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Radical scavenging activity of aaptamine derivatives: A theoretical study

Hoạt tính quét gốc tự do của các dẫn xuất aaptamine: Nghiên cứu lý thuyết

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Abstract

The antioxidant activities of a dataset of 10 aaptamines were performed by Density Functional Theory (DFT). First, the intrinsic thermodynamic parameters such as bond dissociation (BDE), proton affinity (PA) and adiabatic ionization potential (IP_a) were initially investigated in the gas phase and water. Secondly, the radical scavenging activities of HO• and HOO• free radicals were studied via three common mechanisms namely Hydrogen Transfer (HT), Radical Adducts Formation (RAF), and Single Electron Transfer (SET). The results show that **A7** is the most potential scavenger for both radicals and in two media. The HT mechanism is more competitive than the RAF and SET ones. The Quantitative Structure-Activity Relationship (QSAR) reveals that the antioxidant properties (BDE and the Gibbs free energy of reaction of the HT mechanism) exhibit correlation with some key molecular aspects, such as ionization potential, the HOMO-LUMO gap, the absolute hardness and absolute electronegativity of the molecules.

Keywords: aaptamine; radical scavenging activity; Density Functional Theory; HO• radical; HOO• radical.

Tóm tắt

Hoạt tính chống oxy hóa của bộ dữ liệu gồm 10 aaptamin được nghiên cứu bằng Lý thuyết Hàm Mật độ (DFT). Đầu tiên, các thông số nhiệt động học nội tại như năng lượng phân ly liên kết (BDE), ái lực proton (PA) và thế ion hóa đoạn nhiệt (IPa) được kiểm tra ban đầu trong pha khí và nước. Thứ hai, khả năng quét gốc tự do HO• và HOO• được nghiên cứu thông qua ba cơ chế phổ biến: chuyển Hydro (HT), cơ chế cộng gốc tự do (RAF) và chuyển đơn điện tử (SET). Kết quả cho thấy **A7** là chất quét gốc tiềm năng nhất đối với cả hai loại gốc tự do và trong cả hai môi trường. Cơ chế HT cạnh tranh hơn so với RAF và SET. Nghiên cứu mối quan hệ Định lượng Cấu trúc - Hoạt tính (QSAR) cho thấy đặc tính chống oxy hóa (thông qua BDE và năng lượng tự do Gibbs của phản ứng theo cơ chế HT) có sự tương quan với một số đặc điểm phân tử quan trọng, như thế ion hóa, khoảng cách HOMO-LUMO, độ cứng tuyệt đối và độ âm điện tuyệt đối của các phân tử.

Từ khóa: aaptamine; hoạt tính quét gốc tự do; lý thuyết hàm mật độ; gốc tự do HO•; gốc tự do HOO•.

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1. Introduction

Marine organisms have been known as a rich source of unusual compounds with interesting biological activities. In 1982, Nakamura *et al*. isolated Aaptamine for the first time, a natural alkaloid with the unique 1*H*-benzo[*de*]-1,6-naphthyridine scaffold, from tropical sea sponge *Aaptos aaptos* collected off the shores of Okinawa, Japan [1]. Since then, researchers have identified many other aaptaminoids from other sea water. Indeed, aaptamine derivatives were isolated from *Aaptos aaptos* marine sponges collected across the Pacific Ocean, such as Japan, Taiwan, Indonesia [2,3], Malaysia [4], Vietnam [5], and China [6-8].

The aaptamine framework is associated with a broad range of biological activities, with significant focus on its cytotoxic, antimicrobial, antiviral, antioxidant, and recently, neuroprotective (anti-AD) potential. Initially, the ancestor aaptamine was paid attention as an effective competitive α-adrenoceptor antagonist endowed with potential cardiotonic effect [1]. However, the majority of research focuses on the potent cytotoxic activity and anticancer of aaptamines against various cancer cell lines. For example, Shen *et al.* reported the cytotoxicity against murine P-338 and human tumor cells including KB16, A549, HT-29 (colon adenocarcinoma) cell lines [9]. Shaari et al. demonstrated that aaptamine bearing a substitution at C3 has higher toxicity on CEM-SS human T-lymphoblastic leukaemia cells than aaptamine itself [4]. Another group reported the cytotoxic activity of several aaptaminoids against the murine lymphoma L5178Y cell lines (IC50 from 0.9 to 8.3 μM), whereas the most potent compound is demethylaaptamine [10]. Yu *et al*. studied the cytotoxicities of four aaptamine derivatives against six human cancer cell lines, including HL60 (acute leukemia), K562 (chronic leukemia), MCF-7 (breast cancer), KB (nasopharyngeal cancer), HepG2 (liver carcinoma), and HT-29 cells, with IC50 values in the range of 0.03 to 8.5 μM and the HL-60 is the most sensitive cell line [7]. Similarly, five aaptaminoids exhibit the cytotoxic activities against four human cancer cell lines, such as HeLa (cervical cancer), K562, MCF-7, and U937 (lymphoma) cell lines (IC50 values of 0.90–12.32 μM) [8]. Yang *et al.* studied the aromatic ring substituted on thirty new aaptamine analogues and sixteen of them showed their cytotoxicities to four cancer cell lines with IC50 less than 10 μM [11]. Among these analogues, the dimeta methylbenzene-substituted, compound **5i,** showed a significant antiproliferative effect on the extranodal natural killer/T-cell lymphoma (ENKT) cell line SNK-6 with an IC50 value of 0.6 μM, and cytotoxicities to multiple lymphoma cell lines, including Ramos, Raji, WSU-DLCL2, and SU-DHL-4 cells. In these studies, authors tried to suggest the structure-activity relationships, for example, the features like hydroxylation at C-9 and C-3 substitution can influence cytotoxicity [4, 12].

