



Theoretical design of new very potent free radical scavengers

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ABSTRACT

The importance of radical scavengers in health or as preservatives in various media is well-established. Their properties are dependant of different factors such as their ability to donate a hydrogen atom or an electron, but also their lipophilicity and chain length for the protection of membranes. This paper presents new compounds with very potent radical scavenging potencies. The improvement in the magnitude of the quantities which reflect the radical scavenging ability can reach 10 kcal/mol with respect to vitamins C or E or other good radical scavengers such as flavonoids. The lipophilicity of these compounds can be increased by adding a tail at the good position without modifying their ability of donating a hydrogen atom. In the same way, the effect of addition of a sugar which increases the solubility in water is analysed.

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1. Introduction

A lot of degenerative diseases are related to the oxidation of biological components induced by the reactive oxygen species (ROS) produced in the mitochondria [1]. The excess of ROS, called oxidative stress, has been implicated in the pathogenesis of various diseases such as cancer, atherosclerosis, Parkinson and Alzheimer pathologies and has an impact on the body's ageing process [2,3]. In such pattern, free radicals interact with other molecules within cells and cause oxidative damage to proteins, membranes and genes. Antioxidants are molecules able to hinder this oxidation and their role in the maintenance of human health is largely assessed.

On another side, antioxidant molecules, especially phenolic compounds, are known to have the property to counteract lipid peroxidation in various media, vegetable oils or emulsions, liposome and lipoproteins. Lipid oxidation is a challenge in cosmetic or food industry because of the increasing amount of unsaturated fatty acid in the preparations. Lipid oxidation alters the taste and the nutritional quality of the fat but it can also lead to toxic compounds like malondialdehyde or 4-hydroxynonenal [4]. The study of antioxidants able to work inside the lipid media is of utmost importance.

There are different kinds of antioxidants. In biology, they can be signalling molecules which prevent from the inflammatory response or metal chelating compounds. When the oxidation comes from radicals, in every media, the antioxidants are good radical scavengers. A lot of works focused on the measurements of

antioxidant abilities of polyphenolics compounds extracted from vegetables or medicinal plants [5,6]. They used different methods, measuring the efficiency of lipid peroxydation inhibition or evaluating the radical scavenging. They do not always lead to the same results in particular because the peroxydation inhibition is dependant of the lipophilicity of the antioxidant. Thus, in the design of new antioxidants, it is important to take into account the solubility of the molecule in the medium where it must operate. This paper will focus only on the radical scavenging properties of the molecules. It is evident that, for medicinal or food preservative purpose, other properties must be evaluated such as toxicity and metabolism. These properties cannot be evaluated by theoretical calculations and only the first step in the evaluation of antioxidant ability, the radical scavenging capacity, will be evaluated in this paper forthcoming the other requirements to experimental studies.

On a chemical point of view, the radical scavenging abilities depend on three mechanisms. In the first one, the free radical gains a hydrogen atom from the radical scavenger, which becomes a radical:



The occurrence of such a hydrogen transfer (HAT) is determined by the bond dissociation enthalpy (BDE) which measures the strength of the OH bond. In the second mechanism, the radical scavenger gives an electron to the radical:



In that case the ionisation potential (IP) is the significant energy factor of the reaction. If the polyphenol molecule exists in anionic form at physiological pH due to its low pK_a , this

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mechanism has been named Sequential Proton-Loss Electron-Transfer (SPLET) [7,8].



The significant enthalpy related to this reaction can be denoted ETE (electron transfer enthalpy) [9]. It corresponds to the second equation and is equal to the difference between the enthalpies of ΦO^- and ΦO^\cdot . Its occurrence depends on the $\text{p}K_a$ of the compound.

BDE, IP or ETE can be theoretically evaluated with a good accuracy [10–12]. Wright et al. have calculated the BDE of a large variety of substituted phenols with an accuracy of a few kcal/mol. Their calculations were done in the gas phase and it has been further evidenced that calculations including the solvation were still more accurate. In Ref. [12], Lespade et al. have compared the calculated BDE of a series of flavonoids with the experimental antioxidant abilities measured in a stop-flow spectrometer. The good correlation between theory and experiment indicates an accuracy of less than 1 kcal/mol for the relative calculated BDE of this type of compounds. Comparison of theoretical enthalpies with the results of experiments possessing a long stabilization time has pointed out the occurrence of processes (1) and (3) in the DPPH $^\cdot$ radical scavenging by flavonoids in ethanolic solution. The calculations indicate that the second process described by Eq. (2) is not energetically favored. Thus a certain number of studies have shown that the use of theoretical calculations can be of great utility in the investigation of radical scavenging properties of polyphenols. The OH BDE can be calculated with an accuracy of at least a few kcal/mol, which permits a good comparison between the compounds. There are less possibility of comparison between ETE and experimental results, but generally, if the antioxidant is a very weak acid, a low BDE correlates with a low ETE.

