

## Quantum Modeling of Ferric Iron ( $\text{Fe}^{3+}$ )-Condensed Tannins Complexes

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### Abstract

The condensed tannin-iron complex formation is one of the major causes of iron deficiency anaemia. Although, condensed tannins have beneficial virtues for the body and, as for iron, it participates in vital function such as breathing. In order to prevent this complex formation, we have undertaken to understand the complexing mechanism. We use quantum molecular modelling using quantum descriptors (energy gap, ionization energy, hardness, electrophilic index and softness) between ferric iron ( $\text{Fe}^{3+}$ ), major form of iron in the diet and catechin, epicatechin (major form of condensed tannins in diet). Calculations were made in gas phase using density functional theory (DFT) B3LYP/6-311+G (d,p).

The results obtained show that we could have as complexes formed at the level of the organism catechin 4\_BS, Epicatechin 2\_BS that in strong magnetic field; Catechin 5\_HS and Epicatechin 5\_HS in weak field. We also notice that catechin and epicatechin have a low probability of complexing with ferric iron ( $\text{Fe}^{3+}$ ) with the hydroxyl group at position 3 whether in a strong field or a weak field.

In further studies, more in-depth simulations coupled with experimentation, more understanding of these mechanisms will be given hoping to find solutions that would prevent the formation of condensed tannin-iron complexes.

**Keywords:** Dithiobiurets; Nanoparticles; Microbial evaluation

### Introduction

Nowadays it has been found that stable and insoluble complexes in the body are formed between iron and condensed tannins which are plant molecules contained in foods. This is one of the major reasons for iron deficiency anaemia, which is a public health problem, especially as it affects about one third of the world's population today according to World Health Organization [1,2]. Once these complexes are formed, tannins and iron are irreversibly lost in the body [3,4]. Condensed tannins have healing properties for the human body such as their antioxidant power allowing them to play a protective role against cardiovascular and aging diseases such as Alzheimer's [5-7]. Iron is an essential part of the body that participates in many vital functions such as the carrier of oxygen ( $\text{O}_2$ ) and carbon dioxide ( $\text{CO}_2$ ) in the blood [8,9].

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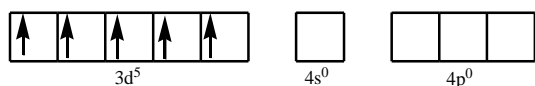
One of the ways to explore to optimize the bioavailability of iron and tannins is to look for alternatives to complex iron-tannin complexing. These require in advance, the understanding of the mechanisms of formation of these complexes.

This problematic lead us during this work to study by quantum molecular modelling using quantum descriptors (energy gap, ionization energy, hardness, electrophilic index and softness), the complexation of  $\text{Fe}^{3+}$  ferric iron (a major form of iron in the diet) and condensed tannin molecules such as catechin and epicatechin (which are also major forms of tannins in the diet) [10-13]. Calculations were made in gas phase using density functional theory (DFT) B3LYP/6-311+G (d,p).

## Materials and Methods

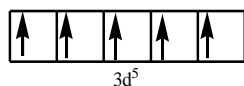
### Presentation of complexes

Ferric iron ( $\text{Fe}^{3+}$ ) is a first-order transition cation that is to say that it has its incomplete d underlayer. With its valence layer  $3d^5 4s^0 4p^0$ , it forms coordination bonds of generally octahedral geometry with the ligands [14,15]. Coordination bonds because the ligands provide free electron pairs that form covalent coordination bonds with the empty atomic orbitals provided by the metal ion ( $\text{Fe}^{3+}$ ). The five 3d orbitals of  $\text{Fe}^{3+}$  are degenerate (same energy) in the isolated state. In the presence of a weak octahedral field created by the six ligands, there is degeneration and the electrons do not match in the 3d orbitals. We thus have five (5) single electrons with a spin state  $S=5/2$  and the resulting complexes are called high spin (HS). In the presence of a strong octahedral field, the electrons pair in the 3d orbitals with a spin state  $S=1/2$  and the resulting complexes are called low spin (BS), S or spin of the electron (FIG. 1).



