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Investigation of free radical scavenging activities of some Isatin Schiff bases (O—H versus N—H). A DFT Study

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ABSTRACT

In the present study we analyze various mechanisms of primary antioxidant action of a series of Schiff bases of isatin and its derivatives. For the purpose, theoretical calculations have been performed by means of density functional theory (DFT), using the hybrid functional M05–2X, range-separated functional LC-ωPBE and 6–31+G (d, p) basis set. The reactivity of these Schiff bases has been investigated and interpreted using chemical reactivity descriptors in gas and solvents phase. The two computational approaches used provide identical mechanisms trends in gas and non -polar phase and they are shown that the hydrogen atom transfer (HAT) mechanism is more favored. In contrast, the polarity of the solvent plays a crucial role in the antioxidant activity mechanism, as a higher solvent polarity enhances the contribution of the sequential proton loss electron transfer (SPLET) mechanism. It is found that the isatin group did not suppress the antioxidant effect of the disubstituted Schiff bases products as suggested by the experimental results.

1. Introduction

Compounds with the structure of azomethine group (–C꞊N–), known as Schiff bases (**SB**), are an important class of compounds in pharmaceutical and biological field [1–4]. They are usually synthesized from the condensation of primary amines and compounds having active carbonyl groups. Recently, several studies focused on their biological activities as antibacterial [5–8], anticancer [9], and antifungal activities [10,11]. Schiff bases also showed potential antioxidant activity to scavenge free radicals. Isatin is an endogenous compound identified in humans. Biological properties of isatin include a range of actions in the brain and offer protection against certain types of infections [12].

Due to its pharmaceutical properties, the Schiff group of isatin has recently had a wide range of uses. Schiff bases of isatin are a significant class of hetero-compounds in organic chemistry, and are known to have a broad range of pharmacological properties including anticonvulsant [13,14], antibacterial, antiviral [3,15–19], antioxidant [20–22], anti-HIV, and antifungal activity [3,15,16,18,23]. Substituted

isatin-thio/carbohydrazones based on Schiff bases are commonly called β -isatin aldehyde-N, N′ -(thio)/carbohydrazones [24]

Recently, new Schiff base derivatives (SB) (Scheme 1) were synthesized from thiocarbohydrazide, isatin, and various substituted aldehydes under reflux in ethanol., [25] The antioxidant activity of these novel Schiff base derivatives was evaluated using the well-established 1, 1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging method, which demonstrated strong reducing activity., [25]

The compounds have been subdivided into two classes, namely (1) monosubstituted thiocarbohydrazone (**SB1-SB5**), (2) disubstituted thiocarbohydrazone products (**SB6-SB8**) in which the second substituent is an isatin. The objective of this study was to synthesize isatin analogs by combining thiocarbohydrazone with different functionalized aldehydes to develop new antioxidant agents. The authors investigated the impact of isatin on the antioxidant activity in the disubstituted thiocarbohydrazone derivatives.

The IC50 values, which represent the concentration of the compound required to reduce the DPPH signal by 50 %, ranged from 10.7 to 37.3

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µM [25] (see Table S1 in Supporting Information). In terms of antioxidant activity, the compounds in the first category followed the order: **SB4 < SB3 < SB2 < SB1 < SB5**, while for the second category, the order was: **SB7 < SB8 < SB6**. If we take into account all compounds, the order is: **SB4 < SB3 < SB2 < SB1 < SB7 < SB5 < SB8 < SB6**. The experimental study concluded that the isatin group in the disubstituted Schiff base derivatives reduced their antioxidant effects, with compounds **SB3** and **SB4** exhibiting the highest antioxidant activity [25]
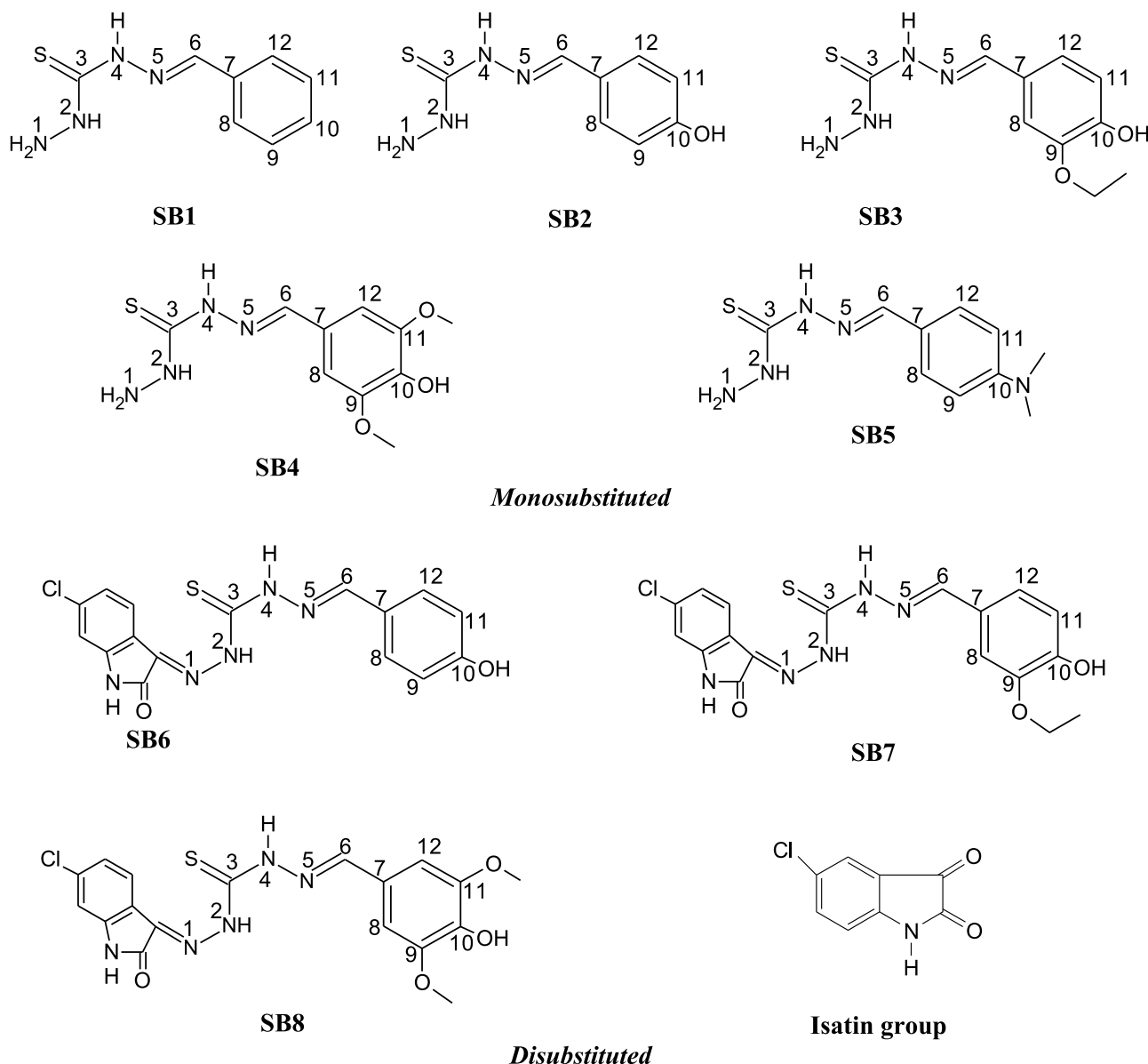
The selection of compounds SB1–SB8 was guided by a systematic approach to explore the relationship between molecular structure and antioxidant activity.

