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ORIGINAL PAPER

Understanding the antioxidant behavior of some vitamin molecules: a first-principles density functional approach

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Abstract The structures, energetics, vertical and adiabatic ionization potentials, electron affinities, and global reactivity descriptors of antioxidant vitamins (both water- and fat-soluble) in neutral, positively charged, and negatively charged states were investigated theoretically. We worked within the framework of first-principles density functional theory (DFT), using the B3LYP functional and both localized (6-311G+(d,p) and plane-wave basis sets. Solvent effects were modeled via the polarizable continuum model (PCM), using the integral equation formalism variant (IEFPCM). From the computed structural parameters, ionization potentials, electron affinities, and spin densities, we deduced that these vitamins prefer to lose electrons to neutral reactive oxygen species (·OH and ·OOH), making them good antioxidants. Conceptual DFT was used to determine global chemical reactivity parameters. The computed chemical hardnesses showed that these antioxidant vitamins are more reactive than neutral reactive oxygen species (ROS), thus supporting their antioxidant character towards these species. However, in the neutral state, these vitamins do not act as antioxidants for O_2^-. The reactivity of vitamins towards ROS depends on the nature of the solvent. Amongst the ROS, ·OH has the greatest propensity to attract electrons from a generic donor. The reactivities of fat-soluble vitamins towards neutral reactive oxygen species were found to be larger than those of water-soluble vitamins towards these species, showing that the former are better antioxidants.

Keywords Density functional theory · Ab initio calculations · Antioxidants · Vitamins · Reactive oxygen species

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Introduction

Vitamins are natural organic substances found in plants and animals. Interestingly, the word "vitamin" is derived from "vital amines," as it was originally thought that these substances were all amines. There are 13 essential vitamins, and they can be classified into two types: water-soluble and fat-soluble [1]. Eight of the water-soluble vitamins are known as the B-complex group: thiamine (vitamin B1), riboflavin (vitamin B2), niacin (vitamin B3), pantothenic acid (vitamin B5), pyridoxine (vitamin B6), biotin (vitamin B7), folic acid (vitamin B9), cyanocobalamin (vitamin B12), and the ninth water-soluble vitamin is ascorbic acid (vitamin C). These vitamins are widely distributed in foods. The fat-soluble vitamins include retinol (vitamin A), calciferol (vitamin D), tocopherol (vitamin E), and phylloquinone (vitamin K).

Vitamins are among the most essential nutrients required by the human body, and their absence causes serious physiological problems. Most vitamins (B-complex vitamins) function as precursors for enzyme cofactor molecules (coenzymes). For example, vitamin B2 is the precursor of several coenzymes, such as flavin mononucleotides (FMN) and flavin adenine dinucleotide (FAD), which play an important role in biological electron transfer. Vitamins also act as coenzymes to carry chemical groups between enzymes. Although these roles in assisting enzyme reactions are the best-known functions of vitamins, they have other important functions as well. One important role of some of the vitamins is as antioxidants that quench the reactive radical intermediates formed during

oxidative reactions. The presence of the reactive oxygen species (ROS) ·OH, ·OOH, and O_2^- can trigger oxidative damage to DNA, proteins, and lipids, causing many serious diseases [2]. Radical-scavenging antioxidants therefore play an important role in inhibiting oxidative damage to macromolecules. In addition to antioxidant enzymes such as superoxide dismutase (SOD), catalase, and peroxidases, several small antioxidant molecules play important roles in this respect. These small molecules are required in regions in which antioxidant enzymes are either absent or are present in only small quantities. These nonenzymatic antioxidants can be separated into oil-soluble and water-soluble antioxidants. In biological systems, the environment is quite heterogeneous. Hydrophilic radical-scavenging antioxidants are required in the cytosol and extracellular fluids, while lipophilic radical-scavenging antioxidants are required in the lipophilic domain. Some of the vitamins that act as radical-scavenging antioxidants are hydrophilic, while others are lipophilic. The antioxidant properties of hydrophilic vitamin C and lipophilic vitamin E [3] have been investigated for decades, and in recent years other hydrophilic and lipophilic vitamins such as vitamin B6 [4] and vitamin A (http://ods.od.nih.gov/factsheets/vitaminA) have also been discovered to show antioxidant behavior.

In recent years, increasing attention has been given to the investigation of biochemical molecules using a wide range of theoretical and experimental tools. In particular, first-principles density functional theory (DFT) studies of many biochemical molecules have been begun. Thus, for example, the structures and energetics as well as the vibrational, electronic, and optical properties of all of the standard amino acids have been analyzed [5, 6]. The mechanisms of action of alkylating drug molecules [7] and NRTIs [8] have been studied using DFT. A few theoretical studies of the antioxidant properties of vitamins also exist. For instance, a DFT study of 4 vitamins and 8 phenolic acids in the gas phase analyzed the factors responsible for antioxidation [9]. The superoxide dismutase (SOD) activities of copper complexes of nicotinic acid (vitamin B3) and related pyridine derivatives were correlated with the theoretical parameters as calculated at the B3LYP/LANL2DZ level of theory [10]. The antioxidant properties of pyridoxine (vitamin B6) were analyzed by studying its reactivity towards the ROS ·OH, ·OOH, and O_2^- at the B3LYP and MPW1B95 level of theory [4]. The effects of the conformation on the acidity of vitamin C have been linked to its antioxidant mechanism through molecular orbital computations of adiabatic energies of deprotonation [11]. Tocopherols and chromones have been investigated using B3LYP, with the results indicating that the chromane structure is responsible for the antioxidant effect of vitamin E [12]. The antioxidant properties of butein have been compared with those of α-tocopherol by calculating and comparing their ionization potentials (IP), bond dissociation energies (BDE), highest occupied molecular orbitals (HOMO), and spin densities [13]. The dynamics of the antioxidant action of vitamin E in vivo have been elucidated [3]. The pro-oxidant effect of vitamin E due to the formation of H_2O_2 through its reaction with HOO· [14] has been studied.

Systematic studies and detailed analyses of various properties of antioxidant vitamins are, however, yet to appear. As may be expected, a knowledge of their ground-state energetics, geometries, as well as their chemical and physical properties is a prerequisite to understanding various crucial aspects of vitamin function and activity.

