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The natural food colorant Peonidin from cranberries as a potential radical scavenger – A DFT based mechanistic analysis

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ABSTRACT

A theoretical evaluation of the antioxidant property of a natural food colorant Peonidin has been performed. The most suitable mechanism for explaining the radical scavenging capacity of Peonidin is the Hydrogen Atom Transfer and the most active site for radical formation is position 3 and is confirmed through Mulliken charge analysis, pKa value evaluation, Bond Dissociation Energy values, and Natural Bond Orbital analysis. Position 3 and 5 in Peonidin exists in blood as deprotonated as their pKa values are lower than the pH of blood. Peonidin is highly reactive than Quercetin and less stable than flavan-3-ols due to the small band gap. Global descriptor analysis shows that PN prefers to accept electrons than to donate. The effect of number of —OH groups and the nature of substituents are well explained through this work.

1. Introduction

About 33 years ago; i.e., in 1985, the concept of Oxidative Stress (OS) has been introduced in the Redox biology and medicine as the introductory chapter 1 in the book ‘Oxidative Stress’ (Sies, 1985). Later in a review article on ‘Biochemistry of oxidative stress’ (Sies, 1986), explain the world of antioxidant and their influence in biological system and then onwards ‘Redox biology’ becomes an interesting area of research among various disciplines like Chemistry, Medicinal Chemistry, Pharmaceutics, Biology, Radiation biology, etc.

The OS is the dangerous situation resulting from the generation of free radicals in the biological system. These free radicals may be Reactive Oxygen Species (ROS) or Reactive Nitrogen Species (RNS). The free radicals are short living fast reactive species. They react rapidly with cellular membrane and causes disorder which ultimately leads to death. In our body, the brain is the part of high metabolic rate, lipid peroxidation, etc., so that brain is highly vulnerable to OS. This drives a scientist to develop some antiradicals to treat brain injury (Masone & Chanforan, 2015). Similarly, most of the electron transport reactions are takes place in mitochondria so that most of the ROS/RNS are generated in mitochondria. Thus antiradicals targeting mitochondria have to be developed. The OS may lead the regular/normal life activities to an abnormal level and lead to AIDS, aging, arthritis, asthma, cancer, cataract, diabetes, neurodegenerative disorders, Alzheimer’s, Parkinson’s disease, heart failure, etc. In order to fight against these ROS/RNS, our body develops a defense mechanism in which certain substance are actively fought against the free radicals called antioxidants (Gupta & Sharma, 2006).

The substances which produced in low concentrations in our body in order to delay the OS produced as a result of oxidation of proteins/lipids, carbohydrates, DNA, etc., are termed as antioxidants. Generally, they are called radical scavengers or antiradicals. They do so either by acting as an antioxidant or as an antireductant. There are 3 categories of antioxidants namely: 1st, 2nd and 3rd line defense antioxidants. The antioxidants present in our body are Vitamin E and C. But the modern lifestyle and food habits make these antioxidants insufficient to neutralize the free radicals generated in the biological system so that we have to depend on medicines (synthetic antioxidants). But this again has some problems because synthetic antioxidants have lots of toxic side effects and are expensive too. In this scenario, chemists forced to discover some natural radical scavengers. The discovery of natural antiradicals replaces the use of synthetic antiradicals because of a number of facts. Natural antiradicals are of low cost, compatibility with dietary intake and no harmful effects in the human body (Sindhi,