Moreover, the antimicrobial, antifungal, and antiviral activities of aaptamines have been reported. For example, Calcul *et al.* showed that aaptamine, isoaaptamine and dimethyl(oxy) aaptamine were effective against Gram (+) (*S. aureus*), Gram (–) (*E. coli, V. anguillarum*) bacterial strains, and a fungus (*C. tropicalis*) [2]. Particularly, the anti-HIV-1 (human immunodeficiency virus type 1) activity of the aapatamine is also reported, with the modification at the C9 position may impact the activity. Antifungal activity against six fungi, with MIC values in the range of 4 to 64 μg/mL. Yu showed anti-HIV-1 activity, with inhibitory rates of 88.0% and 72.3%, respectively, at a concentration of 10 μM [6].

Recently, Miao *et al.* reported the *in vivo* therapeutic effects of aaptamine in a zebrafish

model. In this study, aaptamine acted as a dual AChE and BuChE inhibitor, with treatments of 10 and 20 µM of aaptamines yielding therapeutic effects similar to those of 8 µM donepezil. The dyskinesia recovery rate at the optimal dose reached up to 60%, showing potential use for AD treatment [13].

Although aaptamine derivatives are considered potential natural antioxidants, there is limited literature on this topic. The antioxidant activities of aaptamine and isoaaptamine have been reported early by Takamatsu *et al*., in which two molecules exhibited strong activity in scavenging free DPPH radical, $IC_{50} = 1.8 \times 10^{-5}$ M and 1.6×10^{-5} M, respectively [14, 15]. Beyond direct radical scavenging, the antioxidant properties of aaptamines can also involve chelating oxidative transition metal ions, particularly copper and iron, which helps prevent the formation of harmful reactive hydroxyl radicals. We have performed a computational study that investigates the antioxidant mechanisms of three aaptamine derivatives, including the radical scavenging activity via Hydrogen Atom Transfer (HAT), Single Electron Transfer (SET), Proton Loss (PL), Radical Adduct Formation (RAF) pathways, and Cu-chelating [16]. In cellular studies, aaptamine was found to significantly reduce intracellular Reactive Oxygen Species (ROS) generation and increase the expression of antioxidant enzymes like catalase, SOD, and GPx in UVB-irradiated cells [17]. There is a need for more understanding of the antioxidant activity of these molecules.

In this study, we aim to study the antioxidant activities of ten derivatives of aaptamine (Figure 1) which are seen as potent as antioxidants. First, we screen the thermodynamic properties of the molecules via the Bond Dissociation Energy (BDE), proton affinity (PA), and adiabatic ionization potential (IP_a) parameters. Second, we evaluate the free radical scavenging activities against two common ROS (HO•/HOO• radicals), following mechanisms such as hydrogen transfer (HT), single electron transfer (SET), and radical adduct formation (RAF). Finally, we try to establish the Quantitative Structure-Activity Relationship (QSAR) of the antioxidant activities with some molecular properties for the set of compounds. The results can be helpful for tailoring design and the synthetic process of novel antioxidant molecules.