In the work described in the present paper, we attempted to understand the antioxidant effects of all the vitamins with known antioxidant properties arising due to their interaction with ROS, using first-principles DFT. We first present a detailed study of their ground-state structures and energetics. Chemical properties such as the ionization potentials and electron affinities and reactivity descriptors such as the electronegativities, chemical potentials, chemical hardnesses, chemical softnesses, and electrophilicity indices of vitamin molecules and ROS in the gas phase and in the presence of solvent are then obtained. The spin densities for radical systems have also been computed in order to explain the electron transfer between the vitamins and the ROS.

Theory and computational details

Theory

As the number of electrons (N) in a many-electron system (such as an atom, ion, or molecule) and the external potential $v(\vec{r})$ fix the Hamiltonian of the system, all of its properties may be obtained by varying N and $v(\vec{r})$ appropriately. This approach to analyzing chemical behavior, termed "conceptual DFT" [15–17], has been quite successful in providing a theoretical basis for popular qualitative chemical descriptors such as electronegativity (χ), chemical potential (μ), chemical hardness (η), chemical softness (S), and electrophilicity index (ω), which describe the reactivity of the molecule as a whole [7] and are thus known as global reactivity parameters.

The absolute electronegativity (χ), chemical potential (μ), chemical hardness (η), and chemical softness (S), may be defined as

$$\chi = -\mu = -\left(\frac{\partial E}{\partial N}\right)_{v(\vec{r})} = \left(\frac{\mathrm{IP}+\mathrm{EA}}{2}\right) \quad (1)$$

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{v(\vec{r})} = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_{v(\vec{r})} = \left(\frac{\mathrm{IP}-\mathrm{EA}}{2}\right) \quad (2)$$

$$S = \frac{1}{2\eta}, \quad (3)$$

where $E(N)$ is the electronic energy of the N-electron system.

The ionization potential (IP) and the electron affinity (EA) may be expressed, using the finite difference approximation, as

$$\mathrm{IP} = \mathrm{E(N-1)} - \mathrm{E(N)} \text{and } \mathrm{EA} = \mathrm{E(N)} - \mathrm{E(N+1)}. \quad (4)$$

The global electrophilicity index (ω) [18, 19], given by

$$\omega = \frac{\mu^2}{2\eta}, \quad (5)$$

quantifies the tendency of a molecule to accept electrons from a generic donor.

Computational details

We worked within the density functional theory (DFT) approach [20–22], including the generalized gradient approximation (GGA) to the local spin density approximation (LSDA) [23]. Valence electrons were treated explicitly, and their wavefunctions were expanded in a plane-wave basis set with an energy cut-off of 70 Ry, while core-valence interactions were described by norm-conserving pseudopotentials [24] that have been carefully tested for both convergence and transferability [25–28].

In each case, the vitamin molecule was placed in an orthorhombic simulation cell with sides ranging in length from 6.0 to 26.4 Å. The large size of the cell, which is chosen to be at least twice the largest dimension of the molecule, ensured sufficient reduction of finite-size effects. In order to avoid the spurious interactions with the images of the system in neighboring simulation cells that can occur when periodic boundary conditions are employed, we adopted an isolated cell approach, following the scheme of Barnett and Landmann [29] and refined by Tuckerman [30, 31]. For ionized molecules, a uniformly charged background compensated for the molecular charge.

For the sake of self-consistency within the density functional theory used, as well as to optimize the trial structure constructed, geometry relaxations were carried out on the starting molecule. In this way, the initial guessed system moved to the nearest local minimum of the potential energy surface, representing a stable molecular configuration.

The geometry of the molecule was fully relaxed via direct inversion in iterative subspace (DIIS) [32], as implemented in the CPMD code [33, 34], until the largest component of the ionic forces attained a value $<5\times10^{-4}$ a.u. For these calculations, we used the GGA due to Becke and Lee as well as Yang and Parr [35, 36] (BLYP) for the exchange and correlation functionals, respectively. In order to determine the effect of the basis set employed, the final structure obtained from the plane-wave basis set was reoptimized using the 6-311+G(d,p) basis set in Gaussian 09 [37]. To investigate the effect of the environment (solvent effects) on these molecules, the environment was modeled through the polarizable continuum model (PCM) [38] using the integral equation formalism variant (IEFPCM). The gas-phase structures were reoptimized in the presence of the solvent. The ionization potential and electron affinity of the molecule were then investigated and their vertical and adiabatic values were obtained. Finally, the DFT-based global chemical reactivity descriptors of interest defined earlier were calculated.

Results and discussion

Structural properties

The fully optimized structures of the vitamins and ROS in the gas phase, obtained at the B3LYP level using the 6-311G+(d,p) basis set, are shown in Fig. 1. The total energy of each molecule is also indicated in the figure. Vitamin E, due to its large size, was modeled using a simpler system, following the usual practice in the literature. The long alkyl side chain ($R=C_{16}H_{33}$) of vitamin E can be replaced by a methyl group ($R=CH_3$), since the side chain has been shown to have a negligible effect on the antioxidant properties of tocopherols [39] and ubiquinol [40].

Tables I–X provided in the "Electronic supplementary material" (ESM) specifically indicate the changes in the bond lengths and bond angles in the cations and anions of the vitamin molecules as compared to those lengths and angles in the corresponding neutral molecules. In addition, for some vitamins, the experimental [41–43] and theoretically calculated [44–50] bond lengths and bond angles are available in the literature, and these are given in their respective tables. To the best of our knowledge, no theoretical and experimental data are available for the other molecules. Our results are in good agreement with the available experimental data, giving us confidence in the ability of DFT to accurately describe this class of systems. Our results obtained using a plane-wave basis set and a localized basis set (6-311G+(d,p)) also agree well with other theoretical results gained using localized basis sets. Examination of the geometry-optimized structures of the vitamins shows that the geometrical variation in the cation or anion as compared to the neutral molecule is greater when computed using the localized basis set (6-311G+(d,p)) rather than the plane-wave basis set.

