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Theoretical study of the hydrogen abstraction from vitamin-E analogues. The usefulness of DFT descriptors

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Abstract The activation and reaction energies governing hydrogen atom transfer between α-tocopherol analogues and methylperoxyl radical were determined using the B3LYP/6-311++G(d,p) method. An a priori qualitative estimation of the charge transfer involved in the formation process of the two-fragment reaction between α-tocopherol-like molecules and the methylperoxyl radical was used as a predictive tool to determine antioxidant activity. Consistency between the energetic data and reactivity criterion was nicely reached indicating that the electronic nature of the substituents in the heterocyclic ring in α-tocopherol-like molecules strongly influences the activation and reaction energies.

Keywords Density functional theory · α-Tocopherol · Reactivity · Hydrogen abstraction · Conceptual DFT

Introduction

Biological systems possess many metabolic processes that produce reactive oxygen species (ROS) [1, 2]. ROS are chemical substances that, through specific reactions, lead to oxidative degradation of carbon-based materials. Biological systems regulate the content of ROS thus protecting themselves from oxidative processes. However, external agents, such as radiation and interaction with chemicals, can significantly increase ROS content, thus overcoming the antioxidant capabilities of the system; the result is an

increase in oxidation processes, which is thought to contribute to various different types of sickness, inflammatory injuries, cancer, etc. [1, 3]. In short, the unbalanced ratio between ROS content and protecting antioxidants seems to be at the origin of the so-called oxidative stress that attacks biological structures [4].

Oxidative degradation of carbon-based materials begins with ROS attack on an alkyl group of a lipid molecule, RH, to produce the carbon-centered radical $R^\bullet$ derived from it by removal of a hydrogen atom [4]. Further oxidation reaction of $R^\bullet$ with oxygen—so-called autoxidation—produces a peroxyl radical, $ROO^\bullet$:

$$R^\bullet + O_2 \rightarrow ROO^\bullet \tag{1}$$

$ROO^\bullet$ can extract a hydrogen atom from another hydrocarbon molecule to generate peroxide and another reactive free radical in a propagation process in which new reactive radicals are formed:

$$ROO^\bullet + RH \rightarrow ROOH + R^\bullet \tag{2}$$

The chain of reactions in reactions 1 and 2 can be broken by an important class of compounds, phenolic antioxidants, which inhibit oxidation of materials of biological interest. Phenolic antioxidants (ArOH) have the function of intercepting and reacting with free radicals [5] at a rate faster than that of the hydrocarbon molecule RH in reaction 2, and generate a comparatively unreactive free radical species according to:

$$ROO^\bullet + ArOH \rightarrow ROOH + ArO^\bullet \tag{3}$$

The effectiveness of phenolic compounds as antioxidants is directly related to the rate of reaction 3, which is determined by the barrier height of hydrogen transfer from phenol to the peroxyl free radical [6–9]. One of the most

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important and effective lipid-soluble, chain-breaking, natural antioxidant in human blood plasma is α-tocopherol (Fig. 1a), a major component of vitamin E [10–15]. The present work investigated the antioxidant capability of six α-tocopherol-like molecules (M1–M6) toward the methylperoxyl radical $CH_3OO^\bullet$ (MPR; Fig. 1b). The aim of this investigation was to gain a deeper appreciation of the aptitude of α-tocopherol-like molecules as antioxidants. In this context, we studied reaction (3) with $ROO^\bullet$=MPR and ArOH=M1–M6. These reactions, labeled RX (X=1, 6), describe the MPR + MX reaction of H-atom abstraction from antioxidant MX (X=1, 6) by the methylperoxyl radical, (for example, in Fig. 2: R1 is MPR + M1).

