

# Investigation of the antioxidant and radical scavenging activities of some phenolic Schiff bases with different free radicals

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**Abstract** The antioxidant properties of some phenolic Schiff bases in the presence of different reactive particles such as  $\cdot\text{OH}$ ,  $\cdot\text{OOH}$ ,  $(\text{CH}_2=\text{CH}-\text{O}-\text{O}\cdot)$ , and  $\cdot\text{O}_2$  were investigated. The thermodynamic values,  $\Delta H_{\text{BDE}}$ ,  $\Delta H_{\text{IB}}$  and  $\Delta H_{\text{PA}}$ , were used for this purpose. Three possible mechanisms for transfer of hydrogen atom, concerted proton–electron transfer (CPET), single electron transfer followed by proton transfer (SET-PT), and sequential proton loss electron transfer (SPLET) were considered. These mechanisms were tested in solvents of different polarity. On the basis of the obtained results it was shown that SET-PT antioxidant mechanism can be the dominant mechanism when Schiff bases react with radical cation, while SPLET and CPET are competitive mechanisms for radical scavenging of hydroxy radical in all solvents under investigation. Examined Schiff bases react with the peroxy radicals via SPLET mechanism in polar and non-polar solvents. The superoxide radical anion reacts with these Schiff bases very slowly.

**Keywords** Antioxidant mechanisms · Antioxidant properties · Density functional theory · Phenolic Schiff bases

## Introduction

Schiff bases, as azomethines, are an important class of organic compounds [1–3]. This class of compounds has found application in the broad field of organic chemistry [4–6]. The azomethine group plays an important role in nature, since it is present in various natural and synthetic products. They are responsible for a broad range of biological activities, [7–9] including antibacterial, antifungal, antimalarial, anti-inflammatory, antiviral, anti-proliferative, and antipyretic properties [3, 10]. If these compounds contain phenolic OH group (one or more), they can show radical scavenging activity [11].

Scavenging activity of phenolic compounds, Schiff bases (SBO-H) in this case, is based on their ability to transfer H atom (from OH group) to other free radicals ( $\text{RO}\cdot$ ). Thus the obtained phenolic radicals should be more stable and less reactive than the previous ones.

There are at least three mechanisms [12–14] for this transfer of hydrogen atom: concerted proton–electron transfer (CPET), 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 [15]. 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. Determination of the reaction enthalpies plays a very important role in understanding of these processes. Namely, if a reaction is exothermic, it means that the newly formed radical or intermediate is more stable in

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comparison to the starting radical, and implies that the corresponding reaction path may be favorable. In the case that a reaction is endothermic, one may suppose that this reaction path is not favored [16]. Certainly, to fully understand antioxidant mechanisms it is desirable to examine reaction kinetics too. In the present work the reaction enthalpies were calculated in two ways: in the absence (Electronic supplementary material), and in the presence of a harmful free radical  $RO^{\bullet}$ . Since the latter results describe antioxidant processes more realistically, they are presented in the main text.

In the CPET mechanism:

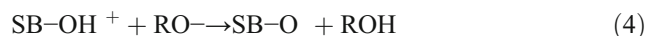
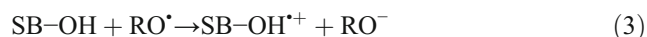


$\Delta H_{BDE}$  can be calculated as follows:

$$\Delta H_{BDE} = H(SBO^{\bullet}) + H(ROH) - H(SBO-H) - H(RO^{\bullet}) \quad (2)$$

where  $H(SBO^{\bullet})$ ,  $H(ROH)$ ,  $H(SBO-H)$ , and  $H(RO^{\bullet})$  represent the enthalpies of the corresponding radicals and molecules.

The SET-PT mechanism takes place in two steps: electron transfer is the first step of this reaction (Eq. (3)), and deprotonation of the generated radical cation (Eq. (4)) is the second step:



This mechanism is characterized with  $\Delta H_{IP}$  and  $\Delta H_{PDE}$ :

$$\Delta H_{IP} = H(SB-OH^{\bullet+}) + H(RO^{-}) - H(SB-OH) - H(RO^{\bullet}) \quad (5)$$

$$\Delta H_{PDE} = H(SB-O^{-}) + H(ROH) - H(SB-OH^{\bullet+}) - H(RO^{-}) \quad (6)$$

where  $H(SB-OH^{\bullet+})$  and  $H(RO^{-})$  stand for the enthalpies of the corresponding species.

As presented in Electronic supplementary material the first step of the SPLET mechanism is energetically notably unfavorable (as it involves charge separation), which is manifested through very large PA values (Table S1). It is reasonable to expect that deprotonation of the phenolic Schiff bases, with the  $pK_a$  values of around 5 [17], will be facilitated in a basic medium, for example at physiological pH of 7.4. For this reason we investigate this mechanism under an assumption that it takes place in a basic environment, implying that some  $SB-O^{-}$  anions are already present in the reaction mixture. Thus, the SPLET mechanism can be presented as follows:



The first step is electron transfer from  $SB-O^{-}$  to an undesired radical where the  $SB-O^{\bullet}$  radical is built, and the second step is reformation of the  $SB-O^{-}$  anion. These processes are described with the  $\Delta H_{ETE}$  and  $\Delta H_{PA}$  values, which can be calculated as follows:

$$\Delta H_{ETE} = H(SB-O^{\bullet}) + H(RO^{-}) - H(SB-O^{-}) - H(RO^{\bullet}) \quad (9)$$

$$\Delta H_{PA} = H(SB-O^{-}) + H(ROH) - H(SB-OH) - H(RO^{-}) \quad (10)$$

The properties of the scavenged radicals play a very important role in the reactions with various antioxidants [18, 19]. Investigation of the effects of various radicals (hydroperoxyl radical ( $^{\bullet}OOH$ ), superoxide radical anion ( $^{\bullet}O_2^{-}$ ), hydroxyl radical ( $^{\bullet}OH$ ), and vinyl peroxy radical ( $CH_2=CH-O-O^{\bullet}$ ) on antioxidant activity of the investigated Schiff bases (1–11), as well as the influence of solvents of different polarity (water, ethanol, and benzene) will significantly contribute to the understanding of the above mentioned processes. These four radicals were chosen because they play an important role in food chemistry and environmental chemistry.