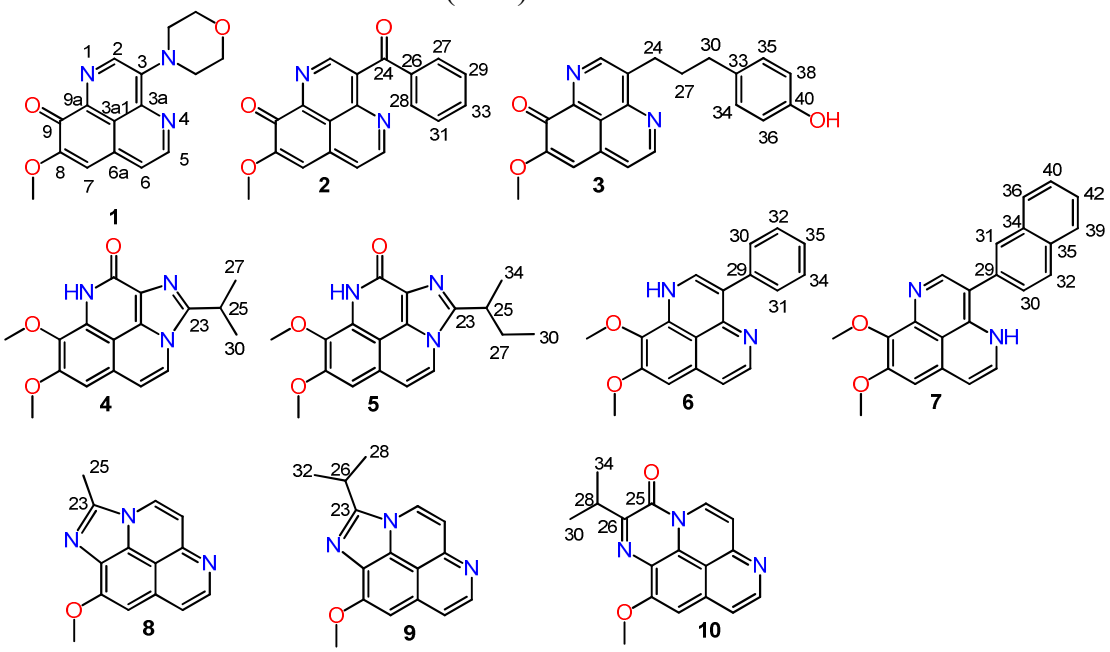

Figure 1. The 2D structures of the studied aaptamine derivatives, with numbering positions of the framework.

2. Computational methods

Optimized structures of aaptamines are obtained using Gaussian G16 Rev. A03 [18]. Density functional theory (DFT) using the M06-2X method [19] combined with 6-311++G(d,p) basis set, was applied. Solvent effects were studied via an implicit approach with a continuum solvent model SMD [20] for water. The enthalpies of the proton and electron in water were -252.31 and -18.98 kcal/mol, respectively, according to the work of Markovic *et al.* [21].

Intrinsic thermodynamic parameters such as bond dissociation energy (BDE), proton affinity (PA), and adiabatic ionization potential (IP_a) were initially investigated. Subsequently, the enthalpy and Gibbs free energy of the reactions with $HO^{\bullet}$/$HOO^{\bullet}$ radicals at 298 K were calculated. The antioxidant activity of the studied compounds was assessed based on common mechanisms, including hydrogen transfer (HT), single electron transfer (SET), and radical adduct formation (RAF). The details of all calculations can be found in our previous studies [16]. The Quantitative Structure – Activity Relationship (QSAR) is then established between the antioxidant activity and several key molecular structural properties such as ionization potential, chemical potential, absolute electronegativity, and absolute hardness.

3. Results and discussion

3.1. Optimized geometries and electronic structures

The optimized geometries and electronic structures, specifically the highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), and electrostatic potential (ESP) maps, of studied aaptamines, **A1**-**A10**, are presented in Figure 2. As seen in Figure 2, the optimized geometries generally reveal a planar structure of the scaffold of aaptamines. For all compounds, the frontier orbitals HOMO and LUMO are evenly distributed across the entire structure, showing very minimal electron delocalization between the frontier molecular orbitals. The exception is **A7**, which shows distinct electron delocalization from the aaptamine rings in the HOMO to the naphthalene group in the LUMO. The ESP maps reveal highly negative charges are mostly distributed on the C=O groups, which tend to attract positively charged species. The highly positive charges are mainly observed on the nitrogen or CH_3 groups, indicating the potential sites that interact with nucleophiles.

