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Characterization of π-stacking interactions between aromatic amino acids and quercetagetin

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ABSTRACT

In the present study, the π-stacking interactions between quercetagetin (QUE), which is one of the most representative flavonol compounds with biological and chemical activities, and some aromatic amino acid (AA) residues has been investigated by the quantum mechanical calculations. The trend in the absolute value of stacking interaction energy $|\Delta E|$ with respect to AAs is HIS > PHE > TYR > TPR. The results show that the sum of donor-acceptor interaction energy between AAs and QUE ($\sum E^2$) and the sum of electron densities ρ calculated at BCPs and CCPs between the rings ($\sum\rho_{BCPs}$ and $\sum\rho_{CCP}$) can be useful descriptors for prediction of the ΔE values of the complexes. The O–H bond dissociation enthalpy (BDE) slightly decreases by the π-stacking interaction, which confirms the positive effect of that interaction on the antioxidant activity of QUE. A reverse trend is observed for BDE when is compared with the $|\Delta E|$ values. A reliable relationship is also observed between the Muliken spin density (MSD) distributions of the radical species and the most convenient O–H bond dissociations. In addition, reactivity is in good correlation with the antioxidant activity of the complexes.

1. Introduction

Flavonoids are polyphenolic compounds that are present in fruits, vegetables, coffee beans, green and black tea, red and white win, herbs and propolis [1]. They have a special importance in the medical and biological sciences due to their biological activities, *e.g.* antiallergic, antioxidant, antiviral, antibacterial and anticancer [2–4]. Three major subfamilies of flavonoids are flavones, flavonols and flavanones. The chemical structure of flavonoid is based on $C_6–C_3–C_6$ carbon framework (subscripts 3 and 6 represent the number of carbon in each ring), consisting of two aromatic benzene rings (rings A and B) linked via an oxygen-containing pyran ring (ring C) [5,3]. There are differences in the degree of pyran ring saturation, in the placement of ring B at the C2 or C3 positions of ring C and the position and the number of hydroxyl groups [3]. Several studies have shown that flavonoids are enzyme inhibitors and are bound to active sites via noncovalent interactions [6–12].

Noncovalent interactions (hydrogen bond, van der Waals, charge transfer, π-stacking, *etc.*) play significant roles in drug design, supramolecular chemistry, materials science and molecular biology [13–18]. Many theoretical and empirical studies have focused on π-stacking interactions because of their biological importance [19–34], especially in the protein-ligand complexes. There is a set of small and large molecules, including aromatic rings, which make such biologically important complexes via π-stacking interactions with aromatic amino acids (AAs) like tryptophan (TRP), tyrosine (TYR), phenylalanine (PHE) and histidine (HIS) [35–39]. The crystal structures also indicate π-stacking interactions between ligands and aromatic AAs in the active sites of enzymes. The T-shaped, edge-to-face, and parallel-displaced stacking configurations are favored energetically in comparison with the sandwich configuration. It should be noted that the parallel displaced configuration is observed more frequently than the T-shaped configuration in the protein structures [26,40].

In recent decades, many computational studies have been performed to characterize the π-stacking interactions in the active sites of proteins, which are highly informative about the nature and importance of these interactions [41–45]. Intermolecular π-stacking interactions are also occurred in the crystal structures of flavonoids due to the planarity, polarity, and aromaticity [46,47].

The inhibition mechanism of cytochrome P450 2C9 (CYP2C9) has previously been investigated via a series of flavonoids [10]. The results demonstrated that all the tested flavonoids are reversible inhibitors of CYP2C9 and among them, 6-hydroxyflavone acts as

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noncompetitive inhibitor and other flavonoids are competitive inhibitors. In addition, the work used computer aided docking and molecular dynamic simulation to characterize the binding sites of flavonoids in CYP2C9. Results indicated that the competitive inhibitors bind to the substrate binding site whereas the noncompetitive inhibitor binds to the allosteric site of the enzyme via a π-stacking interaction with Phe100 residue and the hydrogen bonds with Leu102 and Arg105 residues. The inhibitory mechanism of the β-hydroxyl-acyl carrier protein dehydratase of *Helicobacter pylori* (HpFabZ) by three flavonoids (S)-sakuranetin, quercetin and apigenin has been studied by Zhang and coworkers [11]. These flavonoids were identified to be competitive inhibitors and bind to HpFabZ via two models. In one model, flavonoids act as enzyme inhibitors via noncovalent interactions and are stacked with two residues Tyr100 and Pro112. Elsewhere, Pawlotsky and coworkers [12] investigated the inhibition process of hepatitis C virus RNA-dependent RNA polymerase (HCV RdRp) by six flavonoids. Quercetagetin (QUE), a type of flavonol indicated in Scheme 1, was found to be a more potent inhibitor in comparison with other flavonoids. The X-ray structure of the HCV RdRp-QUE complex shows that QUE binds to allosteric site of enzyme and alter its 3D structure. This binding is done through noncovalent interactions (a hydrogen bond with G238 and a π-stacking interaction with Phe162 residue), which are poorly described by density functionals.