Since the effectiveness of a given antioxidant is directly related to the energy barrier for the hydrogen transfer reaction from the antioxidant molecule MX to the peroxyl free radical MPR, in this work special attention is devoted to the characterization of transition states. On the other hand, electronic properties that are important for characterizing the electronic activity taking place during a chemical reaction are chemical potential and hardness. One novelty of this research is to study the antioxidant activity of α-tocopherol-like molecules in terms of these electronic properties. These will be determined through computational methods based upon density functional theory (DFT) [16–23].
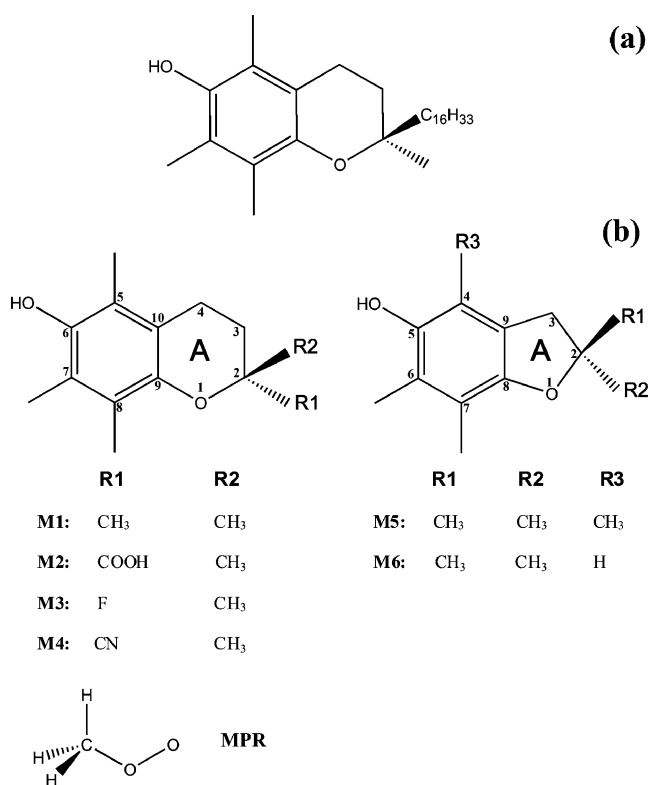

Fig. 1 a α-Tocopherol. b Common molecular skeleton of α-tocopherol-like molecules as antioxidants (M1–M6) and methylperoxyl radical (MPR)

Theoretical background

This section provides definitions for the most relevant theoretical elements used to characterize reaction (3) and for rationalizing the transition states involved in it.

Chemical potential and molecular hardness

The basics of DFT state that energy may be written as a function of N, the total number of electrons, and a functional of $v(\vec{r})$, the external potential: $E \equiv E[N, v(\vec{r})]$ [18, 20, 22, 24, 25]. In this context, chemical potential (μ) and hardness (η), which are very important global properties aimed at describing chemical reactivity [16, 18, 26–28], are defined as:

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{v(\vec{r})} \approx \frac{1}{2}(I + A) \approx \frac{1}{2}(\varepsilon_L + \varepsilon_H) \qquad (4)$$

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{v(\vec{r})} \approx \frac{1}{2}(I - A) \approx \frac{1}{2}(\varepsilon_L - \varepsilon_H) \qquad (5)$$

In numerical applications, μ and η are calculated through the finite difference approximation involving the first ionization potential (I) and electron affinity (A); further approximations, making use of Koopmans (or Janak) [29] theorem, lead to μ and η in terms of the energy of the frontier molecular orbitals HOMO (ε_H) and LUMO (ε_L). Chemical potential is interpreted as the escaping tendency of an electron with respect to an equilibrium distribution, whereas hardness is often interpreted as the resistance of the system to change in its electronic distribution.

In electron transfer reactions, electrons flow from the reactant presenting the higher value of μ to the reactant presenting the lowest value of chemical potential. Following Sanderson's principle of equalization of chemical potential [27], electronic flux continues until chemical potentials equalize to a given value for the whole system. In this context, the larger the difference between the chemical potentials of the reacting molecules, the larger the electronic transfer among them and the reaction is more likely to occur. This is therefore a reactivity criterium in electronic transfer reactions. On the other hand, hard molecules are expected to be less reactive than soft molecules, as stated by the principle of maximum hardness (PMH) [30]: stable molecules are expected to be as hard as possible. In this context, the relative hardness of the systems under study (M1–M6) will provide an absolute criterion for reactivity that will be used in the present analysis of reaction (3).
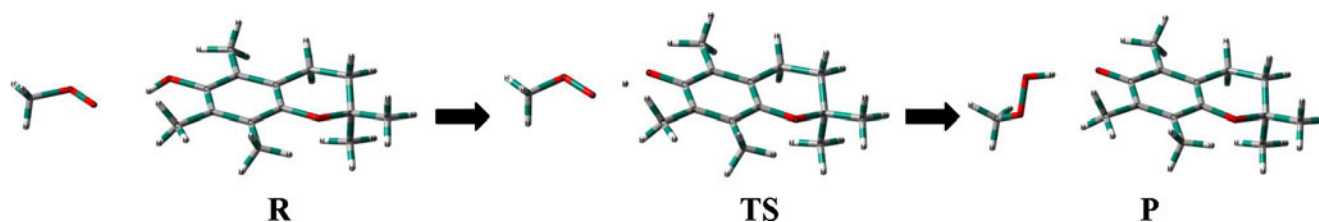
Fig. 2 Reactant (**R**), transition state (**TS**) and product (**P**) structures for the **MPR** + **MX** reaction (**R1**) representing H-atom abstraction from antioxidant **M1** by the methylperoxyl radical