All Schiff bases compounds studies share a common core based on thiocarbohydrazone which are known for their electron-rich systems and pharmacologically active properties. The key variation across the SB1–SB8 series lies in the substitution pattern on the aromatic aldehyde used in the condensation reaction. SB1–SB5 are monosubstituted Schiff bases bearing different functional groups such as –OCH$_2$CH$_3$ (ethoxy) and –N(CH$_3$)$_2$ (dimethylamino) which are either electron-donating or electron-withdrawing. These groups were chosen to examine how electronic effects influence the compounds' radical scavenging ability via hydrogen atom transfer (HAT) or electron transfer-based mechanisms.

SB6–SB8, on the other hand, are disubstituted derivatives in which an isatin moiety is introduced. This substitution introduces significant changes to the electronic distribution and steric environment of the molecule, potentially influencing the hydrogen bond network and intramolecular proton transfer, both of which are critical to antioxidant behavior. Additionally, the substitution was designed to investigate whether the presence of an isatin would enhance or diminish antioxidant capacity, especially when electron-withdrawing groups are present. These structural modifications allowed for a targeted evaluation of how different substituents at key positions modulate bond dissociation energies (BDEs) and other thermodynamic descriptors linked to antioxidant potential. Our numbering of the molecules, sketched in Scheme 1, is SB6–8 = SB2–4 + isatin.

A comparison between compounds **SB2, SB3, SB4** and the derivatives **SB6, SB7**, and **SB8** reveals that the latter are essentially modified versions of the former, with hydrogen replaced by an isatin group. This substitution takes place at a site distant from the reaction center. Furthermore, electron-withdrawing groups are present in

Monosubstituted

Disubstituted

Scheme 1. Structure of the investigated Schiff bases.

compounds **SB3** and **SB4**, which are known to enhance oxidative activity [21,26] Interestingly, the same electron-withdrawing groups are present in compounds **SB7** and **SB8**, prompting the question: why do these groups not exhibit their expected behavior in this case? In other words, what mechanism allows the isatin group to suppress the antioxidant property? Additionally, it is well-established that the scavenging activity of Schiff bases is based on their ability to transfer hydrogen atoms (from either the OH or NH groups) to free radicals. However, the experimental study does not specify which hydrogen atom whether from the O—H or N—H group is abstracted by the DPPH radical. These two questions lead us to study the antioxidant activity of these Schiff bases to interpret the experimental results.

In principle, N–H bond dissociation energy (BDE) may also correlate with the free radical scavenging capacity, since the hydrogen of these groups may be labile according to the chemical environment, stability of resulting radicals and reaction mechanism).

In the present work, we started by determining the physiochemical properties of these Schiff bases with the help of different descriptors (Dipole moment, HOMO, LUMO, Ionization Potential (IP), Electronic affinity (EA), absolute hardness (η)) and the presence of Electron Donating Groups (EDGs) such as --O–CH_2CH_3 and –$N(CH_3)_2$ in ortho position to the OH group on antioxidants.

In a second step, we investigate the free radical scavenging ability of both OH and NH groups by analyzing the competition between them for hydrogen atom transfer (HAT), using separate calculations of bond dissociation energies (BDEs) for each group.
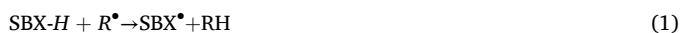
In a third step, the IP, Proton Dissociation Enthalpy (PDE), Proton Affinity (PA) and Electron Transfer Enthalpy (ETE) parameters which characterize the corresponding steps of the single electron transfer followed by proton transfer (SET-PT) and sequential proton loss electron transfer (SPLET) mechanisms will be examined. Finally, the radicals formed after the loss of one H atom, will be also studied according to their electron spin density distribution.

For the purpose, we used two DFT functionals, namely the LC-ωPBE and M05–2X, as suggested by La Rocca *et al.* [27] for an accurate and fast evaluation of energetic parameters related to antioxidant activity.

2. Theoretical background

Free radical scavenging capacity of phenols is generally attributed to the hydrogen atom lability of the OH groups [28–30]; however in some antioxidants, NH groups may provide labile hydrogen [31–38]. Antioxidants **SBX–H** ($X = O$, N) may scavenge free radicals ($R^\bullet$) by H atom transfer through one of the three mechanisms; hydrogen atom transfer (HAT), single electron transfer followed by proton transfer (SET-PT), and sequential proton loss electron transfer (SPLET) The net result of all three mechanisms is the same . They are competitive, implying that the nature of free radicals and polarity of solvents, as well as other reaction conditions, have significant impact on the reaction pathways [39].
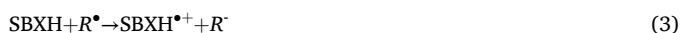
In HAT mechanism: Hydrogen atom transfer (HAT, eq (1)) from antioxidant molecule ($SBX - H$) to radicals ($R^\bullet$).

$$SBX\text{-}H + R^\bullet \rightarrow SBX^\bullet + RH \tag{1}$$

$\Delta H(BDE)$ can be calculated as follows:

$$\Delta H(BDE) = [\mathbf{H}(SBX^\bullet) + H(RH)] - |\mathbf{H}(SBXH) + H(R^\bullet)] \tag{2}$$

The SET-PT mechanism takes place in two steps: the electron transfer is the first step of this reaction (Eq. (3)), and a deprotonation of the generated radical cation (Eq. (4)) is the second step:
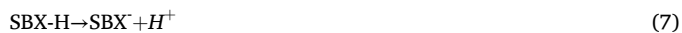
$$SBXH + R^\bullet \rightarrow SBXH^{\bullet+} + R^- \tag{3}$$

$$SBXH^{\bullet+} + R^- \rightarrow SBX^\bullet + RH \tag{4}$$

This mechanism is characterized with $\Delta H(IP)$ and $\Delta H(PDE)$

$$\Delta H(IP) = [\mathbf{H}(SBXH^{\bullet+}) + H(R^-)] - [\mathbf{H}(SBXH) + H(R^\bullet)] \tag{5}$$

$$\Delta H(PDE) = [\mathbf{H}(SBX^\bullet) + H(R)] - [\mathbf{H}(SBXH^{\bullet+}) \text{-} H(R^-)] \tag{6}$$

The SPLET mechanism: Sequential proton loss electron transfer (SPLET). This mechanism involves two steps (7 and 8)

$$SBX\text{-}H \rightarrow SBX^- + H^+ \tag{7}$$

$$SBX^- + R^\bullet \rightarrow SBX^\bullet + R^- \tag{8}$$

This mechanism is characterized with $\Delta H(PA)$ and $\Delta H(ETE)$

$$\Delta H(PA) = [\mathbf{H}(SBX^-) + H(H^+)] - H(SBX\text{-}H) \tag{9}$$

$$\Delta H(ETE) = |\mathbf{H}(SBX^\bullet) + H(e)] - H(SBX^-) \tag{10}$$

From these definitions, it becomes clear that in order to find the total enthalpies of each mechanism we need the enthalpies for the electron, proton, and the H atom. The enthalpy values of the hydrogen atom $H^\bullet$, calculated at (U)M05–2X and (U)LC-ωPBE level of theory amount (-310.9 and -314.9 kcal/mol), independently of the gas or solvent phase, and close to the exact value (-313.7 kcal/mol). The H($H+$) and H ($e-$) enthalpies used are taken from literature: (1.5 and 0.75 kcal/mol) in gas phase, (-208 and -1.6 kcal/mol) in benzene, (-245 and -25 kcal/mol) in water respectively., [40–42] These values may include some not significant variations expected due to different computational levels. All molecular enthalpies have been calculated at 298.15 K.