### Electronic configuration of $\text{Fe}^{3+}$ outer layer ( $3d^5 4s^0 4p^0$ )

#### Configuration of the 3d sub-layer in weak octahedral field (high spin)



#### Configuration of the 3d sub-layer in strong octahedral field (low spin)

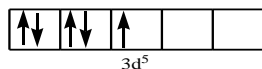


FIG. 1. Different electronic configurations of the  $\text{Fe}^{3+}$  3d sublayer.

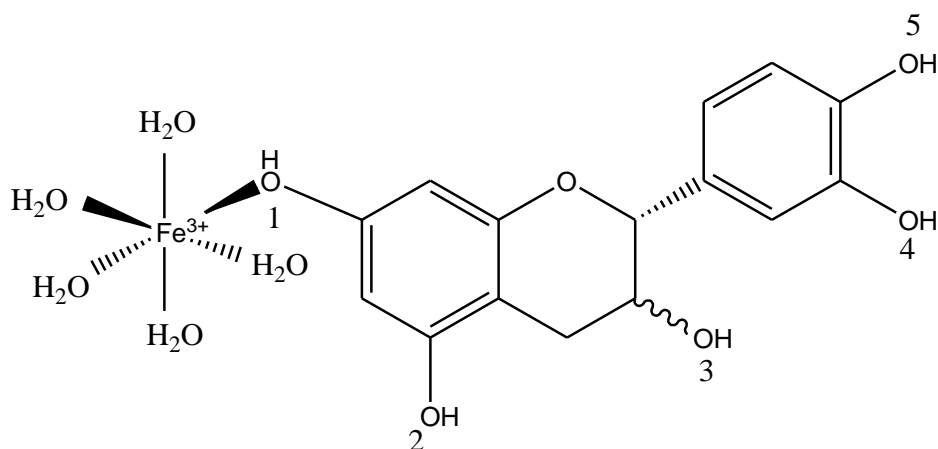


FIG. 2. Octahedral complex between  $\text{Fe}^{3+}$  and catechin/epicatechin.

The calculations will concern the complexes between  $\text{Fe}^{3+}$  and the different hydroxyl groups of catechin and epicatechin (numbered from 1 to 5 in FIG. 2) as well as with water molecules. This is because the formation of the complexes generally takes place at the level of the hydroxyl groups of the condensed tannin molecules [16,17]. The presence of water molecules is explained by the fact that the complexes are generally formed in the duodenum which is an aqueous medium [18].

### Methodology of calculation

Theoretical studies are carried out with the Gaussian 03 calculation software [19]. Calculations were made with the B3LYP/6-311+G (d,p) gas phase method. Complete optimizations were carried out without any symmetry constraint. Harmonic vibration frequencies have been calculated to confirm that the optimized system correctly corresponds to a local minimum that does not have a negative frequency. Subsequently, determination of probable models was made using quantum descriptors (energy gap, ionization energy, hardness, electrophile index and softness described below) based on the results obtained. Below is the summary (TABLE 1) of the calculation parameters.

TABLE 1. Summary table of calculation parameters.

Calculation parameters Complexes Types	Method of calculation	Basis for calculation	Multiplicity $M=2S+1$ With $S=1/2$	Charge
Catechin (1-5)-FeIII_low spin	B3LYP	6-311+G (d,p)	2	+3
Catechin (1-5)-FeIII_high spin	B3LYP	6-311+G (d,p)	6	+3
Epicatechin (1-5)-FeIII_low spin	B3LYP	6-311+G (d,p)	2	+3
Epicatechin (1-5)-FeIII_high spin	B3LYP	6-311+G (d,p)	6	+3

To simplify the notation of complexes, we will call for example the complex Catechin 1-FeIII\_low spin, catechin 1\_BS.

