$[F + \sum(\varepsilon_i)]\phi_i^{\mathrm{Dyson}} = \varepsilon_i\phi_i^{\mathrm{Dyson}} \quad (3)$$

where F is the one-electron Hartree−Fock (HF) operator; ϕ_p^{Dyson} are the eigenfunctions of these equations, that is, the Dyson orbitals, which may be interpreted as an overlap function between the N and $(N \pm 1)$ states; and ε_i are the eigenvalues, which correspond to the electron binding energies of the molecular system. The $\Sigma(\varepsilon_i)$ operator in eq 3 includes electron correlation and orbital relaxation effects that are neglected by the HF operator.

The pole strength (PS) is the norm of the Dyson orbital corresponding to a given electron binding energy, and its values range from 0 to 1. It is commonly used to diagnose the validity of the electron attachment and detachment energies obtained from OVGF and P3 calculations. These approximations remain valid only if the PS values are greater than 0.80−0.85.[48−50] For all the results presented here, the PS values were found to be larger than 0.87, which validates the use of these methods (Tables 2S and 5S in the Supporting Information).

The EPT-based methods provide electron binding energies for ionizations from any orbital from a single calculation, and they permit systematic improvements in incorporation of correlation and relaxation effects.[50] For these reasons, they have emerged as an economic, efficient, and reliable tool for the direct computation of vertical ionization energies from a single calculation.[47] These methods provide a foundation for the efficient and accurate evaluation of ionization energies and electron affinities of large molecules[51] and have been successfully used for predicting the electron binding energies of a large variety of chemical systems,[52−56] ranging from diatomic molecules to nucleotides[57,58] and substituted porphyrins.[59,60] Moreover, EPT calculations have been proven to be capable of predicting ionization energies with average errors smaller than 0.25 eV with respect to the experiments.[61,62]

Table 1. Signed Errors, from Calculations with Different Approaches, and Experimental Values of the First IE (eV) of the Reference Molecules

	approach				
molecule	electronic	Perdew−Levy	OVGF	P3	exptl
EDA	0.08	0.16	−0.24	0.01	8.00[25]
I	0.16	−0.05	−0.08	0.04	9.24[64]
II	0.50	0.34	0.20	0.32	9.15[65]
III	0.21	−0.07	−0.01	0.08	8.87[66]
IV	−0.01	0.06	−0.30	−0.09	7.86[67]
V	0.16	0.68	−0.14	0.01	8.65[25]
VI	0.19	0.55	0.01	0.24	7.86[25]
VII	0.07	0.23	−0.23	0.02	7.70[25]

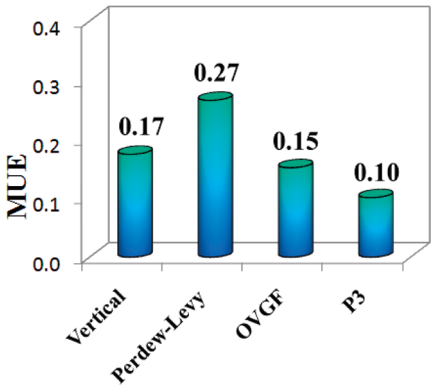


Figure 2. Mean unsigned errors (MUE) obtained from different approaches for the first IE of the reference set of molecules.

RESULTS AND DISCUSSION

Choosing the Best Approach. Because one of the main goals of this work is to accurately predict the ionization energies of edaravone derivatives, the first part of this investigation was focused on testing the accuracy of different approaches. To that purpose, edaravone and a reference set of molecules, which are structurally similar to the edaravone derivatives, were used (Figure 1). The calculated vertical ionization energies obtained when using the electronic, Perdew−Levy, OVGF, and P3 approaches are provided in the Supporting Information (Table 1S). The pole strengths for the OVGF and P3 calculations are also provided in the Supporting Information (Table 2S). The experimental values available for the reference set of molecules and the signed errors, calculated with respect to them, for all the tested approaches are reported in Table 1.

The maximum absolute errors (MAE), within the Perdew−Levy and electronic approaches, were obtained for molecules **V** (0.68 eV) and **II** (0.50 eV). For the EPT-based methods, the maximum absolute errors were found to be significantly lower. For the P3 approach, MAE = 0.32 eV, which corresponds to the IE of molecule **II**; and for the OVGF approach, the MAE = 0.30 eV, which corresponds to molecule **IV**. For EDA, any of the used approaches led to errors that are significantly lower than the only previous theoretical estimation (7.14 eV).[26] In particular, the P3 value is in excellent agreement with the experimental value.

Table 2. Edaravone Derivatives Studied in This Work

species	R1	R3	species	R1	R3
A1	Ph−	$-CH_3$	A2	2−pyridinyl−	$-CH_3$
B1	*p*-OCH_3−Ph−	$-CH_3$	B2	Ph−	$-OCH_3$
C1	*p*-$O(CH_2)_3ONO_2$−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 3. Hammett Sigma Constants (σ) of the Groups Used To Construct the Edaravone Derivatives

group	σ^a	group	σ^a
H	0	SH	0.15
NH_2	−0.66	Cl	0.23
$O(CH_2)_3ONO_2$	NA	CHO	0.42
OH	−0.37	CF_3	0.54
OCH_3	−0.27	CN	0.66
CH_3	−0.17	NO_2	0.78
$CH{=}CH_2$	−0.04	NO	0.91

[a] From ref 70.

The mean unsigned errors (MUE) arising from the calculations of the first vertical IE of the reference molecules with the tested approaches are plotted in Figure 2. All the obtained MUEs are lower than 0.3 eV. The Perdew−Levy approach yielded the largest average error (MUE = 0.27 eV), and the P3 approach yielded the smallest one (MUE = 0.10 eV), followed by the OVGF approach (MUE = 0.15 eV). This is in line with previous studies on the relative performance of these two EPT-based methods, which reported that the mean absolute errors of P3 calculations are to some extent lower than those arising from OVGF calculations, for small organic molecules.[43,63]

On the basis of the better performance of the EPT-based methods, with respect to the other tested approaches, they have been selected for estimating the electron detachment energies of the edaravone derivatives.

First Ionization Energies of Edaravone Derivatives. Even though three nonionic tautomeric forms of edaravone, the keto, the enol, and the amino forms, have been previously proposed,[6,68] it has been estimated that more than 97% of neutral edaravone is in the keto form, regardless of the polarity of the environment.[23] Therefore, this is the only nonionic form that is considered for EDA and its derivatives in the present work. However, because the anionic form has been proposed to have higher antioxidant activity than the neutral one and, on the basis of pK_a considerations,[23] it is expected to exist to a significant extent at a physiological pH, the electron detachment energies of the anions have also been estimated.