The present work focus only the thermodynamic aspect of these reactions, comparing the mechanisms which may be involved in gas phase or solvents. Kinetics aspects are not investigated in the present work, and will the object of further work

3. Computational details

The equilibrium geometries of all Schiff bases (**SB**) and their radicals ($SBX^\bullet$), anions (SBX^-), and radical cations ($SBXH^{\bullet+}$) ($X = O$ or N) were fully optimized with the hybrid meta GGA density functional methods (M05–2X) [43] and range-separated functional LC-ωPBE [44–47]. These two functionals are recommended for general purpose applications in thermochemistry, kinetics, and especially recommended for calculating Bond Dissociation Energies (BDE)., [27]

The optimized structures were confirmed as true minima by vibrational analysis, ensuring the absence of imaginary frequencies. Calculations were performed with the 6–31+G(d, p) basis set [27]. Unrestricted calculations have been applied for open shell systems such as radicals and radical cations. To investigate the effect of the environment (solvent effects), polar (water, ε=78.35) and non-polar (benzene, ε=2.27) solvent effect were evaluated using the SMD model [48]. This model is based on the quantum mechanical charge density of a solute molecule interacting with a continuum description of the solvent. It should be mentioned that all the gas-phase structures were re-optimized in presence of the solvent at the two levels of theory (M05–2X and LC-ωPBE).

Vertical ionization potential (vIP) was determined according to Koopmans' theorem: vIP=$-E_{HOMO}$, vEA=$-E_{LUMO}$. Additionally, absolute hardness (η) and electronegativity (χ) of the compounds were evaluated from HOMO and LUMO energies using the following formulae: η = (vIP – vEA); χ = (vIP + vEA)/2., [49],The molecular electrophicity index (ω) was calculated from $\omega = \chi2/2\eta$ [50]. All calculations were performed using Gaussian 09/16 program suites., [51]

3.1. Benchmarking study of computational method

The DFT method is a powerful and highly valuable computational tool, known for its ability to accurately predict the antioxidant properties., [52] Recently, the Density Functional Theory (DFT) method, combined with the hybrid meta exchange-correlation functional M05–2X [43] and the range-separated functional LC-ωPBE [44,45], has been applied to general-purpose tasks in thermochemistry, kinetics, and

Bond Dissociation Energy (BDE) calculations., [27,53–55] According to reference [27], the functionals LC-ωPBE, M05–2X, and M06–2X exhibit the lowest errors, making them suitable for precise and efficient evaluation of energetic parameters related to antioxidant activity. The 6–31+G(d, p) basis set is used because, as shown in reference [27], results obtained with this set converge closely with those from larger basis sets, with average deviations of <0.04 eV. Thus, the computational methods M05–2X/6–31+G(d, p) and LC–ωPBE/6–31+G(d, p) are appropriate for assessing antioxidant properties.

4. Result and discussion

4.1. Global reactivity descriptors in gas and solvents phase

A quantitative analysis of the investigated molecule reactivity has been performed through calculations of the global reactivity descriptors. The values in gas and solvent (benzene and water) phases are calculated at M05–2X and LC–ωPBE levels of theory and the results are reported in Support Information Tables S2 and S3.

Bond polarity is one of the factors determining the physiochemical property for molecules. Started by gas phase, all compounds are highly polarized and confirm their solubility in the polar solvents (Tables S2). Both functional (LC-ωPBE and M05–2X) show that **SB5** possess the highest value of dipole moment, while SB6 has the smallest one.

Analyzing both non-polar (benzene) and highly polar (water) solvents let us surround the effects obtained with the ethanol solvent used in the experiment. (ref. 25). Incorporation of non-polar solvent (benzene) leads to an increase in the calculated dipole moments (See Tables S2 and S3). A larger increase is in the polar solvent (water), as expected. The relative increase of the dipole moment upon introducing benzene and water are roughly 45 % (with both functionals).

One of the most important descriptors of free radical scavenging activity is the energy of HOMO and LUMO orbitals. It is generally assumed that the better electron-donating ability of the antioxidant molecule can be ascribed to the higher energy of HOMO whereas the better electron accepting ability of the compound is associated with the smaller LUMO. The gas-phase energies of HOMO orbital varied from −8.61 eV for **BS6** to −7.72 eV for **BS5** calculated at LC-ωPBE level of theory and between −7.30 eV for **BS6** to −6.49 eV for **BS5** with hybrid function M05–2X, while the gas-phase energies of LUMO orbital were in the range between −0.48 eV for **BS8** and 0.77 eV for **BS5** with LC-ωPBE functional and varied from −1.68 eV for **BS8** to −0.40 eV for **BS5**. (See Tables S2). Hence, the two functionals show that the molecule **SB5** seems to be the best electron donor, while **BS8** the best electron acceptor from the compounds studied. The gas-phase values of HOMO-LUMO gap increased in the following order: **BS2 < BS1 < BS4 < BS3 < BS5 < BS6 < BS7 < BS8** and in the order (**BS2 < BS1 = BS3 < BS4 < BS5 < BS6 < BS7 < BS8**) with the two functionals meta-hybrid and range separated, respectively. The theoretical prediction regarding the calculated HOMO-LUMO energy gap values suggests that the reactivity of monosubstituted Schiff bases (**SB1** to **SB5**) should be superior over the disubstituted Schiff bases (**SB6** to **SB8**).

A lower Ionization Potential (vIP) in antioxidants facilitates electron donation to free radicals, enhancing their protective effects. However, if the vIP is too low, the molecule may become too reactive, acting as a prooxidant and promoting oxidative damage. This can lead to auto-oxidation and increased free radical production. Therefore, an optimal vIP range is crucial for maintaining antioxidant efficacy without triggering harmful side reactions., [56]

From Tables S2 and S3 it may be seen that the gas-phase and solvated vIP values (benzene and water) calculated for **SB5** (Without Hydroxyl group**)** using meta-hybrid and range separated functions are lower than corresponding values for monosubstituted Schiff bases (**SB1** to **SB5**) and should possess higher free radical scavenging activity in this class of compounds. Among the disubstituted Schiff bases, the vIP value of **BS8** is the lowest and should possess the highest free radical scavenging

activity in this group of compounds (**SB6** to **SB8**).

According to Pearson's maximum hardness principle, [57] molecules with the smallest hardness, i.e. the lowest frontier molecular orbital gap, are the least stable [58], and the most polarized, as shown by Vela and Gazquez., [59] In these molecules, some intermolecular charge transfer between electron donors and electron acceptors can occur up to a significant degree, which may influence the biological activity of the molecule. According to the results in Table S2, the two functionals show that the molecule **SB5** has the lowest hardness for the monosbstitued Schiff bases whereas the **SB8** molecule hardness is the lowest one in the disubstituted Schiff bases group. Thus, molecules **SB5** and **SB8** are the preferred Schiff bases molecules for radical scavenging process for the two groups of molecules.

Generally we can see that the effect of the solvent on the global reactivity descriptors is minor. In several papers, it was shown that reactivity indices calculated in gas phase do not significantly differ from those calculated with PCM and CPCM models., [54,60,61] This is not the case for ionized species (vide infra).

4.2. Frontier molecular orbitals

Frontier molecular orbital analysis is valuable for understanding the role of phenolic antioxidants in neutralizing free radicals., [62] Two key factors that greatly influence bioactivity are highest occupied molecular orbitals (HOMO) and the lowest unoccupied molecular orbitals (LUMO)., [62] To investigate the main atomic contributions to these orbitals, we created plots of the HOMO and LUMO for each Schiff bases.