Energy barriers and the Marcus equation

Energy barriers are often rationalized through the Marcus equation [31]:

$$\Delta E^{\neq} = [E(TS) - E(R)] = \Delta E_o^{\neq} + \frac{1}{2}\Delta E^o + \frac{(\Delta E^o)^2}{16\Delta E_o^{\neq}} \quad (6)$$

where $E(TS)$ and $E(R)$ are the energy of the transition state (TS) and the reactant (R), respectively, $\Delta E^o=[E(P)-E(R)]$ is the reaction energy and from the knowledge of ΔE^o and $\Delta E^{\neq}$ we can obtain Marcus' intrinsic activation energy, $\Delta E_o^{\neq}$ [31], which should be interpreted in terms of electronic and structural properties; in this context, we have suggested in previous works that Marcus' intrinsic barrier can be rationalized in terms of the electronic properties μ and η [32].

Along with the activation energy, the Brönsted coefficient β comes into the picture [33]:

$$\beta = \frac{\partial \Delta E^{\neq}}{\partial \Delta E^o} \Rightarrow \beta = \frac{1}{2} + \frac{\Delta E^o}{8\Delta E_o^{\neq}} \quad (7)$$

This parameter defined within the interval $0\leq\beta\leq1$, may have different interpretations. On the one hand it is a measure of the resemblance of the TS to the products; it can also be interpreted as the position of the TS defined in a reduced reaction coordinate going from 0 at the reactants, to 1 at the products. On the other hand, the Brönsted coefficient can also be viewed as a descriptor of the Hammond postulate (HP) [34], which interrelates the reaction energy with the position of the energy barrier on the potential energy surface. Within the HP framework, an exothermic reaction has a reactant-like TS ($\beta<1/2$), whereas product-like TS ($\beta>1/2$) characterize endothermic processes.

Computational details

In this work, all calculations were carried out at the DFT/B3LYP [35, 36] level of theory with the standard 6–311++G** basis set using the Gaussian03 [37] package. The geometries of **M1–M6** and **MPR** together with the stationary points of reactions **R1–R6** were fully optimized. Frequency calculations were subsequently performed in order to characterize the stationary points as minima or maxima. Radical fragments were calculated using UB3LYP theory. Electronic chemical potential and molecular hardness were calculated by applying Eqs. 4 and 5, respectively, using the frontier orbital energies ε_H and ε_L.

Results and discussion

Table 1 lists the values of chemical potential, $\Delta\mu$ and hardness of molecules **M1–M6** together with μ and η for the radical **MPR**. Note that all molecules present values of μ and η that are quite close to each other. The system **M5** (**M4**) has the largest(lowest) value of μ and the lowest (largest) value of η.

An a priori qualitative estimation of the charge transfer involved in the formation process of the two-fragment reaction between **MX** (X=1,6) and **MPR** can be determined through the following expression:

$$|\Delta\mu|(MX) = |(\mu(MPR) - \mu(MX))| \quad (X = 1, 6) \quad (8)$$

The results are displayed in Table 1. It is interesting to note that, in all cases, the transfer direction is from **MX** to **MPR** so that the radical is acting as an electrophile, whereas antioxidants **M1–M6** act as nucleophiles with different strengths. Within this series, **M5** is the best

Table 1 Electronic properties, chemical potential (μ) and chemical hardness (η) for molecules **M1–M6** and methylperoxyl radical (**MPR**) and charge transfer ($\Delta\mu$) at DFT/B3LYP//6–311++G** level of theory. All values are in kcal mol^{-1}

	M1	M2	M3	M4	M5	M6	MPR
μ	−65.92	−69.98	−70.21	−73.85	−65.39	−66.15	−126.73
η	56.40	56.99	58.65	59.28	55.66	56.99	47.58
$\|\Delta\mu\|$	60.81	56.75	56.52	52.88	61.34	60.58	