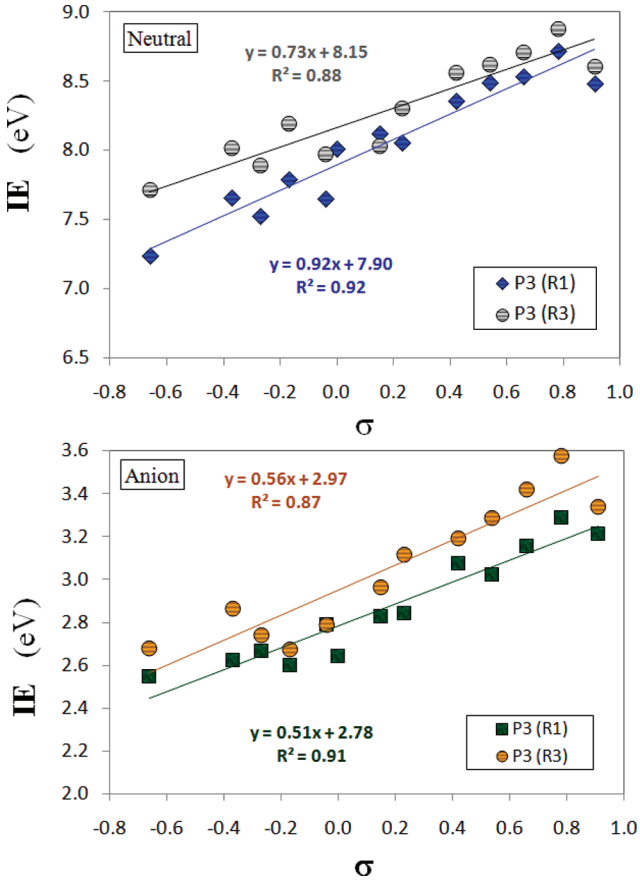


Figure 3. Relationship between the first ionization energies and the Hammett sigma constants (σ).

Table 4. First Ionization Energies (eV) of Edaravone Derivatives

	neutral		anion			neutral		anion	
species	OVGF	P3	OVGF	P3	species	OVGF	P3	OVGF	P3
A1	7.76	8.01	2.47	2.64	A2	8.07	8.34	2.33	2.49
B1	7.27	7.53	2.50	2.67	B2	7.64	7.90	2.57	2.75
C1	7.43	7.71	2.65	2.82					
D1	6.99	7.24	2.37	2.55	D2	7.47	7.72	2.52	2.68
E1	7.53	7.79	2.43	2.60	E2	7.93	8.19	2.48	2.68
F1	7.75	8.06	2.66	2.85	F2	8.01	8.31	2.86	3.12
G1	7.38	7.66	2.44	2.63	G2	7.75	8.02	2.67	2.87
H1	7.39	7.65	2.61	2.79	H2	7.71	7.98	2.60	2.79
I1	7.82	8.12	2.65	2.83	I2	7.75	8.03	2.74	2.97
J1	8.00	8.36	2.88	3.08	J2	8.23	8.57	2.89	3.19
K1	8.14	8.53	2.95	3.16	K2	8.37	8.71	3.09	3.42
L1	8.27	8.72	3.07	3.29	L2	8.50	8.88	3.17	3.58
M1	8.15	8.49	2.84	3.03	M2	8.31	8.62	2.98	3.29
N1	8.12	8.48	3.02	3.21	N2	8.30	8.61	3.03	3.34

The edaravone derivatives studied in this work are presented in Table 2. 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 natures, as is reflected by their Hammett sigma constants

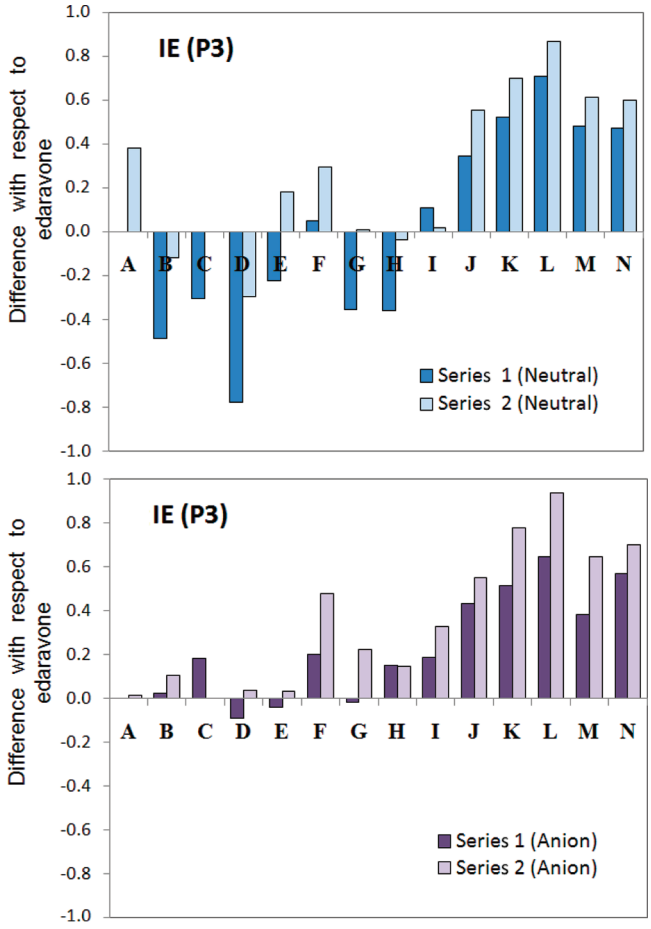


Figure 4. Difference in the first ionization energies (eV) of edaravone derivatives relative to that of edaravone.

