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This article can be cited before page numbers have been issued, to do this please use: D. Hannachi, N. E. H. Amrane, L. Merzoud and H. Chermette, New J. Chem., 2021, DOI: 10.1039/D1NJ01996A.
Exploring the Antioxidant Activity of Thiaflavan Compounds: a Quantum Chemical Study

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Density functional theory calculations at B3LYP level are performed to theoretically investigate the antioxidant properties of 30 thiaflavan compounds. The main theoretical parameters, such as bond dissociation enthalpy, ionization potential, proton dissociation enthalpy, proton affinity, electron transfer enthalpy, aromaticity index and spin density of O-atoms in gas, water and benzene phases have been determined. On the basis of our calculations, the OH groups in A-ring are the main contributors of the antioxidative activities of thiaflavan comparatively to the B-ring. The reactivity of the thiaflavan compounds with the DNA bases is determined and the thymine moiety in DNA is found to be the primary target for reduction. Among the 30 compounds theoretically studied, the ones containing a ferrocene moiety at ring C’ of thiaflavan are the most promising for future applications in the pharmacology field and the food industries.

Introduction

Free radicals are highly reactive and unstable compounds, as they can induce oxidative damage in biological systems such as DNA, RNA, proteins and lipids. They play an important role in various diseases such as cancer, aging, arthritis, cardiovascular disease and neurodegenerative1–3. This destructive reaction can be inhibited by antioxidant compounds capable of scavenging free radicals through electron or proton transfer mechanism. In the literature, three important mechanisms describe antioxidant reactions4,5 as shown in Scheme 1.

(1): Hydrogen atom transfer mechanism (HAT)

According to this mechanism the free radical removes one hydrogen atom from the antioxidant (ArOH), so that the antioxidant compound itself becomes a radical. In this mechanism the BDE (Bond Dissociation Enthalpy) is generally the numerical parameter for estimating the antioxidant activity see (1) in Scheme 1.

Scheme 1. antioxidants mechanisms: (1) HAT, (2) SPLET, (3) SETPT. {ArOH}: antioxidant, (ArO' ): radical, (ArOH+): radical cation, (ArO-): anion, (X' ): free radical.

(2): Sequential proton loss electron transfer (SPLET):

The SPLET is a two-step reaction (see (2) in Scheme 1). In this reaction, the antioxidant dissociates into an anion (ArO-) and a proton. The created ion reacts with the free radical and therefore becomes itself a radical (ArO'). The numerical parameters related with the SPLET mechanism are: PA (Proton Affinity) for the first step and ETE (Electron Transfer Enthalpy) for the second step.

(3): Single-electron transfer followed by proton transfer (SET-PT):

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This mechanism also consists of a two-step reaction (see (3) in Scheme 1). In the SET mechanisms, the antioxidant provides an electron to the free radical and then becomes itself a radical cation (ArOH\(^+\)). A numerical parameter related to this mechanism is the IP (Ionization Potential). In the second step, the antioxidant cationic radical decomposes into a radical (ArO\(^-\)) and a proton. In this mechanism, the proton dissociation enthalpy (PDE) of the antioxidant is the energetic factor for evaluating the antioxidant action.

In 2014 Lai et al. have synthesized and studied the antioxidant properties of several thiaflavan compounds (T2, T5, T6, T8, T9, T10, T13, T14, T16 see Scheme 2) and concluded that:

- The (ArO\(^-\)) radicals are stable like those of curcumin and flavonoid antioxidant derivatives.
- The ferrocene moiety at ring B is beneficial for enhancing abilities of thiaflavans to trap radicals and to inhibit DNA oxidation.
- The antioxidant effectiveness generated by hydroxyl groups or ferrocene moiety at ring B is enhanced by the electron-donating group attached to the ring A.
- The sulfur and oxygen atoms on ring C induce different effects on the antioxidant property of hydroxyl group located at para-positions in ring A. The hydroxyl group at para-position of oxygen atom (position 3) exhibits a higher antioxidant effectiveness than that at the para-position of sulfur atom (position 4). The sulfur atom is beneficial for the hydroxyl group in ring A to quench radicals, while the oxygen atom is beneficial for the hydroxyl group in ring A to inhibit DNA oxidation.

The inhibition effect on DNA oxidation and the ability to scavenge radicals are characteristic properties of antioxidant compounds (see, e.g. ref.\(^7\)). Accordingly, the aim of this work is to perform a quantum chemical investigation to clarify the effects of hydroxyl groups at ring A and B, ferrocene moiety at ring B and ring C’ on the antioxidant effectiveness of 30 thiaflavan gathered in Schemes 2 and 3. One can notice that the difference between \(T7\) and \(T7’\), \(T8\) and \(T8’\), \(T15\) and \(T15’\), \(T19\) and \(T19’\) and \(T25\) and \(T25’\) is only the orientation of H atoms in the clock or anti-clock direction. In the present work, we have attempted to study the interaction between the thiaflavan compounds and DNA bases with the goal to better understand the antioxidant effects to the DNA molecule. To this aim, we assumed that the DNA oxidation inhibition is related to the calculated charge transfer between the thiaflavan molecules and the DNA bases using the \(\Delta N\) method. The values of \(\Delta N\) let estimate the electron donors and electron acceptors characters.