Using the 6-311G+(d,p) basis set, the maximum variations in bond lengths and bond angles upon cation and anion formation were found for vitamin B3 (Table 1). During anion formation, the smallest variations in bond lengths and bond angles were found for vitamin E. Insight into the reasons for these electronic and structural variations upon the acquisition

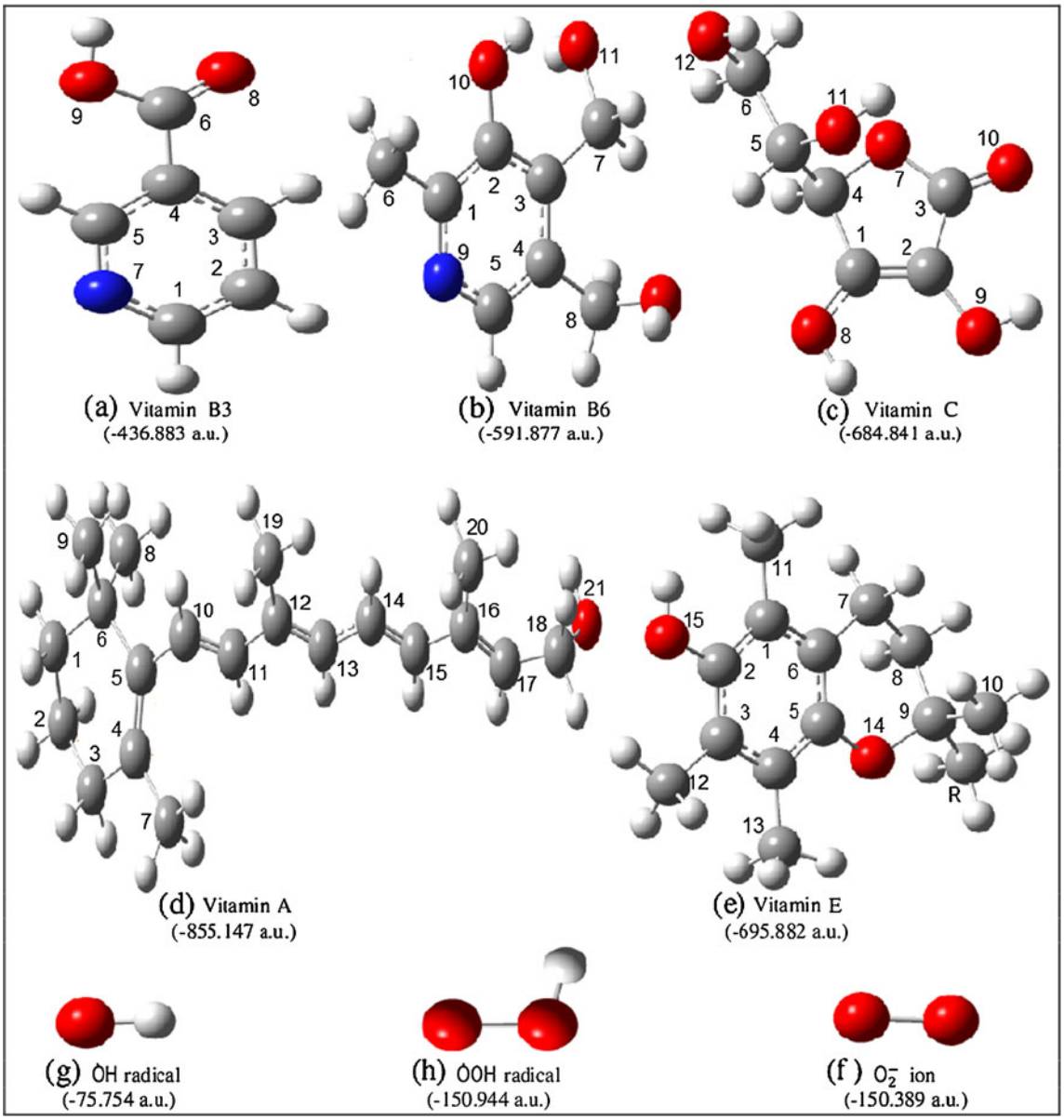

Fig. 1 Optimized structures of molecules calculated at the 6-311G+(d,p) level

of charge can be obtained by examining the molecular orbitals (MOs). Graphical representations of the highest occupied molecular orbitals (HOMO) and the lowest unoccupied molecular orbitals (LUMO) of the vitamins are given in Figs. 2 and 3,

Table 1 Root mean square deviations (RMSDs) in bond lengths (Å) and bond angles (°) in the gas phase

Vitamin	RMSD in bond length				RMSD in bond angle			
	On cation formation		On anion formation		On cation formation		On anion formation	
	Plane waves	6-311 +G(d,p)	Plane waves	6-311 +G(d,p)	Plane waves	6-311 +G(d,p)	Plane waves	6-311 +G(d,p)
B3	0.021	0.068	0.015	0.039	5.008	6.985	0.977	3.627
B6	0.024	0.031	0.005	0.028	1.287	1.799	0.235	1.899
C	0.029	0.032	0.010	0.037	2.287	1.976	0.339	2.712
A	0.018	0.025	0.013	0.025	1.081	1.217	1.474	1.849
E	0.036	0.024	0.003	0.004	1.271	1.457	0.160	0.151

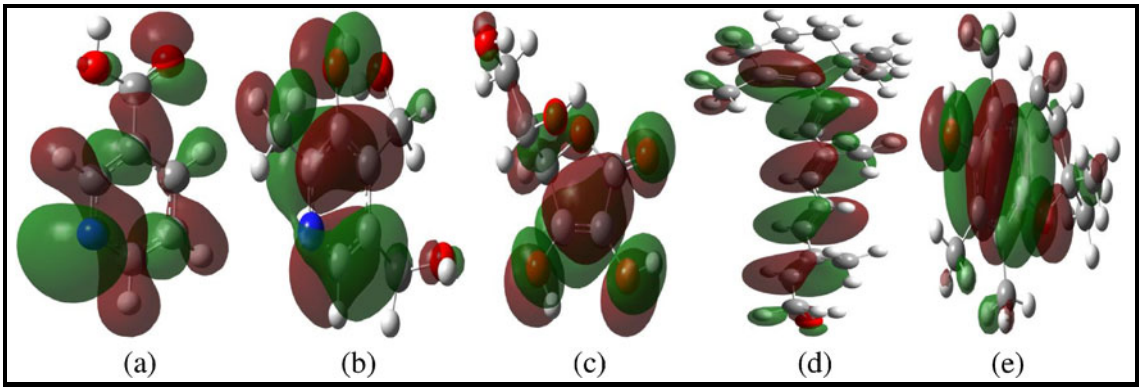

Fig. 2a–e HOMO isosurfaces of vitamins **a** B3, **b** B6, **c** C, **d** A, and **e** E in the neutral state

respectively, and more details on the atomic orbitals that significantly contribute to the MOs are given in the ESM. From the LUMO isosurface of vitamin E (Fig. 3), we can deduce that the electron added during anion formation is not localized on the atoms, so that only a dipole-bound anion can form and there is the least variation during its formation. Analysis of the MOs of vitamin B3 indicates that its LUMO receives its greatest contributions from the $2p_z$ and $3p_z$ orbitals, and hence can easily accommodate an electron during anion formation. In the case of vitamin A, all of the conjugated C–C bonds are altered upon ion formation. This is because the HOMO and LUMO of vitamin A receive their largest contributions from the atomic orbitals of the atoms involved in conjugation. Among the studied molecules, vitamin C has the largest experimental [42, 43] and theoretically calculated [45–50] bond length and bond angle values reported in the literature. In the literature, the bond lengths and bond angles given are mainly for neutral molecules, whereas we have computed the structural parameters for neutrals as well as for ions.