Graphical representations of (HOMO) and (LUMO) with LC-ωPBE/6–31+G (d, p) in the gas phase of the studied Schiff bases are given in Figure S1. From the visuals of this Figure, the HOMO orbitals of all compounds are localized mainly on O—H and on =N—NH groups. Hence, these O—H and =N—NH groups are the most probable reaction sites which can be attacked by free radicals, removing an electron. In contrast, the distribution of LUMOs for all these Schiff bases shows no contribution of the O—H or =N—NH groups. Always from Figure S1 we can see the absence of charge in the isatan-thiocarbohydrazone side for disubstituted Schiff bases HOMOs

4.3. Spin density distributions in (SBX•) radicals (Gas and solvents effects)

The spin density distribution is known to be a property giving a better understanding of the stability of a radical. The electron delocalization and subsequent stabilization of the resulting radicals is one of the elements which controls the ranking of the cleavable OH positions., [27]

As local descriptor of reactivity, the spin density is often considered to be a realistic parameter and provides a better representation of the reactivity. Generally, the more delocalized the spin density of the radical, the easier the radical will be formed, and thus, the lower will be the BDE., [63]

In order to rationalize the differences in BDE and reactivity of the O—H and N—H sites, the spin density distributions of the radicals were calculated. The spin densities of all radicals obtained at two levels of theory (meta-hybrid and range separated) are given in Tables S4-S17 (See Support Information).

The spin densities of (**SBO•**) and (**SBN•**) radicals obtained at M05–2X/6–31 G + (d, p) in gas phase are given in Fig. 1 (**SBO•**) and Figure S2 (**SBN•**).

The spin densities in monosubstituted radicals appear to be more delocalized and extended over the molecules. This facilitates the antioxidant activity of the monosubstituted Schiffs bases compared to disubstituted. (See Fig. 1 and Figure S2 or Tables S4-S17 in Support Information).

Indeed, a simple inspection of the graphical spin densities reported in Fig. 1, shows a large delocalization of the spin density over the different atoms of the systems. (See Fig. 1, S2 and Tables S4-S17 in Support
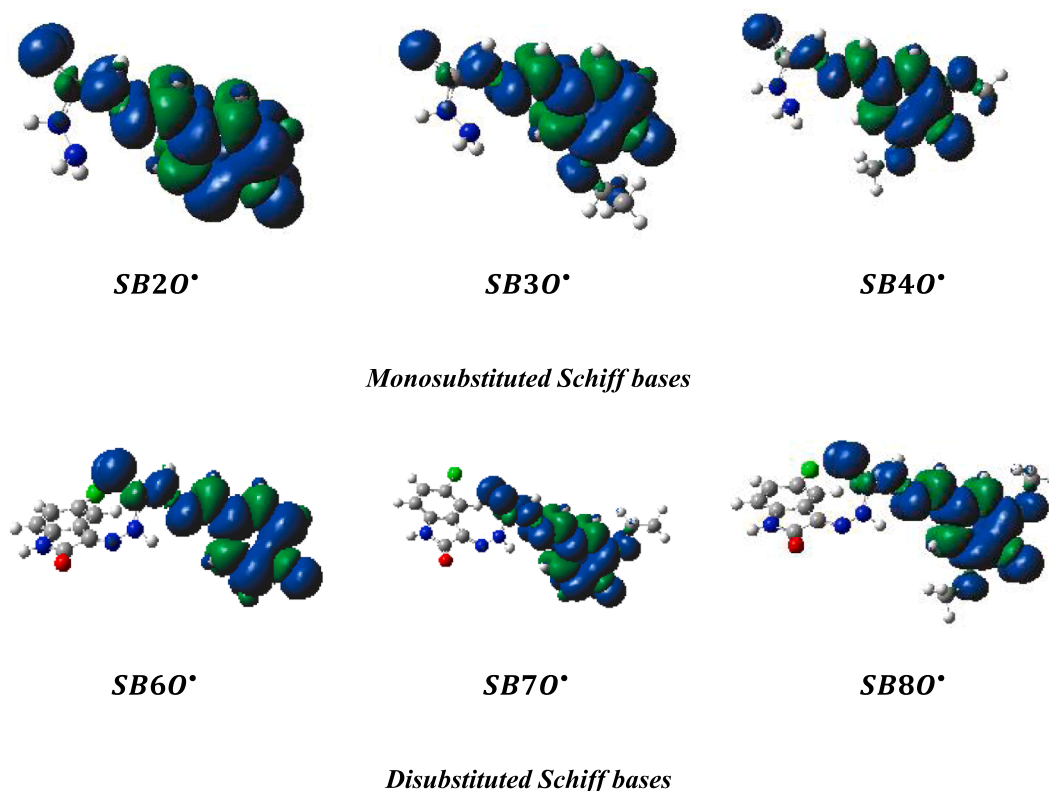
SB2O•   **SB3O•**   **SB4O•**

Monosubstituted Schiff bases

SB6O•   **SB7O•**   **SB8O•**

Disubstituted Schiff bases

Fig. 1. Graphical representation of spin density distribution for **SBO•** radicals at M05–2X/6–31 G + (d, p) level of theory.

Information). The two type formed radicals (**SBO•** and **SBN•**) are predicted to be stable and the corresponding compounds are predicted to be potential antioxidants. The spin densities on the oxygen atom of **SBO•** radicals calculated in gas phase are in a 0.30–0.33 and 0.31–0.35 range with functionals M05–2X and LC–ωPBE respectively.

The effect of non-polar solvent (benzene) and polar solvent (water) on spin densities distribution is also calculated in the same level. Obtained results are summarized in the same Tables (S4-S17). As expected, Tables S4-S17 show that the lowest values of the spin density on the oxygen atom are obtained in polar solvent (water) (0.26–0.29) with the two functionals.

While the spin densities in gas phase on the Nitrogen atom (**SBN•**) are in a 0.45–0.53 and 0.54–0.58 range with the functionals M05–2X and LC–ωPBE respectively. The effect of non-polar solvent (benzene) and polar solvent (water) on spin densities on the Nitrogen atom (**SBN•**) are not very significant, the range is between 0.44–0.59 in benzene and 0.42–0.58 in water. We noted that larger values of spin densities are obtained with LC–ωPBE functional, with respect to M05–2X. In general we note that the calculated spin densities on the Nitrogen atom (**SBN•**) follow the same trends in gas, polar and non-polar phase. From the visuals of Fig. 1, we observed the total absence of the spin density in the isatan thiocarbohydrazone part for disubstituted Schiff bases.

4.4. Descriptors of the antioxidant properties in gas phase

4.4.1. HAT mechanism

Bond Dissociation Enthalpy (BDE) is one of the earliest studied quantities in association with antioxidants with straightforward mechanism. The free radical scavenging capacity has been extensively correlated to O–H BDEs, rationalized by spin density distribution and stability of the radical formed after HAT. In principle, N–H BDE may also correlate with the free radical scavenging capacity, since the hydrogen of these groups may be labile according to the chemical environment, stability of resulting radicals and reaction mechanism.

The minimal value of BDE (BDE min) of the N–H and O–H bonds indicate which group possess the most easily hydrogen can be removed that is which group is targeted for radical attack. For a given system the most stable radical formed by the O–H (N–H) cleavage is the one that shows the lowest BDE.

For the HAT mechanism we calculated the enthalpy for each H (O–H or N–H) independently as if only one H in the molecule reacted with the radical BDE (OH) and BDE (NH). The BDEs values of Schiff bases (**SB**) in gas phase are reported in Figs. 2 and S2 (See also Table S18 in Support Information).

First of all, the BDEs values calculated at LC–ωPBE level of theory are the lowest, excepted for BDE (NH) and BDE (NH) of the **SB7** are the same values (See Table S18). Differences between M05–2X and LC–ωPBE values do not exceed +5 kcal/mol calculated for BDE (OH) of **SB6**.