Moreover, π-stacking interactions may also affect the antioxidant action of flavonoids. In fact, the activity of phenolic antioxidants is not solely dependent on their structures. It may also be affected by the noncovalent interactions in the surrounding environment [2], particularly π-stacking interactions. Thus, it is important to investigate the π-stacking interaction between flavonoids and aromatic AAs and its effect on their antioxidant activity.

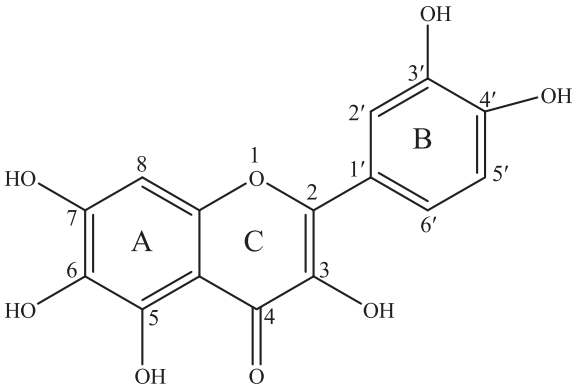
In the present work, the π-stacking interactions of QUE and some amino acids containing five and six-membered aromatic rings have been investigated at the M06-2X/6-311++G(d,p) level of theory. The complexes have been investigated with respect to the energy data and the results of the population analyses. Herein, the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), bond dissociation energies (BDE), and Muliken spin density distribution (MSD) values have been considered to investigate the antioxidant activity of stacked QUE. This study can provide an insight about the magnitude of π-stacking interactions between the aromatic AAs and QUE and their effect on antioxidant activity of QUE, which is useful in biological processes.

2. Computational details

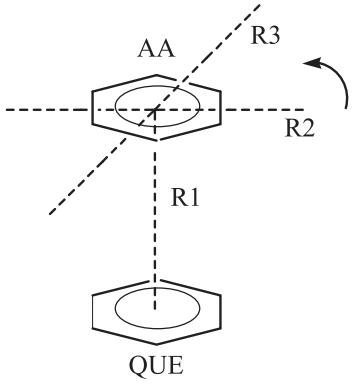
All calculations were carried out using the Gaussian09 program package [48]. All units were fully optimized by the hybrid meta exchange-correction functional M06-2X [49] method in conjunction with the 6-311++G(d,p) basis set. The nucleotide units were modeled by replacing a hydrogen atom with the protein backbone of AAs (indole for TRP, phenol for TYR, benzene for PHE and imidazole for HIS). The initial structures of AA||QUE complexes (where || donates π-stacking interaction) were generated by aligning the centers of rings of units. Four parameters including vertical separation (*R*1), rotational angle (α), and horizontal displacement (*R*2 and *R*3), were considered to determine the optimal complexes (see Scheme 2). The potential energy surface scans were carried out through the single point calculations at the M06-2X/6-311++G(d,p) level to obtain the optimized geometries of the AA||QUE complexes. The preferred *R*1 value was obtained by 0.1 increments and held constant for the remaining calculations. Then, AA was rotated by 360° (12 steps of size 30°) for α increments in right-handed sense about the axis that passes through the centers of rings. Using the optimal values for α and *R*1, the optimal values of *R*2, and *R*3 were determined upon the shift of AA across the face of QUE in 0.1 increments. All the above mentioned steps were performed for three rings of QUE, which specified by A, B and C letters in Scheme 1. After finding the best orientations of AAs relative to the rings A, B and C of QUE, the most stable complexes were obtained by optimization at the M06-2X/6-311++G(d,p) level of theory. No imaginary frequency was found for any of the optimized structures. In addition, single point interaction energies were calculated by the B3LYP-D3 [50,51] dispersion corrected functional as suggested by Grimme for noncovalent contacts [52,53]. The basis set superposition error (BSSE) correction was performed by the counterpoise (CP) method. Also, to investigate the effect of π-stacking interaction on the antioxidant activity of QUE, radical structures of QUE and stacked QUE were optimized at the above mentioned level. The topological properties of electron charge density were calculated by the atoms in molecules (AIM) method [54] using the AIM2000 program package [55] on the wave functions obtained at the HF/6-311++G(d,p) level of theory. The natural bond orbital (NBO) analysis [56] has been performed on those wave functions by the NBO3.1 software [57]. Moreover, MSDs for radical species have also been calculated and interpreted.

3. Results and discussion

The interaction energies (Δ*E*) obtained for each step along the scans of variables, introduced in the previous section, are available in Supplementary material (see Table 1S). The largest Δ*E* values calculated between AAs and the rings A, B and C of QUE are reported in Table 1. The trend in the |Δ*E*| values is B < A < C in stacking



Scheme 1. The structure of quercetagetin (3,5,6,7,3′,4′-hexa hydroxy flavonol).



Scheme 2. Definition of variables in the AA||QUE-C complexes.