Table 2 Energetic parameters for reaction **R1–R6** at DFT/ B3LYP//6–311++G** level of theory. All values are in kcal mol^{-1}. ΔE^o Reaction energy, $\Delta E^{\neq}$ energy barrier, $\Delta E_o^{\neq}$ Marcus' intrinsic activation energy, β Brönsted coefficient

Reaction	R1	R2	R3	R4	R5	R6
ΔE^o	−12.98	−11.63	−11.01	−9.92	−13.89	−12.17
$\Delta E_o^{\neq}$	9.56	10.06	10.23	10.53	9.11	9.52
$\Delta E^{\neq}$	4.17	5.08	5.47	6.16	3.49	4.41
β	0.33	0.36	0.37	0.38	0.31	0.34

nucleophile whereas **M4** is the worst. The $\Delta \mu$ criterium for reactivity in electronic transfer reactions shows that reaction **R5: M5 + MPR** should be the most favored reaction. On the other hand, the hardness criterium indicates that **M5** is the most reactive system among the molecules under study. In summary, the $\Delta \mu$ and hardness criteria indicate that the reactivity of the molecules toward the **MPR** appears to be ordered as **M5 > M1>M6 > M2>M3 > M4**.

Let us now consider the energetic results of the H-transfer reactions displayed in Table 2. It can be observed that all six reactions are thermodynamically favorable, leading to reaction products considerably more stable than the reactants; the thermodynamic control indicate that the feasibility of the H-transfer reaction can be ordered as **R5 > R1>R6 > R2>R3 > R4**. On the other hand, $\Delta E^{\neq}$ values show that the kinetic control is in agreement with thermodynamic criteria, with reaction **R5** the most likely to take place because of its low energy barrier. In contrast, R4, the least exothermic reaction, is the reaction presenting the largest value of $\Delta E^{\neq}$ and therefore exhibiting the lowest probability to take place within this series. These results are in complete agreement with the predicted reactivity of the isolated systems.

In all cases, TS are shifted strongly toward the reactants, thus stressing the degree of similarity expected among these structures. Moreover, the values of the Brönsted coefficient (Table 2) are considerably lower than 0.5, indicating that the structure and properties of the TS should be closer to those of reactants. In this context, all the reactions follow the HP: with early activation barriers, the more exothermic the reaction, the closer the TS is to the reactant, as indicated by Eq. 7. It is important to mention that this result is in complete agreement with the observed structural deviation of the TS with respect to reactants and products. In all cases under study, the TS was found to be structurally much closer to the reactant structure (Fig. 2). Moreover, analysis of structural parameters indicated that most deviation of TS occurs within the aromatic ring. These results validate the use of the Brönsted coefficient as a descriptor of the relative similarity of TS with respect to reactants and products.

Consistency between thermodynamic and kinetic criteria is observed in Fig. 3a, where a nice correlation between $\Delta E^{\neq}$ and ΔE^o ($r^2 = 0.98$) was obtained for the complete series of reactions under study. This results follows the principle of Evans and Polanyi [38], which states that, within a series of closely related atom transfer reactions, the activation energy displays a linear dependence on the reaction energy. Hence, the correlation in Fig. 3a clearly shows that reactions (**R1–R6**) would follow the same mechanism [39].

Moreover, consistency between the energetic data and the $\Delta \mu$ reactivity criterion is also reached, as can be observed in Fig. 3b, c. These correlations can be associated to the electronic nature of the systems involved. Within the strongest nucleophilic systems (**M1**, **M5**, **M6**), the barrier is strongly dependent upon the $\Delta \mu$ value (dashed line in Fig. 3b), whereas in less nucleophilic systems (**M2**, **M3**, **M4**) the $\Delta E^{\neq}$ vs $\Delta \mu$ plot presents a considerably smaller slope (solid line in Fig. 3b). This situation is replicated when looking at the relationship between reaction energy and $\Delta \mu$ in Fig. 3c. In summary, reactions **R1**, **R5** and **R6** are largely favored kinetically and thermodynamically by large, although similar, values of $\Delta \mu$ whereas **R2**, **R3** and **R4** are less favored both kinetically and thermodynamically
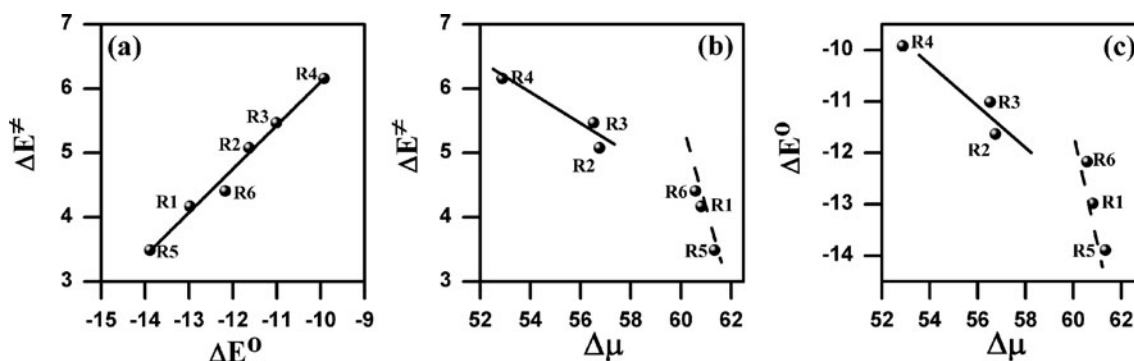