## Computational methods

The equilibrium geometries of all Schiff bases and their radicals, anions, and radical cations were fully optimized by the hybrid density functional method (M05-2X) [20] and 6-311++G(d,p) basis set, [21] as implemented in the Gaussian 09 package [22]. This functional developed by the Truhlar group yields satisfactory performance for thermochemistry and kinetics calculations, of organic, organometallic, and biological molecules. Also, this functional is useful for describing noncovalent interactions in molecules. It is worth mentioning that M05-2X functional nicely reproduces nonplanarity between rings B and C in morin and quercetin [23, 24].

The influence of water ( $\epsilon=78.35$ ), ethanol ( $\epsilon=24.85$ ), and benzene ( $\epsilon=2.27$ ) as solvents was calculated by a solute electron density (SMD) solvation model [25]. This model is based on the quantum mechanical charge density of a solute molecule interacting with a continuum description of the solvent. In this model name “D” stands for “density” and means that full solute electron density is used without defining the partial atomic charges. It should be mentioned that all species under investigation were fully optimized in all solvents used. The nature of the stationary points was determined by the vibrational frequencies obtained from diagonalization of the corresponding Hessian matrices. For this purpose the number of imaginary frequencies was analyzed—0 for minimum.

## Experimental

### Materials and methods

The compounds salicylaldehyde, vanillin, aniline, 4-fluoroaniline, 2-hydroxyaniline, 4-hydroxyaniline, nordihydroguaeretic acid (NDGA), and 2,2-diphenyl-1-picrylhydrazyl (DPPH) were obtained from Aldrich Chemical Co. All common chemicals were of reagent grade. The NMR spectra were run in DMSO on a Varian Gemini 200 MHz spectrometer. Melting points were determined on a Mel-Temp capillary melting points apparatus, model 1001. Elemental microanalyse for carbon, hydrogen, and nitrogen were performed at the Faculty of Chemistry, University of Belgrade.

### Synthesis of Schiff bases

The procedure for synthesis of the Schiff bases (1–5), as well as their corresponding spectral characterization are given in reference [11].

### DPPH free radical scavenging assay

The determination of the DPPH free radical scavenging activity of the examined compounds was performed according to methodology described in ref. [26]. The investigated Schiff bases (1–5) were reacted with the stable DPPH radical in ethanol solution. Briefly, 1 mL (0.1 mM) of DPPH solution in ethanol was mixed with an equal volume of the tested compound (20  $\mu$ L of compound solution in DMSO and 980  $\mu$ L of ethanol). The sample is left at room temperature for 30 and 60 min. After the period of incubation the absorbance was measured at 517 nm. Ethanol was used as the control solution. IC<sub>50</sub> values represent the concentration necessary to obtain 50 % of a maximum scavenging capacity. NDGA was used as an appropriate standard possessed 96 % activity at 0.1 mM.

## Results and discussion

The most stable conformers of the phenolic Schiff bases 1–11 [11, 27] are presented in Fig. S1. The conformers of the compounds 1–5 were described in our previous paper [11]. Antioxidant activity of these compounds was determined on the basis of the IC<sub>50</sub> results which are presented in Fig. 1. The IC<sub>50</sub> values for the compounds 1–5 were obtained with the DPPH test, while the corresponding data for the compounds 6–11 were collected from literature. It was found that compounds 2, 3, and 9 are very good radical scavengers, 6–8, 10, and 11 are slightly less active, whereas Schiff base 1 is poor radical scavenger [11]. The reactions of 1–11 with some free

radicals of importance in food and environmental chemistry: hydroxyl radical ( $\cdot$ OH), hydroperoxyl radical ( $\cdot$ OOH), superoxide radical anion ( $\cdot$ O<sub>2</sub>), and vinyl peroxy radical (CH<sub>2</sub>=CH–O–O $\cdot$ ) were investigated. The calculated reaction enthalpies for all three antioxidant mechanisms (CPET, SET-PT, and SPLET) of all Schiff bases are presented in Tables 1, 2, 3, 4, and 5. The preferred mechanism of radical scavenging activity of Schiff bases with the investigated free radicals can be estimated on the basis of  $\Delta H_{\text{BDE}}$ ,  $\Delta H_{\text{IP}}$ ,  $\Delta H_{\text{PDE}}$ ,  $\Delta H_{\text{PA}}$ , and  $\Delta H_{\text{ETE}}$  values. The lowest of these thermodynamic values designates which mechanism may be dominant. An inspection of Tables 1, 2, 3, 4, and 5 reveals that the  $\Delta H_{\text{ETE}}$  values are often positive (corresponding reactions are endothermic), which would indicate that, in spite of the negative  $\Delta H_{\text{PA}}$  values, the SPLET mechanism can be discarded. However, it should be emphasized that small positive  $\Delta H$  values (<40 kJ mol<sup>-1</sup>) do not necessarily mean that the corresponding free radical scavenging reactions should be neglected. These endothermic processes may represent significant reaction pathways if they do not require high activation energies [28].