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Abbreviations: OS, Oxidative Stress; ROS, Reactive Oxygen Species; RNS, Reactive Nitrogen Species; PG, Pelargonidin; CY, Cyanidin; DP, Delphinidin; PN, Peonidin; PT, Petunidin; MA, Malvidin; DFT, Density Functional Theory; HF, Hartree Fock; HAT, Hydrogen Atom Transfer; ET-PT, stepwise electron transfer-proton transfer; SPLET, sequential proton loss electron transfer; BDE, Bond Dissociation Energy; PES, Potential Energy Scanning; CM, continuum models; IEF-PCM, integral equation formalism polar continuum models; SCRF, Self-Consistent Reaction Field; SE, Semi-Empirical; FMO, Frontier Molecular Orbital; HOMO, highest molecular orbital; LUMO, lowest unoccupied orbital; VIP, Vertical Ionization Potential; VEA, Vertical Electron Affinity; NBO, natural bond orbital; NAO, natural atomic orbitals; NHO, natural hybrid orbitals; SET, single electron transfer; AIP, Adiabatic Ionization Potential; SETPT, single-electron transfer followed by proton transfer; PDE, Proton Dissociation Enthalpy; PA, proton affinity; ETE, Electron Transfer Enthalpy; NPA, Natural Population Analysis

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Gupta, Sharma, & Bhatnagar, 2013).

Studies have shown that the major class of natural products; flavonoids are potential antiradicals. Anthocyanidins, a widely distributed class of flavonoids, are major constituents of vascular plants and are harmless water-soluble natural pigments with bright color. This makes their wide acceptance as a good natural food colorant. They also found to have the capacity to chelate metal ions in biological systems (Mosquera, Estévez, Bugarín, 2015; Sakata, Saito, & Honda, 2006). The acyl-glycosides of these are called anthocyanins. Pelargonidin (PG), Cyanidin (CY), Delphinidin (DP), Peonidin (PN), Petunidin (PT) and Malvidin (MV) are the most common anthocyanidins in which PN is studied and explained in the present article. Studies have shown that they have antioxidant (Mosquera, 2008, 2010; Tănasie & Medeleanu, 2012), anticancer and antidiabetic capacities (Castañeda-ovando, Pacheco-hernández, Páez-hernández, Rodríguez, & Galán-vidal, 2009). But the relationship of the structures of anthocyanidins and the properties that they have shown is not completely understood. In this scenario, detailed structural analyses of anthocyanidins are particularly relevant.

Different anthocyanidins differ in the number of —OH groups and glycosidic linkages. Their abundance in plants follows the order CY = 50%, DP = PG = PN = 12%, and PT = MV = 7% respectively. The isolated anthocyanidins are highly unstable and because of the enormous applications, the studies regarding the stability of anthocyanidins are very important. The affinity towards pH, metal ions, temperature, concentration, light, etc., makes them unstable in the free state. As the use of synthetic colorants have been increased to a great extent and become a great threat to human health because of their toxicity; the development of some natural food colorant is particularly relevant in the area of food industry.

Cranberries are one of the major crops in certain American states and Canadian provinces. They are red in color and processed into juices, jams and also as dried fruits. Cranberry sauce is served as a traditional accompaniment to Turkey at Christmas dinner in the United Kingdom and Canada. The title compound PN is the color pigment in Cranberry and is one of the principal anthocyanidins. The basic structure of anthocyanidins consists of an aromatic ring [A] bonded to a heterocyclic ring [C] that contains an oxygen which is also bonded by a C—C bond to a third aromatic ring [B] (Fig. S1). They belong to polyphenolic groups containing at least one —OH group in the benzene ring. The title compound, PN is a naturally existing anthocyanidin and belongs to phytonutrient family. PN is a well-known antioxidant found in berries, cherries, etc., with bright color. The name PN is derived from 'Peony' a plant with a pink colored flower. It is the presence of PN which gives color to Peony flower. PN also imparts blue/blue-green color to the flowers in 'Morning Glory'. How the same compound gives a different color to these two flowers is due to the difference in pH at which they grow. At acidic pH, PN is purple in color while in alkaline pH it is blue in color and the optimum pH for planting Peony is in the range 6–7 and that for Morning glory is in the alkaline pH range.

As PN is a promising antioxidant, the present study involves a theoretical/computational investigation on the structural effects of PN on its antiradical property. Most of the studies are based on its glycoside derivative so that evaluation on the structure of parent compound is significant. Since computational investigations give a clear cut idea and deep insight into the radical scavenging activity of PN, we have used computational approach and are explained in the following sections.