**Scheme 2.** Structures of the thiaflavan Ti (i= 1 to 24)

1. The thiaflavan antioxidant Ti (i= 1 to 24) with the following characteristics:
   - The sulfur and oxygen atoms on ring C induce different effects on the antioxidant property of hydroxyl group located at para-positions in ring A.
   - The ferrocene moiety at ring B is beneficial for enhancing abilities of thiaflavans to trap radicals and to inhibit DNA oxidation.
   - The antioxidant effectiveness generated by hydroxyl groups or ferrocene moiety at ring B is enhanced by the electron-donating group attached to the ring A.
   - The sulfur and oxygen atoms on ring C induce different effects on the antioxidant property of hydroxyl group located at para-positions in ring A.
   - The sulfur atom is beneficial for the hydroxyl group in ring A to quench radicals, while the oxygen atom is beneficial for the hydroxyl group in ring A to inhibit DNA oxidation.

The present paper is then organized as follows: In Section 1, some computational details and definitions are given; in Section 2, the interaction between the molecules and the DNA is studied; in Section 3, antioxidant parameters is discussed; the paper ends with some concluding remarks.
Theory and computational details

Theory

Conceptual Density Functional Theory (DFT) supplies many reactivity indices to chemist researchers, which can successfully be used for describing and predicting chemical reactivity. Global descriptors such as electronegativity (χ), chemical potential (μ), chemical hardness (η), electrophilicity index (ω) are now widely used.

The electronic chemical potential refers of an atom or molecule to the escaping tendency of electrons from equilibrium, which is approximated by:

\[ \mu = \frac{1}{2} (\varepsilon_H + \varepsilon_L) = -\chi \]  

The hardness (η) expresses the resistance of a molecular system to change its number of electrons.

\[ \eta = \varepsilon_L - \varepsilon_H \]  

In these equations, ε_H at ε_L are the energies of the highest occupied and the lowest unoccupied molecular orbitals (HOMO and LUMO), respectively.

The global electrophilicity index (ω) introduced by Parr et al. expresses the ability of a molecule to accept electrons from the surroundings, it is given by the following equation:

\[ \omega = \frac{\mu^2}{2\eta} \]  

The fraction of the transferred electron (ΔN) from the nucleophile (Nu) to electrophile (E) can be estimated according to Pearson and co-workers:

\[ \Delta N = \frac{\mu_{Nu} - \mu_{E}}{\omega (\mu_{Nu} + \omega)} \]  

Computational details

All DFT calculations were carried out using Gaussian 09 program packages developed by Frisch co-workers. The water, benzene and gas phase geometries of neutral compounds (ArOH) and the corresponding radical (ArO •), ionic (ArO −) and radical cationic (ArOH +) structures were optimized using the Becke’s three-parameter Lee-Yang-Parr hybrid functional (B3LYP) functional without any constraints. Stuttgart-Dresden basis sets and pseudopotential were applied to Fe and the Pople-style basis 6-311G* was applied to H, C, O and S atoms.

The solvent effects were modeled by employing the PCM18 continuum solvent model based on the optimized gas-phase geometries. The harmonic vibrational frequencies are calculated at the same level of theory for the four states (neutral compounds (ArOH), radical (ArO•), ionic (ArO−) and radical cationic (ArOH+) to confirm that the optimized geometries correctly correspond to local minima and to estimate the free energy.

The reaction enthalpies related to HAT, SET-PT and SPLET mechanisms are usually denoted as follows:

\[ BDE = H(ArO) + H(H) - H(ArOH) \]

The ionization potential (IP) and proton dissociation enthalpy (PDE) are calculated to describe the SET-PT mechanism. The calculated equations for IP and PDE are:

\[ IP = H(ArOH^+) + H(e^-) - H(ArOH) \]

\[ PDE = H(ArO) + H(H^+) - H(ArOH^+) \]

The proton affinity (PA) of ArO• anion are used to characterize the reaction enthalpy of the first step of SPLET. The calculated equation for PA is:

\[ PA = H(ArO^-) + H(H^+) - H(ArOH) \]

The electron transfer enthalpy (ETE) is related to the second step of SPLET. The calculated equation for ETE is:

\[ ETE = H(ArO) + H(e^-) - H(ArO^-) \]

The calculated enthalpies for electron (e), proton (H+) and hydrogen atom (H2) in the gas phase are 0.75, 1.484 and -312.28 kcal/mol, respectively. The antioxidant molecules are inside the body and have to be functional in a biological membrane, where unsaturated lipids (non-polar media) as well as in physiological liquids (polar media). To study the antioxidant mechanism correctly, we will calculate the antioxidant parameters in water (polar) and non-polar environments such as benzene.

Results and Discussion

Reactivity

The values of the dipole moment, the chemical potential (μ, eV), the chemical hardness (η, eV) and electrophilicity index (ω, eV) calculated for each of the thiaflavan T1 to T24 and for the DNA bases in gas and solvent phases, are given in Table 1.
The chemical potential ($\mu$) of the thiaflavan ranges from -3.503 to -3.113 eV, whereas for the DNA bases the values range from -4.402 to -3.515 eV and decrease following the order Thymine > Cytosine > Adenine > Guanine in gas and solvent phases. The DFT results are in agreement with the experimental tendency. According to the absolute scale of global electrophilicity power ($\omega$) proposed by Domingo et al., the DNA bases can be classified as strong electrophiles (1.18 to 1.83 eV). Besides, the thiaflavan compounds T1 to T24 display a moderate electrophilicity power in gas and solvent phases.
On the other hand the computed hardness of the DNA bases follows the order: Thymine > Adenine > Guanine > Cytosine and the thiaflavan ones range from 4 to 5.3 eV. Among the thiaflavan compounds, T1 to T15 have the largest hardness with respect to the T16 to T24 in water, benzene and gas, respectively. The hardness of Ti (i= 1 - 24) decreases with the increase in the number of OH substitutions in the ring. We can see that the T14 and T15 are more stable than T2 and T7, respectively, and T8’ than T8, T7 than T7’ and T19 than T19’.