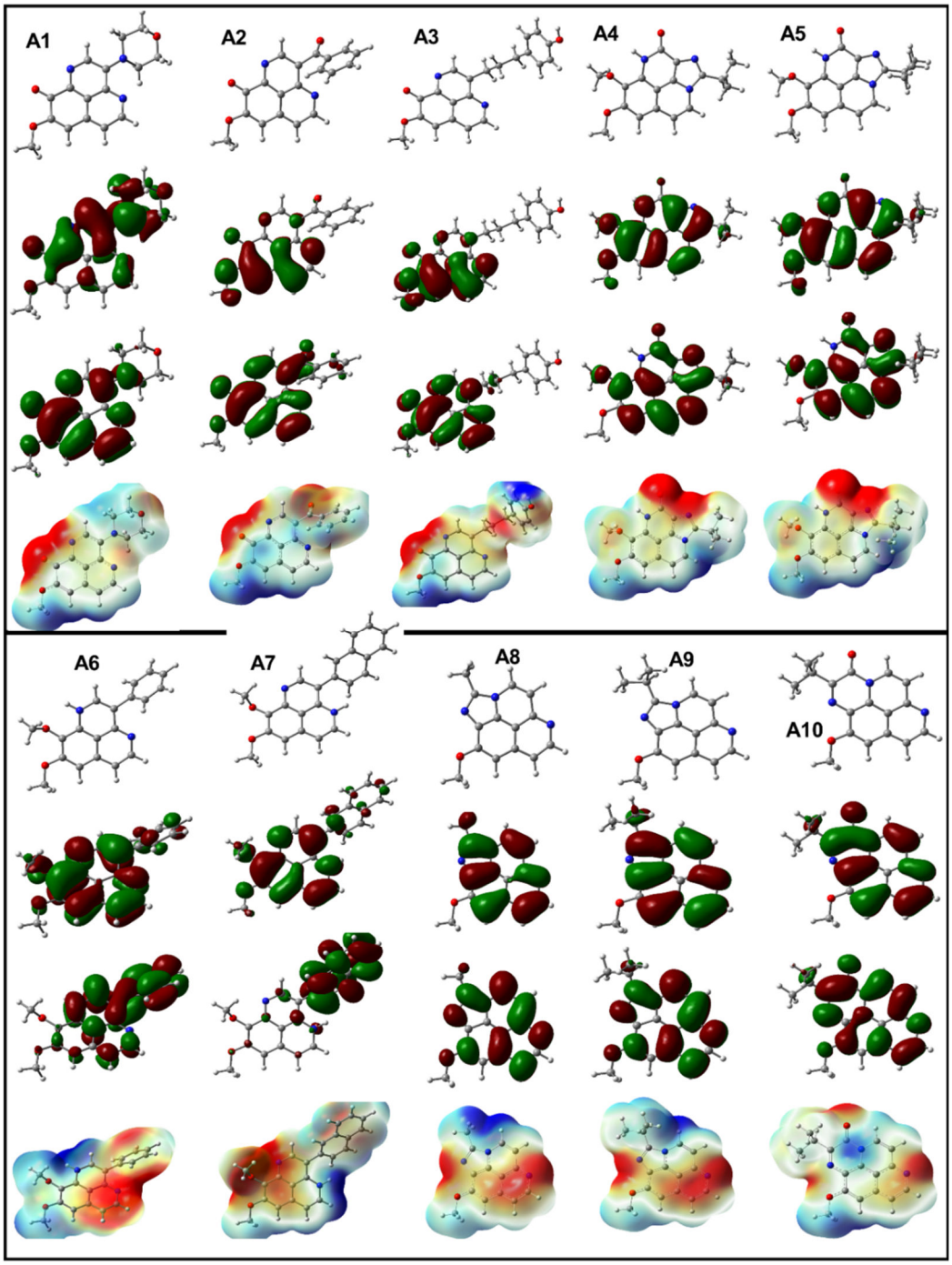

Figure 2. Optimized geometry and electronic structures, including HOMO, LUMO, ESP maps (from top to bottom) of the studied aaptamines

3.2. Thermodynamic parameters

Intrinsic thermochemical properties of these molecules, including the bond dissociation energy (BDE), proton affinity (PA), and adiabatic ionization potential (IP_a) are given in Table 1. The lower the value, the better the antioxidant activity is. Although dissociation and proton loss for all H-atoms were evaluated, only the lowest values, those corresponding to the most probable H-transfer and proton transfer, are reported for clarity. As shown in Table 1, the lowest BDE values are found for **A7** at H28 (N-H), with values of 276.35 kJ mol^{-1} in the gas phase, and 295.43 kJ mol^{-1} in water, respectively. This BDE of other compounds in water varies by +9 to -50 kJ mol^{-1} in comparison

with the value in gas, suggesting that the polar solvent has minimal impact on breaking C-H or N-H bonds. In contrast, the PA values are 3.7 to 8.7 times higher in the gas phase than in water, consistent with the behavior of the charged particles (protons) in a polarized solvent. The lowest PA is also found for **A7** (1362.65 kJ mol^{-1}, at H28) in the gas phase, and for **A3** (155.77 kJ mol^{-1} at H25, adjacent to the aaptamine ring) in water. Similar to PA, IP_a values are higher in the gas phase than in water, ranging from 607.81 to 826.13 kJ mol^{-1} in the gas phase, and from 560.11 to 704.13 kJ mol^{-1} in water. Interestingly, the lowest IP_a is also found at **A7**, suggesting that the compound **A7** is the most favored for electron transfer. Overall, **A7** is the highest potent antioxidant molecule.