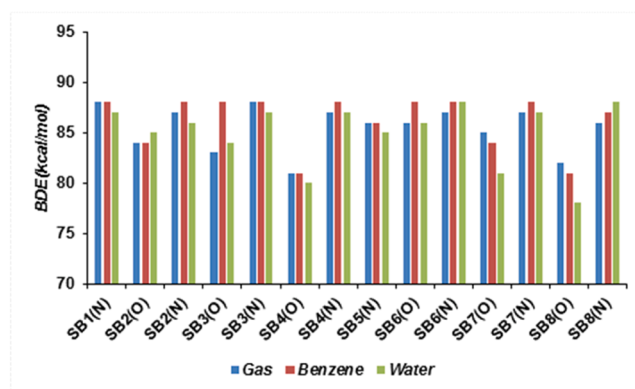As we noticed in introduction, our compounds are subdivided into

Fig. 2. Bond dissociation energies (BDE, kcal/mol) for all Schiff bases computed using M05–2X functional in gas and solvent phases. The same property calculated with the LC–ωPBE functional is given in Fig. S2. The solvent contribution is discussed in Section 4.5.1.

two groups; monosubstituted Schiff bases (**SB1-SB5**) and disubstituted Schiff bases (**SB6-SB8**). In the following parts, we discussed each group separately and finally, we will give a general summary of the two groups together.

Firstly, in the group containing monosubstituted compounds (**SB1-SB5**), the O—H (N—H) bond dissociation enthalpies (BDEs) grow in the following order for the two functionals (See Figs. 2 and S2 or Table S18 in Support Information):

LC-ωPBE: *SB4(O) < SB2(O) < SB3(O) < SB3(N) < SB4(N)=SB5(N) = SB2(N) < SB1(N)*

M05–2X: *SB4(O) < SB3(O) < SB2(O) < SB5(N) < SB4(N)= SB2(N) < SB3(N)= SB1(N)*

The BDEs values and the order cited above with two functionals (LC-ωPBE and M05–2X) indicate also that an abstraction of the H atom in O—H bond results in lower BDE values than the abstraction of the H atom from N—H bond (See Figs. 2, S2 or Table S18 in Support Information). This result shows that O—H of compound **SB4** has the least BDE (OH) value and it has a higher radical scavenging reactivity than other compounds (**SB1** to**SB5**) in gas phase. This result is in excellent agreement with the experimental results where the IC_{50} values for monosubstituted products follows the order of (**SB4 < SB3 < SB2 < SB1 < SB5**)., [25] We note that the order with the functional M05–2X is more consistent with the experimental results. (See order with M05–2X, LC-ωPBE and experiment order)

The compounds (**SB1** and **SB5**) having no OH group, can only be active from their NH group. However the N–H BDEs of these two compounds are higher than 85 kcal/mol (See Table S18 in Support Information) making these compounds inefficient to scavenge DPPH. Indeed, the BDE of DPPH—H is ca. 80 kcal/mol [64,65], thus for these compounds the thermodynamic balance of Eq. (1) is positive with DPPH. Then, it appears that the DPPH as radical scavenging reagent is not convenient for evaluating the antioxidant features of compounds like **SB1** and **SB5**.

We can see that the compound **SB5**, having an electron-donating group (**EDG**) (dimethylamine –N(CH₃)₂) in the ring increases the BDE (NH), making this compound more active compared to **SB1 (**not substituted in any position).

Secondly, in the group comprising the disubstituted compounds (**SB6-SB8**), the O—H (N—H) bond dissociation enthalpies (BDEs) grow in the following order for the two functionals (See Figs. 2, S2 or Table S18 in Support Information):

LC-ωPBE**: *SB8(O)=SB7(O) < SB6(O) =SB8(N)=SB6(N)= SB7(N)*

M05–2X: SB8(O) < SB7(O) < SB6(O)= SB8(N) < SB6(N) < SB7(N)

Again, this order indicates that the abstraction of the H atom in O—H bond results in lower BDE value than the abstraction of the H atom N—H bond. (See Figs. 2, S2 or Table S18)

This result shows that O—H of compound **SB8** has the least BDE value and it shows higher radical scavenging reactivity than other derivatives in gas phase. This result is partially confused with the experimental result where the IC_{50} values for disubstituted Schiff bases follow the order of (**SB7 < SB8 < SB6**)., [25] (See Table S1 in Support Information)

4.4.2. SPLET mechanism

The sequential proton loss electron transfer (SPLET) two-step reaction is reported in Figs. 3, 4, S4 and S5. (See Table S18 in Support information). As presented in the theoretical background section, this mechanism involves two steps (PA and ETE). The PAs values calculated at LC-ωPBE level of theory are slightly higher than those calculated with the M05–2X function, the max difference is 17 kcal/mol for **SB3** (O—H). In our previous work this difference did not exceed 5.1 kcal/mol., [55] . Indeed, the "large" difference between the two functionals for all eight
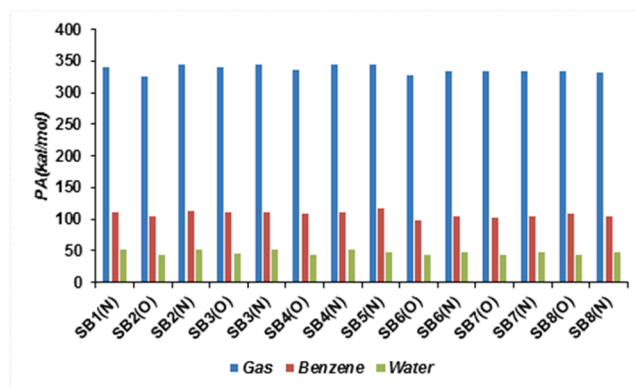

Fig. 3. Proton affinity (PA, kcal/mol) for all Schiff bases computed using M05–2X functional in gas and solvent phases. The same property calculated with the LC-ωPBE functional is given in Fig. S4. The solvent contribution is discussed in Section 4.5.2.
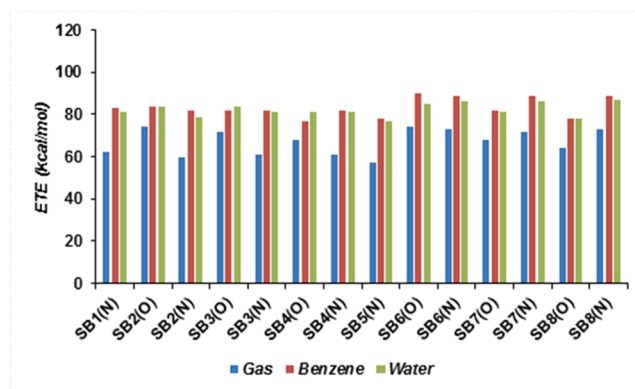

Fig. 4. Electron transfer enthalpy (ETE, kcal/mol) for all Schiff bases computed using M05–2X functional in gas and solvent phases. The same property calculated with the LC-ωPBE functional is given in Fig. S5. The solvent contribution is discussed in Section 4.5.2.

compounds is typical of the different behaviour of the functionals within the introduction of a solvation model in case of a polar solvent. Whereas the numbers are quite similar in gas phase or non-polar phase, such as benzene, they differ in water medium. This is clear in Table S17 for PDE or ETE energies of most of the eight compounds. This is difficult to properly explain the difference according to the dim construction of the M05–2X functional. Fortunately, that do not change the trends.

Firstly, in the group comprising the monosubstituted compounds (**SB1-SB5**), the Proton affinities (PAs) value shows approximately the same order for the two levels of theory (the order of two molecules **SB3** and **SB4** only are different for the two functional) and increasing in this order: (See Figs. 3 and S4 or Table S17 in Support Information):

LC-ωPBE: *SB2(O) < SB4(O) < SB3(O)=SB1(N) < SB3(N)=SB4(N) < SB2(N)=SB5(N)*

M05–2X: *SB2(O) < SB3(O) < SB4(O) < SB1(N)=SB3(N)=SB4(N) < SB2(N) < SB5(N)*

Whatever the functional used the PAs are smaller for the proton transfer from O—H than from N—H. This means that the proton transfer from O—H of **SB2** is more probable than from all O—H and N—H of other Schiff bases. For the **SB5** Schiff base (which has no O—H bond), its high PA goes with considerably lower ETE (See the paragraph of the ETE discussion below or See Figs. 4 and S5) in comparison to the rest of studied compounds. Therefore, the deprotonated form of the **SB5 (N—H)** compound should be the best electron donor from the

thermodynamic point of view.

