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Theoretical study of the structure and acidity of condensed tannin monomers

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ABSTRACT

Low level of polyphenols absorption is due among other things to the formation of irreversible complexes between non-heminic iron (Fe^{2+}, Fe^{3+}) and these polyphenols through their hydroxyl groups. Understanding of these complexes formation mechanisms led us to explore hydroxyl groups acidity of these polyphenols monomers (catechin, epicatechin, gallocatechin and epigallocatechin) mainly found in food. Quantum chemistry modelling, more precisely the functional density theory (DFT) method, associated to 6-311G (d, p) base was used in gas phase. Spectroscopic, thermodynamic descriptors and geometric parameters resulting from calculations showed a slight stability of catechin compared to epicatechin and gallocatechin compared to epigallocatechin. As for the acidity of these monomers hydroxyl groups, the results show that it decreases similarly as follows: $O_{4'} > O_5 > O_7 > O_{5'} > O_3$ for Catechin and epicatechin; $O_{3'} > O_5 > O_{4'} > O_7 > O_{5'} > O_3$ and $O_{3'} > O_{4'} > O_5 > O_7 > O_{5'} > O_3$ respectively for gallocatechin and epigallocatechin.

Keywords: Catechin, Epicatechin, Gallocatechin, Epigallocatechin, Acidity, DFT.

INTRODUCTION

Catechin, epicatechin, gallocatechin and epigallocatechin are condensed tannins monomer found in abundance in human nutrition. They are found in fruits and vegetables but also in chocolate and wine. Their study got a great interest since they had not only anticancer properties but also cardiovascular effects (Rein et al., 2000; Martin and Andriantsitohaina, 2002; Raju et al., 2014). In addition, they are used in the prevention of ulcers and hormone-dependent diseases (Funatogawa et al., 2004; Ruggiero et al., 2006; Gerber and Berta, 2006; Lainé et al., 2007). Several scientific studies have shown that inorganic or non-heminic iron (Fe^{2+}, Fe^{3+}) inhibits intestinal absorption of condensed tannins from food by formation of insoluble and irreversible complexes. (Roberta et al., 2002; Seigo et al., 2002; Scalbert et al., 2002; Jeremy, 2003; Mourad et al., 2007). It's established that this phenomenon occurs between phenolic hydroxyls of tannins and inorganic iron (Tapiero H. et al., 2002; Manach C. et al., 2004). Any solution aimed at avoiding formation of these complexes in order to optimize absorption of tannins requires first, precise knowledge of mechanisms of action. However, process of complex formation between condensed tannins and inorganic iron is not yet clearly established. Knowing that hydroxyl groups of

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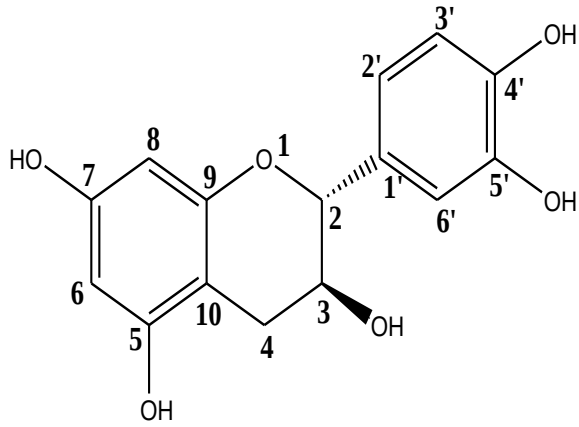
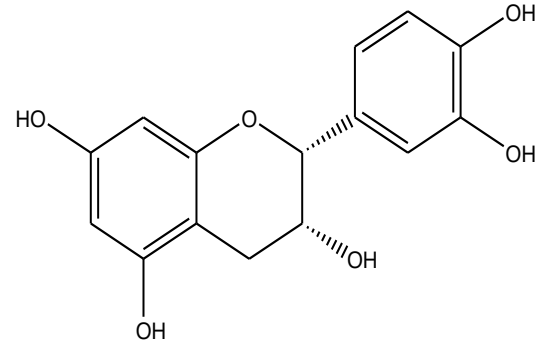
tannins are the sites of non heminic iron binding, our objective during this work is to study preferential sites at these hydroxyl groups. This, by theoretical determination of these hydroxyl groups acidity of monomers (catechin, epicatechin, gallocatechin and epigallocatechin). Theoretical calculations of quantum chemistry using functional density theory (DFT) method, associated to 6-311G (d,p) base allowed us to carry out this study.