Chattaraj, Lee, and Parr26 have established that a variety of acid–base reactions do follow the HSAB principle summarized as: “hard likes hard and soft likes soft”. From this principle, it is anticipated that thiaflavan compounds would prefer to react with the DNA bases having the closest hardness values.

It is well-established that the oxidative damage of DNA bases is a rather complicated operation related to charge transport and reactions controlled by a combination of entropy, enthalpy, steric and other factors.27 The charge transfer (ΔN) between the T1 to T24 molecules and the DNA bases has been calculated and reported in Table 2 and Figure 1.

**Table 2:** Calculated charge transfer between the thiaflavan Ti (i= 1 to 24) molecules and the DNA bases (A: Adenine, C: Cytosine, G: Guanine and T: Thymine) in gas and solvent phases.

|     | Gas          | Water        | Benzene       |
|-----|--------------|--------------|---------------|
|     | A/Ti C/Ti G/Ti T/Ti | A/Ti C/Ti G/Ti T/Ti | A/Ti C/Ti G/Ti T/Ti |
| T1  | 0.022 0.035 0.009 0.052 | 0.023 0.034 0.011 0.042 | 0.023 0.035 0.008 0.047 |
| T2  | 0.024 0.037 0.011 0.054 | 0.024 0.035 0.012 0.043 | 0.024 0.036 0.009 0.048 |
| T3  | 0.030 0.042 0.016 0.06  | 0.029 0.039 0.017 0.047 | 0.029 0.041 0.014 0.053 |
| T4  | 0.026 0.038 0.013 0.055 | 0.026 0.037 0.014 0.044 | 0.026 0.037 0.011 0.050 |
| T5  | 0.024 0.036 0.011 0.053 | 0.024 0.035 0.013 0.043 | 0.025 0.036 0.010 0.049 |
| T6  | 0.026 0.039 0.013 0.056 | 0.027 0.038 0.015 0.046 | 0.027 0.039 0.012 0.051 |
| T7  | 0.027 0.04 0.014 0.058  | 0.028 0.039 0.016 0.047 | 0.028 0.04 0.013 0.052 |
| T7’ | 0.026 0.04 0.013 0.057  | 0.028 0.039 0.016 0.047 | 0.027 0.039 0.012 0.052 |
| T8  | 0.027 0.04 0.014 0.057  | 0.028 0.039 0.016 0.047 | 0.029 0.041 0.014 0.053 |
| T8’ | 0.026 0.039 0.013 0.056  | 0.028 0.038 0.016 0.046 | 0.027 0.039 0.013 0.051 |
| T9  | 0.024 0.036 0.011 0.054  | 0.023 0.034 0.011 0.042 | 0.024 0.035 0.009 0.048 |
| T10 | 0.024 0.037 0.011 0.054  | 0.026 0.037 0.014 0.045 | 0.026 0.038 0.011 0.05 |
| T11 | 0.028 0.041 0.015 0.058  | 0.028 0.039 0.016 0.047 | 0.028 0.04 0.013 0.052 |
| T12 | 0.027 0.04 0.014 0.057  | 0.027 0.038 0.015 0.046 | 0.027 0.039 0.012 0.051 |
| T13 | 0.031 0.044 0.018 0.061  | 0.033 0.044 0.021 0.053 | 0.032 0.044 0.017 0.057 |
| T14 | 0.032 0.045 0.019 0.062  | 0.035 0.046 0.023 0.054 | 0.034 0.046 0.019 0.059 |
| T15 | 0.031 0.044 0.018 0.061  | 0.035 0.046 0.023 0.054 | 0.034 0.046 0.02 0.059 |
| T15’| 0.029 0.042 0.016 0.06  | 0.035 0.046 0.023 0.054 | 0.033 0.045 0.018 0.057 |
| T16 | 0.015 0.029 0.001 0.047  | 0.013 0.025 0.0004 0.033 | 0.014 0.027 -0.001 0.04 |
| T17 | 0.015 0.028 0.006 0.047  | 0.014 0.026 0.001 0.034 | 0.014 0.027 -0.001 0.041 |
| T18 | 0.023 0.037 0.009 0.055  | 0.019 0.031 0.006 0.039 | 0.021 0.034 0.005 0.047 |
| T19 | 0.017 0.03 0.002 0.049  | 0.015 0.027 0.002 0.036 | 0.016 0.029 0.0003 0.042 |
| T19’| 0.016 0.03 0.002 0.049  | 0.022 0.034 0.009 0.043 | 0.016 0.029 0.0001 0.042 |
| T20 | 0.021 0.035 0.007 0.054  | 0.02 0.032 0.007 0.041 | 0.021 0.034 0.005 0.047 |
| T21 | 0.015 0.029 0.0005 0.048 | 0.013 0.026 0.0006 0.034 | 0.014 0.027 -0.001 0.041 |
| T22 | 0.020 0.033 0.004 0.047  | 0.013 0.026 -0.002 0.039 | 0.017 0.030 0.001 0.043 |
| T23 | 0.021 0.034 0.005 0.0488 | 0.014 0.027 -0.001 0.040 | 0.018 0.031 0.001 0.044 |
| T24 | 0.021 0.034 0.005 0.047  | 0.0141 0.026 -0.001 0.040 | 0.018 0.031 0.002 0.044 |
Figure 1. Calculated charge transfer between the thiaflavan Ti (i = 1 to 24) molecules and the DNA bases A (triangle): Adenine, C (Square): Cytosine, G: (Circle) Guanine and T (star): Thymine) in gas and solvent phases (black: gas, blue: water and red: benzene).