(σ)[69](Table 3). Their σ values range from −0.66 for the $-NH_2$ group to 0.91 for −NO. In addition, the A2 and C1 derivatives have been included because they have been already synthesized.[5,24] Both of them are proposed to have higher antioxidant activity than edaravone.[5,24]

The ionization energies of the studied compounds are expected to be influenced by the presence of the substituents, in accordance with their electronic effect. As the electron withdrawing power of the group increases, the ionization energies are expected to decrease, while, as the electron-donor power increases, the ionization energies are expected to increase. The studied compounds follow this trend for substitutions at both the R1 and the R3 sites. This is shown in Figure 3, where the relationship between the first IE and the Hammett sigma constant is presented. Another regularity that arises from the analysis of the results presented in Table 4 is that the first ionization energies of the edaravone derivatives modified in site R1 are systematically lower than those of the derivatives modified with the same substituent in site R3. This trend appears for both the neutral and the ionic forms of the studied compounds and occurs regardless of the electronic nature of the substituent group. The only exceptions to this trend are as follows: structures I in the neutral form (IE(I1) > IE(I2)) and structures H in the anionic form (IE(I1) ≈ IE(I2)). The IE values obtained within the EPT approaches are presented in Table 4, and the corresponding PS values are reported in Table 5S in the Supporting

Table 5. Proton Affinities (in kcal/mol) of the Edaravone Derivative Anions

species	PA	species	PA
A1	332.03	A2	332.73
B1	333.52	B2	328.66
C1	328.90		
D1	334.80	D2	334.02
E1	332.93	E2	329.73
F1	327.91	F2	322.43
G1	332.55	G2	328.15
H1	329.74	H2	329.77
I1	328.15	I2	327.53
J1	323.63	J2	320.44
K1	321.72	K2	314.06
L1	319.53	L2	311.51
M1	324.22	M2	317.46
N1	320.58	N2	312.60

Information. The values obtained with the other approaches are also reported in the Supporting Information (Tables 3S and 4S).

To analyze in more detail the electron donating capability of the edaravone derivative, with respect to the parent molecule, the differences in the first ionization energies relative to that of edaravone have been plotted in Figure 4. In general, the effect of the substituent is in the same direction, regardless of the substitution site (R1 or R3). The only exceptions for the neutral forms of the derivatives are structures E and G. The first ionization energy of G1 is significantly lower than that of edaravone (0.36 eV), while the first ionization of G2 is practically the same as that of edaravone (higher by 0.01 eV). Therefore, when the substituent is the −OH moiety, its influence on the IE values is substantial when the substitution takes place in the phenyl ring, but its influence is negligible when the substitution takes place in the pyrazolin ring. For structures E1 and E2, the analysis is different. Because E1 has a methyl group in the phenyl group and another one in the pyrazolin group, it has an extra methyl group as compared to edaravone (R1). On the other hand, E2 has one fewer methyl group than edaravone. Because this group has an electron-donating character, the IE value of E1 is lower than that of edaravone, while the IE value of E2 is higher than that of edaravone. The exceptions for the anionic forms are structures D, E, and G. The IE of D1 is moderately lower than that of EDA (∼0.1 eV), while the IE of D2 is very similar to that of edaravone, though slightly higher (0.04 eV). The effect of the substituent on the IE values of E1 and E2 is almost negligible, but the values are of opposite signs. For the G structures, the substitution in R1 leaves the IE almost unchanged, while the IE of R2 is higher than that of EDA by 0.22 eV.

The effects of the substituents on the IE values of the neutral species are in line with the Hammet sigma constants; that is, those substituents with negative values of σ lower the IE of the derivative with respect to that of edaravone, while those groups with positive values of σ increase the IE with respect to that of edaravone. However, for the anions, this trend is not as apparent. All the anionic derivatives, except D1, E1, and G1, have higher IE values than that of EDA's anion.

In the particular case of derivatives A2 and C1, which cannot be characterized by the Hammet sigma constants, in their neutral forms, the IE of A2 is 0.38 eV higher than that of EDA, while the IE of C1 is 0.31 eV lower than that of EDA. Regarding their anionic forms, the IE of A2 is very similar to that of EDA, while the IE of C1 is higher than that of EDA by 0.18 eV. Therefore, the facility for electron-donation is not responsible for the higher antioxidant activity of A2 reported by Nakagawa et al.[5] This suggestion is supported by the oxidation potentials estimated by these authors,[5] as they found them to be identical for A2 and EDA. Moreover, these authors found that the relationship between the antioxidant activity and the oxidation potential was not simply proportional, but V-shaped, and they proposed that the efficiency of A2 for radical scavenging is due to the increase of its anion form.[5] On the other hand, the higher antioxidant activity of C1 reported by Chegaev et al.[24] can be rationalized in terms of IE.

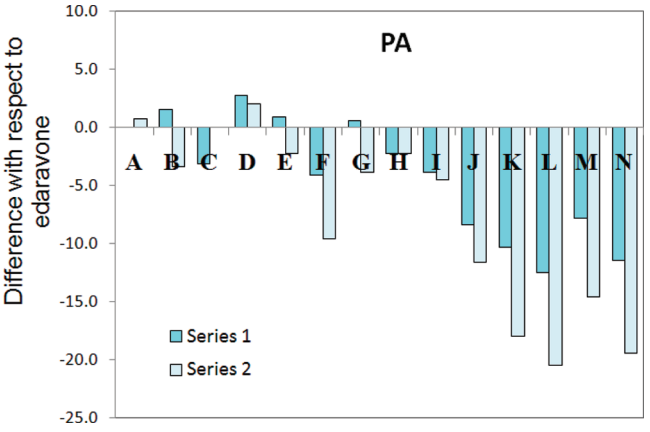


Figure 5. Difference in the proton affinities (kcal/mol) of edaravone derivatives relative to that of edaravone.

Proton Affinities. A key quantity that allows the estimation of the relative ease of deprotonation of a series of compounds is the proton affinity of the base involved in the protonation−deprotonation equilibrium. The PA of the species A^- is defined as the negative of the molar enthalpy change (ΔH), at 298.15 K, of the hypothetical gas-phase reaction:

$$A^-(g) + H^+(g) \rightarrow HA(g)$$

In this work, A^- and HA represent the anionic and neutral forms of the studied species, and the PA has been used to evaluate the proclivity of the edaravone derivatives to form the corresponding anions. Even though PA is by definition in the gas phase, the solvents effects are not taken into account; PA values are very helpful and have been widely used for describing large varieties of chemical systems.[71] Moreover the experimental data concerning PA has increased dramatically in the last decades.

The calculated values of PA are reported in Table 5. They have not been compared with other results because this is the first report on the PA of these compounds. In general, for every pair of derivatives with an identical substituent, the PA is higher for that with the substituent in R1. The only exception to this trend was found for structures H (substituent, —CH═CH_2), with PA values for H1 and H2 that are practically the same (Table 5).

