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Theoretical insights on the antioxidant activity of edaravone free radical scavengers derivatives

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ABSTRACT

The prediction of antioxidant properties is not straightforward due to the complexity of the *in vivo* systems. Here, we use theoretical descriptors, including the potential of ionization, the electrodonating power and the spin density distribution, to characterize the antioxidant capacity of edaravone (EDV) derivatives. Our computations reveal the relationship between these parameters and their potential bioactivity as free radical scavengers. We conclude that more efficient antioxidants could be synthesized by tuning the R_1 and R_2 positions of the EDV structure, rather than modifying the R_3 group. Such modifications might improve the antioxidant activity in neutral and deprotonated forms.

1. Introduction

In biological systems free radicals ($R^{\cdot}$) are one of the natural intermediate products in cellular activity [1,2]. In normal conditions, the $R^{\cdot}$ concentration is balanced by several antioxidant enzymes, e.g., the superoxyde–dismutaze enzyme, a powerful free radicals scavenger naturally presented in the body [3]. However, a lack of such enzyme might induce irreversible effects on the cell processes. One of the most critical phenomena is the oxidative intrastrand cross-links of DNA either photoinduced [4] or initiated by reactive oxygen species, as the hydroxyl free radical [5]. The uncontrolled amount of $R^{\cdot}$ is actually involved in many other pathologies including degenerative diseases [6,7] and cardiovascular disorders [8]. To partially (or even completely) mitigate the side effects of such highly reactive species, external antioxidant molecules have been proposed to be used as dietary supplements as well as novel drugs. It is therefore not surprising that the vast literature is devoted to novel treatments of neurodegenerative diseases with antioxidants [9].

The edaravone [3-methyl-1-phenyl-2-pyrazolin-5-one (EDV)], see Figure 1, is one of those promising compounds with strong neuroprotective and antioxidant abilities. EDV was first synthesized in 1986 by Watanabe [10] and only 14 years later was recognized as an efficient drug in the treatment of cerebral thrombosis and embolism [11] among many other successful medical applications [12–19]. Unfortunately, the mechanism behind EDV's beneficial properties is not yet fully understood, which in turn impede the development of more efficient EDV derivatives within systematic routes of synthesis. Three possible mechanisms are known to neutralize $R^{\cdot}$, namely, single electron transfer [SET, Eq. (1)], allylic hydrogen abstraction [AHA, Eq. (2)] and radical addition to a double bond [RA, Eq. (3)]:

$$\mathrm{EDV} + R^{\cdot} \rightarrow EDV^{\cdot +} + R^{-} \quad (1)$$

$$\mathrm{EDV} + R^{\cdot} \rightarrow EDV^{\cdot}(-H) + R - H \quad (2)$$

$$\mathrm{EDV} + R^{\cdot} \rightarrow [EDV - R]^{\cdot} \quad (3)$$

The preponderant mechanism of an antioxidant varies according to the chemical nature of the antioxidant and of the free radical, the media polarity, the pH,... [20–24]. For EDV, a series of theoretical studies has been carried out to distinguish its antioxidant mechanisms. For instance, Pérez-González and Galano proposed a sequential electron proton transfer, in which the deprotonated form of the EDV [EDV $(-H)^{-}$] is generated at an early stage followed by a SET, as the main antioxidant channel at physiological pH [25]. This theoretical hypothesis is consistent with experiment [14,26–29]. Indeed, the neutral EDV is much less (bio) reactive than the anionic EDV $(-H)^{-}$ form [26,27]. These data indicate that the EDV's reactivity, and consequently its antioxidant activity, might be controlled by tuning the acid–basic equilibrium as illustrated on Figure 2.

However, antioxidant capacity is an evasive descriptor for computational chemistry since (i) there is no explicit measure of this parameter and (ii) the complexity of the biological environment.

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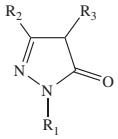

Figure 1. Active center of the edaravone derivatives. $R_1 = Ph, R_2 = CH_3$, $R_3 = H$ is the standard EDV.

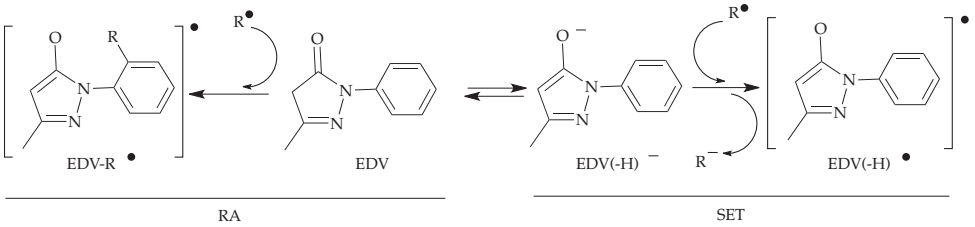

Figure 2. The central double arrow stands for the acid–basic equilibrium at physiological pH (7.4), while the extremes summarize the possible radical scavenging mechanisms of EDV: RA for neutral EDV (left) and SET for the deprotonated form (right).