MATERIALS AND METHODS

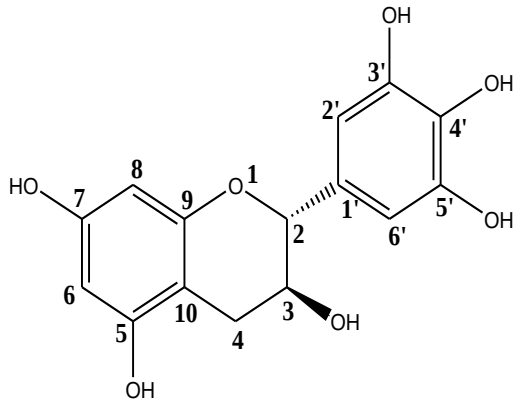
The Acer predator processor runs the calculations. Catechin, epicatechin, gallocatechin and epigallocatechin molecules (Figure 1) were drawn by GaussView 5.0 software (Frisch et al. 2003). Calculations were made in gas phase using the functional density theory method (DFT) with functional hybrid B3lyp, associated to 6-311G (d,p) base, incorporated in the GAUSSIAN-03 program (Frisch et al., 2003). Initial geometries have been optimised. Gibbs free energies (G) are obtained from frequencies calculation.



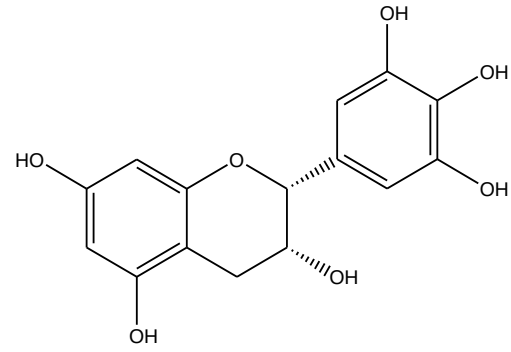
Catechin



Epicatechin



Gallocatechin



Epigallocatechin

Figure 1: structures of catechin, epicatechin, gallocatechin and epigallocatechin.

RESULTS

Geometric parameters

Figure 1 shows the structures of catechin, epicatechin, gallocatechin and epigallocatechin. Bond lengths and measured dihedral angles are contained in Table 1. C-O bond lengths of catechin derivatives varied very little compared to those of epicatechin. Dihedral angle O_1-C_2-$C_{1'}$-$C_{6'}$ is smaller in epicatechin compared to catechin. It's also smaller in epigallocatechin compared to gallocatechin. Same remarks are made at the dihedral angle O_1-C_2-$C_{1'}$-C_2.

Theoretical frequencies

Catechin and epicatechin are composed of 35 atoms, they have $(3N - 6 = 99)$ normal modes of vibration. Gallocatechin and epigallocatechin had 36 atoms which gave 102 normal modes of vibration. We are particularly interested in νO-H elongations because oxygen atoms are preferred sites for complexation with iron. Values are contained in Tables 2 and 3. In general, νO-H elongations range from 3786 cm^{-1} to 3850 cm^{-1}.

Stability

Gibbs energy (G), at computational level B3LYP / 6-311G (d, p), helps to discuss relative stability of catechin and its derivatives. Table 4 summarises its values; ΔG is difference between Gibbs energy of catechin and epicatechin on one hand and on other hand between gallocatechin and epigallocatechin. The data in Table 4 show relative stability of catechin and gallocatechin compared to epicatechin and epigallocatechin, respectively.

Acidity

Catechin, epicatechin, gallocatechin and epigallocatechin have hydrogenated sites (hydroxyl groups) which may be deprotonated. Choice of the site of deprotonation depends of strength of acid. ΔG variation of associated reaction ($AH \rightarrow A^- + H^+$) helps to evaluate acidity of oxygen atoms of catechin and its derivatives (Remko, 2003):

$\Delta G = \Delta H - T\Delta S$

$\Delta G = G(A^-) + G(H^+) - G(AH)$

$G(H^+) = 2{,}5RT - TS°(H^+) = 1{,}48 - 7{,}76 = -628\ \text{Kcal.mol}^{-1}$ in gas phase

With: **AH**: acid molecule; $\mathbf{A^-}$: deprotonated molecule; **G:** Gibbs energy or free enthalpy reaction; **ΔG:** variation of free enthalpy reaction; **T:** temperature; **R:** perfects gas constant; **S°**: standard entropy reaction; **ΔS**: variation of entropy reaction.

Table 1: Bond lengths (Å) and dihedral angles (°).