The relative values of PA, compared to that of edaravone, are plotted in Figure 5. As this figure shows, most of the studied derivatives have lower proton affinities than edaravone, which indicates that they should be more prompt to deprotonate than the parent compound. The exceptions are B1, D1, E1, G1, A2,

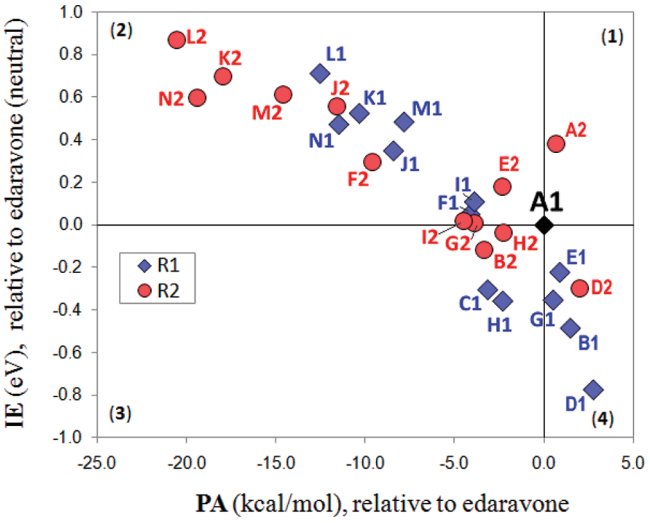


Figure 6. Ionization energies vs proton affinities of the studied derivatives relative to edaravone.

and D2. However, the PA values of A2, E1, and G1 are very similar to that of edaravone. Analyzing the effect of the substitution on the PA for each pair of derivatives, with identical substituent groups, it can be noticed that it is the same (increase or decrease) in most of the studied cases. The exceptions are structures B, E, and G. In these three cases, the substitution in R1 increases the PA value, while the substitution in R3 decreases the PA value, with respect to that of edaravone. As expected, the PA values of all the edaravone derivatives with electron-withdrawing substituents, that is, groups with positive σ values, are lower than that of EDA, and this effect is stronger for substitutions in R3 than it is for substitutions in R1. For electron-donating substituents, the only one that has the same effect on the PA value (increase with respect to edaravone) regardless of the substitution site is $-NH_2$, that is, the group with the most negative value of σ. For the other groups with negative σ, the substitution in R1 increases the PA, while the substitution in R3 decreases the PA.

First Ionization Energies vs Proton Affinities. According to the above discussions and in line with chemical intuition, modifications of edaravone with electron-withdrawing groups lead, in general, to derivatives with ionization energies higher than that of EDA, and therefore, such derivatives are expected to be less efficient as electron donors, that is, less efficient as antioxidants through the SET mechanism, than edaravone. At the same time, the presence of electron-withdrawing groups decreases the proton affinity and therefore increases the fraction of the anionic form. Logically, modifying EDA with electron-donating groups has the opposite effects: the resulting derivatives have lower ionization energies and higher proton affinities than those of edaravone.

The efficiency of these compounds as free radical scavengers has been associated with both low ionization energies and large fraction of the anionic form (more active than the neutral one). Therefore, designing edaravone derivatives with better performance as antioxidants than edaravone itself, on the basis of these two properties, is a challenge because groups with a strong electron-donating or electron-withdrawing character have the opposite effect. Accordingly, it may be hypothesized that substituents with weak or moderate electron-donating or electron-withdrawing characters are the best candidates for modifying edaravone to produce better antioxidants.

Figure 6 shows a plot that allows comparing, simultaneously, both the IE and PA values of the studied derivatives with respect to edaravone (A1). The structures located in quadrant 1 have higher IE values and higher PA values than those of edaravone. Accordingly, it might be expected that they behave as poorer antioxidants than edaravone. However, the only compound located in this quadrant is A2, which has been previously reported to be a better free radical scavenger than edaravone.[5] Accordingly, it seems that, at least for this compound, IE and PA are not enough to explain the observed behavior, and more extensive and detailed analyses of the involved chemical processes are needed. Moreover, this suggests that even though the ease of donating electrons and the fraction of the anionic form are key factors to the antioxidant activity of edaravone and its derivatives, they are not necessarily the only ones ruling such activity. In our opinion, the importance of other factors would increase as the importance of the SET process decreases, compared to other possible mechanisms of action such as hydrogen transfers or radical adduct formation.

The species in quadrant 2 (Figure 6) have higher IE values but lower PA values than those of edaravone. This means that they are expected to deprotonate more easily than EDA and, therefore, to have larger fractions of the anionic form, but as neutral species, they are less able to donate electrons. Species in quadrant 4 have just the opposite characteristics: they have lower IE values but higher PA values than those of EDA.

Species in quadrant 3 have just the desired behavior: lower IE values and lower PA values than those of edaravone. Therefore, they are expected to be better free radical scavengers than their parent molecule is through the SET mechanism. One of these species is C1, which is one of the compounds synthesized by Chegaev et al.[24] and described as having better antioxidant activity than edaravone. Therefore, in this case, the analysis of IE and PA seems to be enough to explain the observed behavior, and therefore, it seems that the SET mechanisms play a key role in the free radical scavenging activity of this compound.

Species H1 and H2, both with the $—CH{=}CH_2$ group as substituent, are also located in quadrant 3 (Figure 6). On the basis of IE and PA values alone, they are both predicted to be better antioxidants than EDA. The σ value of this group is almost zero (-0.04), which supports the hypothesis that substituents with weak electronic effects would produce better SET antioxidants. In addition, H1 is predicted to be better than H2, indicating a larger effect of the structure modification with this group when it takes place at site R1, compared to R3. In fact, H1 has values of both IE and PA that are significantly lower than those of edaravone, while the PA of H2 is lower than that of EDA but its IE is almost the same as that of EDA.