Ionization potential and electron affinity

Table 2 gives the ionization potentials and the electron affinities (both vertical and adiabatic) for each vitamin molecule and ROS, as calculated by us using plane-wave and 6-311G+(d,p) basis sets. The vertical ionization potential (electron affinity) is the difference in the total energies of the neutral and positively (negatively) charged molecules, where their molecular geometries were optimized in the neutral state. The adiabatic ionization potential (electron affinity) was calculated as the difference in the total energies of the relaxed neutral cluster and the relaxed positively (negatively) charged cluster with the same topology. Also given for comparison is one experimental [51] and a few theoretical [9] values obtained from the literature for the ionization potential. The results are found to be dependent on the type of basis set used. The IPs obtained using the plane-wave basis set are lower than those obtained using the 6-311G+(d,p) basis set. The computed vertical IP values for vitamins in the gas phase obtained using the 6-311G+(d,p) basis set range from 6.738 to 9.821 eV, whereas the vertical IP values computed using 6-311G+(d,p) basis set for ROS, ·OH (16.346 eV), and ·OOH (12.646 eV) are higher than all of those for the vitamin molecules. For all molecules, the adiabatic ionization potential is found to be lower than the corresponding vertical ionization potential. Similar trends were also observed in our study of amino acids [5], alkylating drugs [7], NRTIs [8], and antiherpes [52]. We note that the mean difference between the vertical and

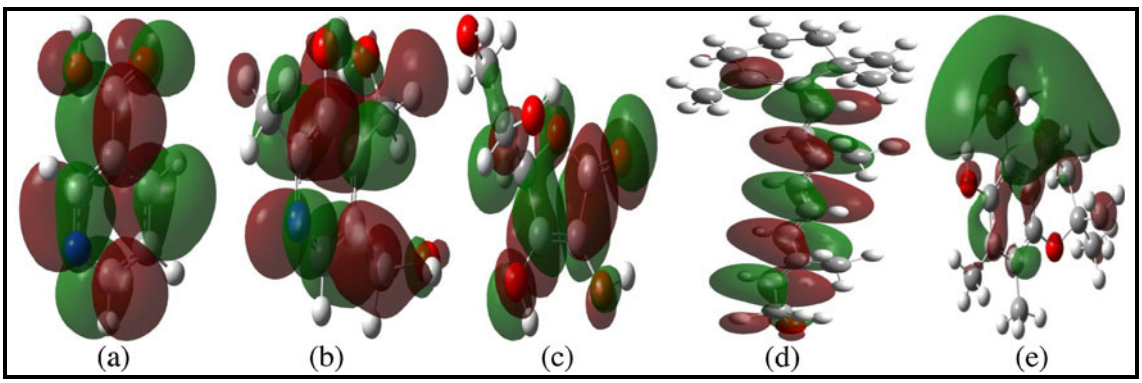

Fig. 3a–e LUMO isosurfaces of vitamins **a** B3, **b** B6, **c** C, **d** A, and **e** E in the neutral state

Table 2 Calculated ionization potentials (IP, eV), electron affinities (EA, eV), and global chemical reactivity descriptors for the vitamin molecules and reactive oxygen species (ROS): electronegativity (χ) (eV), chemical potential (μ) (eV), chemical hardness (η) (eV), chemical softness (S) (eV), electrophilicity index (ω) (eV), and dipole moments (D.M.) in the gas phase, water ($\epsilon = 78.36$), and enzymatic environment ($\epsilon = 2.23$), as calculated using 6-311G+(d,p) and plane-wave (in parentheses) basis sets

Molecules	Medium	IP (eV)		ΔIP	EA (eV)		ΔEA	η	S	$\chi = -\mu$	ω	D.M
		Vertical	Adiabatic		Vertical	Adiabatic						(D)
Vitamin B3	Gas	9.821	9.175	0.646	0.380	0.662	0.280	4.720	0.106	5.100	2.756	0.719
		(9.292)	(8.722)	(0.570)	(0.146)	(0.582)	(0.436)	(4.573)	(0.109)	(4.719)	(2.434)	
			*(8.92) [9]									
	$\epsilon = 78.36$	7.801	7.146	0.655	2.386	2.659	0.273	2.707	0.185	5.094	4.792	0.954
Vitamin B6	Gas	8.376	7.841	0.535	−0.111	0.191	0.302	4.243	0.118	4.132	2.012	1.996
		(8.030)	(7.673)	(0.357)	(0.579)	(0.638)	(0.059)	(3.726)	(0.134)	(4.305)	(2.487)	
		**(8.12) [51]	*(7.81) [9]									
	$\epsilon = 78.36$	6.436	6.183	0.253	1.546	1.903	0.358	2.445	0.204	3.991	3.257	3.148
Vitamin C	Gas	8.957	8.631	0.326	−0.079	0.355	0.433	4.518	0.111	4.439	2.181	2.733
		(8.474)	(8.214)	(0.260)	(0.702)	(0.718)	(0.016)	(3.886)	(0.129)	(4.588)	(2.708)	
			*(8.14) [9]									
	$\epsilon = 78.36$	6.788	6.480	0.308	1.541	2.127	0.586	2.624	0.191	4.164	3.305	3.333
Vitamin A	Gas	6.738	6.346	0.391	0.611	1.052	0.442	3.063	0.163	3.674	2.203	2.667
		(5.996)	(5.826)	(0.170)	(0.806)	(0.877)	(0.071)	(2.595)	(0.193)	(3.401)	(2.232)	
	$\epsilon = 2.23$	5.916	5.640	0.276	1.445	1.809	0.364	2.235	0.224	3.680	3.030	2.970
Vitamin E	Gas	7.044	6.684	0.359	−0.645	−0.612	0.033	3.844	0.130	3.199	1.331	2.804
		(6.595)	(6.330)	(0.265)	(0.479)	(0.479)	(0.000)	(3.058)	(0.164)	(3.537)	(2.052)	
	$\epsilon = 2.23$	6.172	5.852	0.321	0.118	0.129	0.011	3.027	0.165	3.145	1.634	3.264
·OH	Gas	16.346	16.223	0.123	1.753	1.747	−0.006	7.296	0.069	9.049	5.612	1.833
		(13.674)	(13.594)	(0.080)	(1.213)	(1.215)	(0.002)	(6.231)	(0.080)	(7.444)	(4.433)	
	$\epsilon = 78.36$	12.817	12.716	0.101	5.198	5.191	−0.007	3.809	0.131	9.007	10.649	2.049
	$\epsilon = 2.23$	14.372	14.263	0.109	3.659	3.652	−0.007	5.356	0.093	9.016	7.588	1.931
·OOH	Gas	12.646	12.154	0.492	0.529	1.038	0.508	6.058	0.083	6.588	3.582	2.383
		(11.633)	(11.328)	(0.305)	(1.009)	(1.165)	(0.156)	(5.312)	(0.094)	(6.231)	(3.756)	
						**(1.16) [60]						
						**(1.19) [60]						
						**(1.08) [61]						
	$\epsilon = 78.36$	9.507	9.001	0.506	3.698	4.188	0.490	2.904	0.172	6.603	7.505	2.778
	$\epsilon = 2.23$	10.895	10.394	0.501	2.277	2.770	0.493	4.309	0.116	6.586	5.033	2.559
O_2^-	*$\epsilon = 78.36$*	5.895	5.380	0.515	1.416	1.937	0.521	2.239	0.223	3.655	2.983	–