Geometric parameters	Catechin	Epicatechin	Gallocatechin	Epigallocatechin
O_1-C_2	1,44	1,44	1,44	1,44
O_1-C_9	1,37	1,37	1,37	1,37
O_3-C_3	1,42	1,42	1,42	1,42
O_5-C_5	1,37	1,37	1,37	1,37
O_7-C_7	1,36	1,37	1,36	1,37
O_3-$C_{3'}$	-	-	1,38	1,37
$O_{4'}$-$C_{4'}$	1,38	1,38	1,37	1,37
$O_{5'}$-$C_{5'}$	1,36	1,36	1,36	1,36
C_2-$C_{1'}$	1,52	1,52	1,52	1,52
O_1-C_2-$C_{1'}$-$C_{6'}$	166,08	155,46	166,5	154,12
O_1-C_2-$C_{1'}$-$C_{2'}$	-13,22	-24,50	-12,87	-26,09

Table 2: IR Frequencies (cm^{-1}) and Intensities of O-H Elongations of Catechin and Epicatechin.

Elongations O-H	Catechin		Epicatechin	
	Frequency	IR intensity	Frequency	IR intensity
νO_3-H	3808	30	3797	26
νO_5-H	3836	67	3835	66
νO_7-H	3833	65	3833	64
νO_4-H	3850	83	3850	84
νO_5-H	3789	114	3789	117

Table 3: IR Frequencies (cm^{-1}) and Intensities of O-H elongations of gallocatechin and epigallocatechin.

O-H Elongations	Gallocatechin		Epigallocatechin	
	Frequency	IR intensity	Frequency	IR intensity
νO_3-H	3808	29	3788	20
νO_5-H	3836	68	3836	68
νO_7-H	3833	65	3833	65
νO_3-H	3848	66	3846	67
νO_4-H	3806	108	3805	108
νO_5-H	3787	112	3786	131

Table 4: Gibbs energies of catechin and its derivatives.

Compounds	G (a.u)	ΔG (Kcal. mol^{-1})
Catechin	-1031,404	0
Epicatechin	-1031,403	0,628
Gallocatechin	-1106,64581	0
Epigallocatechin	-1106,64478	0,646

(a.u): atomic unit; 1 a.u = 627,51 kcal/mol.

Table 5: Acidity of Catechin and Epicatechin.

Compounds	G (a.u)	ΔG (Kj.mol^{-1})
Catechin	-1031,404	
Catechin (O_3-anion)	-1030,814	1548,8
Catechin (O_5-anion)	-1030,857	1435,9
Catechin (O_7-anion)	-1030,853	1446,3
Catechin ($O_{4'}$-anion)	-1030,868	1407,0
Catechin($O_{5'}$-anion)	-1030,846	1464,8
Epicatechin	-1031,403	
Epicatechin (O_3-anion)	-1030,821	1527,8
Epicatechin (O_5-anion)	-1030,854	1442,8
Epicatechin (O_7-anion)	-1030,850	1451,6
Epicatechin ($O_{4'}$-anion)	-1030,870	1399,1
Epicatechin ($O_{5'}$-anion)	-1030,849	1454,3

(a.u): atomic unit; 1 u.a = 2625 kj/mol

Table 6: Acidity of gallocatechin and epigallocatechin.

Compounds	G (au)	ΔG (Kj/mol)
Gallocatechin	-1106,646	
Gallocatechin (O_3-anion)	-1106,057	1546,1
Gallocatechin(O_5-anion)	-1106,102	1428,0
Gallocatechin (O_7-anion)	-1106,098	1438,5
Gallocatechin($O_{3'}$-anion)	-1106,109	1409,6
Gallocatechin($O_{4'}$-anion)	-1106,100	1433,3
Gallocatechin($O_{5'}$-anion)	-1106,087	1467,4
Epigallocatechin	-1106,645	
Epigallocatechin (O_3-anion)	-1106,063	1527,8
Epigallocatechin(O_5-anion)	-1106,099	1433,3
Epigallocatechin (O_7-anion)	-1106,095	1443,8
Epigallocatechin($O_{3'}$-anion)	-1106,112	1399,1
Epigallocatechin($O_{4'}$-anion)	-1106,103	1422,8
Epigallocatechin($O_{5'}$-anion)	-1106,091	1454,3