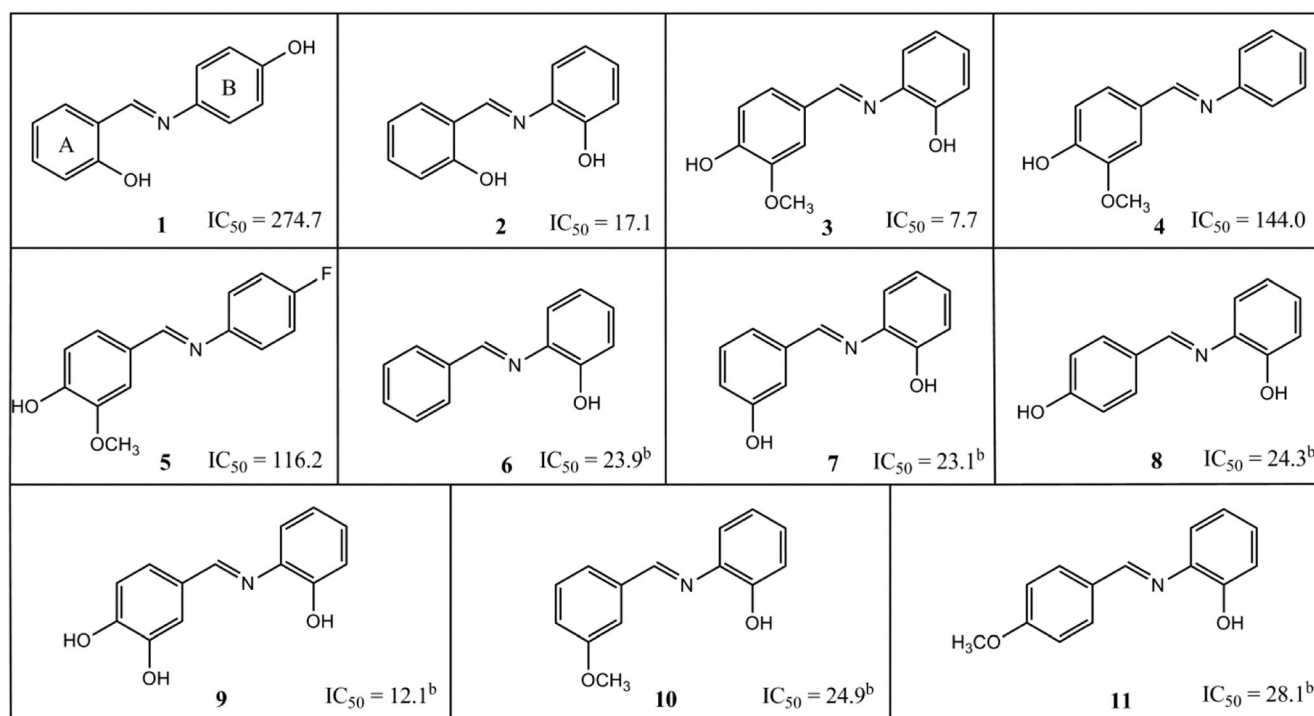
### Antioxidant mechanisms of Schiff bases with hydroxyl radical

In Table 1, the thermodynamic data regarding the reactions of 1–11 with hydroxyl radical in all solvents are collected. All reactions of Schiff bases with  $\cdot$ OH are exothermic in all solvents when CPET and SPLET are operative mechanisms. It should be noted that  $\Delta H_{\text{BDE}}$  and  $\Delta H_{\text{IP}}$  are almost constant in both polar solvents. On the other hand,  $\Delta H_{\text{BDE}}$  slightly increases, while  $\Delta H_{\text{PA}}$  and  $\Delta H_{\text{IP}}$  significantly decrease in non-polar solvent benzene (Table 1).

On the basis of the values of enthalpy of reactions of Schiff bases with  $\cdot$ OH (Table 1) it is clear that SPLET and CPET are competitive. Generally speaking, the lowest values of reaction enthalpies are for the *p*-OH group in ring A of 9, 3–5, and 8. In the absence of this hydroxyl group, *m*-OH in ring B is more reactive in comparison to other hydroxyl groups.

### Antioxidant mechanisms of Schiff bases with hydroperoxyl and vinyl peroxy radicals

The thermodynamic data for all reactions of Schiff bases with hydroperoxyl and vinyl peroxy radicals in different solvents are collected in Tables 2 and 3. The latter radical is less reactive, and may mimic lipid peroxy radicals LOO $\cdot$  which are abundantly formed in biological systems. Obtained results are different in comparison to hydroxy radical, since both peroxy radicals are less reactive species. Analysis of data from Tables 2 to 3 indicates that, in general, the values of thermodynamic parameters are slightly higher for vinyl peroxy radical, which is in agreement with its lower reactivity in comparison to the peroxy radicals. The values for a certain



**Fig. 1** Structure of the investigated Schiff bases and their  $IC_{50}$  values ( $\mu M$ ). The values labeled with <sup>b</sup> are taken from ref. [27]

**Table 1** Calculated reaction enthalpies ( $kJ mol^{-1}$ ) for the reactions of Schiff bases with hydroxyl radical

M05-2X/6-311+G(d,p)