In the second group comprising disubstituted compounds (**SB6-SB8**), the Proton Affinities (PAs) values show also approximately the same order with the two levels of theory and increasing in this order (**SB6(O) < SB8(N) < SB6(N) = SB7(N) < SB7(O) < SB8(O)**))

For the group comprising disubstituted Schiff bases (**SB6- SB8),** the slightly higher PA of the **SB6** (O—H) molecule shown by the two functionals means that this molecule is the most reactive from the thermodynamic point of view. The two functionals show that **SB8** (O—H) is the least reactive among them.

In the second step (ETE) of SPLET, electron transfer takes place. The M05–2X functional gives the highest values. The max differences between LC-ωPBE and M05–2X values is 14 kcal/mol shown for **SB3** (O—H**)**. (See Figs. 4, S5 or Table S18 in Support Information)

In the group comprising the monosubstituted Schiff bases (**SB1-SB5),** the ETE values decrease in order:

LC-ωPBE: **SB5(N) < SB2(N)=SB3(N)=SB4(O)=SB4(N) < SB3(O) < SB1(N) < SB2(O)**

M05–2X: **SB5(N) < SB2(N) < SB3(N)=SB4(N) < SB1(N) < SB4(O) < SB3(O) < SB2(O)**

In the second group comprising the disubstituted Schiff bases (**SB6- SB8),** the ETE values decrease according to the order:

LC-ωPBE: **SB8(O) < SB7(O) < SB6(O) < SB6(N) =SB7(N)=SB8(N)**

M05–2X: **SB8(O) < SB7(O) < SB7(N) < SB6(N)= < SB8(N) < SB6(O)**

An excellent linear correlation between the ETE descriptor, which expresses the electron transfer enthalpy of the anion **SBX⁻ (X = O** or **N),** and the HOMO energy of the anions is obtained for the two class of Schiff bases. (See Fig. 5)

4.4.3. SET-PT mechanism

In the SET-PT mechanism, electron donation initiates the process, and IP stands as a crucial parameter indicating the electron donation capability. The ionization potential (IP) illustrates the easiness of electron donation of the compounds. It is well known that molecules with lower IP values are more active. In Figs. 6, 7, S7 and S8 the calculated IPs and PDEs are presented. The IPs values calculated at M05–2X level of
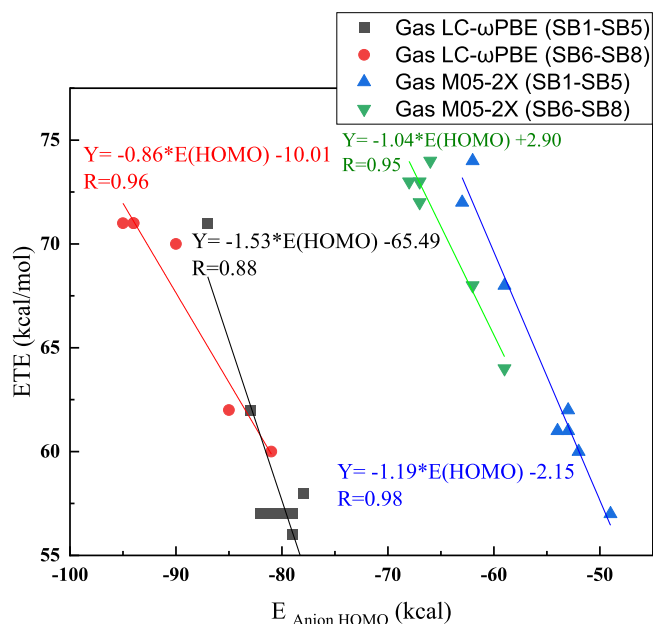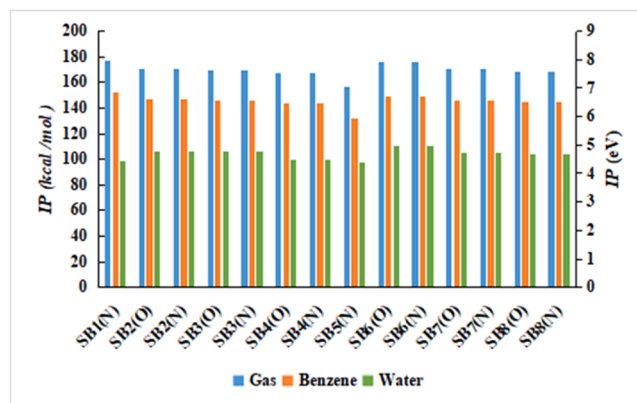

Fig. 6. Ionization potential (IP, kcal/mol and eV) for **SB** compounds computed using M05–2X functional in gas and solvent phases. The same property calculated with the LC-ωPBE functional is given in Fig. S7. The solvent contribution is discussed in Section 4.5.3.

Fig. 7. Proton dissociation enthalpy (PDE, kcal/mol) for **SB** compounds computed using M05–2X functional in gas and solvent phases. The same property calculated with the LC-ωPBE functional is given in Fig. S8. The solvent contribution is discussed in Section 4.5.3.
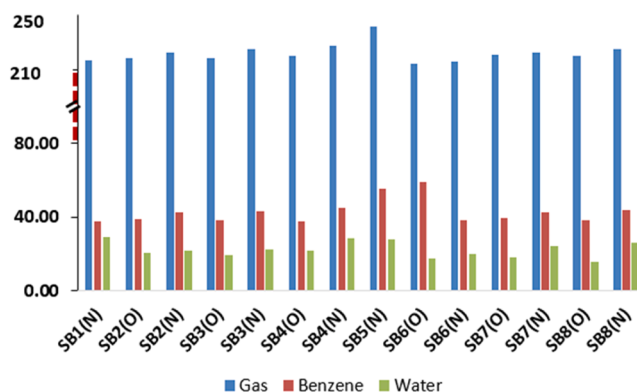
theory are slightly lower than those calculated with LC-ωPBE (See Fig. 6 and Figure S6 or Table S18). Differences between LC-ωPBE and M05–2X values do not exceed +4 kcal/mol)

Not surprisingly, the two functionals LC-ωPBE and M05–2X give the same order for both groups of Schiff bases (**SB5 < SB4 < SB3 < SB2 < SB1**) and (**SB8 < SB7 < SB6**) (See Fig. 6, S6 or Table S18). This order indicates that the two molecules **SB5** (N—H), **SB8** should be more easily ionizable, leading to better electron-transfer rate between free radicals and antioxidants.

In the SET-PT mechanism, the second step involves proton donation from the cation radical, a process characterized by the PDE measuring the tendency of deprotonation of radical cations formed in the first step. A lower PDE value signifies a stronger proton- donating ability of the cation radical. The calculated PDE values for all Schiff bases are presented in Figs. 7 and S8. For this descriptor, no significant difference between the functionals is obtained, with a difference being at most 6 kcal/mol for **SB7** (O—H).

For the group of monosubstituted Schiff bases (**SB1-SB5**) gas-phase PDEs values follow different order with the two functionals:

LC-ωPBE: **SB2(O) < SB4(O) < SB1(N) < SB2(N) < SB3(O) < SB3(N) < SB4(N) < SB5(N)**

M05–2X: **SB1(N) < SB2(O)=SB3(O) < SB4(O) < SB2(N) < SB3(N) < SB4(N) < SB5(N)**

Fig. 5. Linear correlations between ETE values and E_{HOMO} (Anion). The same correlation in solvents is given in Fig. S6.