### Global descriptors of the reactivity

These are reactivity parameters that qualify the stability of a molecular system.

**Energy gap**

The Energy Gap ( $\Delta E$ ) is a comparative criterion of molecules that measures the global reactivity of a molecular structure and therefore its stability. This is the difference between the energy of the HOMO (Molecular Orbital containing higher energy electrons easier to yield) and the energy of the LUMO (Electron Acceptable Lowest Molecular Orbital).

$$\Delta E = E_{LUMO} - E_{HOMO}$$

A molecule with a low energy gap is easily polarisable and generally has significant chemical activity, very low kinetic stability [20].

**Ionization energy**

Ionization energy (IE) is defined as the energy needed to pull an electron out of a system. It is the energy needed to move from the neutral molecule (N electrons) to cation (N-1 electrons); therefore a high value of ionization energy indicates that the system does not lose its electrons easily and is therefore more stable.

$$EI = -E_{HOMO}$$

**Hardness ( $\eta$ )**

Hardness is defined as the resistance of a molecular system to electron transfer (load transfer), whether it is an electron gain or loss. It thus measures the stability of the system. Thus, the higher the hardness of the molecular system, the more stable it is [21].

$$\eta = \left( \frac{\partial^2 E}{\partial N^2} \right)_{v(\bar{r})} = \left( \frac{\partial \mu}{\partial N} \right)_{v(\bar{r})} = \left( \frac{EI - AE}{2} \right) = \frac{E_{LUMO} - E_{HOMO}}{2} = \frac{\Delta E}{2}$$

**Softness**

This is the opposite of hardness. It corresponds to the ability of an atom or molecule to retain an acquired charge [22,23]. The higher the overall softness of a system, the less resistant it is to electron transfer (load) and therefore less stable. It's the opposite of hardness [23,24].

$$S = \frac{1}{\eta} = \left( \frac{\partial N}{\partial \mu} \right)_{v(\bar{r})} = \frac{2}{\Delta E}$$

**Electrophilic index ( $\omega$ )**

It defines the energy stabilization of a molecular system due to the transfer of electrons. The system is more stable if its electrophilic index is higher.

$$\omega = \frac{\mu^2}{2\eta}$$

## Results and Discussion

Note that all quantum descriptors are expressed in electron volt (eV).

### Low spin complex

#### Catechin complexes

TABLE 2. Catechin\_FeIII\_BS\_DFT\_6-311+G(d,p) in electron volts (eV).

Molecules/Parameters of Reactivity	$\Delta E$	EI	$\eta$	S	$\omega$
Catechin1_BS	1,87448	13,86935	0,93724	1,06696	78,37136
Catechin2_BS	4,33151	13,74089	2,16576	0,46173	145,0882
Catechin3_BS	0,77412	13,70389	0,38706	2,58359	34,32006
Catechin4_BS	4,82101	14,04238	2,41051	0,41485	163,0714
Catechin5_BS	4,01044	13,83015	2,00522	0,49870	140,1938

**Energy gap ( $\Delta E$ ):** According to TABLE 2, catechin4\_BS model is more stable. Which would give us a decreasing order of stability as follows: Catechin4\_BS> Catechin2\_BS> Catechin5\_BS> Catechin1\_BS> Catechin3\_BS.

**Ionisation energy (EI):** The Catechin4\_BS model seems to be the most stable. So we would have a descending order of decreasing stability: Catechin4\_BS> Catechin2\_BS> Catechin5\_BS> Catechin1\_BS> Catechin3\_BS.

**Hardness ( $\eta$ ):** The Catechin4\_BS model has the highest value and therefore the most probable model. So we would have a descending order of decreasing stability: Catechin4\_BS> Catechin2\_BS> Catechin5\_BS> Catechin1\_BS> Catechin3\_BS.