The other species located in quadrant 3 is B2. The substituent group in this case is $-OCH_3$, which has moderate electronic effects ($\sigma = -0.25$), but the substitution site is R3, which seems to fade its overall influence on the analyzed properties, compared to R1. In fact, changing the substitution site to R1 (derivative B1) causes an increase in PA that moves the location of the species to quadrant 4. According to this analysis, the antioxidant activity of B2 is predicted to be higher than that of EDA, provided that the major mechanism of reaction is SET.

pK_a Values. As mentioned above, even though proton affinities provide relevant information on the intrinsic propensity of a chemical species to deprotonate, this property does not take

Table 6. pK_a Values of Edaravone Derivatives and Estimated Fractions of the Anionic Form (fa) in Aqueous Solution at Physiological pH

species	pK_a	fa	species	pK_a	fa
A1	6.9[a]	0.76	A2	6.64	0.85
B1	7.54	0.42	B2	6.19	0.94
C1	7.18	0.63			
D1	7.32	0.54	D2	9.52	0.01
E1	7.31	0.55	E2	5.17	0.99
F1	6.57	0.87	F2	3.00	~1.00
G1	7.40	0.50	G2	5.82	0.97
H1	6.67	0.84	H2	6.26	0.93
I1	7.12	0.66	I2	4.80	~1.00
J1	6.14	0.95	J2	2.39	~1.00
K1	5.85	0.97	K2	0.27	~1.00
L1	5.48	0.99	L2	−2.60	~1.00
M1	5.88	0.97	M2	0.47	~1.00
N1	5.71	0.98	N2	−0.31	~1.00

[a] From ref 24.

into account the effects of the solvent. To include such effects, we have estimated the pK_a values. For this purpose, we have used the proton exchange method, also known as the isodesmic method or the relative method.[72] It involves the reaction scheme

$$HA + Ref^- \leftrightarrow A^- + HRef$$

where HRef/Ref^- is the acid/base pair of a reference compound, which should be structurally similar to the system of interest. Within this approach, the pK_a is calculated as

$$pK_a(HA) = \frac{\Delta G_s}{RT \ln 10} + pK_a(HRef) \quad (4)$$

where the experimental value of the reference acid, HRef, is used. In our case, we have chosen HRef = edaravone, which has been reported to have pK_a = 6.9.[24]

The pK_a values estimated for the species studied in this work are reported in Table 6, together with the fraction of their anion form (fa) at physiological pH. To calculate fa, we have obtained the acid constants (K_a) from the pK_a values:

$$K_a = 10^{-pK_a} \quad (5)$$

Then, using the definition of the equilibrium constant, for the deprotonation equilibrium ($HA \leftrightarrow A^- + H^+$)

$$K_a = \frac{[A^-][H^+]}{[HA]} \quad (6)$$

The fraction of the anion can be easily obtained as

$$fa = \frac{K_a}{K_a + [H^+]} \quad (7)$$

where $[H^+]$ is calculated from the pH. At physiological pH (7.4), $[H^+] = 3.98 \times 10^{-8}$ M.

In addition to the pK_a of edaravone, Chegaev et al.[24] also reported the pK_a values of structures B1 (pK_a = 7.06) and C1 (pK_a = 7.11). The values estimated in the present work for these derivatives agree well with the experimental values. This agreement supports the reliability of the pK_a values reported here for the first time for the other compounds. However, the pK_a values

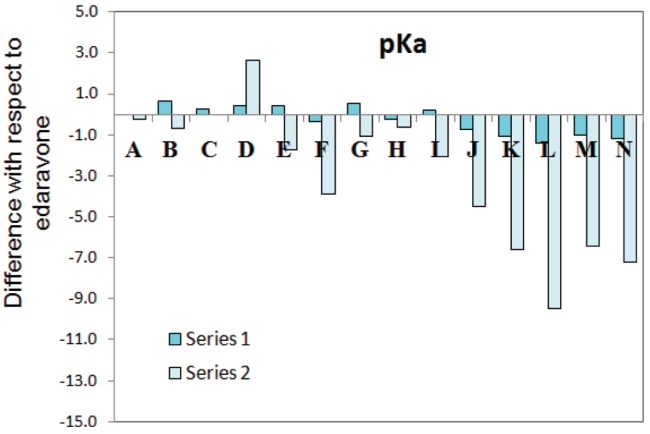


Figure 7. Difference in the pK_a of edaravone derivatives relative to that of edaravone.

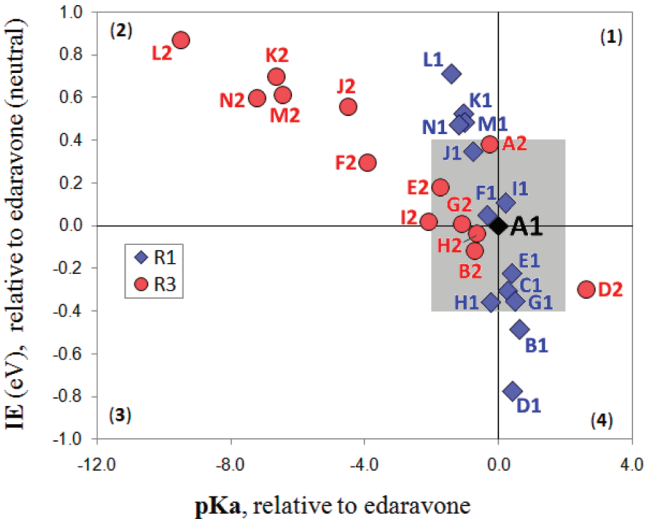


Figure 8. Ionization energies vs pK_a values of the studied derivatives relative to edaravone.

obtained for species K2, L2, M2, and N2 are very low, even negative. Therefore, further estimations of their pK_a values are highly recommended. In any case, the main purpose of the pK_a estimations in the present work is to use them for comparison with that of edaravone. Such relative values are trustworthy, regardless of the accuracy of the individual pK_a values, since a cancellation of errors is expected because of the structure similarities.[73−75]

It was found that the influence of the modifications in site R3 on the pK_a values of the studied species is stronger than that of modifications in R1. It was found that the range of pK_a value variation for species of series 1 is ~2 units of pK_a, while this range is ~12 units of pK_a for series 2. This seems to be a logical finding because in series 2 the substitution site (R3) is very close to the deprotonated site, while in series 1 (R1) the substitutions would mainly modify the electronic properties of the phenyl moiety.

The values of pK_a for the studied derivatives, relative to that of edaravone itself, are plotted in Figure 7. Comparing this figure with Figure 5, it can be seen that, even when the trends are the same as those found for PA, the solvation has an influence on the relative ease of deprotonation. One of the main differences is

that, while the PA of A2 is slightly higher than that of EDA, its pK_a is slightly lower. This indicates that A2 would have a larger fraction of the anionic form than EDA (Table 6), which supports the proposal of Nakagawa et al.[5] and might justify its higher antioxidant activity. Another difference concerns derivatives C1 and I1. Their PA values are significantly lower than that of EDA, but their pK_a values are slightly higher (0.28 and 0.22 units of pK_a, respectively) than that of EDA. Figure 7 also shows that, in general, the presence of the solvent increases the effect of the substituent groups in R1, with respect to substitutions in R3, regarding the ease of deprotonation.