Schiff base*	Water					Ethanol					Benzene				
	CPET		SET-PT		SPLET	CPET		SET-PT		SPLET	CPET		SET-PT		SPLET
	$\Delta H_{BDE}$	$\Delta H_{IP}$	$\Delta H_{PDE}$	$\Delta H_{PA}$	$\Delta H_{ETE}$	$\Delta H_{BDE}$	$\Delta H_{IP}$	$\Delta H_{PDE}$	$\Delta H_{PA}$	$\Delta H_{ETE}$	$\Delta H_{BDE}$	$\Delta H_{IP}$	$\Delta H_{PDE}$	$\Delta H_{PA}$	$\Delta H_{ETE}$
1-A	-88.1	91.9	-179.9	-59.5	-28.6	-87.1	105.7	-192.8	-61.9	-25.2	-75.6	304.7	-380.3	-103.6	28.0
1-B	-143.4		-235.3	-92.2	-51.2	-143.0		-248.7	-95.7	-47.3	-138.3		-442.9	-152.4	14.2
2-A	-105.3	101.9	-207.2	-96.8	-8.5	-98.0	119.3	-217.3	-78.1	-19.9	-90.3	320.0	-410.2	-131.9	41.6
2-B	-141.0		-242.9	-81.5	-59.5	-133.5		-252.8	-92.9	-40.6	-123.8		-443.8	-139.5	15.6
3-A	-141.9	83.4	-225.3	-101.3	-40.6	-141.1	96.7	-237.8	-104.7	-36.3	-131.2	289.8	-421.0	-159.7	28.5
3-B	-130.5		-214.0	-71.6	-59.0	-129.7		-226.5	-73.8	-55.9	-120.2		-410.0	-113.2	-7.0
4-A	-144.0	92.1	-236.0	-95.5	-48.4	-143.2	105.5	-248.8	-98.5	-44.7	-134.0	299.0	-432.9	-147.1	13.2
5-A	-143.8	91.3	-235.1	-96.4	-47.4	-143.0	105.0	-248.0	-99.6	-43.5	-133.3	301.5	-434.8	-151.0	17.7
6-B	-129.4	96.7	-226.1	-73.5	-55.9	-128.6	110.3	-238.9	-75.6	-53.0	-118.1	308.4	-426.5	-113.2	-4.9
7-A	-122.7	98.7	-221.5	-91.0	-31.8	-122.3	112.3	-235	-94.2	-28.1	-117.4	309.2	-426.6	-145.8	28.3
7-B	-128.9		-227.6	-74.1	-54.8	-128.0		-240	-76.0	-51.9	-117.2		-426.4	-111.7	-5.5
8-A	-133.2	85.7	-218.9	-109.1	-24.0	-132.9	99.1	-232.0	-113.2	-19.7	-129.4	293.5	-422.9	-175.8	46.4
8-B	-129.9		-215.6	-71.3	-58.6	-129.1		-228.2	-73.2	-55.8	-118.9		-412.5	-109.0	-9.9
9-A3	-148.5	87.8	-236.3	-116.4	-32.1	-148.4	101.2	-249.6	-120.5	-27.9	-147.6	295.2	-442.8	-182.9	35.3
9-A4	-158.2		-246.0	-129.5	-28.7	-158.2		-259.3	-134.0	-24.2	-158.1		-453.3	-202.0	43.9
9-B	-129.4		-217.2	-71.3	-58.1	-128.4		-229.6	-73.1	-55.3	-117.2		-412.5	-107.4	-9.9
10-B	-129.3	97.6	-226.9	-73.9	-55.4	-128.3	111.1	-239.4	-75.7	-52.6	-117.4	306.4	-423.9	-110.5	-7.0
11-B	-130.2	83.8	-214.0	-70.8	-59.4	-129.3	97.0	-226.4	-72.7	-56.7	-118.6	288.9	-407.6	-107.9	-10.8

\* The numbers denote the compounds in Figs. 1 and S1, whereas A and B stand for the A and B rings. A3 and A4 denote the positions 3 and 4 on the A ring. The same holds for Tables 2, 3, and 4

**Table 2** Calculated reaction enthalpies (kJ mol<sup>-1</sup>) for the reactions of Schiff bases with peroxy radical

M05-2X/6-311+G(d,p)

