Computational and Theoretical Chemistry xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Computational and Theoretical Chemistry

journal homepage: www.elsevier.com/locate/comptc

Lycopene, oxidative cleavage derivatives and antiradical activity

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ARTICLE INFO

Article history:
Received 13 September 2015
Received in revised form 31 October 2015
Accepted 2 November 2015
Available online xxxx

Keywords:
Antioxidant
Radical scavengers
Carotenoids
Oxidative cleavage
Cancer

ABSTRACT

The principal aim of this investigation is to study free radical scavenger capacity of oxidized derivatives of lycopene (LYC) that were reported before as bioactive derivatives/metabolites. The electron transfer mechanism is analyzed in terms of its ionization energies and electron affinities. Lambda maximum (λ_{max}) values are also included. Electron affinity increases and ionization energy decreases as the number of carbon atoms in the backbone and the number of conjugated double bonds augment. The presence of OH improves the electron donor capacity, whereas the presence of the aldehyde group raises the electron acceptor capacity. Di-aldehyde derivatives appear as the best electron acceptors among the molecules investigated. The increased power to accept electrons on the part of the oxidized derivatives may influence anti-cancer properties. Here we report the electronic differences between these molecules. This information will aid in the understanding of different possible mechanisms that may be involved in the prevention of some illnesses like cancer, as reports exist indicating that some of these metabolites can be formed in vivo and are biologically active.

1. Introduction

Lycopene (LYC) is a red carotenoid that can be produced by some plants and microorganisms [1]. It is a natural compound that is omnipresent in the diet of humans all over the world as it is present not only in tomatoes and derivatives but also in watermelon, guava, pink grapefruit and papaya, among others [2,3]. LYC has been shown to exhibit a considerably high antioxidant capacity [4–14] and is associated with a wide spectrum of potentially beneficial health outcomes [15–25]. In this sense, anti-cancer potential is considered to exist [17–25] particularly against prostate cancer [22,23], although causality has not been clearly established due to inherent difficulties. In contrast to the effect of β-carotene among certain risk groups, in the case of LYC there is no observed association between elevated risk of lung cancer and its long-term use as a dietary supplement [24].

LYC has a highly unsaturated structure and can thus be easily oxidized. A typical methodology for obtaining oxidative cleavage derivatives of carotenoids consists in the use of potassium permanganate as an oxidizing agent. For instance this has been used with LYC and β-carotene [26,27] although studies on the interaction of LYC oxidative cleavage derivatives with oxidizing agents are lacking. However, it has recently been shown that the cleavage of β-carotene into a number of these derivatives is accompanied by noticeable changes not only in color but also in antioxidant capacity [28]. More importantly, mammals are known to codify oxygenase enzymes that catalyze the oxidative cleavage of provitamin A carotenoids into retinoids (usually referred to as β,β-carotene 15,15′-monooxygenase 1) and of both provitamin A and non-provitamin A carotenoids (like LYC). The latter enzyme (usually termed as β,β-carotene 9′,10′-dioxygenase) cleaves the carotenoids eccentrically at both the 9,10 and 9′,10′ double bonds, producing oxidized non-volatile apocarotenoids, as well as oxidized volatile cleavage products [29]. Interestingly, the presence of some cleavage oxidative metabolites from LYC has been reported in human plasma [30].

Currently it is thought that these cleavage oxidative metabolites may be biologically active and be involved in some of the actions traditionally attributed to the parent carotenoids [31,32]. Some of the products of LYC that may present bioactive properties include apo-lycopenals, apo-carotenedials, apo-lycopenones, carboxylic acids and epoxides [33–37]. Therefore, a mixture of LYC oxidation products has manifested an enhanced ability to inhibit the growth of leukemia cells [33]. On the other hand, apo-10′-lycopenoic acid appears to promote lung cancer cell growth activity and to suppress lung tumorigenesis [35].

Some efforts have been made to correlate the chemical structure of these compounds with their reactivity [36]. It appears that chemical reactivity is related to the position of the first methyl

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http://dx.doi.org/10.1016/j.comptc.2015.11.001
2210-271X/

group (with respect to the terminal aldehyde group) and the number of carbon atoms in the backbone chain. The optimal backbone has 12 carbon atoms and the most active derivatives are those with the methyl group located at a distant position. Fig. 1 shows the chemical structure of possible bioactive lycopene cleavage derivatives.

There are several reports concerning the antiradical activity of LYC and it has been reported that one of the mechanisms is the electron transfer reaction between carotenoids and the reactive oxygen species. The electron transfer reaction with the superoxide anion is special, given that in this case the carotenoids accept rather than donate electrons. From this perspective, the antiradical activity of carotenoids against the superoxide ion is related to the capacity to prevent the formation of reactive oxygen species [6,12–14]. It has been reported that very high doses of β-carotene supplementation can increase the risk of lung cancer among smokers and other risk groups [24]. LYC was also included in this investigation, and it has been proved that there is no correlation between cancer risk and the doses of lycopene; however nothing is known about the bioactive derivatives of lycopene.

Even though there are reports about the antiradical activity of lycopene and carotenoids and about the activity of lycopene bioactive derivatives as anticancer substances, little if anything is known about the correlation between the electronic structure and the capacity of lycopene derivatives to prevent oxidative stress. In this report, optimized structures of bioactive derivatives are reported. The oxidized derivatives of LYC used in this investigation are included in Fig. 1, and were reported before [37] as bioactive derivatives/metabolites. Additional derivatives, including mono and di-aldehyde derivatives, are also included to emphasize the trend according to the functional groups. The electron transfer mechanism is analyzed in terms of the ionization energies (IE) and electron affinities (EA). In order to analyze the correlation between the presence of conjugated doubles bonds (cdb) and the emission–absorption spectra, lambda maximum (λ_{max}) values are also included.