Our results indicate that these molecules act as electron donors (ΔN>0) in gas and solvent phases, and the thymine has the maximum accepting power to interact with the Ti compounds, with respect to the cytosine, adenine and guanine (see Figure 1). Exceptions are the cases of the interaction of {T16, T17 and T21 in benzene} and {T22, T23 and T24 in water) compounds which are more inclined to react with the guanine. The negative ΔN indicates that these compounds act as electron acceptors only with the guanine in benzene and water.

Thus, our quantum chemical calculations indicate that the thymine moiety in DNA has the largest ΔN value and the guanine has the smallest value (in water, benzene and gas) hence oxidation reactions should be commonly found to occur primarily at the guanine site. This result agrees well with the experimental and calculation results of alkylating drug molecules28,29.

Antioxidant activity

The quantum chemical calculations of antioxidant parameters BDE, IP, PA, PDE and ETE for thiaflavan compounds (T1 to T24) have been determined in the gas phase as well as in water and benzene.

Ionization potential

The calculated ionization potentials (IPs) for thiaflavan compounds are given in Table 3. All the thiaflavans can easily donate an electron (IP>0) and they can be sorted in the following order: T13-T15, T16-T24 and T1-T12 in all environments, namely water, benzene and gas phases.

Table 3a: The rate constant (k) for thiaflavans in scavenging ABTS⁺, DPPH and galvinoxyl radicals. BDE, IP, PA, PDE and ETE [kcal/mol] values calculated in gas phase at B3LYP/6-311G++/SDD level of theory

| Ti     | j-R      | BDE  | IP    | PDE  | PA    | ETE  | Experimental (k x 10³ M⁻¹s⁻¹) |
|--------|----------|------|-------|------|-------|------|-----------------------------|
|        |          |      |       |      |       |      | ABTS⁺ DPPH Galvinoxyl radical |
| T1     | 3-OH     | 75.97| 169.00| 221.47| 338.99| 51.48|                             |
| T2     | 4-OH     | 77.14| 169.13| 222.52| 338.55| 53.10| 0.168 - -                   |
| T3     | 1-OH     | 79.98| 164.41| 230.08| 334.74| 59.74| 0.202 - -                   |
| T4     | 1-OH     | 79.62| 163.54| 230.59| 331.35| 62.77| 8.92 0.043 0.025           |
| T5     | 3-OH     | 75.95| 168.45| 222.00| 338.71| 51.75|                             |
| T6     | 4-OH     | 77.10| 167.96| 223.64| 338.55| 53.05| 10.8 0.069 0.034           |
| T7     | 3-OH     | 69.79| 165.08| 219.21| 329.48| 54.81|                             |
| T7'    | 4-OH     | 70.50| 164.75| 220.25| 329.07| 55.93|                             |
| T8     | 2-OH     | 73.61| 162.68| 225.43| 325.66| 62.45|                             |
| T8'    | 1-OH     | 74.91| 164.69| 224.72| 327.54| 61.87|                             |
| T9     | 3-OH     | 75.61| 166.68| 223.44| 338.63| 51.49| 11.7 1.18 0.52             |
| T10    | 4-OH     | 77.10| 167.66| 223.94| 338.23| 53.38| 16.7 1.61 0.57             |
| T11    | 1-OH     | 73.84| 167.66| 220.68| 325.88| 62.46|                             |
| T12    | 2-OH     | 79.83| 163.60| 230.73| 334.06| 60.27|                             |
|        | 4-OH     | 70.48| 163.60| 221.38| 328.14| 56.84|                             |
| Ti   | j-R     | HAT  | SET-PT | SPLET | BDE  | IP  | PDE  | PA     | ETE     | BDE  | IP  | PDE  | PA     | ETE     |
|------|---------|------|--------|-------|------|-----|------|--------|---------|------|-----|------|--------|---------|
| T13  | 3-OH    | 75.82 | 143.77 | 246.56 | 338.79 | 51.54 | 0.16  | -     | -      | 22.9  | 0.124 | 0.084 | DOI: 10.1039/D1NJ01996A |
| T14  | 4-OH    | 77.07 | 143.00 | 248.57 | 338.14 | 53.43 | 0.18  | -     | -      | 22.9  | 0.124 | 0.084 | DOI: 10.1039/D1NJ01996A |
| T15  | 4-OH    | 69.63 | 143.53 | 240.60 | 329.32 | 54.80 | 0.18  | -     | -      | 22.9  | 0.124 | 0.084 | DOI: 10.1039/D1NJ01996A |
| T15’ | 3-OH    | 70.17 | 145.65 | 239.03 | 328.52 | 56.15 | 0.18  | -     | -      | 22.9  | 0.124 | 0.084 | DOI: 10.1039/D1NJ01996A |
| T16  | 3-OH    | 76.31 | 160.07 | 230.75 | 334.15 | 56.66 | 4.89  | 0.0071 | 8.14  | 0.031 | 0.084 | DOI: 10.1039/D1NJ01996A |
| T17  | 4-OH    | 77.01 | 159.88 | 231.64 | 333.49 | 58.02 | 0.18  | -     | -      | 22.9  | 0.124 | 0.084 | DOI: 10.1039/D1NJ01996A |
| T18  | 1-OH    | 76.50 | 155.02 | 239.99 | 331.66 | 59.35 | 0.18  | -     | -      | 22.9  | 0.124 | 0.084 | DOI: 10.1039/D1NJ01996A |
| T19  | 3-OH    | 69.35 | 158.02 | 225.84 | 325.16 | 58.69 | 0.18  | -     | -      | 22.9  | 0.124 | 0.084 | DOI: 10.1039/D1NJ01996A |
| T19’ | 4-OH    | 69.57 | 158.03 | 226.04 | 324.46 | 59.61 | 0.18  | -     | -      | 22.9  | 0.124 | 0.084 | DOI: 10.1039/D1NJ01996A |
| T20  | 1-OH    | 76.61 | 155.55 | 235.56 | 330.07 | 61.05 | 0.18  | -     | -      | 22.9  | 0.124 | 0.084 | DOI: 10.1039/D1NJ01996A |
| T21  | 2-OH    | 80.75 | 158.04 | 237.22 | 335.45 | 59.80 | 0.18  | -     | -      | 22.9  | 0.124 | 0.084 | DOI: 10.1039/D1NJ01996A |
| T22  | 1-OH    | 70.76 | 158.35 | 226.92 | 324.72 | 59.34 | 0.18  | -     | -      | 22.9  | 0.124 | 0.084 | DOI: 10.1039/D1NJ01996A |
| T23  | 1-OH    | 70.67 | 157.17 | 228.00 | 322.09 | 63.09 | 0.18  | -     | -      | 22.9  | 0.124 | 0.084 | DOI: 10.1039/D1NJ01996A |
| T24  | 3-OH    | 76.24 | 157.31 | 233.43 | 334.06 | 56.68 | 0.18  | -     | -      | 22.9  | 0.124 | 0.084 | DOI: 10.1039/D1NJ01996A |