First Ionization Energies vs pK_a Values. A new map, simultaneously showing the ease of deprotonation and the electron-donating ability of the studied compounds, has been constructed (Figure 8). The solvent effects have been included by replacing PA values with pK_a values. Because IE values are usually estimated from experiments in gas phase, we have keep them that way. Logically, the differences between the relative pK_a values and the relative PA values are reflected in this graphic. In this plot, we have included an "ideal" rectangle (colored in gray) that intends to highlight those derivatives that we predict to be as good as, or even better than, edaravone itself for scavenging free radicals. This zone was constructed on the basis of the errors that might arise from calculations, according to the following reasoning. It has been established that theoretical prediction of accurate pK_a values is a challenging task and that mean absolute deviations smaller than 2 units of pK_a are reasonably accurate.[72] Therefore, we have used this threshold to limit the ideal zone. Even though EPT methods are capable of predicting IE values within approximately 0.25 eV of the experimental values,[76] their accuracy within the continuum solvent models is not clear yet. That is another reason why we have used gas phase IE values in this section. Therefore, we have increased the limit of possible errors to 0.4 eV to construct the ideal rectangle shown in Figure 8.

According to the map shown in this figure, derivatives H1, H2, and B2 are expected to have the best antioxidant activity among all the studied compounds. This statement is based on their location in the IE vs pK_a map. They are all located inside the ideal rectangle and also in quadrant 3. Derivatives C1, E1, F1, G1, H, I1, J1, A2, E2, and G2 are also expected to be good candidates for that purpose, because, even though they are not in quadrant 3, they are all located inside the ideal rectangle. All of them are recommended for scavenging free radicals as efficiently as, or even more efficiently than, edaravone itself, at least when the SET mechanism plays an important role in such activity.

This map (Figure 8) also explains the results reported by Chegaev et al.[24] and by Nakagawa et al.[5] for derivatives C1 and A2, respectively. The higher antioxidant activity of the C1 derivative, compared to that of EDA, can be rationalized in terms of its lower IE, while the higher antioxidant activity of the A2 derivative, compared to that of EDA, can be justified by its lower pK_a, which led to a higher fraction of the anionic form (0.85 vs 0.76).

CONCLUSIONS

The electron-donating capability and the ease of deprotonation of 26 edaravone derivatives have been evaluated in this work. They had been previously proposed as key factors in the antioxidant activity of this kind of compounds. The first ionization energies have been used to assess the electron-donating capability, and the proton affinity (PA) and the pK_a have been used to evaluate the ease of deprotonation.

A reference set of molecules, which are structurally similar to edaravone derivatives, was used to test the suitability of different approaches to accurately reproduce experimental IE. EPT-based methods were identified as the ones with best performance, and they were selected for estimating the ionization energies of the edaravone derivatives. In particular, the P3 approximation led to the lowest mean unsigned error (MUE = 0.10 eV).

Low ionization energies and a large fraction of the anionic form (more active than the neutral one) are both desirable for edaravone derivatives intended to act as efficient free radical scavengers. Even though this means that designing edaravone derivatives with better performance as antioxidants than edaravone itself is a challenge (groups with strong electron-donating or electron-withdrawing characters have the opposite effect on producing edaravone derivatives with low ionization energies and higher proton affinities), we have identified a set of derivatives that are recommended for this purpose. They are derivatives H1, H2, and B2, which are proposed to be the best candidates, and also C1, E1, F1, G1, H, I1, J1, A2, E2, and G2. All of them are recommended for scavenging free radicals as efficiently as, or even more efficiently than, edaravone itself, at least when the SET mechanism plays an important role in such activity.

ASSOCIATED CONTENT

Supporting Information. Calculated IE values obtained by electronic, Perdew−Levy, OVGF, and P3 approaches, pole strengths for the OVGF and P3 calculations, and Cartesian coordinates of the optimized structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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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 the doctoral fellowship.

REFERENCES

(1) Watanabe, T.; Tahara, M.; Todo, S. *Cardiovasc. Ther.* **2008**, *26*, 101.
(2) Yamamoto, Y.; Kuwahara, T.; Watanabe, K.; Watanabe, K. *Redox Rep.* **1996**, *2*, 333.
(3) Wang, L.-F.; Zhang, H. -Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3789.
(4) Abe, S.; Kirima, K.; Tsuchiya, K.; Okamoto, M.; Hasegawa, T.; Houchi, H.; Yoshizumi, M.; Tamaki, T. *Chem. Pharm. Bull.* **2004**, *52*, 186.
(5) Nakagawa, H.; Ohyama, R.; Kimata, A.; Suzuki, T.; Miyata, N. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5939.
(6) Lin, M.; Katsumura, Y.; Hata, K.; Muroya, Y.; Nakagawa, K. *J. Photochem. Photobiol., B* **2007**, *89*, 36.
(7) Anzai, K.; Furuse, M.; Yoshida, A.; Matsuyama, A.; Moritake, T.; Tsuboi, K.; Ikota, N. *J. Radiat. Res.* **2004**, *45*, 319.
(8) Sasano, N.; Enomoto, A.; Hosoi, Y.; Katsumura, Y.; Matsumoto, Y.; Shiraishi, K.; Miyagawa, K.; Igaki, H.; Nakagawa, K. *J. Radiat. Res.* **2007**, *48*, 495.