Also given for comparison are the vertical and adiabatic ionization potentials as well as the adiabatic electron affinities obtained from the literature (* theoretical and ** experimental)

adiabatic IP values of the vitamins is 0.451 eV when using the 6-311G+(d,p) basis set. Our computed IPs for the antioxidant vitamins follow the same order (vitamin A < vitamin E < vitamin B6 < vitamin C < vitamin B3) as that obtained by Mohajeri et al. using the B3LYP/6-31G(d,p) basis set [9]. For vitamin B6, our (vertical) IP values [8.376 eV from the 6-311G+(d,p) basis set and 8.030 eV from the plane-wave basis set] are in good agreement with the (vertical) experimental value (8.12 eV) obtained from charge-transfer spectra [51]. Our computed (adiabatic) IP (7.841 eV) obtained using the 6-311G+(d,p) basis set also agrees well with the result of a previous (adiabatic) theoretical calculation performed using the B3LYP/6-31G(d,p) method (7.81 eV) [9]. For vitamin B3 and vitamin C, it is again clear that our results agree well (to within 0.198 eV and 0.074 eV, respectively) with those obtained in previous calculations [9]. Among the vitamins, the largest difference (0.646 eV) between the vertical and the adiabatic IP is found for vitamin B3. This observation is consistent with the fact that there is the greatest structural variation on cation formation for this molecule, as well as the delocalized character of its HOMO. The electron transfer between the antioxidant and the radical can be determined from the IP and EA. A lower IP means a higher probability of losing an electron. Vitamin B6, although not previously classified as an antioxidant compound, has recently been shown to have highly effective antioxidant properties [53]. An earlier DFT study [4] of vitamin B6 also showed it to be a possible quencher of radicals. The low adiabatic ionization potential value obtained by us for vitamin B6 (7.841 eV) confirms the results of those studies. Finally, we note that the vertical and adiabatic IPs of fat-soluble vitamins (≈6.4–7.0 eV) are lower than those of water-soluble vitamins (≈8–10 eV).

Experimental results for a real biological environment in which the vitamins are surrounded by solvent molecules are scarce. To study how polar and nonpolar environments affect the IPs and EAs of the vitamins, we computed vertical and adiabatic IPs and EAs using Gibbs free energy changes in a dielectric continuum with a dielectric constant of either 78.36 (aqueous) or 2.23 (CCl_4). The aqueous medium was used for water-soluble vitamins, whereas CCl_4 was chosen as the nonpolar medium for the fat-soluble vitamins. The solvent was found to have appreciable effect on the energetics of the molecules studied. The average decrease in the vertical and the adiabatic IP of water-soluble vitamins is 2.043 and 1.946, respectively, whereas it is 0.847 and 0.769 for fat-soluble vitamins. Although there is an appreciable decrease in the IP in the presence of solvent, but the order remains similar to that seen in the gas phase, i.e., vitamin A < vitamin E < vitamin B6 < vitamin C < vitamin B3. For neutral ROS, the average decrease in the vertical and the adiabatic IP in aqueous medium is 3.334 and 3.330, respectively, and 1.863 and 1.860 in CCl_4. As the solvent plays a crucial role in deciding the reactivities of the ionic species, the study was only done in the aqueous medium for O_2^-. The IP of O_2^- in the aqueous medium was found to be lower than those seen for the vitamins.

Experimental determination of the electron affinities (EA) for chemical systems such as drugs and biomolecules is a challenge [8]. To the best of our knowledge, there are no available experimental electron affinity values for vitamins and ROS. Hence, theoretical calculations of the EAs are particularly useful, as the EAs are essential not only for evaluating reactivity descriptors but also for explaining phenomena such as donor–acceptor interactions. The EA, along with the IP, is a crucial influence on the electron transfer between the antioxidant and the radical: a higher EA means a higher probability of gaining an electron. The method most commonly employed for the theoretical determination of EAs is DFT. It can be applied to a larger range of atoms and molecules [54] than any other ab initio method currently in use can. In addition to the conventional ab initio methods (SCF, CI, MPn, and CC), other theoretical methods for predicting EAs include Green's function methods [55], those based on the extended Koopmans' theorem [56], electron propagator approximations [57], and calculations using known experimental half-wave reduction potentials [58]. EAs obtained with DFT methods are fairly accurate (within 0.2 eV or less) in most cases [54].