**Softness (S):** The lowest value is the Catechin4\_BS model with 0,41485 eV. That would be the most likely model. This would give a descending order of stability: Catechin4\_BS> Catechin2\_BS> Catechin5\_BS> Catechin1\_BS> Catechin3\_BS.

**Electrophilic index ( $\omega$ ):** The Catechin4\_BS model would be the most stable. So we would have Catechin 4\_BS> Catechin2\_BS> Catechin5\_BS> Catechin 1\_BS> Catechin3\_BS as order of decreasing stability.

### Complexes of epicatechin (TABLE 3)

TABLE 3. Epicatechin FeIII\_BS\_DFT\_6-311+G (d, p) in electron volts (eV).

Molecules/Reactivity Parameters	$\Delta E$	EI	$\eta$	S	$\omega$
EpiCatechin1_BS	1,62143	13,77573	0,81071	1,23348	68,13701
EpiCatechin2_BS	4,36063	14,22741	2,18031	0,45865	158,21715
EpiCatechin3_BS	0,53984	13,89518	0,26992	3,70479	25,05503
EpiCatechin4_BS	1,73217	13,62662	0,86608	1,15462	70,51281
EpiCatechin5_BS	1,73135	13,85355	0,86568	1,15517	73,01323

**Energy gap ( $\Delta E$ ):** The Epicatechin2\_BS model seems the most stable. This would therefore induce a decreasing order of stability as follows: Epicatechin2\_BS> Epicatechin4\_BS> Epicatechin5\_BS> Epicatechin1\_BS> Epicatechin3\_BS.

**Ionization energy (EI):** EpiCatechin2\_BS could be the most stable. The order of decreasing stability would be as follows: EpiCatechin2\_BS> EpiCatechin3\_BS> EpiCatechin1\_BS> EpiCatechin5\_BS> EpiCatechin4\_BS.

**Hardness ( $\eta$ ):** The EpiCatechin2\_BS model has the highest value so the most likely model. This would give a descending order of stability: EpiCatechin2\_BS> EpiCatechin4\_BS> EpiCatechin5\_BS> EpiCatechin1\_BS> EpiCatechin3\_BS.

**Softness (S):** The lowest value is the EpiCatechin2\_BS model and would therefore be the most likely model. The decreasing stability would then be: EpiCatechin2\_BS> EpiCatechin1\_BS> EpiCatechin4\_BS> EpiCatechin5\_BS> EpiCatechin3\_BS.

**Electrophilic index ( $\omega$ ):** The EpiCatechin2\_BS model would be most likely. This would give EpiCatechin2\_BS> EpiCatechin5\_BS> EpiCatechin4\_BS> EpiCatechin1\_BS> EpiCatechin3\_BS as a decreasing order of stability.

### High spin complexes (HS)

#### Catechin complexes (TABLE 4)

TABLE 4. Catechin\_FeIII\_HS\_DFT\_6-311+G(d,p) in electron volts (eV).

Molecules/Reactivity Parameters	$\Delta E$	EI	$\eta$	S	$\omega$
Catechin1_HS	466,320	1,371,097	233,160	0,42890	15,095,943
Catechin2_HS	460,361	1,361,110	230,180	0,43444	14,720,080
Catechin3_HS	458,211	1,395,477	229,106	0,43648	15,584,012
Catechin4_HS	490,292	1,389,137	245,146	0,40792	16,041,304
Catechin5_HS	513,420	1,413,381	256,710	0,38954	17,172,446

**Energy gap ( $\Delta E$ ):** The model Catechin5\_HS has the highest value so would be the most stable. So, we would have a descending order of stability as follows: Catechin5\_HS> Catechin4\_HS> Catechin1\_HS> Catechin2\_HS> Catechin3\_HS.

**Ionization energy (EI):** The EpiCatechin5\_HS model would be the most stable. The decreasing stability order would give: EpiCatechin5\_HS> EpiCatechin3\_HS> EpiCatechin4\_HS> EpiCatechin1\_HS> EpiCatechin2\_HS.