In the second group comprises disubstituted Schiff bases (**SB6-SB8**) gas-phase PDEs values follow also different order with the two functionals:

LC-ωPBE: **SB6(O) < SB7(O) < SB8(O) < SB6(N) < SB7(N) < SB8(N)**

M05–2X: **SB6(O) < SB6(N) < SB7(O) < SB8(O) < SB7(N) < SB8(N)**

The two functionals LC-ωPBE and M05–2X indicates that the lowest PDE is for **SB6** (O—H) reflect its higher tendency to deprotonation.

Finally, by analyzing HAT, SPLET and SET-PT reaction mechanisms, it is clear that both pathways (SPLET and SET-PT) involve greater energies required to occur with respect to the HAT one. Consequently, the HAT mechanism is predicted to be more favored in gas phase due to the facility of the hydrogen atom transfer and the formation of the **SBX•** radical in a single step. The BDE reaction mechanism indicates also that an abstraction of the H atom in O—H bond results in lower BDE value than the abstraction of the H atom **N—H** bond. On the other hand, the two functionals M05–2X and LC-ωPBE show that the compound **SB4** (O—H) has the highest antioxidant activity among monosubstituted Schiff bases according to the calculated descriptors mentioned above for the three proposed mechanisms, in agreement with experimental results., [25] On the contrary, **SB8** (O—H) Schiff base shows the highest antioxidant activity among the disubstituted ones, in disagreement with experimental results., [25].

The remark of the isatin group suppresses the antioxidant effect of the disubstituted Schiff bases products in experimental study [25] is not always verified, because if we order all Schiff bases (monosubstituted and disubstituted) (see the order below) we find that the two disubstituted Schiff bases **SB7** (O—H) and **SB8** (O—H) show the highest antioxidant activity among the majority of the monosubstituted Schiff bases (**SB2** and **SB3**) (result proved by LC-ωPBE functional). The M05–2X showing that only **SB8** (O—H) has a highest antioxidant among all monosubstituted Schiff bases excepted **SB4** (O—H). (See Figs. 2 and S2 or Tables S18 in Support information)

LCωPBE: **SB4(O) < SB8(O)=SB7(O) < SB2(O) < SB6(O) < SB3(O) < SB3(N) < SB2(N)=SB4(N)=SB5(N) < SB1(N) < SB6(N)=SB8(N)**

M05–2X: **SB4(O) < SB8(O) < SB3(O) < SB2(O) < SB7(O) < SB6(O)= SB5(N)=SB8(N) < SB2(N)= SB4(N)=SB6(N)=SB7(N) < SB3(N)= SB1(N)**

Thus, it can be said that the isatin group did not suppress the antioxidant effect of the disubstituted Schiff bases products as suggested by the experimental results. These findings confirm that the electron-donating groups play the same role as they do with the monosubstituted Schiff bases.

4.5. Solvent effects on antioxidant activity

It is well known that the polarity of the surrounding media has a great influence on the free radical scavenging activity of phenolic compounds., [66] Polar solvent is expected to affect free radical scavenging activity of the compounds studied. In our previous study [55] we discovered that in ionizing solvents phenols react with radicals essentially via SPLET mechanism., [55] That are why in our calculations we have incorporated solvent effects within the framework of SMD approach. SMD implicit model was chosen for calculations in the solution phase due to its applicability to either charged or uncharged solute in any solvent or liquid medium., [67] Water is polar solvent with the tendency to involve hydrogen-bonding interactions, while Benzene is non-polar solvent with small or zero dipole moment and zero hydrogen bond donating ability. Reaction enthalpies in benzene and water are summarized in Table S16 in Support Information and Figs. 2–4, 6, 7 above and in S2, S4-S7. All reactions of Schiff bases are endothermic in two solvents in three mechanisms (HAT, SETPT and SET-PT).

4.5.1. HAT reaction enthalpies in polar and non –polar solvents

Compared the O–H (N—H) BDEs related to the HAT mechanism (Figs. 2, S2 and Table S18 in Support Information), BDE values slightly change in solvents because in the HAT process there is no charged species stabilized by polar solvents or destabilized by non-polar ones. In general, bond dissociation enthalpies are not considerably affected by the environment [68,69] as it can be also seen from the BDE values in Figs. 2 and S2.

Again similarly to the gas phase medium, the BDE values calculated at LC-ωPBE level of theory in two solvents are generally the lowest compared to M05–2X values (except for N—H bond for disubstituted Schiff bases (**SB6-SB8**). (See Figs. 1, 2 or Table S18 in Support Information).

Differences between LC-ωPBE and M05–2X values do not exceed 5 and 6 kcal/mol in benzene and water solvents respectively. (See Table S18 in Support Information).

Firstly, the O—H(N—H) bond dissociation enthalpies (BDEs) in non-polar solvent (Benzene) grow in the same order shown in gas phase with the two functionals for disubstituted Schiff base, while the order is slowly changed between the two Schiff bases **SB2**(O—H) and **SB3** (O—H) for the monosubstituted Schiff bases. (See Figs. 2 and S2 or Table S18 in Support Information): Again, in non-polar solvent (Benzene) the BDE reaction mechanism indicates that an abstraction of the H atom in O—H bond results in lower BDE value than the abstraction of the H atom N—H bond. The two Schiff bases **SB4** (O—H) and **SB8** (O—H) have the highest antioxidant activity among the monosubstituted and disubstituted Schiff bases respectively.

Secondly, in polar solvent (water), the results also show that the lowest BDE is involved in the O—H bond compared N—H bond. The highest H-donation ability of the O—H bonds is observed for **SB4** (O—H) and **SB8** (O—H) for the two classes of monosubstituted and disubstituted Schiff bases molecules, respectively.

However, we notice that the values of O—H or (N—H) bond dissociation enthalpies (BDEs) in solvents (benzene and water) are very close to the BDEs gas values (Figs. 2 and S2 or Table S18 in Support Information).

4.5.2. SPLET reaction enthalpies in polar and non-polar solvents

Contrary to the BDEs case, and as this mechanism involves charged species, the solvent has a large impact on the reaction enthalpies in the SPLET case [70–72] (See Figs. 3, S4 or Table S18 in Support Information). The PAs values calculated at M05–2X level of theory are lower than LC-ωPBE values (See Table S18).

Differences between LC-ωPBE and M05–2X values do not exceed 6 kcal/mol in benzene, and 5 kcal/mol in water solvents respectively. The PA values have been decreased in the two solvents. However, this reduction is extremely large in polar one (water). Proton affinities in non-polar solvent (benzene) are lower than the corresponding gas-phase PAs by 222–234 kcal/mol, the average shift is between 228 and 229 kcal/mol (with the two range separated and hybrid functionals). In polar solvent (water), a very large decrease in PA (297 kcal/ mol) can be observed with LC-ωPBE functional. In general: PAs (water) < PAs (benzene) < PAs (gas). Thus, polar solvent can speed up the rate determining step of SPLET and make the deprotonation easier than the non-polar solvent.

We can see that, non-polar solvent-phase (benzene) PAs follow in general the same trend as the gas-phase ones. In polar solvent (water) PAs do not follow identical trend as the gas-phase ones.

Electron transfer enthalpies (ETE) in the solution-phase are higher than corresponding gas-phase values using two approaches of calculations. (See Fig. 4 and Fig. S5 or Table S18 in Support Information). As shown in gas phase, the ETEs values calculated at M05–2X level of theory are generally higher than LC-ωPBE values (Excepted for **SB7** (O—H) in benzene and for **SB2** (O—H), **SB5** (N—H) in water) (See Fig. 4, Fig. S5 or Table S17).