The computed vertical and adiabatic EAs are found to be dependent on the type of basis set used. The computed EA values for vitamins are lower than those for the neutral ROS ·OH and ·OOH in the same media. The lower IPs of the vitamins than those of the neutral ROS and the higher EAs of the neutral ROS compared to those of the vitamins support the antioxidant behavior of the vitamins. EAs computed using a plane-wave basis set in the gas phase for vitamins and neutral ROS are found to be positive. On the other hand, vertical EAs of vitamins obtained using a localized basis set (6-311G+(d,p) are found to be positive only for B3 and A. The adiabatic EA is only found to be negative for vitamin E. The adiabatic EA of vitamin E is even found to be lower than its vertical EA. A degree of understanding of the EAs may be obtained by examining the MOs and the geometry relaxation upon anion formation, as shown in Table 2. The negative adiabatic EA which is lower than the value of the vertical EA occurs because the LUMO of vitamin E has antibonding character, as found in the NBO analysis (Fig. 3). The maximum difference between the vertical and the adiabatic EA (0.282 eV) is seen for vitamin B3. The maximum RMSDs in bond length and bond angle upon anion formation are also observed for vitamin B3, and are due to the delocalized nature of its LUMO (Fig. 3). The presence of the medium (solvent) significantly influences the EA. The vertical and the adiabatic EAs of water-soluble vitamins in aqueous medium and those of fat-soluble vitamins in CCl_4 medium are found to be positive. Interestingly,

the EAs of ROS (including O_2^-) in aqueous medium are found to be positive, indicating the possibility that O_2^{2-} can exist in the aqueous medium. Although the EA of O_2^- in the aqueous medium is positive, it is, however, found to be lower than those of the water-soluble vitamins.

Spin density

Apart from the structural parameters and energetics, another informative quantity which is useful for determining the electron transfer between the antioxidant vitamin and the ROS is the spin density. For a vitamin molecule to be effective as an antioxidant, its radical cation (which is generated after the transfer of the electron to the ROS) should be stable. The stability of the free radical depends on the degree of delocalization of the unpaired electron. The spin densities of the radical cations before (vertical) and after (adiabatic) vitamin relaxation are shown in Fig. 4. The computed spin density distributions on individual atoms in the gas phase and in the respective solvent medium are given in Table 3. The effectiveness of the antioxidant nature of vitamins is well evidenced by the extent of delocalization (Fig. 4) of the radical on the conjugated part of the vitamin cation (in most cases). In the case of vitamin B3, the electron gets localized on the nitrogen atom (spin = 0.756) after relaxation, making it the least effective antioxidant.

Global chemical reactivity descriptors

A quantitative analysis of the reactivity of the molecule was performed by determining the global reactivity descriptors using the accurately evaluated vertical ionization potentials and electron affinities. The values of the global reactivity descriptors, calculated for each of the vitamin molecules and the reactive oxygen species using the vertical IPs and EAs, are given in Table 2.

Hardness is a direct measure of the stability of the molecule, and softness provides a measure of its reactivity. The computed chemical hardness (η) is found to be lower in the solvent medium than in the gas phase. The computed η values of water-soluble vitamins [3.726–4.573 eV using the plane-wave basis set and 4.243–4.720 eV using 6-311G+(d,p)] in the gas phase are found to be higher than those of the fat-soluble vitamins (2.595–3.058 eV using the plane-wave basis set and 3.063–3.844 eV using 6-311G+(d,p)). In the presence of the solvent, the computed η values of the water-soluble vitamins (2.445–2.707 eV) are comparable to those of fat-soluble vitamins (2.235–3.844 eV). The η values of the ROS ·OH, and ·OOH are 6.231 and 5.312 eV, respectively (using the plane-wave basis set), 7.296 and 6.058 eV, respectively [using 6-311G+(d,p) in the gas phase], which reduce to 5.356 and 4.309 eV in CCl_4 medium, and 3.809 and 2.904 eV in aqueous medium. Hence, the presence of the solvent increases the reactivities of the vitamins and ROS.

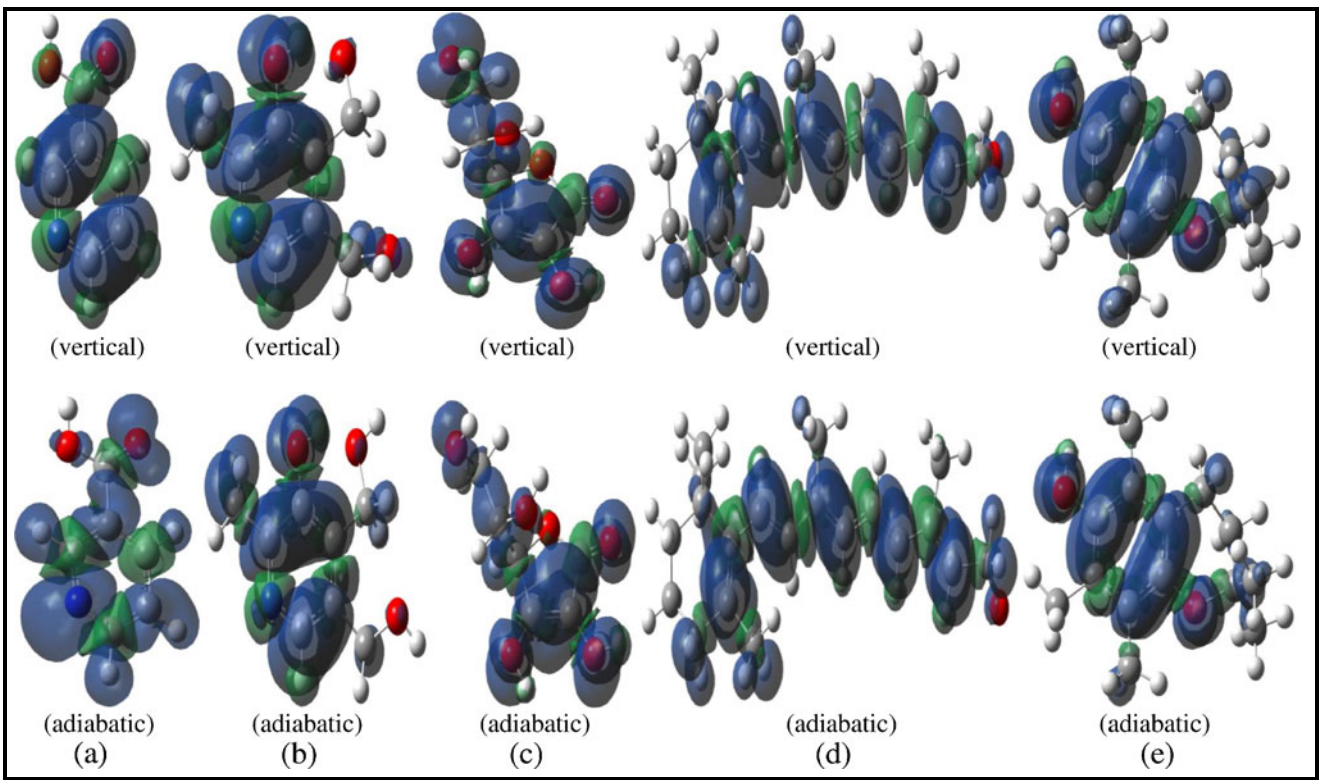

Fig. 4 Spin density plots for radical cations of vitamins **a** B3, **b** B6, **c** C, **d** A, and **e** E in the gas phase