Schiff base	Water					Ethanol					Benzene				
	CPET	SET-PT		SPLET		CPET	SET-PT		SPLET		CPET	SET-PT		SPLET	
	$\Delta H_{\text{BDE}}$	$\Delta H_{\text{IP}}$	$\Delta H_{\text{PDE}}$	$\Delta H_{\text{PA}}$	$\Delta H_{\text{ETE}}$	$\Delta H_{\text{BDE}}$	$\Delta H_{\text{IP}}$	$\Delta H_{\text{PDE}}$	$\Delta H_{\text{PA}}$	$\Delta H_{\text{ETE}}$	$\Delta H_{\text{BDE}}$	$\Delta H_{\text{IP}}$	$\Delta H_{\text{PDE}}$	$\Delta H_{\text{PA}}$	$\Delta H_{\text{ETE}}$
1-A	47.9	184.5	-137.0	-16.5	64.4	48.8	198.0	-149.2	-18.3	67.1	58.8	385.7	-326.9	-50.2	109.0
1-B	-7.4		-192.3	-49.2	41.8	-7.1		-205.1	-52.1	45.0	-3.8		-389.5	-99.0	95.2
2-A	30.7	194.9	-164.3	-53.9	84.5	37.9	211.6	-173.6	-34.4	72.4	44.2	401.0	-356.8	-78.5	122.6
2-B	-5.0		-199.9	-38.5	33.5	2.4		-209.2	-49.2	51.7	10.6		-390.4	-86.1	96.7
3-A	-5.9	176.5	-182.3	-58.3	52.5	-5.1	189.0	-194.2	-61.1	56.0	3.2	370.8	-367.6	-106.3	109.5
3-B	5.5		-171.0	-28.6	34.1	6.2		-182.8	-30.2	36.4	14.2		-356.6	-59.8	74.0
4-A	-8.0	185.1	-193.1	-52.6	44.6	-7.3	197.8	-205.1	-54.9	47.6	0.5	380.0	-379.5	-93.8	94.2
5-A	-7.8	184.4	-192.2	-53.4	45.6	-7.1	197.3	-204.4	-55.9	48.8	1.1	382.5	-381.4	-97.6	98.8
6-B	6.6	189.7	-183.1	-30.6	37.1	7.4	202.6	-195.3	-31.9	39.3	16.3	389.5	-373.1	-59.8	76.2
7-A	13.3	191.8	-178.5	-48.0	61.3	13.6	204.6	-191.0	-50.6	64.2	17.0	390.0	-373.2	-92.4	109.4
7-B	7.1		-184.6	-31.1	38.3	8.0		-196.6	-32.4	40.4	17.2		-373.0	-58.3	75.5
8-A	2.8	178.8	-176.0	-66.2	69.0	3.0	191.4	-188.4	-69.6	72.6	5.0	374.6	-369.5	-122.4	127.5
8-B	6.1		-172.7	-28.3	34.4	6.9		-184.5	-29.6	36.5	15.5		-359.1	-55.7	71.1
9-A3	-12.5	180.9	-193.4	-73.4	60.9	-12.5	193.4	-206.0	-76.9	64.3	-13.2	376.2	-389.4	-129.5	116.4
9-A4	-22.2		-203.0	-86.5	64.3	-22.2		-215.7	-90.4	68.1	-23.7		-400.0	-148.6	124.9
9-B	6.6		-174.2	-28.3	35.0	7.5		-185.8	-29.4	36.9	17.2		-359.1	-54.0	71.1
10-B	6.7	190.7	-183.9	-30.9	37.7	7.6	203.4	-195.8	-32.1	39.7	17.0	387.5	-370.5	-57.1	74.0
11-B	5.8	176.9	-171.1	-27.8	33.6	6.6	189.3	-182.7	-29.0	35.6	15.8	370.0	-354.2	-54.5	70.3

thermodynamic quantity are mutually very similar in the two polar solvents ( $\Delta H_{\text{BDE}}$  and  $\Delta H_{\text{IP}}$  values are almost identical for both radicals in water and ethanol). One may assume that these two radicals obey the SPLET mechanism in all three solvents, where the reactions of heterolytic cleavage of the O-H bond (PA values) are particularly exothermic in benzene. The order of reactivity of the investigated compounds is the same as in the case of hydroxyl radical (Table 2).

#### Antioxidant mechanisms of Schiff bases with superoxide radical anion

In the case of the reactions of Schiff bases with superoxide radical anion  $\Delta H_{\text{BDE}}$  has large positive values in all solvents. Furthermore, these values are almost identical in all used solvents. All these facts show, in accordance with our expectations, that CPET is not a plausible mechanism for the reactions of Schiff bases and superoxide radical anion in polar and non-polar solvents. In polar solvents the reaction enthalpies for the other two mechanisms are endothermic, except for  $\Delta H_{\text{PA}}$  value for compound **9** (Table 4). The  $\Delta H_{\text{PA}}$  values significantly decrease in nonpolar solvent, except for **10** and **11**. One can suppose that all compounds, except for **10** and **11**, can undergo the SPLET mechanisms with the superoxide radical anion

in suitable solvents. However, we cannot claim, just on the basis of endothermicity of the reactions, that other Schiff bases will not obey the SPLET mechanism. Such assumption needs to be confirmed or negated with the activation energy values.

Our results show that the superoxide radical anion is not particularly reactive. This finding is in agreement with the well-known fact that the superoxide radical anion is in equilibrium with its protonated form, the hydroperoxyl radical, whose  $\text{p}K_{\text{a}}$  is 4.9 [29–31].



Thus, at physiological pH most of the  $\text{O}_2^{\cdot-}/\text{HO}_2^{\cdot}$  radical pair exists in the dissociated form, which is less reactive than its conjugate acid. In addition,  $\text{O}_2^{\cdot-}$  can react with  $\text{H}_2\text{O}_2$  to generate singlet oxygen and the hydroxyl radical, which are much more powerful oxidants.

Taking into account the  $\Delta H_{\text{IP}}$  values (Tables 1, 2, 3, and 4) one can suppose that SET-PT is not the operative scavenging mechanism with the radicals under investigation [32, 33]. Namely,  $\Delta H_{\text{IP}}$  values increase with the decreasing dielectric constant of used solvents. Apparently, the first step of the SET-PT mechanism, formation of the radical cation in the presence of free radicals (Eqs 3 and 5), is too endothermic. It is known that radical cations, which are odd-electron positive



**Table 3** Calculated reaction enthalpies (kJ mol<sup>-1</sup>) for the reactions of Schiff bases with vinylperoxy radical