**Hardness ( $\eta$ ):** The Epicatechin5\_HS model would be most likely. This would induce a decreasing order of stability: Epicatechin5\_HS> Epicatechin4\_HS> Epicatechin1\_HS> Epicatechin2\_HS> Epicatechin3\_HS.

**Softness (S):** The Epicatechin5\_HS model has the lowest value and therefore would be the probable model. The decreasing stability would therefore be: Epicatechin5\_HS> Epicatechin4\_HS> Epicatechin1\_HS> Epicatechin2\_HS> Epicatechin3\_HS.

**Electrophilic index ( $\omega$ ):** The Epicatechin5\_HS model might be most likely. Which would induce Epicatechin5\_HS> Epicatechin4\_HS> Epicatechin1\_HS> Epicatechin3\_HS> Epicatechin2\_HS as order of decreasing stability.

**Complexes of Epicatechin (TABLE 5)**

TABLE 5. Epicatechin\_FeIII\_HS\_DFT\_6-311+G (d, p) in electron volts (eV).

Molecules/Parameters de Reactivity	$\Delta E$	EI	$\eta$	S	$\omega$
Epicatechin1_HS	4,63871	13,61845	2,31935	0,43115	148,05562
Epicatechin2_HS	4,56932	13,51261	2,28466	0,43770	144,01003
Epicatechin3_HS	4,13778	13,92021	2,06889	0,48335	145,29171
Epicatechin4_HS	4,71952	13,77110	2,35976	0,42377	153,64250
Epicatechin5_HS	4,89312	13,92728	2,44656	0,40874	161,23693

**Energy gap ( $\Delta E$ ):** The Epicatechin5\_HS model seems most likely. Which would therefore give us a descending order of stability as follows: Epicatechin5\_HS> Epicatechin4\_HS> Epicatechin1\_HS> Epicatechin2\_HS> Epicatechin3\_HS.

**Ionization energy (EI):** The Epicatechin5\_HS model would be the most stable. The order of decreasing stability would give: Epicatechin5\_HS> Epicatechin3\_HS> Epicatechin4\_HS> Epicatechin1\_HS> Epicatechin2\_HS.

**Hardness ( $\eta$ ):** The Epicatechin5\_HS model would be most likely. This would induce a descending order of stability as follows: Epicatechin5\_HS> Epicatechin4\_HS> Epicatechin1\_HS> Epicatechin2\_HS> Epicatechin3\_HS.

**Softness (S):** The Epicatechin5\_HS model has the lowest value and therefore would be the probable model. The decreasing stability would therefore be: Epicatechin5\_HS> Epicatechin4\_HS> Epicatechin1\_HS> Epicatechin2\_HS> Epicatechin3\_HS.

**Electrophilic index ( $\omega$ ):** The Epicatechin5\_HS model might be most likely. Which would induce Epicatechin5\_HS> Epicatechin4\_HS> Epicatechin1\_HS> Epicatechin3\_HS> Epicatechin2\_HS as order of decreasing stability.

**Discussion**

These results show us that the preferred complexation sites at the level of the monomers of condensed tannins (catechin, epicatechin) with the Ferric Iron ( $Fe^{3+}$ ) are a function of the strength of the ligand. Thus, when ligands behave in strong ligands, the probable low spins complexes are Catechine4\_BS for Catechin and Epicatechine2\_BS for Epicatechin. In the case of weak ligands (weak field), the probable high spins complexes are Catechin5\_HS for catechin and Epicatechin5\_HS for epicatechin. Regardless of the type of complexation (High or Low Spin), catechin and epicatechin are found to have a low probability of complexing to ferric iron ( $Fe^{3+}$ ) with the hydroxyl grouping in position 3. This low probability would be due to the position behind the plane (epicatechin) and in front of the plane (catechin) of the hydroxyl group at position 3 [16,17].