Table 3 Spin density distributions of radical cations of vitamins in the gas phase. The values obtained in the respective solvents are given in parentheses

Vitamin B3			Vitamin B6			Vitamin C			Vitamin A			Vitamin E		
	Vertical	Adiabatic		Vertical	Adiabatic		Vertical	Adiabatic		Vertical	Adiabatic		Vertical	Adiabatic
C_1	0.294 (0.282)	−0.037 (−0.033)	C_1	0.247 (0.253)	0.264 (0.273)	C_1	0.168 (0.223)	0.230 (0.258)	C_1	0.005 (0.004)	0.007 (0.007)	C_1	0.044 (0.045)	0.030 (0.032)
C_2	0.311 (0.377)	0.081 (0.086)	C_2	0.227 (0.237)	0.191 (0.192)	C_2	0.233 (0.281)	0.306 (0.311)	C_2	0.003 (0.003)	0.003 (0.003)	C_2	0.231 (0.232)	0.262 (0.260)
C_3	−0.152 (−0.154)	−0.032 (−0.030)	C_3	0.001 (0.015)	0.065 (0.086)	C_3	−0.035 (−0.029)	−0.029 (−0.019)	C_3	−0.010 (−0.010)	−0.021 (−0.021)	C_3	0.005 (0.007)	−0.012 (−0.010)
C_4	0.382 (0.336)	0.080 (0.072)	C_4	0.065 (0.040)	0.007 (−0.018)	C_4	−0.023 (−0.037)	−0.038 (−0.046)	C_4	0.222 (0.220)	0.301 (0.300)	C_4	0.048 (0.050)	0.060 (0.061)
C_5	0.257 (0.283)	−0.028 (−0.040)	C_5	0.292 (0.300)	0.313 (0.327)	C_5	0.038 (0.014)	0.023 (0.014)	C_5	−0.034 (−0.048)	−0.067 (−0.071)	C_5	0.224 (0.228)	0.225 (0.227)
C_6	−0.067 (−0.050)	−0.008 (−0.001)	C_6	−0.001 (−0.004)	−0.008 (−0.011)	C_6	0.002 (0.004)	0.006 (0.002)	C_6	−0.007 (−0.004)	0.001 (0.001)	C_6	0.067 (0.062)	0.082 (0.080)
N_7	−0.090 (−0.092)	0.756 (0.812)	C_7	−0.003 (−0.004)	−0.002 (−0.002)	C_7	0.004 (0.014)	0.009 (0.022)	C_7	−0.029 (−0.030)	−0.032 (−0.032)	C_7	−0.011 (−0.010)	−0.010 (−0.010)
O_8	0.113 (0.059)	0.103 (0.043)	C_8	0.006 (0.006)	0.015 (0.015)	C_8	0.126 (0.174)	0.131 (0.155)	C_8	0.005 (0.004)	−0.003 (−0.004)	C_8	0.013 (0.012)	0.009 (0.009)
O_9	−0.005 (0.008)	0.003 (0.000)	N_9	−0.089 (−0.091)	−0.095 (−0.101)	N_9	0.192 (0.248)	0.201 (0.224)	C_9	0.009 (0.009)	0.003 (0.003)	C_9	−0.007 (−0.007)	−0.011 (−0.011)
			O_{10}	0.221 (0.224)	0.217 (0.217)	O_{10}	0.103 (0.098)	0.093 (0.072)	C_{10}	0.193 (0.206)	0.197 (0.203)	C_{10}	0.001 (0.002)	0.004 (0.003)
			O_{11}	−0.001 (−0.001)	0.001 (−0.001)	O_{11}	0.023 (0.005)	0.013 (0.004)	C_{11}	0.043 (0.037)	0.035 (0.034)	C_{11}	0.003 (0.003)	0.004 (0.004)
			O_{12}	0.007 (0.004)	0.002 (0.001)	O_{12}	0.160 (0.008)	0.053 (0.004)	C_{12}	0.104 (0.109)	0.066 (0.65)	C_{12}	0.007 (0.007)	0.006 (0.006)
									C_{13}	0.126 (0.132)	0.137 (0.144)	C_{13}	0.002 (0.002)	0.003 (0.002)
									C_{14}	0.003 (−0.004)	−0.034 (−0.043)	O_{14}	0.202 (0.197)	0.190 (0.188)
									C_{15}	0.189 (0.200)	0.216 (0.229)	O_{15}	0.129 (0.129)	0.122 (0.123)
									C_{16}	−0.053 (−0.060)	−0.072 (−0.078)	C_{16}	0.021 (0.020)	0.013 (0.13)
									C_{17}	0.218 (0.222)	0.246 (0.244)			
									C_{18}	−0.017 (−0.017)	−0.020 (−0.019)			
									C_{19}	−0.010 (−0.011)	−0.007 (−0.007)			
									C_{20}	0.001 (0.002)	0.002 (0.003)			
									O_{21}	0.014 (0.011)	0.001 (0.002)			

To get the complete picture of a charge-transfer reaction, chemical descriptors such as the Mulliken electronegativity (χ) need to be taken into account. There are several proposed mechanisms [12] for the quenching of free radicals by vitamins: hydrogen atom transfer (HAT), single-electron transfer followed by proton transfer (SET-PT), and sequential proton loss electron transfer (SPLET). The common feature amongst all of these mechanisms is charge transfer.