Fig. 3 a Plot of activation energy ($\Delta E^{\neq}$) vs reaction energy (ΔE^o) for reactions **R1–R6**. **b** Plot of activation energy ($\Delta E^{\neq}$) vs charge transfer descriptor ($\Delta \mu$) for reactions **R1–R6**. **c** Plot of reaction energy (ΔE^o) vs charge transfer descriptor $\Delta \mu$ for reactions **R1–R6**. All values in kcal mol^{-1}

by a relatively lower electronic transfer among the reactants. Accordingly, the nature of substituents as electron donor or withdrawing, in particular in the position R1 present in the heterocyclic ring **A** (see Fig. 1b), play a fundamental role: all electron donating groups, e.g., methyl groups, decrease the activation and reaction energies in the order **R6 < R1 < R5**, and electron withdrawing substituents like COOH, F and CN increase the activation and reaction energies of hydrogen abstraction in **R2**, **R3** and **R4**, respectively.

Using $\Delta\mu$ as a criterion of nucleophilicity for antioxidant systems, it can be observed that the average nucleophilic power of the series is $\overline{\Delta\mu} = 58.15$ kcal mol^{-1}. Within the series, **M2** is the molecule presenting the closest nucleophilic activity to the average value of the six systems. Also, **R2** presents a value of $\Delta E^{\neq}$ that is closest to the mean value, $\overline{\Delta E^{\neq}} = 4.80$ kcal kcal mol^{-1}. In this context, **M2** (and **R2**) may be seen as pivotal to the system, defining the turning point from high nucleophilic power to low nucleophilic power. This observation has a sound chemical basis: while **M1**, **M5** and **M6** present electron donor substituents with respect to **M2**, **M3** and **M4** present at least one electron-withdrawing substituent. This represents an important difference when characterizing the electronic activity of the whole system. Taking **M2** as a reference, substitution by methyl groups (**M1**, **M5** and **M6**) stabilizes the phenoxyl free radical generated, lowers the barrier, and makes the reaction more exothermic, as shown in Table 2. On the other hand, substitution by withdrawing groups COOH (**M2**), F (**M3**) and CN (**M4**) increases the reaction barrier and makes the reaction less exothermic.

Concluding remarks

From electronic structure calculations on six α-tocopherol-like molecules at the B3LYP/6–311++G** level of theory, we can conclude that: (1) the reactions of hydrogen abstraction from vitamin-E analogues from methylperoxyl radical follow the Hammond postulate, i.e., all reactions are exothermic with early activation barriers and have TS structurally close to the reactants; (2) $\Delta\mu$ is an excellent parameter for the estimation of the charge transfer involved in the formation process of the two-fragment reaction between **MX** (X=1,6) and **MPR**, and can be used as a predictive tool to determine antioxidant activity; (3) a good linear relationship between activation energy and reaction energy is found, which can be used to understand the mechanistic behavior of hydrogen abstraction from antioxidant molecules; (4) consistency between energetic data and the $\Delta\mu$ reactivity criterion was also reached. These correlations are associated with the electronic nature of the systems involved, with the strongest nucleophilic systems increasing electronic transfer to the methylperoxyl radical, lowering the barrier and leading to a more exothermic reaction; (5) the electronic nature of the substituents in the heterocyclic ring strongly influences the activation and reaction energies, with electron withdrawing substituents in the heterocyclic ring of α-tocopherol-like molecules decreasing antioxidant activity and donor substituents increasing this activity.

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