

ANTIOXIDANT ACTIVITY OF SOME SCHIFF BASES: EXPERIMENTAL AND THEORETICAL STUDY

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Abstract: Ten hydroxyl-substituted Schiff bases with the different number and position of hydroxyl group on the two aromatic rings (A and B rings) was synthesized and have been under experimental and theoretical investigation of antioxidant activity. DPPH method was used for experimental examination of antioxidant activity, and DFT method for theoretical investigation in polar and non polar solvents.

Key words: Schiff bases, antioxidant activity, DPPH, DFT

Introduction

Schiff bases have been known since 1864 when Hugo Schiff reported the condensation of primary amines with carbonyl compounds (Ashraf et al., 2011). Antitumor, antiviral, antifungal and antibacterial activities of this compounds (Radecka-Paryzek et al., 2007) found application in medicine and pharmacy. Due to these biological properties, Schiff bases are used as basic materials for synthesis of antibiotics, antiallergics, antitumors and antifungal drugs (Lozier et al., 1975). It has also been reported that Schiff bases of salicylaldehydes have influence in plant growth, and show some antimicrobial and antimycotic activity (Ashraf et al., 2011). They are interesting to medicine because they have the ability to rebuild hemoglobin, red blood cells and white blood cells, also it's proved that they are useful in treatment of AIDS and diabetes (Brodowska and Lodyga-Chruscinska, 2014). It was shown that some Schiff bases act as effective antioxidants and potential drugs that can prevent disease caused by free radical damage.

Material and methods

Schiff bases (1-10) were prepared according to procedure in the literature with some modification (Tunç et al., 2009). In our case, aldehyde (salicylaldehyde, vanillin)

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(1 mmol), corresponding aromatic amine (aniline, 4-fluoroaniline, 4-nitroaniline, toluidine, 2-hydroxyaniline, 3-hydroxyaniline, 4-hydroxyaniline) (1 mmol), and 3 ml of methanol were placed in flask and stirred at 70 °C for 3h. After completion of the reaction, the solvent was evaporated, and final product obtained recrystallization from ethanol. Schiff bases were obtained in 90-97% yield.

In this study, the free radical scavenging activity of the examined Schiff bases was performed using the DPPH method. In brief, 1mL (0.1 mm) solution of DPPH in methanol was mixed with an equal volume of the tested compound (20 mL of compound solution in DMSO and 980 mL of methanol). The reaction mixture is left at room temperature for 20 and 60 min. After incubation the absorbance was measured at 517 nm. As control solution, methanol was used. IC_{50} values represent the concentration necessary to obtain 50% of a maximum scavenging capacity nordihydroguareric acid (NDGA). NDGA was used as positive control with 96% activity at 0.1 mM.

All calculations in this paper were performed using the Gaussian program package (Frisch et al., 2009). The equilibrium geometries of all Schiff bases and corresponding radicals, radical cations, and anions were optimized by the empirical exchange-correlation M05-2X functional and split-valence basis set 6-311+G(d,p). To evaluate the impact of different solvents: water, methanol, and benzene, the continuum solvation model CPCM was used.

Results and discussion

In the reaction of aldehyde (salicylaldehyde or vanillin) and aromatic amine (aniline, 4-fluoroaniline, 4-nitroaniline, toluidine, 2-hydroxyaniline, 3-hydroxyaniline or 4-hydroxyaniline), in methanol, was synthesized a series of ten Schiff bases (1-10, Fig. 1), of which compound 10 is newsynthesized. These compounds were applied for evaluation of their antioxidative activity.

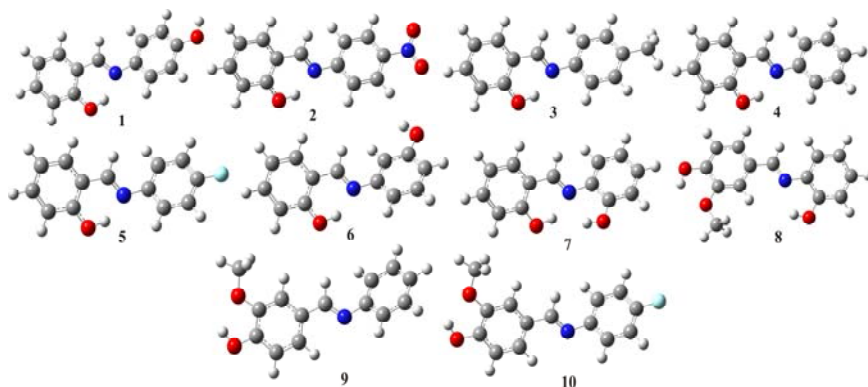


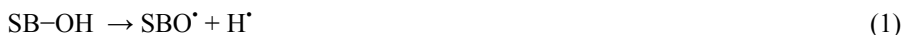
Figura 1: Optimizovane geometrije ispitivanih šifovih baza. Predstavljene su najstabilniji izomeri svakog jedinjenja.

Figure 1: Optimized geometries of the investigated Schiff bases. Each compound is presented with its most stable isomer.

The DPPH free radical scavenging activity of Schiff bases 1-10 was determined, Table 1. It was shown through IC₅₀ values that compounds 7 and 8 interact well with DPPH, and exhibit high activity. Compounds 1, 9, and 10 show somewhat activity and compounds 2-6 exhibit poor antioxidative activity. Therefore, compounds 8 and 7 with activity slightly lower than the reference compound NDGA, can be considered as good antioxidants.