**Table 3b:** BDE, IP, PA, PDE and ETE [kcal/mol] values calculated in water and benzene phases at B3LYP/6-311G++/SDD level of theory.
**Bond dissociation enthalpy**

Bond dissociation enthalpy is an important parameter related to the breaking of O-H bond resulting in the abstraction of H atom. The highest BDE value indicates the lowest antioxidant activity.

The calculated BDEs in gas and solvent phases are reported in Table 3. Firstly, the calculated BDE values in gas and solvent phases show a nice correlation with experimental results presented by Lai and co-workers of rate constant (ln (k)) for thiaflavans in scavenging [(ABTS)•+] (2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonate) cationic radical) see Figure 2. These lines provide a trend between the BDE and PDE and (available) experimental ln (k).

**Figure 2.** Correlation between BDE and PDE values calculated in water rate constant and available experimental (ln (k)) for thiaflavans in scavenging ABTS•+

On the other hand, comparing between gas, polar and non-polar phase BDE values, no dramatic differences are found (all are less than 5 kcal/mol). However, one can notice that the O–H BDE values of thiaflavans are lower than that at A ring. The calculated BDEs in gas and solvent phases are reported in Table 3. Firstly, the calculated BDE values in gas and solvent phases show a nice correlation with experimental results presented by Lai and co-workers of rate constant (ln (k)) for thiaflavans in scavenging [(ABTS)•+] (2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonate) cationic radical) see Figure 2. These lines provide a trend between the BDE and PDE and (available) experimental ln (k).

The high BDE values of T3-R1, T4-R1, T5-R1, T6-R1, T11-R1, T12-R2 and T22-R2 compounds indicate that a single hydroxyl group at 1 or 2-position in ring B exhibits a weak ability to donate its hydrogen atom. On the other hand, the BDE value of T2-R4, T6-R4 and T17-R4 compounds is higher than that of T1-R3, T3-R3 and T6-R3 compounds (~1.14 kcal/mol). Our calculation shows that the bond dissociation enthalpy of single O-H group at B ring is about 5 kcal/mol higher than that at A ring.

Therefore, the hydroxyl groups at A ring play a key role in scavenging radicals and antioxidant effectiveness.

On the other hand, this result shows that the hydrogen atom transfer from ring A of two hydroxyl group at 3 and 4-position is easier than that of B- ring of two OH group at 1 and 2-position, this clearly proves that the ring A has to be considered as the primary target for radical attack in thiaflavans.