Electronegativity (χ), which is the negative of the chemical potential (μ), is a measure of the tendency of the molecule to attract electrons. The computed χ values for vitamins (≈3–5 eV) are lower than those for the neutral ROS. The χ of ·OH [≈9 eV in different media when the 6-311G+(d,p) basis set is used, and 7.444 eV in the gas phase when the plane-wave basis set is used) is higher than the χ of ·OOH (≈ 6.6 in different media when the 6-311G+(d,p) basis set is used; and 6.231 eV when the plane-wave basis set is used). This suggests that, among the ROS, ·OH has the greatest tendency to extract an electron from the vitamin molecules, which in turn explains its highly reactive nature [59]. It is interesting to note that the presence of solvent and the polarity of the solvent are found to have negligible effects on the electronegativities of the vitamin and neutral ROS, but they are expected to have a considerable effect on the electronegativities of ionic species such as O_2^-. μ, which is a measure of the tendency of electron to escape, is found to be higher for the fat-soluble vitamin A (−3.401 eV in the gas phase when the plane-wave basis set is used, and −3.674 and −3.680 eV in the gas phase and in the solvent medium when the 6-311G+(d,p) basis set is used) and vitamin E (−3.537 eV in the gas phase when the plane-wave basis set is used, and −3.199 and −3.145 eV in the gas phase and in the solvent medium when the 6-311G+(d,p) basis set is used) than for the water-soluble vitamins B3 (−4.719 eV in the gas phase when the plane-wave basis set is used, and −5.100 and −5.094 eV in the gas phase and the solvent medium when the 6-311G+(d,p) basis set is used), B6 (−4.305 eV in the gas phase when the plane-wave basis set is used, and −4.132 and −3.991 eV in the gas phase and the solvent medium when the 6-311G+(d,p) basis set is used], and vitamin C (−4.588 eV in the gas phase when the plane-wave basis set is used, and −4.439 and −4.164 eV in the gas phase and the solvent medium when the 6-311G+(d,p) basis set is used). This suggests that fat-soluble vitamins are more likely to release electrons to neutral ROS than water-soluble vitamins are.

To get an idea of the extent of the electron transfer (partial) between two molecules, which depends on the ionization potentials and the electron affinities of both the molecules, we have computed the differences in the Mulliken electronegativities between the vitamins and ROSs (Table 4). The larger the difference in electronegativity, the greater the charge transfer. This electronegativity difference from neutral ROS is greater for fat-soluble vitamins then for water-soluble vitamins. Among the fat-soluble vitamins, vitamin E is found to have a larger electronegativity difference from neutral ROS then vitamin A does. Among the water-soluble vitamins, the electronegativity difference from neutral ROS is largest for vitamin B6, followed by vitamin C, and is smallest for vitamin B3. Among the ROS, ·OH is found to have greater electronegativity differences from both fat-soluble and water-soluble vitamins than ·OOH does. The solvent is found to have a negligible effect on the difference in χ between the vitamins and ROS. The computed negative χ between the vitamins and charged ROS (O_2^-) in aqueous medium confirms that, on their own, vitamins are incapable of converting O_2^- to O_2^2.

Another useful reactivity descriptor, the electrophilicity index (ω), quantifies the tendency of a molecule to soak up electrons. Hence, the higher the electrophilicity index, the greater the propensity of the complex to attract electrons from a generic donor molecule. Several authors [19] have shown that this parameter allows quantitative classification of the global electrophilic character of a molecule within the reactivity scale. The electrophilicities (ω) of the neutral ROS ·OH (5.612, 7.588, and 10.649 eV in the gas phase, CCl_4 medium, and aqueous medium, respectively, as obtained using the 6-311G+(d,p) basis set, or 4.433 eV in the gas phase using the plane-wave basis set) and ·OOH (3.582, 5.033, and 7.505 eV in the gas phase, CCl_4 medium, and aqueous medium, respectively, as obtained using

Table 4 Calculated differences in electronegativity between vitamins and ROS ($\Delta\chi = \chi_{ROS} - \chi_{vitamin}$) in the gas phase and in solvent

Vitamin	Gas phase				Solvent medium		
	6-311G+(d,p)		Plane-wave basis set		6-311G+(d,p)		
	·OH	·OOH	·OH	·OOH	·OH	·OOH	O_2^-
B3	3.949	1.488	2.725	1.512	3.913	1.509	−1.439
B6	4.917	2.456	3.139	1.926	5.016	2.612	−0.336
C	4.610	2.149	2.856	1.643	4.843	2.439	−0.509
A	5.375	2.914	4.043	2.830	5.336	2.906	–
E	5.850	3.389	3.907	2.694	5.871	3.441	–

the 6-311G+(d,p) basis set, or 3.756 eV in the gas phase using the plane-wave basis set) are found to be higher than those of all the vitamins. The high ω values of ·OH are in keeping with its highly reactive nature [59], as mentioned earlier. The ω values of vitamins in the gas phase range from 2.232 to 2.708 eV when obtained using the plane-wave basis set and from 1.331 to 2.756 eV using the 6-311G+(d,p) basis set. The ω values of water-soluble vitamins in aqueous medium range from 3.257 to 4.792 eV and those of fat-soluble vitamins in CCl_4 range from 1.634 to 3.030 eV. This is consistent with the fact that the vitamins act as scavengers by donating electrons to the ROS, and this effect is enhanced in the presence of the solvent.

Conclusions

We have carried out detailed first-principles density functional calculations of the structures and energetics, ionization potentials, electron affinities, spin densities, and various DFT-based global chemical reactivity descriptors of interest for antioxidant vitamins—vitamin A, vitamin B3, vitamin B6, vitamin C, and vitamin E molecules—in both neutral and charged states. Our results are in good agreement with the few relevant experimental results reported in the literature and previous theoretical calculations, giving us confidence in the ability of DFT to accurately describe these systems and providing a benchmark for further experiments. Thus, our study has expanded the application of reactivity indices to these molecules. The variations in structural parameters observed during cation and anion formation and the relaxation in energy calculated from the vertical and adiabatic values of ionization potential and electron affinity indicate that these vitamins prefer to lose electrons to neutral reactive oxygen species. However, we found that these neutral-state vitamins do not act as antioxidants for the ionic reactive oxygen species (O_2^-). The reactivities (antioxidant behavior) of the vitamins and ROS were found to depend on the nature of the medium. In the presence of a solvent, the reactivity increased. The fat-soluble vitamins were found to be better antioxidants than the water-soluble vitamins.

We note that the probability that the antioxidant reaction will take place is given by the reaction rate constant, which is dependent on the reaction energy barrier. Although our study represents a vital first step towards the detailed investigation of the antioxidant mechanisms of vitamin molecules with antioxidizing properties, several other factors (such as the nature of the environment) would obviously be expected to play important roles in such complex biochemical processes.

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