Schiff base	Water					Ethanol					Benzene				
	CPET		SET-PT		SPLET	CPET		SET-PT		SPLET	CPET		SET-PT		SPLET
	$\Delta H_{\text{BDE}}$	$\Delta H_{\text{IP}}$	$\Delta H_{\text{PDE}}$	$\Delta H_{\text{PA}}$	$\Delta H_{\text{ETE}}$	$\Delta H_{\text{BDE}}$	$\Delta H_{\text{IP}}$	$\Delta H_{\text{PDE}}$	$\Delta H_{\text{PA}}$	$\Delta H_{\text{ETE}}$	$\Delta H_{\text{BDE}}$	$\Delta H_{\text{IP}}$	$\Delta H_{\text{PDE}}$	$\Delta H_{\text{PA}}$	$\Delta H_{\text{ETE}}$
1-A	51.8	158.4	-106.6	13.9	37.9	52.7	170.5	-117.7	13.1	39.6	63.1	342.1	-279.0	-2.3	65.4
1-B	-3.5		-161.9	-18.8	15.3	-3.1		-173.6	-20.7	17.5	0.5		-341.6	-51.1	51.6
2-A	34.6	168.4	-133.9	-23.5	58.0	41.9	184.1	-142.2	-3.0	44.9	48.5	357.4	-308.9	-30.5	79.0
2-B	-1.1		-169.5	-8.1	7.0	6.4		-177.7	-17.8	24.2	14.9		-342.5	-38.1	53.1
3-A	-2.0	150.0	-151.9	-27.9	26.0	-1.2	161.5	-162.7	-29.6	28.5	7.6	327.2	-319.7	-58.3	65.9
3-B	9.4		-140.6	1.8	7.6	10.1		-151.4	1.3	8.9	18.6		-308.7	-11.8	30.4
4-A	-4.1	158.6	-162.7	-22.2	18.1	-3.4	170.3	-173.7	-23.4	20.1	4.8	336.4	-331.6	-45.8	50.6
5-A	-3.9	157.9	-161.8	-23.0	19.1	-3.2	169.8	-172.9	-24.5	21.3	5.5	338.9	-333.5	-49.7	55.1
6-B	10.5	163.2	-152.8	-0.2	10.6	11.3	175.1	-163.8	-0.5	11.8	20.7	345.9	-325.2	-11.9	32.5
7-A	17.2	165.3	-148.1	-17.6	34.8	17.5	177.1	-159.5	-19.2	36.7	21.3	346.6	-325.3	-44.4	65.8
7-B	11.0		-154.2	-0.8	11.8	11.9		-165.2	-1.0	12.9	21.6		-325.0	-10.4	31.9
8-A	6.7	152.3	-145.6	-35.8	42.5	7.0	163.9	-156.9	-38.2	45.1	9.4	331.0	-321.6	-74.5	83.9
8-B	10.0		-142.3	2.1	7.9	10.8		-153.1	1.8	9.0	19.8		-311.1	-7.7	27.5
9-A3	-8.6	154.4	-163.0	-43.0	34.4	-8.6	165.9	-174.5	-45.4	36.8	-8.8	332.6	-341.5	-81.6	72.7
9-A4	-18.3		-172.6	-56.1	37.8	-18.3		-184.3	-58.9	40.6	-19.4		-352.0	-100.7	81.3
9-B	10.5		-143.8	2.1	8.5	11.4		-154.5	2.0	9.4	21.5		-311.1	-6.0	27.5
10-B	10.6	164.2	-153.5	-0.5	11.2	11.5	175.9	-164.4	-0.6	12.2	21.3	343.8	-322.5	-9.1	30.4
11-B	9.7	150.4	-140.7	2.6	7.1	10.5	161.8	-151.3	2.4	8.1	20.1	326.4	-306.2	-6.5	26.7

species, can be formed in different ways: by means of UV and visible light [34–38] and chemical oxidants [39–41], as well as in electrochemical processes [42–44] and metal-catalyzed oxidations [45–48]. In addition, radical cations can be obtained from electron-rich cyclopropanes, arylalkenes, and dienes using appropriate oxidizing agents [49]. It is clear that intermediate radical cations are formed under extreme conditions, and these processes cannot be expected to occur in vivo, but only in vitro. Once formed radical cations can react with Schiff bases:



For this reaction  $\Delta H_{\text{IP}}$  value can be calculated as follows:

$$\begin{aligned} \Delta H_{\text{IP}} = & H(\text{SB-OH}^+) \\ & + H(\text{ROOH}) - H(\text{SB-OH}) - H(\text{ROOH}^+) \quad (12) \end{aligned}$$

$\Delta H_{\text{IP}}$  values for formation of radical cations of investigated Schiff bases with hydroperoxyl and vinyl peroxy radical cations are presented in Table 5. All  $\Delta H_{\text{IP}}$  values are negative, which means that newly formed radical cations of Schiff bases are more stable than the starting radical cations. The second step of the SET-PT mechanism is deprotonation of the radical cation with different bases [50]. Since all  $\Delta H_{\text{PDE}}$  values

indicate that the second step of the SET-PT mechanism is exothermic (Tables 3 and 4), one can assume that, provided that radical cations of Schiff bases are obtained in the reaction (11), SET-PT can be the dominant scavenging mechanism.

### SAR and QSAR analysis

The structure activity relationship (SAR) examines the relationships between the structure of chemical compounds and their biological activity. A brief SAR study of the examined compounds can relate their chemical structure and antioxidant activity. On the basis of the measured  $\text{IC}_{50}$  values in Fig. 1 it is clear that the position of the OH groups, and to which aromatic ring they are bound, A or B, are of crucial importance to antioxidant capacity of the observed compounds. On the basis of the number and position of the OH groups the antioxidant Schiff bases can be divided into two groups.