Moreover, only few studies are devoted to the characterization and chemical rationalization of functional groups to enhance the beneficial effects of EDV, as two recent works focused on ionization potential (IP) and electronic affinities (EA) to characterize the EDV activity [30,31]. Interestingly, IP and EA can be combined to obtain the so-called the electroaccepting (ω^+) and particularly the electrodonating (ω^-) refined indexes which better capture the free radical scavenging phenomena [32,33]. These parameters can be used to quantify the propensity of a molecule to donate or to accept a charge within a complex environment [34].

In the present contribution we select a wide panel of EDV derivatives (Table 1) aiming to provide a general conclusion on the interplay between chemical structure and EDV antioxidant activity. More specifically, we compute standard IP and EA values as well as the more refined ω^+ and ω^- descriptors to analyze this relation depending on functional groups (R_1, R_2, R_3). The impact of the polarity of the surrounding is also assessed to investigate its contribution on the EDV antioxidant activity. Spin densities as a product of the electron transference to the free radical have been computed to further rationalize the antioxidant action of EDV derivatives.

This Letter has been organized as follows: in the next section we introduce the selected computational protocol necessary to determine antioxidant properties of EDV derivatives. Results and discussion are then divided into four subsections: we first present both the vertical and adiabatic IP, EA, ω^+ and ω^- of neutral EDV in gas phase; second we investigate the effect of the pH influence on ω^- quantities by including the deprotonated forms EDV $(\text{-H})^-$; third the solvent effects on the antioxidant activity are evaluated; and lastly we rationalize the stability of the products generated during the free radical deactivation on base of the unpaired electron delocalization.

2. Computational methods

The properties of the EDV derivatives to donate or accept an electron have been first estimated through the simple IP and EA values. IP (EA) is the difference between the energy of a cationic (neutral) species and the energy of its neutral (anionic) state. Those properties have been evaluated for all listed EDV in their neutral (i.e., protonated) forms as well as in their anionic (i.e., deprotonated) counterparts. Aiming to provide a complete picture of the electronic structure, IP and EA have been computed by considering both the vertical (vert) and adiabatic (adia) approaches. In the former, both IP and EA are computed by considering a fix geometry while in the latter both oxidized and reduced species are also optimized prior to computing the respective magnitudes. Although IP and EA are well defined magnitudes, ω^- and ω^+ are more complex as it is the ratio between the addition of IP and EA and the difference between them [34]:

Table 1
Edaravone derivatives designed by varying the three functional groups (R_1, R_2 and R_3, see Fig. 1) on the EDV's basic structure. Cp and Ch stands for cyclopentyl and cyclohexyl substituents, respectively.

	R_1	R_2	R_3
I (=EDV)	Ph–	$-CH_3$	H
II	*p*-CH_3O–Ph–	$-CH_3$	H
III	*p*-Cl–Ph–	$-CH_3$	H
IV	*p*-NO_2–Ph–	$-CH_3$	H
V	Ch–	$-CH_3$	H
VI	2-Pyridinyl–	$-CH_3$	H
VII	Ph–	$-CF_3$	H
VIII	Ph–	–Ph	H
IX	Ph–	*p*-OCH_3–Ph–	H
X	Ph–	*p*-NO_2–Ph–	H
XI	Ph–	CH_3OCONH–	H
XII	Ph–	PhOCONH–	H
XIII	Ph–	CpNHCONH–	H
XIV	Ph–	Isopropenyl-	H
XV	Ph–	–Benzyl	H
XVI	Ph–	$-CH_3$	Isobutyl–
XVII	Ph–	$-CH_3$	Ph–
XVIII	Ph–	$-CH_3$	Cyclopropyl–
XIX	Ph–	$-CH_3$	PhCO–
XX	Ph–	$-OCH_3$	H
XXI	*p*-NH_2–Ph–	$-CH_3$	H
XXII	Ph–	$-NH_2$	H
XXIII	*p*-CH_3-Ph–	$-CH_3$	H
XXIV	Ph–	H	H
XXV	Ph–	–Cl	H
XXVI	*p*-OH–Ph–	$-CH_3$	H
XXVII	Ph–	–OH	H
XXVIII	*p*-CH_2=CH–Ph–	$-CH_3$	H
XXIX	Ph–	$-CH{=}CH_2$	H
XXX	*p*-SH–Ph–	$-CH_3$	H
XXXI	Ph–	–SH	H
XXXII	*p*-CHO–Ph–	$-CH_3$	H
XXXIII	Ph–	–CHO	H
XXXIV	*p*-CN–Ph	$-CH_3$	H
XXXV	Ph–	–CN	H
XXXVI	Ph–	$-NO_2$	H
XXXVII	*p*-CF_3	$-CH_3$	H
XXXVIII	*p*-NO–Ph–	$-CH_3$	H
XXXIX	Ph–	–NO	H