Antioxidative activity of Schiff bases (SB-OH) is directly related to their ability to release hydrogen atoms. A few different mechanisms of free radical scavenging are known: hydrogen atom transfer (HAT), single electron transfer followed by proton transfer (SET-PT), and sequential proton loss electron transfer (SPLET).

HAT mechanism is the only one which consists of one step in which hydrogen atom is transferred to free radical.



SET-PT and SPLET mechanisms consist of two steps. In SET-PT mechanism, the first step is characterized by process in which one electron is lost and radical cation is created, whereas in the second step radical cation is deprotonated and corresponding radical is formed.



In SPLET mechanism, the first step is deprotonation of parent molecule. In the second step the anion formed loses an electron and corresponding radical is formed.



These mechanisms are described by thermodynamical parameters: bond dissociation enthalpy (BDE) related to Eq. (1), ionization potential (IP) related to Eq. (2.1), proton dissociation enthalpy (PDE) related to Eq. (2.2), proton affinity (PA) related to Eq. (3.1), and electron transfer enthalpy (ETE) related to Eq. (3.2).

BDE, IP, PDE, PA and ETE values were determined from total enthalpies of the individual species, as follows:

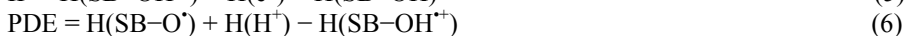


Tabela 1. Izračunati termodinamički parametri (kJ mol^{-1}) antioksidativnih mehanizama i eksperimentalne osobine Šifovih baza

Table 1. Calculated thermodynamical parameters (kJ mol^{-1}) of antioxidative mechanisms and experimental properties for Schiff bases

	HAT		SET-PT			SPLET				IC ₅₀ (μM)
	BDE		IP	PDE		PA		ETE		
Methanol	A	B		A	B	A	B	A	B	
1	407	351	542	56	0	183	149	414	392	186.3
2	406		624	-28		168		428		>500
3	406		559	38		181		416		>500
4	407		584	13		180		417		>500
5	407		586	11		179		419		>500
6	407	366	566	32	-9	178	152	419	404	>500
7	396	360	555	31	-4	167	152	419	399	18.8
8	353	364	533	11	22	140	171	403	384	5.3
9	351		542	0		146		395		86.2
10	351		541	0		146		396		68.8
Water										
1	412	356	522	71	16	191	159	401	379	
2	411		603	-12		177		415		
3	411		539	53		189		403		
4	412		564	29		189		404		
5	412		566	27		188		405		
6	412	371	546	47	7	187	161	406	391	
7	401	365	535	47	11	176	161	406	386	
8	358	369	513	26	37	150	179	389	371	
9	356		522	15		155		381		
10	356		521	16		155		382		
Benzene										
1	415	352	636	189	126	465	416	359	345	
2	414		661	163		434		390		
3	415		650	174		464		360		
4	416		665	161		462		363		
5	415		639	186		457		368		
6	417	367	661	165	115	458	426	368	350	
7	400	367	651	159	125	437	429	373	347	
8	359	370	621	148	159	409	456	360	324	
9	357		630	136		422		345		
10	357		633	134		418		349		

On the basis of values of thermodynamical parameters: BDE, IP, PDE, PA, and ETE, prevailing antioxidative mechanism of Schiff bases in a corresponding solvent can be predicted. The lowest value for some parameter tells us which reaction mechanism is thermodynamically more probable. The obtained results show that compounds 2-6 have significantly higher BDE, IP, and PA values than other compounds under investigation. The values of thermodynamical parameters undoubtedly show that negligible antioxidative activity can be expected for these compounds.

Schiff bases with OH groups in *para* position have the smallest BDE values (compounds 1, 8-10). Table 1 shows that BDE values of Schiff bases with hydroxyl group in *para* position are lower than those with hydroxyl groups in *meta* and *ortho* positions. On the basis of our results, molecules with only one *ortho* OH group in the ring A (compounds 2-5) have generally the highest IP values. Introducing another OH group in the ring B in *meta*, *ortho*, or *para* position (compounds 6, 7, and 1), additionally reduces the IP value.

Conclusion

Theoretical results are in agreement with experimental IC_{50} values. Mutual comparison of BDE, IP, and PA values reveal that IP values are the largest, indicating that SET-PT mechanism is not a favourable reaction path in all investigated solvents. In polar solvents, water and methanol, PA values are significantly lower than the corresponding BDEs. It means that the SPLET mechanism is a dominant reaction pathway in polar solvents. On the other hand, the low PA values show that Schiff bases easily undergo heterolytic dissociation of OH bonds and yield the corresponding phenoxide anions. It means that under physiological conditions (pH of 7.4) it is reasonable to expect SPLET mechanism to be the main reaction path. BDE and PA values show that HAT and SPLET mechanisms are competitive in nonpolar solvent benzene.

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ANTIOKSIDATIVNA AKTIVNOST NEKIH ŠIFOVIH: EKSPERIMENTALNA I TEORIJSKA ISPITIVANJA

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Izvod: Sintetisano je deset različitih hidroksi-supstituisanih Šifovih baza, koje imaju različit broj i položaj hidroksilnih grupa koje se nalaze na dva aromatična prstena (prsten A i B). Ispitana je njihova antioksidativna aktivnost, eksperimentalnim i teorijskim metodama. Za eksperimentalna ispitivanja antioksidativne aktivnosti korišćena je DPPH metoda, dok su teorijska ispitivanja u polarnim i nepolarnim rastvaračima urađena DFT metodom.

Ključne reči: Šifove baze, antioksidativna aktivnost, DPPH, DFT

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