The first group is without OH group in the *ortho* position on ring B (compounds 1, 4, and 5,  $\text{IC}_{50}$  between 116 and 275  $\mu\text{M}$ ). The compounds 4 and 5 do not have any OH group on ring B, and the structure of their ring A is the same. The difference between them is that there is F in the *para* position of ring B in 5, which reduces the value of  $\text{IC}_{50}$  because the inductive effect of fluorine is stronger than the resonance

**Table 4** Calculated reaction enthalpies (kJ mol<sup>-1</sup>) for the reactions of Schiff bases with superoxide radical anion

M05-2X/6-311+G(d,p)

Schiff base	Water					Ethanol					Benzene				
	CPET		SET-PT		SPLET	CPET		SET-PT		SPLET	CPET		SET-PT		SPLET
	$\Delta H_{\text{BDE}}$	$\Delta H_{\text{IP}}$	$\Delta H_{\text{PDE}}$	$\Delta H_{\text{PA}}$	$\Delta H_{\text{ETE}}$	$\Delta H_{\text{BDE}}$	$\Delta H_{\text{IP}}$	$\Delta H_{\text{PDE}}$	$\Delta H_{\text{PA}}$	$\Delta H_{\text{ETE}}$	$\Delta H_{\text{BDE}}$	$\Delta H_{\text{IP}}$	$\Delta H_{\text{PDE}}$	$\Delta H_{\text{PA}}$	$\Delta H_{\text{ETE}}$
1-A	133.7	410.4	-276.7	69.3	64.4	135.3	439.2	-303.9	68.2	67.1	154.3	855.3	-701.0	45.3	109.0
1-B	78.4		-332.0	36.6	41.8	79.4		-359.8	34.4	45.0	91.6		-763.7	-3.5	95.2
2-A	116.5	420.4	-303.9	32.0	84.5	124.4	452.8	-328.4	52.0	72.4	139.7	870.6	-730.9	17.0	122.6
2-B	80.8		-339.6	47.3	33.5	88.9		-363.9	37.2	51.7	106.1		-764.5	9.4	96.7
3-A	80.0	402.0	-322.0	27.5	52.2	81.4	430.3	-348.9	25.4	56.0	98.7	840.4	-741.7	-10.8	109.5
3-B	91.3		-310.7	57.2	34.1	92.7		-337.6	56.3	36.4	109.7		-730.7	35.7	74.0
4-A	77.9	410.6	-332.8	33.2	44.6	79.2	439.0	-359.9	31.6	47.6	95.9	849.6	-753.6	1.7	94.2
5-A	78.0	409.9	-331.9	32.4	45.6	79.4	438.5	-359.1	30.6	48.8	96.6	852.2	-755.5	-2.1	98.8
6-B	92.4	415.2	-322.8	55.3	37.1	93.8	443.8	-350.0	54.6	39.3	111.8	859.1	-747.2	35.7	76.2
7-A	99.1	417.3	-318.2	37.8	61.3	100.1	445.8	-345.7	35.9	64.2	112.5	859.8	-747.4	3.1	109.4
7-B	93.0		-324.3	54.7	38.3	94.4		-351.4	54.1	40.4	112.7		-747.1	37.2	75.5
8-A	88.6	404.3	-315.7	19.6	69.0	89.5	432.6	-343.1	16.9	72.6	100.5	844.2	-743.6	-26.9	127.5
8-B	91.9		-312.4	57.5	34.4	93.4		-339.3	56.9	36.5	111.0		-733.2	39.8	71.1
9-A3	73.3	406.4	-333.1	12.4	60.9	74.0	434.7	-360.7	9.6	64.3	82.3	845.9	-763.5	-34.0	116.4
9-A4	63.7		-342.7	-0.7	64.3	64.2		-370.4	-3.9	68.1	71.8		-774.1	-53.1	124.9
9-B	92.4		-313.9	57.5	35.0	94.0		-340.7	57.0	36.9	112.7		-733.2	41.5	71.1
10-B	92.6	416.2	-323.6	54.9	37.7	94.1	444.6	-350.5	54.4	39.7	112.5	857.1	-744.6	38.4	74.0
11-B	91.6	402.4	-310.8	58.0	33.6	93.1	430.5	-337.5	57.5	35.6	111.3	839.6	-728.3	41.0	70.3

effect. The IC<sub>50</sub> value of **1** higher than 200 μM suggests that this compound is biologically inactive [51], while the other two compounds are very modest antioxidants.

The second group comprises the compounds with the OH group in the *ortho* position on ring B (**2**, **3**, **6–11**, IC<sub>50</sub> between 7.7 and 28.1 μM). These compounds show good antioxidant activity, where the following order is observed: **3**>**9**>**2**>**6**≈**7**≈**8**≈**10**>**11**. The IC<sub>50</sub> values for **3** and **9** are slightly higher

than the corresponding values for flavones and flavonols. For example, the IC<sub>50</sub> value of **3** is 7.7, while the corresponding value for quercetin is 5.1 [51], which is consistent with the BDE values in water of 358 (Table S1) and 333 kJ mol<sup>-1</sup>, respectively [50]. In the most active Schiff bases **3** and **9**, the two sp<sup>3</sup> oxygen atoms are *ortho* to each other in ring A, which makes the compounds particularly active. This positive impact of both electron donating groups is in agreement with

**Table 5** Calculated reaction enthalpies (kJ mol<sup>-1</sup>) for the reactions of Schiff bases with radical cation

Schiff base	Water		Ethanol		Benzene	
	HOOH <sup>•+</sup>	CH <sub>2</sub> CHOOH <sup>•+</sup>	HOOH <sup>•+</sup>	CH <sub>2</sub> CHOOH <sup>•+</sup>	HOOH <sup>•+</sup>	CH <sub>2</sub> CHOOH <sup>•+</sup>
<b>1</b>	-161.0	-54.9	-164.6	-56.7	-216.8	-85.9
<b>2</b>	-151.0	-44.9	-151.0	-43.1	-201.5	-70.6
<b>3</b>	-169.5	-63.3	-173.6	-65.6	-231.7	-100.7
<b>4</b>	-160.8	-54.7	-164.8	-56.8	-222.5	-91.6
<b>5</b>	-161.6	-55.4	-165.4	-57.4	-220.0	-89.0
<b>6</b>	-156.2	-50.1	-160.0	-52.0	-213.1	-82.1
<b>7</b>	-154.2	-48.0	-158.0	-50.1	-212.3	-81.3
<b>8</b>	-167.2	-61.0	-171.2	-63.3	-227.9	-97.0
<b>9</b>	-165.1	-58.9	-169.2	-61.2	-226.3	-95.3
<b>10</b>	-155.3	-49.1	-159.2	-51.3	-215.1	-84.1
<b>11</b>	-169.1	-62.9	-173.3	-65.3	-232.6	-101.6