Table 1. Bond dissociation energy (BDE, kJ mol-1), proton affinity (PA, kJ mol-1), and adiabatic ionization potential (IPa, kJ mol-1) of studied Aaptamines, calculated in gas phase and water using M06-2X/6-311G++(d,p) level of theory.

Cp	BDE (kJ mol^{-1})		PA (kJ mol^{-1})		IP_a (kJ mol^{-1})	
	gas	water	gas	water	gas	water
A1	333.67 (H27/37)	283.72 (H29/34)	1430.26 (H35)	362.54 (H35)	716.51	628.39
A2	373.51 (H22)	387.06 (H20)	1460.30 (H30)	321.50 (H30)	826.13	704.13
A3	340.79 (H26)	313.67 (H26)	1400.30 (H25)	155.77 (H25)	772.99	694.67
A4	319.82 (H26)	326.10 (H26)	1451.09 (H21)	165.98 (H21)	709.90	634.59
A5	324.05 (H26)	330.54 (H26)	1449.67 (H21)	166.23 (H21)	706.80	633.79
A6	320.33 (H17)	297.57 (H17)	1381.22 (H17)	163.59 (H17)	633.54	563.12
A7	276.35 (H28)	295.43 (H28)	1362.65 (H28)	361.79 (H25)	607.81	560.11
A8	337.57 (H28)	346.48 (H28)	1498.21 (H28)	259.83 (H28)	722.12	625.97
A9	318.74 (H27)	325.43 (H27)	1521.30 (H24)	280.45 (H24)	716.26	625.80
A10	304.01 (H29)	312.29 (H29)	1466.58 (H29)	240.50 (H29)	729.73	637.56

3.3. Radical scavenging activities

To investigate the free radical scavenging activity of the aaptamines, the standard enthalpy (Δ_rH^0, kJ mol^{-1}) and Gibbs free energy of reaction (Δ_rG^0, kJ mol^{-1}) for reactions with HO$^\bullet$/HOO$^\bullet$ radicals were calculated. Three main mechanisms were considered, including the hydrogen transfer (HT), single electron transfer (SET), and radical adduct formation (RAF) reactions. The results for HT, SET, and RAF are summarized in Tables 2, 3, and 4, respectively. Given the numerous possible sites for H-abstraction and C/N-addition in each compound, only the most potential results are presented here.

3.3.1. HT mechanism

Several key observations can be drawn for the HT reaction (Table 2). First, the Δ_rH^0 and Δ_rG^0 of the HT reaction are lower with the HO$^\bullet$ radical compared to those with the HOO$^\bullet$ radical. This aligns with the known reactivity of free radicals, as HO$^\bullet$ is the most reactive among reactive oxygen species (ROS). Second, while the environmental effects have minimal impact on HO$^\bullet$-scavenging, HOO$^\bullet$ radical scavenging reactions are more favorable in water than in the gas phase. For example, only two compounds, **A6** and **A7**, show spontaneous and exothermic HOO$^\bullet$-scavenging in the gas phase, with negative Δ_rH^0 and Δ_rG^0 energy, values being -

2.97/-4.75 and -13.55/-13.87 kJ mol^{-1} for **A6** and **A7**, respectively. However, in water, all studied compounds (except **A2**) exhibit negative Δ_rH^0 and Δ_rG^0 energy for HOO•-scavenging, indicating these reactions are exothermic and thermodynamically favorable in aqueous conditions. Third, the most promising antioxidants via the HT mechanism in the gas phase are **A7** and **A6**, with Δ_rG^0 for HO• scavenging of -169.09 and -178.20 kJ mol^{-1}, respectively. In water, **A1**, **A7**, and **A6** are the most potential antioxidants via the HT mechanism.

Table 2. Enthalpy (Δ_rH^0, kJ mol^{-1}) and Gibbs free energy of reaction (Δ_rG^0, kJ mol^{-1}) of the HT reaction between aaptamines and HO•/HOO• radicals in the gas phase and water at the most potential positions.

Cp	GAS					WATER				
	Pos.	HO•		HOO•		Pos.	HO•		HOO•	
		Δ_rH^0	Δ_rG^0	Δ_rH^0	Δ_rG^0		Δ_rH^0	Δ_rG^0	Δ_rH^0	Δ_rG^0
A1	H27	-116.20	-120.86	46.10	43.47	H29	-184.91	-188.67	-87.33	-89.37
A2	H22	-76.67	-81.05	85.63	83.28	H20	-80.32	-85.37	17.26	13.94
A3	H26	-139.08	-141.82	23.22	22.52	H26	-159.18	-158.72	-61.60	-59.42
A4	H26	-128.15	-134.73	34.14	29.60	H26	-139.35	-146.30	-41.77	-46.99
A5	H26	-125.54	-130.51	36.76	33.82	H26	-135.95	-141.90	-38.37	-42.59
A6	H17	-165.26	-169.09	***-2.97***	***-4.75***	H17	-171.94	-174.84	-74.36	-75.53
A7	H28	-175.85	-178.20	***-13.55***	***-13.87***	H28	-172.35	-176.98	-74.78	-77.67
A8	H28	-114.99	-116.98	47.30	47.35	H28	-124.36	-125.93	-26.79	-26.63
A9	H27	-129.54	-135.84	32.75	28.50	H27	-141.18	-146.98	-43.60	-47.67
A10	H29	-143.57	-150.56	18.73	13.77	H29	-152.73	-160.11	-55.16	-60.80