This paper is devoted to the design of compounds possessing low BDE or ETE, which is of utmost interest in chemistry of conservatives. This design is a consequence of an observation made in Ref. [12]: the comparison of the charges on the oxygen atoms of the flavonoid series indicates that, when the hydroxyl group is not embedded in a hydrogen bond, the higher is the Mulliken charge of the oxygen atom, the lower the corresponding BDE is calculated. This observation can be linked to a comment of Heijnen et al. [13] on substituted phenols. They have found that the ability of a compound to scavenge peroxyxynitrite correlates with the electron donating activity of the substituent groups and concluded that the electron donation from the substituent to the oxygen of the hydroxyl group weakens the O–H bond.

Thus, this paper is devoted to theoretical calculations of BDE and ETE of compounds which have high Mulliken charges on the oxygen atom of a hydroxyl group. Then, the effect of the addition of a lipophilic tail or a sugar is examined in order to propose potent hydrophilic and lipophilic radical scavengers.

2. Computational details

The calculations of the BDE and ETE are performed with methods analogous to what is exposed in the paper of Wright, Johnson & Di Labio [10]. All the calculations have been conducted by using the Gaussian 09 packages [14].

2.1. BDE

The BDE is the enthalpy related to the HAT mechanism (Eq. (1)):
 $\text{R}^\cdot + \Phi\text{OH} \rightarrow \text{RH} + \Phi\text{O}^\cdot$

The enthalpy of a species ΦOH is estimated as:

$$\begin{aligned} H(\Phi\text{OH}) = & E_0(\Phi\text{OH}) + \text{ZPE}(\Phi\text{OH}) + \Delta H_{\text{trans}}(\Phi\text{OH}) \\ & + \Delta H_{\text{rot}}(\Phi\text{OH}) + \Delta H_{\text{vib}}(\Phi\text{OH}) + \text{RT} \end{aligned} \quad (5)$$

where E_0 is the calculated total electronic energy, ZPE the zero point energy, and the other terms correspond to the thermal contributions of the enthalpy originating from the translation, rotation or vibrations of the molecule. The five last terms are evaluated in frequency calculations performed by Gaussian. The BDE being a local property, the molecule can be considered in two parts by using the ONIOM procedure implemented in Gaussian package. First, the geometries of the whole molecules and radicals are optimised within the density functional theory (DFT) approach with the B3LYP exchange correlation potential and a small basis set: 6-31+G(d). The unrestricted open-shell approach (UB3LYP) is used for radical species. The enthalpies $H(\Phi\text{OH})$ and $H(\Phi\text{O}^\cdot)$ are evaluated at the same level of calculations by performing a frequency calculation. Then the difference between the electronic energies of the radical and molecule $E_0(\Phi\text{OH}) - E_0(\Phi\text{O}^\cdot)$ is calculated by optimisation of the geometry of the two species with the ONIOM procedure, by describing the OH bond with a large basis set: 6-311+G(2d,2p) and the remaining part of the molecule with the small one: 6-31+G(d). The BDE corresponds to this energy difference between the two species corrected from the difference of enthalpies minus the enthalpy of the hydrogen radical. As in the paper of Wright et al. [10], the enthalpy of the H $^\cdot$ radical has been taken equal to 0.49764 hartrees. With Gaussian 09 code, it is possible to combine the ONIOM method with the self-consistent reaction field polarised continuum model (SCRFP-PCM) [15,16] which mimics the solution in solvents by building a cavity of overlapping spheres. The calculations have been performed in ethanol solution to compare the results with the BDEs of the flavonoids series [12]. It has been verified that the values of the BDE in water are very similar. The use of ONIOM procedure leads to small errors of less than 0.3 kcal/mol except for very few cases. It is possible to describe a larger part of the molecule with the large basis set to avoid the errors. This procedure allows the calculations of large molecules with a good precision. In the case of small molecules with no tail or sugar substituent, the ONIOM procedure has not been used. The geometries of the entire molecules and radicals have been optimised with the larger basis set.

As reported in Ref. [12], these calculations generally underestimate slightly the absolute value of the BDE. The BDE of phenol in the gas phase is calculated 85.6 kcal/mol to compare with the experimental value 86.5 kcal/mol. For DPPH, the discrepancy is higher 76.3 versus 80 kcal/mol.

2.2. ETE

For the calculation of the electron transfer, the geometries of the molecule and radical are optimised with the same method and basis set B3LYP/6-31+G(d) (UB3LYP/6-31+G(d)). The zero point energies (ZPEs) are calculated within the same level of calculations. The electron transfer corresponds to the difference between the single point energies B3LYP/6-311+G(2d,2p)//B3LYP/6-31+G(d) (UB3LYP/6-311+G(2d,2p)//UB3LYP/6-31+G(d)) corrected from the ZPE. Contrary to the BDE, the electron transfers are completely different in solution or gas phase. The solvent effects are evaluated in the framework of self-consistent reaction field polarised continuum model (SCRFP-PCM) [15,16] implemented in Gaussian package.

3. Results

Before studying synthetic radical scavengers, it is interesting to evaluate the antioxidant abilities of natural compounds present in

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