2. Materials and method

2.1. Materials

The present work has used a computational approach to study the structure and properties of an anthocyanidin, PN. The input structures are drawn by using the Gaussview-5.0 graphical user interface. All the computational works have been carried out through Gaussian 09 software package (Frisch et al., 2009). The present work uses DFT-B3LYP as the level of theory with 6-31 + G (d, p) as the basis set.

2.2. Computational methodology

Computational chemistry is a set of techniques for investigating chemical problems on a computer by the implementation of suitable software. The quantum mechanical calculations have been iteratively solved by the programmes as per the keywords and the properties can be computed. These are green because it does not require any chemicals and is less time-consuming. Almost all the properties can be calculated computationally with considerable accuracy. Once the computers and software are built up there are no other requirements and consequently is economic too. The same set up can be used for different types of property calculations. These are the merits of computational methods. Before going to synthesize the compound in the laboratory and analyzing its properties, it is better to carry out a theoretical study on the structure and properties of the compound. In doing so, we could get an idea about the factors on which the properties depend and how we can tailor them accordingly.

Density Functional Theory (DFT) is one of the major and most often used computational tools to solve the chemical problems. DFT is, analogously to Hartree Fock (HF) method, an independent-particle model, and is comparable to HF computationally, but provides significantly better results. The main disadvantage of DFT is that there is no systematic approach to improving the results towards the exact solution. The level of theory adopted was B3LYP, which consists of Becke's exchange functional (Becke, 1993) in conjunction with Lee-Yang –Parr correlational functional (Lee, Yang, Parr, 1988) and the basis set used is 6-31 + G (d, p).

Before going to the details of the computational methodology adopted here, some literature reviews have to be pointed. From literature, different peoples use a different level of theory and basis sets for the structural calculations of anthocyanidin; of which DFT-B3LYP is the most commonly used level of theory. There are lots of studies on anthocyanidins, especially on CY, DP, and MA and which includes both antioxidant and excited states studies (Cacelli, Ferretti, & Prampolini, 2016; Guzmán, Santiago, & Sánchez, 2009; Lu, Qiang, Faliang, Zhang, Zhang, 2014; Nagaoka, Bandoh, Nagashima, & Ohara, 2017; Sakata et al., 2006; Tănasie & Medeleanu, 2012). Laura and et al. have studied the radical scavenging activity of anthocyanidins via hydrogen atom transfer (HAT), stepwise electron transfer-proton transfer (ET-PT) and sequential proton loss electron transfer (SPLET) mechanisms. In all their papers the calculations were done by using Gaussian 03 software package. They have compared the calculations in different levels of theory and basis sets. Also, they have analyzed the —OH Bond Dissociation Energy (BDE) values at different positions in the anthocyanidin moiety and have found that position 3 is the site for the stable radical formation and having lowest BDE value for most of the anthocyanidins. But in some cases especially with solution phase, position 4′ also shows lowest BDE value. They have studied neutral, anionic and cationic forms of anthocyanidins for the radical scavenging capacity (Este & Mosquera, 2007; Mosquera, 2008, 2009, 2010). In all these, the commonly used method was found to be DFT/B3LYP as higher methods do not show much variation in results (Este & Mosquera, 2007; Mosquera, 2008, 2009, 2010). So here in our case also we have chosen the same method and the methodology is as follows.

At first, a Potential Energy Scanning (PES) has been performed on the dihedral connecting the rings [B] and [C] and the lowest energy conformer has been identified for further analysis. The PES diagram is shown in Fig. S3. In order to find out the best basis set and level of theory, geometry optimization studies are carried out with different basis sets and levels of theory. The geometric parameters are given in Tables S1 & S2. To best of our knowledge, there is no available experimental data for PN as all are associated with its glycoside derivatives. So we have compared the geometric parameters of PN under