(9) Yamamoto, Y.; Yanagisawa, M.; Tak, N. W.; Watanabe, K.; Takahashi, C.; Fujisawa, A.; Kashiba, M.; Tanaka, M. *Redox Rep.* **2009**, *14*, 251.
(10) Higashi, Y.; Jitsuikia, D.; Chayamab, K.; Yoshizumia, M. *Recent Pat. Cardiovasc. Drug Discovery* **2006**, *1*, 85.
(11) Inokuchi, Y.; Imai, S.; Nakajima, Y.; Shimazawa, M.; Aihara, M.; Araie, M.; Hara, H. J. *J. Pharmacol. Exp. Ther.* **2009**, *329*, 687.
(12) Saini, A. K.; Patel, R. J.; Sharma, S. S.; Kumar, A. *Pharmacol. Res.* **2006**, *54*, 6.
(13) Saini, A. K.; Kumar, A.; Sharma, S. S. *Eur. J. Pharmacol.* **2007**, *568*, 164.
(14) Zhang, N.; Komine-Kobayashi, M.; Tanaka, R.; Liu, M.; Mizuno, Y.; Urabe, T. *Stroke* **2005**, *36*, 2220.
(15) Noora, J. I.; Uedab, Y.; Ikeda, T.; Ikenoue, T. *Neurosci. Lett.* **2007**, *414*, 5.
(16) Kono, H.; Woods, C. G.; Maki, A.; Connor, H. D.; Mason, R. P.; Rusyn, I.; Fujii, H. *Free Radical Res.* **2006**, *40*, 579.
(17) Sujatha, K.; Shanthi, G.; Selvam, N. P.; Manoharan, S.; Perumal, P. T.; Rajendran, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4501.
(18) Fan, X.; Zhang, X.; Zhou, L.; Keith, K. A.; Kern, E. R.; Torrence, P. F. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3224.
(19) 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.
(20) 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.
(21) Markovic, V.; Eric, S.; Juranic, Z. D.; Stanojkovic, T.; Joksovic, L.; Rankovic, B.; Kosanic, M.; Joksovic, M. D. *Bioorg. Chem.* **2011**, *39*, 18.
(22) Kakiuchi, Y.; Sasaki, N.; Satoh-Masuoka, M.; Murofushi, H.; Murakami-Murofushi, K. *Biochem. Biophys. Res. Commun.* **2004**, *320*, 1351.
(23) Pérez-González, A.; Galano, A. *J. Phys. Chem. B* **2011**, *115*, 1306.
(24) 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.
(25) Vondrak, T.; Bastl, Z. J.; Böhm, S. *J. Chem. Soc., Perkin Trans. 2* **1988**, 641.
(26) (a) Wang, L. F.; Zhang, H. Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3789. (b) Tiwari, A. K. *Curr. Sci.* **2004**, *86*, 1092.
(27) 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.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M. Rega; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R. E.; Stratmann, O.; Yazyev, A. J.; Austin, R.; Cammi, C.; Pomelli, J. W.; Ochterski, R.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision A.08; Gaussian, Inc.: Wallingford CT, 2009.
(28) Zhao, Y.; Schultz, N. E.; Truhlar, D. G. *J. Chem. Theory Comput.* **2006**, *2*, 364.
(29) Zavala-Oseguera, C.; Alvarez-Idaboy, J. R.; Merino, G.; Galano, A. *J. Phys. Chem. A* **2009**, *113*, 13913.
(30) Velez, E.; Quijano, J.; Notario, R.; Pabón, E.; Murillo, J.; Leal, J.; Zapata, E.; Alarcón, G. *J. Phys. Org. Chem.* **2009**, *22*, 971.
(31) Vega-Rodriguez, A.; Alvarez-Idaboy, J. R. *Phys. Chem. Chem. Phys.* **2009**, *11*, 7649.
(32) Galano, A.; Alvarez-Idaboy, J. R. *Org. Lett.* **2009**, *11*, 5114.
(33) Black, G.; Simmie, J. M. *J. Comput. Chem.* **2010**, *31*, 1236.
(34) Furuncuoglu, T.; Ugur, I.; Degirmenci, I.; Aviyente, V. *Macromolecules* **2010**, *43*, 1823.
(35) Galano, A.; Macías-Ruvalcaba, N. A.; Campos, O. N. M.; Pedraza-Chaverri, J. *J. Phys. Chem. B* **2010**, *114*, 6625.
(36) Galano, A.; Francisco-Marquez, M.; Alvarez-Idaboy, J. R. *Phys. Chem. Chem. Phys.* **2011**, *13*, 11199–11205.
(37) Galano, A. *Theor. Chem. Acc.* DOI: 10.1007/s00214-011-0958-0. Published Online First: May 22, 2011.
(38) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378.
(39) Koopmans, T. *Physica* **1933**, *1*, 104.
(40) Perdew, J. P.; Parr, R. G.; Levy, M.; Balduz, J. L., Jr. *Phys. Rev. Lett.* **1982**, *49*, 1691.
(41) Perdew, J. P.; Levy, M. *Phys. Rev. B* **1997**, *56*, 16021.
(42) von Niessen, W.; Schirmer, J.; Cederbaum, L. S. *Comput. Phys. Rep.* **1984**, *1*, 57.
(43) Ortiz, J. V. *J. Chem. Phys.* **1996**, *104*, 7599.
(44) Herman, M. F.; Freed, K. F.; Yeager, D. L. *Adv. Chem. Phys.* **1981**, *48*, 1.
(45) Ortiz, J. V. *Adv. Quantum Chem.* **1999**, *35*, 33.
(46) Linderberg, J.; Öhrn, Y. *Propagators in Quantum Chemistry*, 2nd ed.; Wiley-Interscience: Hoboken, NJ, 2004.
(47) Mishra, M. K.; Medikeri, M. N. *Adv. Quantum Chem.* **1996**, *27*, 225.
(48) Dolgounitcheva, O.; Zakrzewski, V. G.; Ortiz, J. V.; Ratovski, G. V. *Int. J. Quantum Chem.* **1998**, *70*, 1037.
(49) Ortiz, J. V. *Int. J. Quantum Chem.* **2003**, *95*, 593.
(50) Singh, R. K.; Ortiz, J. V.; Mishra, M. K. *Int. J. Quantum Chem.* **2010**, *110*, 1901.
(51) Flores-Moreno, R.; Ortiz, J. V. *J. Chem. Phys.* **2009**, *131*, 124110.
(52) Ortiz, J. V. *Computational Chemistry: Reviews of Current Trends*; Leszczynski, J., Ed.; World Scientific: Singapore, 1997.
(53) Ortiz, J. V.; Zakrzewski, V. G.; Dolgounitcheva, O. *Conceptual Perspectives in Quantum Chemistry*; Kluwer: Dordrecht, 1997.
(54) Ferreira, A. M.; Seabra, G.; Dolgounitcheva, O.; Zakrzewski, V. G.; Ortiz, J. V. *Quantum−Mechanical Prediction of Thermochemical Data*; Kluwer: Dordrecht, 2001.
(55) Flores-Moreno, R.; Zakrzewski, V. G.; Ortiz, J. V. *J. Chem. Phys.* **2007**, *127*, 134106.
(56) Galano, A. *Theor. Chem. Acc.* DOI: 10.1007/s00214-011-0958-0. Published Online First: May 22, 2011.
(57) Zakjevskii, V. V.; King, S. J.; Dolgounitcheva, O.; Zakrzewski, V. G.; Ortiz, J. V. *J. Am. Chem. Soc.* **2006**, *128*, 13350.
(58) Zakjevskii, V. V.; Dolgounitcheva, O.; Zakrzewski, V. G.; Ortiz, J. V. *Int. J. Quantum Chem.* **2007**, *107*, 2266.
(59) Dolgounitcheva, O.; Zakrzewski, V. G.; Ortiz, J. V. *J. Am. Chem. Soc.* **2005**, *127*, 8240.
(60) Dolgounitcheva, O.; Zakrzewski, V. G.; Ortiz, J. V. *J. Phys. Chem. A* **2005**, *109*, 11596.
(61) Flores-Moreno, R.; Ortiz, J. V. *J. Chem. Phys.* **2008**, *128*, 164105.
(62) Flores-Moreno, R.; Melin, J.; Dolgounitcheva, O.; Zakrzewski, V. G.; Ortiz, J. V. *Int. J. Quantum Chem.* **2010**, *110*, 706.
(63) Dolgounitcheva, O.; Zakrzewski, V. G.; Ortiz, J. V. *J. Chem. Phys.* **2001**, *114*, 130.
(64) Average from all the vertical ionization energies reported by NIST: (a) Howell, J. O.; Goncalves, J. M.; Amatore, C.; Klasinc, L.; Wightman, R. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 3968. (b) Kovac, B.; Mohraz, M.; Heilbronner, E.; Boekelheide, V.; Hopf, H. *J. Am. Chem. Soc.* **1980**, *102*, 4314. (c) Kaim, W.; Tesmann, H.; Bock, H. *Chem. Ber.* **1980**, *113*, 3221. (d) Sell, J. A.; Kupperman, A. *Chem. Phys.* **1978**, *33*, 367. (e) Kobayashi, T. *Phys. Lett.* **1978**, *69*, 105. (e) Klasinc, L.; Novak, I.; Scholz, M.; Kluge, G. *Croat. Chem. Acta* **1978**, *51*, 43. (f) Schmidt, W. *J. Chem. Phys.* **1977**, *66*, 828. (g) Gower, M.; Kane-Maguire, L. A. P.; Maier, J. P.; Sweigart, D. A. *J. Chem. Soc., Dalton Trans.* **1977**, 316. (h) Bock, H.; Kaim, W.; Rohwer, H. E. *J. Organomet. Chem.* **1977**, *135*, 14. (i) Clar, E.; Schmidt, W. *Tetrahedron* **1976**, *32*, 2563. (j) Kobayashi, T.; Nagakura, S. *J. Electron Spectrosc. Relat. Phenom.* **1975**, *7*, 187. (k) Bischof, P. K.; Dewar, M. J. S.; Goodman, D. W.; Jones, T. B.