(a.u): atomic unit; 1 u.a = 2625 kj/mol

DISCUSSION

Catéchines, epicatechin, gallocatechin and epigallocatechin have different geometric parameters. In fact, the C_7-O_7 bond is 1,36 Å in catechin and gallocatechin. It is 0,01 Å longer in epicatechin and epigallocatechin. This difference is explained by fact that the O_3-H bond is in front of plane in catechin and in gallocatechin and behind plane in epicatechin and in epigallocatechin. C4'-O4' bond is 1,38 Å in catechin and epicatechin. It is 0,01 Å shorter in gallocatechin and epigallocatechin. This inequality is due to presence of hydroxyl group O_3'-H in gallocatechin and in epigallocatechin. Dihedral angle O1-C2-C1'-C6' is 166,08 ° in catechin and is 10,62 smaller in epicatechin. It is 166,5 ° in gallocatechin and is 11.96 smaller in epigallocatechin. Dihedral angle O1-C2-C1'-C2' is -13,22 ° in catechin and is 11,28 smaller in epicatechin. It is -12,87 ° in gallocatechin and is 13,22 smaller in epigallocatechin. Orientation of the O_3-H bond thus influences the value of the dihedral angles (Ana et al., 2006; Hong et al., 2018).

O-H (νO-H) elongations of catechin and its derivatives appear between 3786 cm^{-1} and 3850 cm^{-1}. The νO_4'-H elongation is observed at 3850 cm^{-1} in catechin and epicatechin, at 3806 cm^{-1} in gallocatechin and at 3805 cm^{-1} in epigallocatechin. This difference is explained by the presence of the hydroxyl group $O_{3'}$-H in gallocatechin and in epigallocatechin. (νO_5-H) elongation is virtually identical in the four compounds. It comes out at 3836 cm^{-1} in catechin, gallocatechin and epigallocatechin and at 3835 cm^{-1} in epicatechin. νO_7-H elongation appears at 3833 cm^{-1} in the four compound. νO_3-H elongation is least intense. It appears at 3808 cm^{-1} in catechin and gallocatechin, at 3797 cm^{-1} in epicatechin and at 3788 cm^{-1} in epigallocatechin (Jayshree et al., 2010).

Difference between the frequencies of catechin and epicatechin on one hand and gallocatechin and epigallocatechin on other hand is certainly due to fact that O_3-H bond is in front of or behind plane. Elongation $\nu O_{5'}$-H is most intense. It was released at 3789 cm^{-1} in catechin and epicatechin, at 3787 cm^{-1} in gallocatechin and 3786 cm^{-1} in epigallocatechin.

With regard to stability, results in Table 4 show that catechin is more stable than epicatechin with an energy difference of 0.628 Kcal/mol; similarly, gallocatechin is more stable than epigallocatechin with an energy difference of 0.646 Kcal/mol.

Acid nature of oxygen atoms of catechin and its derivatives is related to the ΔG value. Lower it is, more oxygen in the position is acid. Under these conditions, $O_{4'}$ oxygen atom is most acid site of catechin, followed by O_5 oxygen atom. Oxygen atom $O_{4'}$ is also most acid site of epicatechin. Definitively, in catechin and epicatechin acidity of oxygen atoms varies in same direction. The descending order is $O_{4'}$> O_5> O_7> $O_{5'}$> O_3. The oxygen atom $O_{3'}$ is most acid site of gallocatechin, then oxygen O_5, after oxygen $O_{4'}$. In general, in gallocatechin, the acidity of oxygen atoms decreases in order $O_{3'}$> O_5> $O_{4'}$> O_7> $O_{5'}$> O_3. Oxygen $O_{3'}$ is also most acid site of epigallocatechin, followed by oxygen O_4'. Decreasing order of epigallocatechin acidity oxygen atoms is $O_{3'}$> $O_{4'}$> O_5> O_7> $O_{5'}$> O_3. The oxygen atom O_3 is thus least acid site of catechin and its derivatives (Ana et al., 2006; Jayshree et al., 2010; Hong et al., 2018).

Conclusion

The acidity of catechin and epicatechin decreased in the order $O_{4'}$ > O_5> O_7 > $O_{5'}$> O_3 while that of gallocatechin and epigallocatechin decreased in the order $O_{3'}$ > O_5> $O_{4'}$ > O_7 > $O_{5'}$ > O_3 and $O_{3'}$ > $O_{4'}$ > O_5 > O_7 > $O_{5'}$> O_3. Knowing the theoretical acidity order of the different hydroxyl groups of the monomers, we will focus our researches to modelize different models of polyphenol inorganic iron complexes likely to be formed in the human organism according to these results. In a second step, complexation sites of inorganic iron will also be modelized to possibly reduce affinity of these condensed tannins with respect to iron.

COMPETING INTERESTS

The authors declare that there are no competing interests.

AUTHORS' CONTRIBUTIONS

Bioinformatics calculations were carried out by KDY, BAA and LAB. Results interpretation was done by KDY, BAA and BRN. Finally, manuscript writing was done by KDY, BAA and MVS.

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