3.3.2. SET mechanism

Table 3 provides the enthalpy (Δ_rH^0, kJ mol^{-1}) and Gibbs free energy of reaction (Δ_rG^0, kJ mol^{-1}) for the SET reaction between aaptamines and HO• and HOO• radicals in both gas and aqueous phases. For the SET reaction, only the electron transferred from **A6** and **A7** to the HO• radical is exothermic and spontaneous in water, with negative Δ_rH^0 (-47.95 and -50.92 kJ mol^{-1}) and Δ_rG^0 values (-47.58 and -51.96 kJ mol^{-1}). These results suggest that **A6** and **A7** are promising radical scavenger in water via the SET mechanism.

Table 3. Enthalpy (Δ_rH^0, kJ mol^{-1}) and Gibbs free energy of reaction (Δ_rG^0, kJ mol^{-1}) of the SET reaction between aaptamines and HO•/HOO• radicals in both gas and aqueous phases.

Cp	GAS				WATER			
	HO•		HOO•		HO•		HOO•	
	Δ_rH^0	Δ_rG^0	Δ_rH^0	Δ_rG^0	Δ_rH^0	Δ_rG^0	Δ_rH^0	Δ_rG^0
A1	561.23	560.32	621.12	619.36	17.33	16.62	110.15	108.67
A2	670.86	668.76	730.75	727.80	93.05	92.13	185.86	184.18
A3	617.73	617.85	677.61	676.88	83.60	91.73	176.42	183.78
A4	554.63	552.90	614.52	611.94	23.53	22.29	116.35	114.34
A5	551.51	552.48	611.40	611.52	22.76	22.54	115.57	114.59

A6	478.27	478.06	538.15	537.08	***-47.95***	***-47.58***	44.89	44.47
A7	452.54	454.63	512.44	513.68	***-50.92***	***-51.96***	41.89	40.09
A8	566.84	565.66	626.72	624.70	14.90	14.13	107.72	106.18
A9	561.00	559.39	620.88	618.43	14.77	13.24	107.57	105.29
A10	574.45	572.33	634.34	631.37	26.48	25.69	119.30	117.74

3.3.3. RAF mechanism

Finally, the addition of HO$^\bullet$ and HOO$^\bullet$ to the non-saturated positions is reported in Table 4 for the most potential positions. As anticipated, the RAF reactions with HO$^\bullet$ are exothermic and spontaneous in both the gas phase and water, with very little effect of the environments. In contrast, for HOO$^\bullet$-addition, only two reactions at C2 (**A6**) and C5 (**A7**) are spontaneous in the gas phase, with $\Delta_r H^0/\Delta_r G^0$ values being -49.50/-0.14 and -58.86/-7.49 kJ mol^{-1}, respectively. Furthermore, the HOO$^\bullet$-scavenging activities via the RAF mechanism are unfavorable in water, all $\Delta_r G^0$ energy is positive. These results indicate that **A6** and **A7** are potent antioxidants via RAF mechanism in the gas phase but not in water.

Overall, a comparison of the enthalpy and Gibbs free energy across the three mechanisms reveals that the HT channel is the most favorable pathway for the reactions of aaptamines, a conclusion that holds in both environments.

Table 4. Enthalpy ($\Delta_r H^0$, kJ mol^{-1}) and Gibbs free energy of reaction ($\Delta_r G^0$, kJ mol^{-1}) of the RAF reaction between aaptamines and HO$^\bullet$/HOO$^\bullet$ radicals in the gas phase and water at the most potential positions.