**Proton Dissociation Enthalpies**

The PDE represents the reaction enthalpies of the second step in SETPT mechanisms which is responsible for the production of radical cation (ArOH•+) from the neutral (ArOH) compound by loss of one electron followed by the deprotonation of the radical cation. The PDE values let suggest the thermodynamically preferred hydroxyl group for deprotonation from [ArOH•+] as shown in Figure 2, the correlation between PDE and 10 experimental values of rate constant (k) for thiaflavans in scavenging [ABTS•+] is fairly good in both gas and solvent phases (correlation coefficient is 0.914).

As shown in Figure 2, the correlation between BDE and PDE values indicates the antioxidant effectiveness. To the best of our knowledge, the PDE value of thiaflavan antioxidants has not been studied previously. The average calculated PDE of T1 to T24 compounds in water, benzene and gas phase are about 11, 38 and 229 kcal/mol, respectively (see tables 3a-b). The calculated PDEs are dramatically lower in water and in benzene than in gas phase confirming that the solvation facilitates the electron donation, particularly with a polar medium. We can attribute these results to the enhanced stability of the radical cation in a polar medium, as expected from the electrostatic interactions between its charge and the polar solvent. The delocalization and conjugation of the n-electrons of the Ti molecules is also larger in polar medium. On the other hand, the dipole moments of the Ti optimized geometries are higher in water than the
The computed PA values for the various Ti compounds in the gas and solvents phases are reported in Table 3. The highest values in gas phase of PA for Ti compounds in different positions of hydroxyl group (OH=R j=1 to 4) are found for the molecules with a single hydroxyl group in a ring A and B (T1, T2, T5-R3, T6-R4, T9-R3, T10, T12, T13, T14, PA= 338 kcal/mol). The lowest PA values are found in the compounds of’ C’ ring and two OH group attached to the same (A or B) ring (T23-R1>T24-R1>T22> T21-R4>T19-R4> T20-R4, PA= 322-324 kcal/mol). We can attribute these results to the formation of an intramolecular hydrogen bond between the hydrogen atom of hydroxyl and C=O group ((C2-O-H and C1=O) and (C3-O-H and C4-O)). This may also be related to the fact that the ring C’ leads to a better resonance between the A-C’-B-rings (see Scheme 2) which make these molecules yielding high reactivity (also these compounds have the lowest values of γ see Table 1) and the corresponding radicals are more stable (this point is discussed in the next section -Mulliken spin density-, vide infra).

On the other hand, the structure of these molecules shows a co-planarity between A, C’ and B-rings (torsion angle between the three rings equal to “6 ˚”). The presently calculated average PA value for a Ti compounds in water, benzene and gas reaches 33, 96 and 331 kcal/mol, respectively.

Furthermore, our calculation indicates that the PA values in polar media are lower than BDE and IP values for all thiaflavan compounds. This result shows that, in water, the SPLET mechanism should dominate, from the thermodynamic point of view. On the other hand, the BDE values are lower than the PA and IP in benzene and gas phase, respectively for all Ti compounds.

According to our DFT calculations, the orientation of H atoms in the gas phase, respectively for all Ti compounds.

The stability of the formed free radical (ARO) plays a key role in the antioxidant activity of a molecule. The spin densities of the antioxidant free radical can provide some information about the stability of (ARO) and the kinetics of the free radical scavenging reaction. The more delocalized the spin density in the antioxidant radical, the easier the antioxidant radical formed. A lower spin density corresponds to a decrease of the BDE value82.

Table 4, which gathers Mulliken spin densities of O-atom of various free radicals of thiaflavan compounds formed after H abstraction shows that the Mulliken spin density in water is lower than those of the benzene and gas, respectively.

| Ti     | j-O*     | Gas      | Water    | Benzene  |
|--------|----------|----------|----------|----------|
| T1     | 3-O*     | 0.454    | 0.383    | 0.421    |
| T2     | 4-O*     | 0.451    | 0.369    | 0.414    |
| T3     | 1-O*     | 0.502    | 0.449    | 0.476    |
| T4     | 1-O*     | 0.499    | 0.446    | 0.473    |
| T5     | 1-O*     | 0.502    | 0.449    | 0.476    |
| T6     | 4-O*     | 0.454    | 0.382    | 0.420    |
| T13    | 3-O*     | 0.452    | 0.381    | 0.419    |
| T14    | 4-O*     | 0.447    | 0.366    | 0.410    |
| T15    | 4-O*     | 0.427    | 0.347    | 0.391    |
| T15'   | 3-O*     | 0.387    | 0.340    | 0.366    |
| T16    | 3-O*     | 0.408    | 0.320    | 0.370    |
| T17    | 4-O*     | 0.401    | 0.293    | 0.355    |
| T18    | 1-O*     | 0.398    | 0.303    | 0.360    |
The Mulliken spin density on the O- atom in water is high on the \{T21-2-O, T22-3-O, T5-1-O, T6-1-O, T4-1-O, T11-1-O, T8-2-O, T9-1-O, T8'-1-O, T10-1-O, T9-3-O, T1-3-O, T5-3-O, T13-3-O\} with values in the 0.458 – 0.381 range then the \{T2-4-O, T10-4-O, T6-4-O, T14-4-O, T15-4-O, T7-3-O, T5'-3-O, T11-4-O, T12-4-O, T16-3-O, T7'-4-O, T24-3-O, T23-1-O, T11-1-O, T22-1-O, T23-1-O, T17-4-O, T23-4-O, T20-1-O\} provide values in 0.369 – 0.285 range \} and \{T19-3-O, T21-4-O, T19'-4-O, T21-4-O, T20-4-O\} give values amounting 0.277 to 0.248. This means that the formation of radicals \{T19-3-O, T21-4-O, T19'-4-O, T20-4-O\} are more favorable for spin density localization than the formation of other thiaflavan radicals. This also means that the stabilization of the \{T19-3-O, T21-4-O, T19'-4-O, T20-4-O\} radicals are higher than the other thiaflavan radicals.