**Correlation between quantum descriptors: Pearson correlation (n)**

The Pearson correlation (n) analyses the different significant correlations between the quantum descriptors that characterize the stabilizers of our complex models in strong field (low spin) and low field (high spin).

**Models of low spin catechin****TABLE 6. Pearson matrix of low spin catechin complex descriptors.**

Variables	$\Delta E$	EI	$\eta$	S	$\omega$
$\Delta E$	1	0,539	1,000	-0,916	0,997
EI	0,539	1	0,539	-0,560	0,572
$\eta$	1,000	0,539	1	-0,916	0,997
S	-0,916	-0,560	-0,916	1	-0,940
$\omega$	0,997	0,572	0,997	-0,940	1

**Models of high spin catechin****TABLE 7. Pearson matrix of high spin catechin complex descriptors.**

Variables	$\Delta E$	EI	H	S	$\omega$
$\Delta E$	1	0,736	1,000	-1,000	0,921
EI	0,736	1	0,736	-0,727	0,942
H	1,000	0,736	1	-1,000	0,921
S	-1,000	-0,727	-1,000	1	-0,915
$\Omega$	0,921	0,942	0,921	-0,915	1

**Models of low spin epicatechin****TABLE 8. Pearson matrix of low spin epicatechin complex descriptors.**

Variables	$\Delta E$	EI	H	S	$\omega$
$\Delta E$	1	0,728	1,000	-0,763	0,998
EI	0,728	1	0,728	-0,183	0,701
$\eta$	1,000	0,728	1	-0,763	0,998
S	-0,763	-0,183	-0,763	1	-0,798
$\omega$	0,998	0,701	0,998	-0,798	1

**Models of high spin epicatechin****TABLE 9. Pearson matrix of high spin epicatechin complex descriptors.**

Variables	$\Delta E$	EI	H	S	$\omega$
$\Delta E$	1	-0,107	1,000	-0,999	0,758
EI	-0,107	1	-0,107	0,155	0,567
$\eta$	1,000	-0,107	1	-0,999	0,758
S	-0,999	0,155	-0,999	1	-0,725
$\omega$	0,758	0,567	0,758	-0,725	1



Generally, TABLES 6, 7 and 8 show us that the energy gap ( $\Delta E$ ) is positively correlated with ionization energy (EI), hardness and electrophilic index ( $\omega$ ). They similarly reflect the stability of the different complex models (the higher these quantities are, the more the complexes are stable). On the other hand, softness (S) is negatively correlated with other quantum descriptors. This would mean that they evolve inversely, thus expressing the stability differently (the lower the softness, the more stable the system, while the more the other descriptors have higher values the more stable the system). Specifically, the same observations could be made with TABLE 9 except that the energy gap ( $\Delta E$ ) is very slightly correlated with the ionization energy (EI) even though they similarly reflect the stability of different models.

## Conclusion

At the end of our study, we can say that ferric iron ( $\text{Fe}^{3+}$ ) could also make strong-field (low spin) and low-field (high-spin) complexes with condensed tannin monomers (catechin, epicatechin) in the body in general and the duodenum in particular. Quantum descriptors such as energy gap, ionization energy, hardness, electrophilic index and softness have indicated to us that in strong field, probable complex models that could more easily form are Catechin4\_BS and Epicatechin2\_BS. In weak field, we would have Catechin5\_HS and Epicatechin5\_HS. Catechin and epicatechin would be less complexed with ferric iron ( $\text{Fe}^{3+}$ ) with the hydroxyl grouping in position 3 in both strong and weak fields.

Subsequent studies of biological simulations associated with experimental studies on the assay of sacrificed guinea pigs, for which radioactively labeled catechin, epicatechin and ferric iron will be contained in upstream foods, will be conducted to better understand the formation phenomenon of complexes. This will allow us to consider appropriate solutions to prevent these complexations.

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