Cp	**Pos.**	**GAS**				**WATER**			
		HO$^\bullet$		**HOO$^\bullet$**		**HO$^\bullet$**		**HOO$^\bullet$**	
		$\Delta_r H^0$	**$\Delta_r G^0$**	**$\Delta_r H^0$**	**$\Delta_r G^0$**	**$\Delta_r H^0$**	**$\Delta_r G^0$**	**$\Delta_r H^0$**	**$\Delta_r G^0$**
A1	**2**	-29.34	-19.21	-25.23	24.94	-26.76	-16.56	-14.72	35.01
	6	-29.14	-19.38	-23.90	22.73	-31.19	-21.91	-24.78	26.29
	7	-30.78	-20.35	-33.48	15.84	-33.18	-22.88	-34.08	17.60
	8	-30.64	-20.75	-21.46	27.44	-30.18	-19.72	-10.54	41.63
A2	**1**	-29.30	-17.97	-12.01	44.26	-19.50	-8.38	30.84	86.80
	3	-37.06	-26.24	-35.70	18.80	-33.30	-22.57	-22.81	33.85
	6	-31.71	-21.93	-32.06	14.62	-33.97	-24.13	-32.46	16.07
	7	-31.50	-21.65	-37.91	11.47	-35.02	-25.04	-40.79	8.96
	8	-31.00	-21.00	-22.71	26.39	-30.66	-21.07	-12.02	38.40
A3	**3**	-36.43	-25.78	-22.55	26.44	-33.76	-22.74	-27.85	28.67
	6	-30.93	-21.32	-29.41	17.13	-33.28	-23.23	-30.35	21.19
	7	-31.09	-21.42	-36.81	12.55	-34.04	-23.73	-37.28	13.21
	8	-30.97	-21.23	-22.18	26.04	-31.26	-20.62	-14.05	36.43
A4	**5**	-36.58	-26.88	-34.74	18.13	-33.78	-23.80	-35.91	13.45
	9	-36.49	-26.17	-34.74	18.13	-33.82	-23.52	-23.58	27.52
	C23	-38.18	-27.64	-38.26	14.92	-33.65	-23.01	-17.20	34.07
A5	**5**	-37.02	-27.46	-46.39	0.81	-34.30	-24.04	-37.75	12.12
	9	-36.48	-26.26	-34.75	17.84	-34.30	-23.74	-22.98	28.83
	C23	-36.35	-25.47	-53.28	0.67	-32.24	-21.25	-7.42	47.95

A6	**2**	-32.43	-22.75	**-49.50**	**-0.14**	-32.66	-22.57	-39.65	10.69
	9	-34.44	-24.11	-30.48	23.86	-31.69	-20.71	-13.42	39.81
A7	**5**	-37.47	-27.18	**-58.86**	**-7.49**	-33.69	-23.59	-43.06	**7.03**
	8	-30.04	-19.58	-9.43	41.85	-22.98	-13.01	13.24	63.29
	9	-40.66	-29.80	-50.99	2.23	-36.50	-25.95	-33.35	18.48
A8	**2**	-35.59	-25.87	-36.81	10.61	-33.40	-23.59	-28.40	16.28
	C23	-36.72	-26.07	-41.16	11.45	-33.77	-23.62	-28.13	22.38
A9	**2**	-35.38	-25.67	-36.26	11.44	-33.00	-22.78	-27.64	21.03
	C23	-38.41	-27.90	-37.99	14.94	-34.22	-23.49	-19.42	33.47
A10	**2**	-35.53	-25.10	-41.14	11.33	-33.38	-23.01	-22.10	28.37
	C25	-31.53	-22.96	56.09	102.63	-20.67	-9.84	22.60	73.29
	C26	-34.00	-23.27	-37.07	16.56	-28.71	-17.98	-25.45	24.23

3.4. Quantitative Structure-Activity Relationship (QSAR)

We attempted to establish the Quantitative Structure-Activity Relationship (QSAR) for the antioxidant capacity of aaptamines based on various molecular parameters. Figure 3 illustrates the correlation between bond dissociation energy (BDE) and Gibbs free energy ($\Delta_r G^o$) in the main reaction mechanism (HT reaction) with respect to key molecular properties, such as ionization potential, chemical potential, absolute electronegativity, and absolute hardness.

The results indicate that both BDE and $\Delta_r G^o$ energies tend to increase with higher ionization potential and greater absolute electronegativity (Figure 3A, 3C), although the regression linear fitting is obtained only with R^2 = 0.51-0.59. For example, **A7** and **A6** exhibit lowest IP value along with lowest BDE and $\Delta_r G^o$ values, whereas **A2** and **A3**, which have the highest IP, also show the highest BDE and $\Delta_r G^o$ values. Regarding chemical potential of the molecules, BDE and $\Delta_r G^o$ seem to decrease as the chemical potential increases (Figure 3B); the trend is inverse compared to the ionization potential and electronegativity. Indeed, the molecules with the lowest chemical potential, such as **A2** and **A3**, show the highest BDE and $\Delta_r G^o$ values. In contrast, **A6** and **A7** exhibit the highest chemical potential, reflecting their ability to participate in reactions, yet they show the lowest BDE and $\Delta_r G^o$ values. Unfortunately, our observation indicates that BDE and $\Delta_r G^o$ do not demonstrate a clear correlation with absolute hardness, a parameter directly linked to molecular stability (Figure 3D). In general, we propose that the OCH_3-substitution at C8 and C9 positions plays an important role, while introducing a functional group with an aromatic system at C3 could be key to enhancing the antioxidant activity of aaptamines.