This result indicates that the Ti radicals having ring C' and hydroxyl and C=O groups on the ring A (R3 and R4) are predicted to be stable compounds and consequently to be potential antioxidants. As can be seen from Table 3, the Mulliken spin atomic densities agree well with the BDE results.

### NICS aromaticity index

The nucleus independent chemical shift (NICS) index is the most popular ty indices\(^{33}\). Since its introduction in 1996\[^{46}\] the NICS index is widely used to characterize the aromaticity and anti-aromaticity of rings\[^{35-39}\] clusters\[^{40-49}\] transition states\[^{46-51}\] transition metal complexes\[^{52}\] originally, the NICS was calculated at the ring center and described as the negative value of the isotropic shielding constant\[^{34,52}\]. In this work, NICS\(_zz\) (1) index is calculated at 1Å above the ring center giving the out-of plane component NICS\(_zz\) (1) for T1 to T25 of thiaflavan antioxidants structures. The NICS analysis is applied to identify the aromaticity of structures, which may reflect their stability. Noted that the strongly negative values indicate the aromaticity and the positive values indicate anti-aromaticity.

### Table 5: NICS\(_zz\) aromaticity index

|    | T1    | T2    | T3    | T4    | T9    | T10   | T11   | T12   | T13   | T14   | T15   | T16   | T17   |
|----|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| NICS\(_zz\) | 19.37 | 19.38 | 19.90 | 14.23 | -5.31 | 7.40  | -5.18 | 7.93  | 19.38 | 11.55 | 7.3  | 1.83  | 16.50 |




Noted that the aromaticity is related to molecular properties such as a biological activities and behavior in various ways\[^{52}\]. The impact of aromatic rings on properties such as solubility, and bioactivities suggests that the presence of more than three aromatic rings may not be optimal for viable drugs meant. All the studied molecules have aromatic 6-membered ring. Therefore, a possibility to relate NICS aromaticity index with the antioxidative properties of the studied molecules is examined. The obtained results, presented in Table 5, show that the OH groups affect the chemical shift in the molecule. Noted that most extended conjugation leads to more stability. However, the aromaticity inside the carbon of ring A is very weak, and the A ring is anti-aromatic.
This result indicates that the hydrogen atom transfer from ring A of two hydroxyl group at 3 and 4-position is easy. On the other hand, the chemical shift inside the carbon of ring B is also weak but less than in the A-ring confirming that ring A should be considered the primary target for radical attack in thiaflavans. Furthermore, the NICS(1) results obtained for C-ring indicate that this ring is always aromatic and, therefore, more stable. Antioxidant activity being due to the capacity to eliminate reactive oxygen species by trapping the free radicals. Based on the NICS analysis, we thus obtained a relationship between the NICS and the hydroxyl groups related to antioxidant activity. Therefore, the lowest value of the enthalpy of dissociation corresponds to the decrease of the aromaticity. This information underlines the importance of aromaticity and the BDE indices, indicating the antioxidant behavior and thus the biological activities.

**Design of the best thiaflavan antioxidants**

The experimental results display that the transition metal complexes show encouraging antioxidant activity and sometimes the ligand exhibits more potent in vitro antioxidant capacity than its complexes.

Towards the design of better thiaflavan antioxidants, we investigated the influence of ferrocenyl group at the B-ring, C’-ring and the position/number of OH group in A and B rings on the BDE, IP, PA, PDE, and ETE of T1 to T24 compounds. Our DFT calculations show that the effectiveness of thiaflavan antioxidants increases in case of:

1. The presence of two hydroxyl groups in the A-ring (3 and 4-positions).
2. The presence of a ring C’.
3. The presence of a ferrocene moiety at ring B. The relevance of the Fe(II)/Fe(III) redox couple in ferrocene is certainly an actor in the efficiency of the T25 thiaflavan system. This has been already suggested by Zai-Qun Liu and Arezki et al. who even suggest that the redox couple of Fe(II)/Fe(III) may control the antioxidative property of the molecule.

According to this study, we can conclude that the best thiaflavan antioxidants are those shown in Scheme 3. The calculated reactivity indices of these compounds (Table 6) show that the T25 and T25’ have the lowest chemical potential and largest electrophilicity index among all the studied thiaflavan compounds (see Table 6 and 1). According to the absolute scale of global electrophilicity power, the T25 and T25’ can be classified as moderate electrophiles.

**Table 6:** Calculated chemical potential (\(\mu\), eV), chemical hardness (\(\eta\), eV), electrophilicity index (\(\omega\), eV) of T25.
Table 7 presents the calculated BDE, IP, PA, PDE and ETE values in gas phase as well as in solvents for of T25 and T25'. By comparison, it can be deduced that the BDE values are lower than the PA and IP values of these compounds (PA and IP are the first step of the SPLET and SETPT process, respectively) in benzene and gas phase.