In non-polar solvent (benzene), this increase cannot be considered as

uniform with an average value amounting 16.3 and 18.3 kcal/mol with M05–2X and LC-ωPBE functionals, respectively.

For the two functionals, the ETEs in polar solvent (water) are higher than gas-phase values by 13–20 kcal/mol (M05–2X) and 13–25 kcal/mol (LC-ωPBE). The average shift cannot be also considered as uniform with an average value amounting 15.1 and 17.4 kcal/mol with M05–2X and LC-ωPBE functionals, respectively.

A linear correlation between the ETE descriptor calculated using the M05–2X and LC-ωPBE functionals is observed in both non-polar (benzene) and polar (water) solvents. Furthermore, the HOMO energy of the anions supports that the transferred electron originates from the HOMO, as expected.

However this correlation is less apparent in polar media for the monosubstituted class of Schiff bases (**BS1-BS5**) and this could be related to the anion solvation contribution. (See Figure S6).

4.5.3. SET-PT reaction enthalpies in polar and non-polar solvents

Calculated IPs and PDEs illustrating the solvent effect on the SET-PT mechanism are presented in Figs. 6, 7 above and S7, S8 in support information (See also Tables S18 in Support Information). The IP values are smaller in the two solvents (benzene and water) with respect to the gas phase. The reduction is quite large in polar solvent (water). It is due to the stabilization of charged systems created in the first step of the SET-PT mechanism by polar solvents. Additionally, the delocalization of the spin densities is larger in the polar media (discussed above in spin densities section). Unlike the gas phase, the IPs values calculated at M05–2X level of theory are not almost lower than the LC-ωPBE values (See Fig. 6 and Fig. S6 or Table S18). In benzene the decrease IP values is in the 18 to 32 and 23 to 25 kcal/mol with both LC-ωPBE and M05–2X functionals, respectively. In water the decrease is larger, in average of 65.7 kcal/mol with the two hybrid and range separated functionals (M05–2X and LC-ωPBE).

The second important parameter of the SET-PT route is the PDE. Dramatically reduced PDEs values are observed in polar and non-polar solvents. This reduction in PDEs values is due to the two charged species (H^+ and $\mathbf{SB}^{\bullet+}$) which can be stabilized by polar solvents. PDEs in benzene are lower by the average of 187.7 and 186.2 kcal/mol with M05–2X and LC-ωPBE respectively, than the corresponding gas-phase values. In water, the average is of 206.5 and 181.2 kcal/mol with M05–2X and LC-ωPBE, respectively, than the corresponding gas-phase values.

In general PDEs (water) < PDEs (benzene) < PDEs (gas) at M05–2X level of theory (See Fig. 7 and Fig. S8). But at LC-ωPBE level of theory this order is slightly distorted with the PDEs (water) not always smaller than that of PDEs (benzene) (See Fig. 7 and Fig. S8)

By analyzing three reactions mechanisms HAT, SPLET and SET-PT in solvents, we can see that the trends may change in solvents. From comparison of the calculated enthalpies in non-polar media (benzene) it can be noticed that HAT mechanism is the most thermodynamically preferred.

Again, in non-polar solvent, if we order all BDEs values of Schiff bases (monosubstituted and disubstituted, we find the same result found in gas phase (see the order below)

LCωPBE:*SB4(O)=SB8(O)<SB7(O)<SB2(O)=SB3(O)<SB6(O) < SB3 (N) < SB2(N)=SB4(N)=SB5(N) < SB1(N) < SB7(N)=SB8(N) < SB6 (N)*

M05–2X: *SB4(O)=SB8(O) < SB3(O) < SB2(O)=SB7(O) < SB5(N) < SB8(N) < SB1(N)= SB2(N) = SB3(N)= SB4(N)= SB6(N)= SB6(O)= SB7(N)*

We found that the two disubstituted Schiff bases SB7(O—H) and **SB8** (O—H) show the highest antioxidant activity among the majority of monosubstituted Schiff bases (**SB**1,SB2,SB3 and **SB5**) (result proved by the two functionals LC-ωPBEand M05–2x). (See Figs. 2 and S2 or Tables S18 in Support information)

It is clear that polar solvents dramatically influence PDE and PAs: this discloses that the HAT process can be more probable in benzene solution (non-polar solvent in general), where IPs and PAs are still higher than BDEs for both O—H and N—H bonds.

According to the comparison of the calculated enthalpies in polar media (water) that supports ionization it can be noticed that SPLET mechanism is the most thermodynamically preferred one. Polar solvent (water) induces significant changes in enthalpies of charged species, which dominantly affects SET-PT and SPLET energetics. In polar solvents (water), very large decrease in PAs are found and they are considerably lower than for BDEs

5. Concluding remarks

In this work, we carried out detailed first-principles DFT calculations on the frontier molecular orbitals, spin densities, and various DFT-based global chemical reactivity descriptors of interest for eight Schiff base (**SB**) compounds: five monosubstituted Schiff bases (**SB1–SB5**) and three disubstituted Schiff bases (**SB6–SB8**). The theoretical predictions regarding the calculated HOMO-LUMO energy gap suggest that the reactivity of the monosubstituted Schiff bases (**SB1** to **SB5**) is superior to that of the disubstituted Schiff bases (**SB6** to **SB8**).

When comparing the computed global reactivity descriptors in the gas phase, as well as in polar and non-polar solvents, it is found that the Schiff bases **SB5** and **SB8** are the most suitable for the charge-transfer mechanism in the monosubstituted and disubstituted Schiff base categories, respectively. Based on these results, three main antioxidant mechanisms HAT, SET-PT, and SPLET were considered to analyze the antioxidative capacity of the Schiff base compounds in the gas, benzene, and water phases.

In gas phase, the antioxidant properties of these Schiff bases are governed by the hydrogen atom transfer (HAT) mechanism. The BDE reaction mechanism also indicates that abstraction of the H atom from the O—H bond results in a lower BDE value than the abstraction from the N—H bond. According to the two functionals, M05–2X and LC-ωPBE, we found that the compound **SB4** (O—H) exhibits the highest antioxidant activity among the monosubstituted Schiff bases. This result is in line with the experimental findings. On the other hand, **SB8** (O—H), shows the highest antioxidant activity among the disubstituted compounds, which apparently contradicts the experimental results.

When we order all the Schiff bases (both monosubstituted and disubstituted), we find that the two disubstituted Schiff bases, **SB7** (O—H) and **SB8** (O—H), exhibit higher antioxidant activity than the majority of the monosubstituted Schiff bases (**SB2** and **SB3**). Therefore, we can conclude that the isatin group does not suppress the antioxidant effect of disubstituted Schiff bases, which is inconsistent with the conclusion raised by experimentalists. The same results are observed in a non-polar solvent (benzene). This raises the point that because radical reactions are often subject to kinetic barriers, transition states calculations driving the kinetic process may support an influence of the kinetics, responsible of a different antioxidant efficiency. Such calculations are in progress. On the other hand, some check of the experimental results may also be necessary to fully establish an efficiency scale among the Schiff bases as antioxidant molecules.

Additionally, the dipole moments of all the investigated compounds show their highly polarized nature. As a result, the mechanism involved in the antioxidant properties of these Schiff bases in a polar solvent (water) is Sequential Proton-Loss Electron-Transfer (SPLET). Thus, these molecules exhibit the best antioxidant activity in polar solvents.

CRediT authorship contribution statement

Habiba Boudiaf: Methodology, Investigation, Data curation, Conceptualization. **Nadjia Latelli:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Roumaissa Khelifi:** Data curation. **Salima Hamadouche:** Data

curation. **Lynda Merzoud:** Methodology, Data curation, Conceptualization. **Christophe Morell:** Data curation. **Henry Chermette:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.chphi.2025.100904.

Data availability

No data was used for the research described in the article.

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