Although the dataset is limited, and the influence of molecular structure and functional groups on the investigated activities cannot be fully captured, the observed trends may still provide valuable guidance for designing novel antioxidants based on the aaptamine framework.

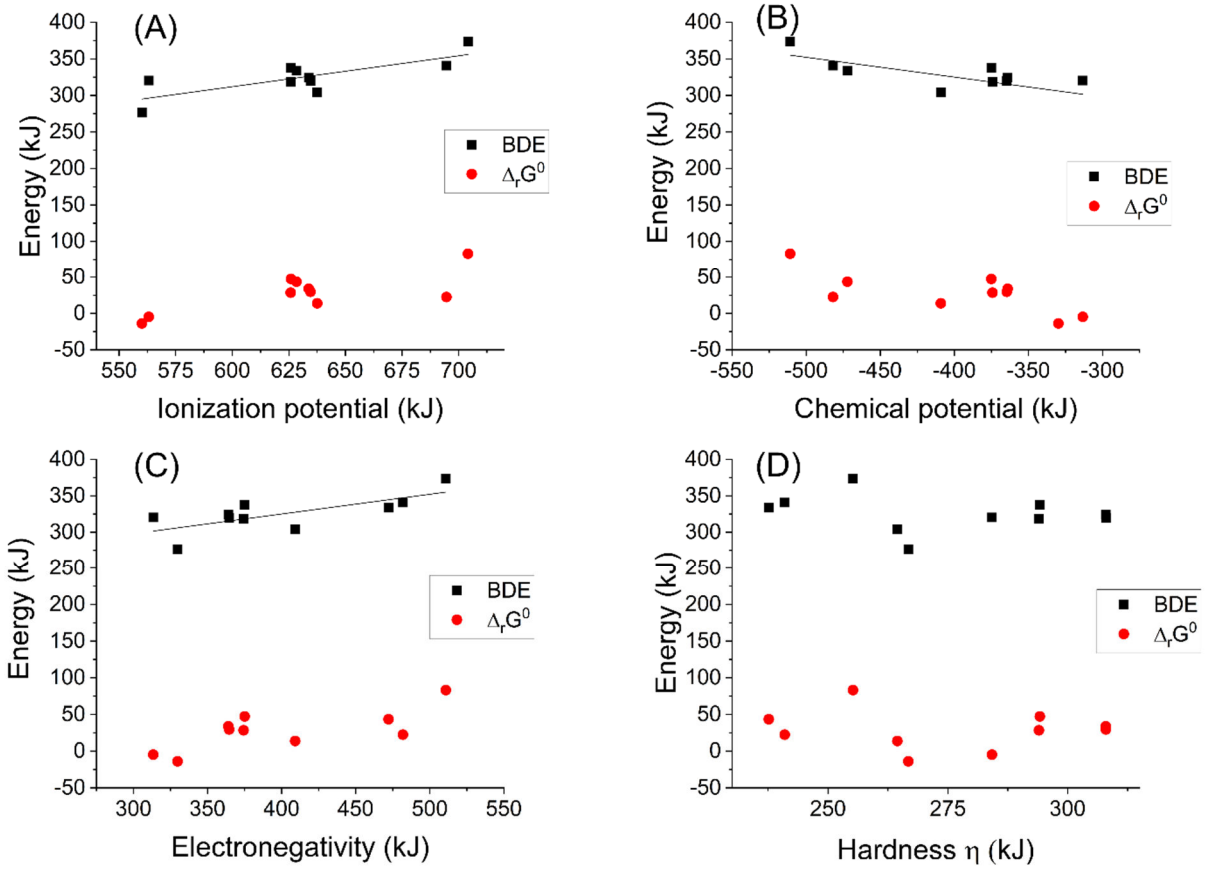

Figure 3. The Quantitative Structure-Activity Relationship (QSAR) for antioxidant activity of the studied aaptamines. The energy of BDE and $\Delta_r G^0$ for HT reaction (kJ) of the HOO•-scavenging activity in the gas phases are given in relationship with (A) ionization potential, (B) chemical potential, (C) electronegativity, and (D) absolute hardness of the aaptamine molecules.

4. Conclusion

In conclusion, we performed a theoretical study on the antioxidant activities of ten aaptamine derivatives. The results indicated **A7** are the most potent scavengers, with the HT mechanism identified as the most favorable channel in both gas and aqueous environments. Notably, **A7** emerged as the most potent compound, demonstrating strong scavenging activity against HO• and HOO• radicals across all three mechanisms, in two media (gas, water). Our study may prove valuable in the search for novel antioxidant compounds based on unusual framework, and can be readily applied in computer-aided drug design.

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