**Table 7**: BDE, IP, PA, PDE and ETE [kcal/mol] values calculated in water and benzene phases with B3LYP/6-311G++/SDD level of theory

| Ti  | j-OH  | Gas     | Water   | Benzene |
|-----|-------|---------|---------|---------|
| BDE | T25   | 4-OH    | 68.99   | 66.11   | 70.56   |
|     | T25'  | 3-OH    | 65.16   | 63.77   | 68.95   |
| IP  | T25   | 4-OH    | 142.91  | 98.62   | 121.18  |
|     | T25'  | 3-OH    | 140.87  | 98.63   | 119.016 |
| PA  | T25   | 4-OH    | 325.63  | 31.42   | 91.40   |
|     | T25'  | 3-OH    | 325.27  | 27.4    | 92.147  |
| PDE | T25   | 4-OH    | 240.59  | 26.16   | 49.20   |
|     | T25'  | 3-OH    | 238.80  | 23.81   | 52.97   |
| ETE | T25   | 4-OH    | 57.87   | 93.36   | 78.98   |
|     | T25'  | 3-OH    | 54.39   | 94.97   | 79.84   |

Consequently, the HAT mechanism is predicted to be more favored in gas and non-polar media and SPLET process in polar media (see Table 7). On the other hand, our calculation indicates that the BDE value of T25' is lower by ~5 kcal/mol than the smallest BDE value among all Ti (i=1 to 24) compounds. Furthermore, the BDE value shows that the hydroxyl groups at 3-position play a key role in scavenging radicals and exhibiting antioxidant effectiveness.

The Mulliken spin atomic density (see Scheme 4) appears to be slightly more delocalized for radicals issued from the 4-position (C4=O4) than for the 3-position (C3=O3) with values equal to 0.477 and 0.437, respectively (see Scheme 4).

This means that the formation of C3=O3 radical is more favorable for a spin density localization than the formation of C4=O4 thiaflavan radical. The intramolecular hydrogen bond between the hydroxyl hydrogen atom and the C=O group of T25' (C4=O-H and C3=O) is always slightly smaller than that of T25 (C3-O-H and C4=O) in all gas, benzene and water phases. Therefore, the BDE values are lower in 3-position than in the 4-position.

In the end, we can conclude that the thiaflavan T25' is an attractive object for future studies of antioxidant activity.

**Conclusions**

In this work, for the first time the antioxidative properties of thiaflavan and thiaflavan-ferrocene in gas, water and benzene phases have been studied from a theoretical point of view.

The calculated molecular properties (chemical potential, hardness and electrophilicity index) of DNA and thiaflavan compounds clearly confirm that the thiaflavans mostly act as electron donors in their interaction with DNA. Our results confirm that the thymine moiety in DNA is the primary target for the thiaflavan drugs.

Based on the above results, three main antioxidant mechanisms, namely HAT, SET-PT and SPLET were taken into account.
to analyze the antioxidative capacity of thiaflavan compounds in gas, water and benzene phases. The DFT calculation shows nice correlation between BDE and PDE values calculated in gas and solvent phases and experimental data of rate constant (ln(k)) for thiaflavans in scavenging ABTS⁺.

As for the HAT mechanism, from the magnitude of the lowest BDE values, in gas and solvent phases, the two hydroxyl groups in the same ring A or B (3-4-position in the A ring and 1-2-position in the B ring) have higher H-atom donation ability than a single hydroxyl group in A or B ring. Our result indicates that hydroxyl groups at A ring play the key role in scavenging radicals and exhibiting antioxidant effectiveness.

For the SET-PT mechanism, in the studied environments, the antioxidant activity of the investigated compounds reveals that PDE values of T13 to T15 (ferrocene moiety at ring B) are the highest compared to the other thiaflavans compounds.

For the SPLET mechanism, in the studied phases, from the PA of the investigated compounds, we can conclude that the rings B and C' show the strongest antioxidant activity of all the cases.

We have seen that the HAT mechanism is more favorable than the SPLET and the SET-PT in gas and benzene phases. On the other hand, the calculation carried out in polar media indicates that the SPLET mechanism is more preferable than the HAT and SET-PT mechanisms.

From the calculated results, OH groups in A-ring contribute mainly to the antioxidative activities as compared with B-ring. On the other hand, in thiaflavan, the dihydroxyl groups in ring A are more active sites for trapping radicals in the 3-position than in the 4-position.

Furthermore, the calculation of aromaticity index confirms that ring A should be considered the primary target for radical attack in thiaflavans.

Our DFT calculations also reveal that the best antioxidant is T25’ which has two hydroxyl groups in the A-ring (3 and 4-position), C'-ring and a ferrocene moiety at ring B.

This work provides an impetus and a benchmark to outlook experiments, for a determination of the detailed properties of T25' and this compound is then an attractive object for future studies of antioxidant properties.

Author Contributions

All the authors discussed the results.

Dounizied Hannachi: project initiation, conceptualization, calculations supervision, data interpretation, draft writing.
Nour El Houda Amrane: calculations achievements, data interpretation, draft writing.
Lynda Merzoud: calculations, data interpretation, draft writing.
Henry Chermette: calculations, data interpretation, draft writing.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors gratefully acknowledge the GENCI/ CINES for HPC resources/computer time (Project cpt2130), and the PSMN of the ENS-Lyon for computing resources.

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