the literature data on the structure–antioxidant activity relationships of polyphenols with the catechol and guaiacol moieties. Similar behavior of **3** and **9** is not surprising, since the only difference between these two compounds is on the A ring, where in **3** this ring is guaiacol-like, and in **9** it is catechol-like. Small difference in the IC<sub>50</sub> values is in accordance with the antioxidant activity of other similar pairs of compounds, such as caffeic and ferulic acids, or protocatechuic and vanilic acids [52]. The SAR analysis revealed that only those Schiff bases with the OH group in the *ortho* position of the ring B exhibit notable antioxidant activity. For this reason, these compounds (**2**, **3**, **6–11**) were further subjected to the quantitative structure-activity relationship (QSAR) analysis.

QSAR is an analytical application that can be used to interpret the quantitative relationship between the activities of a particular molecule and its structure. Some generally accepted principles as correct data selection and partition, selection of molecular descriptors, testing of the models' complexity and robustness, model validation and model accuracy estimation, are used in the development of QSAR models [53, 54]. QSAR models are to be simple and should rely on descriptors with clear physicochemical interpretation.

In our previous paper [54] BDE and number of neighboring OH groups were used as good descriptors for describing the antioxidant capacity of polyhydroxy phenolic compounds. In this paper the number of neighboring oxygen atoms instead of neighboring OH groups were used as molecular descriptors, Eq. (13).

$$IC_{50} = A \times BDE + B \times nO + C \quad (13)$$

In the above equation *R* is the correlation coefficient, *s* the standard error of estimate, *F* is Fisher's F-value, while A, B, and C represent corresponding fitting coefficients.

Obtained results, Table 6, with the *R* values of 0.90 for all radicals under investigation, show good agreement between the IC<sub>50</sub> values on one side, and BDE and the number of neighboring oxygen atoms on the other side. In this way BDE and the number of neighboring oxygens proved to be properly selected descriptors for describing antioxidant activity of the phenolic Schiff bases. The type of the radical does not influence the correlation quality. However, the examined sample is too small to derive any general conclusion.

**Table 6** The obtained results with QSAR analysis

A	B	C	<i>R</i>	<i>s</i>	<i>F</i>	Radical
0.1 (±0.2)	−5.5 (±2.7)	42.7 (±31.7)	0.897	3.73	10.2	OH
0.1 (±0.2)	−5.5 (±2.7)	23.0 (±1.8)	0.897	3.73	10.2	OOH
0.1 (±0.2)	−5.6 (±2.7)	22.5 (±2.4)	0.895	3.75	10.1	CH <sub>2</sub> =CHOO
0.1 (±0.2)	−5.6 (±2.7)	10.4 (±21.9)	0.895	3.73	10.2	OO

## Conclusion

In this paper, the antioxidant properties of phenolic Schiff bases in the presence of <sup>•</sup>OH, <sup>•</sup>OOH, (CH<sub>2</sub>=CH–O–O<sup>•</sup>), and <sup>•</sup>O<sub>2</sub> were investigated. Using the thermodynamic values: Δ*H*<sub>BDE</sub>, Δ*H*<sub>IP</sub>, Δ*H*<sub>PDE</sub>, Δ*H*<sub>PA</sub>, and Δ*H*<sub>ETE</sub>, the CPET, SET-PT, and SPLET mechanisms were considered.

The Δ*H*<sub>IP</sub> values reveal that SET-PT is not an operative antioxidant mechanism when Schiff bases react with radicals under investigations. Changing the reaction conditions, when the reactive particle is not radical but radical cation, then the SET-PT mechanism can be the dominant mechanism, because Δ*H*<sub>IP</sub> values are lower than Δ*H*<sub>BDE</sub> and Δ*H*<sub>PA</sub>.

On the basis of the values in Table 1, one may suppose that SPLET and CPET are competitive mechanisms for radical scavenging of hydroxy radical in all solvents under investigation. The CPET is dominant in polar solvents, while SPLET prevails in benzene.

Two peroxy radicals, <sup>•</sup>OOH and CH<sub>2</sub>=CH–O–O<sup>•</sup>, (Tables 2 and 3), unlike hydroxyl radical, will react via SPLET mechanism in polar and nonpolar solvents.

The results presented in Table 4 lead to an assumption that investigated phenolic Schiff bases will not react with superoxide radical anion in nonpolar solvents. Moreover, these Schiff bases will react with superoxide radical very slowly.

The obtained results provide a fruitful field for further research, for example, mechanistic investigations of the antioxidant properties of Schiff bases. Such investigation will provide the rate constants through activation energies, which will contribute to either confirmation or denial of all assumptions derived from this thermodynamic study.

The SAR analysis reveals that the position of the OH groups plays a very important role in the antioxidant activity of the investigated Schiff bases. Actually, only the compounds with OH group in the *ortho* position on the ring B exhibit notable antioxidant activity. The QSAR analysis showed that BDE values and number of neighboring oxygen atoms are good descriptors of antioxidant activity of the phenolic Schiff basis.

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