J. Organomet. Chem. **1974**, *82*, 89. (l) Schafer, W.; Schweig, A. *Angew. Chem.* **1972**, *84*, 898. (m) Klessinger, M. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 525. (n) Bock, H.; Wagner, G.; Kroner, J. *Chem. Ber.* **1972**, *105*, 3850. (o) Carlson, T. A.; Anderson, C. P. *Chem. Phys. Lett.* **1971**, *10*, 561. (p) Bock, H.; Fuss, W. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 182. (q) Gleiter, R.; Heilbronner, E.; Hornung, V. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 901.

(65) (a) Daamen, H.; Oskam, A.; Stufkens, D. J.; Waaijers, H. W. *Inorg. Chim. Acta* **1979**, *34*, 253. (b) Cradock, S.; Findlay, R. H.; Palmer, M. H. *Tetrahedron* **1973**, *29*, 2173.

(66) Average from the two vertical ionization energies reported by NIST:(a) Ramsey, B. G. *J. Org. Chem.* **1979**, *44*, 2093. (b) Cradock, S.; Findlay, R. H.; Palmer, M. H. *Tetrahedron* **1973**, *29*, 2173.

(67) Streets, D. G.; Hall, W. E.; Ceasar, G. P. *Chem. Phys. Lett.* **1972**, *17*, 90.

(68) Ono, S.; Okazaki, K.; Sakurai, M.; Inoue, Y. *J. Phys. Chem. A* **1997**, *101*, 3769.

(69) Hammett, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 96.

(70) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

(71) See, for example: (a) Moser, A.; Range, K.; York, D. M. *J. Phys. Chem. B* **2010**, *114*, 13911. (b) Bera, N. C.; Maeda, S.; Morokuma, K.; Viggiano, A. A. *J. Phys. Chem. A* **2010**, *114*, 13189. (c) Liu, M.; Yang, I.; Buckley, B.; Lee, J. K. *Org. Lett.* **2010**, *12*, 4764. (d) Mulder, R. J.; Guerra, C. F.; Bickelhaupt, F. M. *J. Phys. Chem. A* **2010**, *114*, 7604. (e) Rosenberg, M.; Ottosson, H.; Kilsa, K. *J. Org. Chem.* **2010**, *75*, 2189. (f) de Petris, G.; Cartoni, A.; Rosi, M.; Barone, V.; Puzzarini, C.; Troiani, A. *Chem. Phys. Chem.* **2011**, *12*, 112.

(72) Ho, J.; Coote, M. L. *Theor. Chem. Acc.* **2010**, *125*, 3.

(73) Ho, J.; Coote, M. L. *Theor. Chem. Acc.* **2010**, *125*, 3.

(74) Rebollar-Zepeda, A. M.; Campos-Hernández, T.; Ramírez-Silva, M. T.; Rojas-Hernández, A.; Galano, A.*J. Chem. Theory Comput.* DOI: 10.1021/ct2001864. Published ASAP: July 28, 2011.

(75) Casasnovas, R.; Fernandez, D.; Ortega-Castro, J.; Frau, J.; Donoso, J.; Muñoz, F. *Theor. Chem. Acc.* DOI 10.1007/s00214-011-0945-5. Published Online First: May 6, 2011.

(76) Flores-Moreno, R.; Ortiz, J. V. *J. Chem. Phys.* **2009**, *131*, 124110.