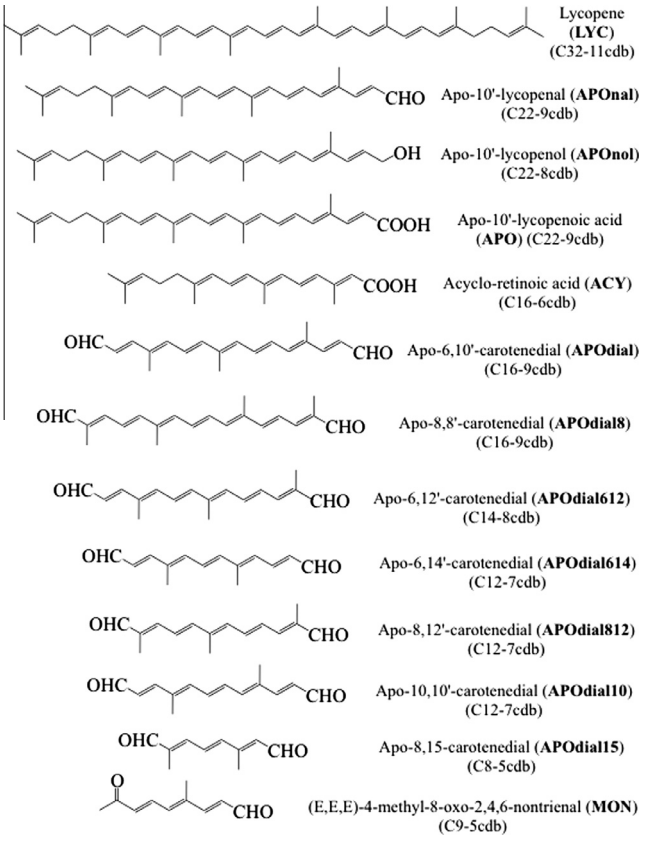

Fig. 1. Molecular structures of lycopene and its bioactive derivatives used in this investigation.

2. Computational details

Gaussian 09 implementation [38] is used to calculate geometry optimization and electronic properties of twelve bioactive derivatives of LYC (Fig. 1). LYC is included for comparison. Initial geometries are fully optimized at B3LYP/6-31G(d) level of theory [39,40]. In order to verify optimized minima, harmonic analyses are performed and local minima are identified (zero imaginary frequencies). The λ_{max} values are obtained by applying time-dependent density functional theory (TDDFT) at CAM-B3LYP/6-311+g(d,p) level of theory [41].

CAM-B3LYP is a relatively new Coulomb-attenuated hybrid exchange–correlation functional that adequately predicts molecular charge-transfer spectra [41]. Likewise, qualitatively good predictions for the spectra of porphyrin, some oligoporphyrins, and chlorophyll were reported; as well as concurring very well with complete-active-space plus second-order Møller–Plesset perturbation theory and symmetry-adapted cluster configuration interaction calculations [42,43]. With this methodology, λ_{max} for LYC in gas phase is 507 nm but if heptane is considered as the solvent, it is equal to 541 nm. The experimental value in hexane is 472 nm. Comparing these two last values, the error is 14%. As we intend to assess tendencies and the differences between the values associated with different functional groups, but are not interested in the exact value of λ_{max}, we consider that we can use these results for the purpose of comparison.

In order to investigate the single electron transfer mechanism, vertical ionization energy (IE) and vertical electron affinity (EA) are obtained from single point calculations of cationic and anionic molecules, using the optimized structure of the neutrals and the B3LYP/6-311+g(d,p) level of theory. A useful tool defined previously is the Full Electron Donor Acceptor Map (FEDAM) [12–14,44,45] In this map (see Fig. 2) IE and EA are plotted and allow us to classify substances as either donors or acceptors of electrons. Electrons will be transferred from molecules located down to the left of the map (good electron donors) to those molecules that are up to the right (good electron acceptors).

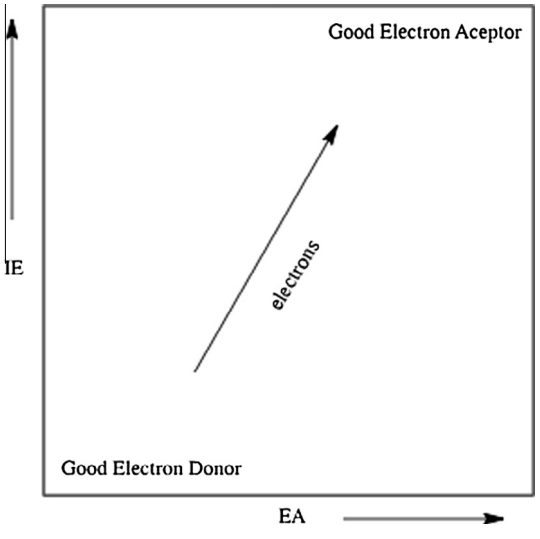

Fig. 2. Full electron donor–acceptor map.

Please cite this article in press as: A. Martínez, A.J. Melendez-Martínez, Lycopene, oxidative cleavage derivatives and antiradical activity, Comput. Theoret. Chem. (2015), http://dx.doi.org/10.1016/j.comptc.2015.11.001